Aromatic Organolithium Reagents Bearing Electrophilic Groups. Preparation by Halogen–Lithium Exchange[1]

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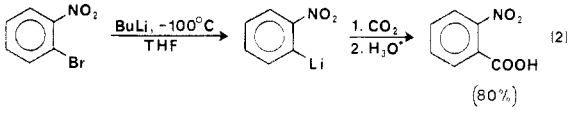
The discovery that aryllithium reagents could be generated by halogen–lithium exchange (eq 1)[3,4]

$$\mathrm{ArX} + \mathrm{RLI} \rightarrow \mathrm{ArLi} + \mathrm{RX} \qquad (1)$$

prompted Gilman et al. to extend this exchange reaction to the preparation of aryllithium reagents bearing electrophilic groups.[5–8] Although these new reagents held great synthetic promise, they were, with the exception of lithium *p*-lithiobenzoate,[6] prepared in uniformly unsatisfactory yields resulting in postponement of their application in organic synthesis for two decades. The observation by Köbrich and Buck[9] that *o*-nitrobromobenzene in tetrahydrofuran at about −100 °C exchanged rapidly and cleanly with butyllithium (eq 2)



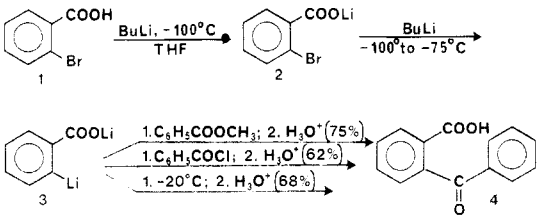
(2)

showed that the lithium–halogen exchange reaction was still rapid at −100 °C and suggested that at such a low temperature unwanted side reactions of the new organolithium reagent might be inhibited.

Reagent Formation

The Köbrich and Buck[9] conditions, suitably modified, have permitted the preparation of many aromatic organolithium reagents bearing electrophilic groups by halogen–lithium (usually bromine–lithium) exchange. Table I[10–17] lists some reagents that reacted with at least one electrophile and presumably could react with others. The functional groups used successfully have in common that at −100 °C their rate of reaction with butyllithium (or *tert*-butyllithium) lags well behind the rate of halogen–lithium exchange. Low temperature is important in achieving satisfactory yields, a dramatic illustration being the yield of (4-cyanophenyl)lithium,

Scheme I



which rose from 17%[7] to 83% (Table I) with a decrease in reaction temperature of only 30 °C (from −70 °C to −100 °C).

Not all reagents prepared in this laboratory have been included in Table I. In some instances irreversible inter- and intramolecular reaction intervened too rapidly during exchange to permit reaction with an external electrophile; in others, our focus on intramolecular reactions led us to omit a thorough study of the intermediates. In theory, intermolecular interaction (self-condensation) should be possible when the substituents are present in the ortho, meta, or para relationship to the lithio group, and this has been illustrated by the formation of *o*-, *m*-, and *p*-benzoylbenzoic acid (vide infra). With certain ortho-substituted reagents, it has been shown that intramolecular addition or condensation leads to products containing a new ring.

Interest in the various interactions characteristic of ortho-substituted reagents has led to a great preponderance of these in Table I.

The time required for the halogen–lithium exchange varies from hours in the case of lithium *o*-bromobenzoate to only a few minutes for *o*-bromobenzyl chloride. If the time required for exchange is too great,

William E. Parham was born in Denton, TX, in 1922 and received his B.A. degree from Southern Methodist University in 1943 (Honorary Doctor of Science, 1966). At the University of Illinois his research for the Ph.D. degree (awarded in 1946) was carried out under the direction of the late Professor R. C. Fuson. He joined the faculty of the University of Minnesota, where he reached the rank of Professor in 1955 and Chief of the Division of Organic Chemistry in 1958. In 1972 he became R. J. Reynolds Industries Professor of Chemistry at Duke University, where the work described in this account was done. His other research interests have included heterocyclic chemistry, the chemistry of halocyclopropanes, and pharmaceutical agents. Long interested in synthetic methods, he was Treasurer of *Organic Synthesis* at the time of his death. A vigorous outdoorsman, he spent his long vacation each year at his summer home at Deer Lake in northern Minnesota. It was there that the end came unexpectedly on May 21, 1976.

Charles K. Bradsher was born in Petersbury, VA. He received the A.B. degree from Duke University in 1933. His research for the Ph.D. degree of Harvard (1937) was done under the direction of L. F. Fieser. After a postdoctoral research appointment at the University of Illinois (with Professor R. C. Fuson), he joined the faculty of Duke University, where he reached the rank of James B. Duke Professor of Chemistry in 1965. He retired from teaching and active research in 1979. His research interests have included cyclization and cycloaddition and the chemistry of aromatic systems having a bridgehead nitrogen.

(1) Aromatic organolithium reagents bearing electrophilic groups may also be generated by direct lithiation. Important advances in this field have been made by P. Beak and V. Snieckus, who have collaborated on an Account of the research of their two groups (*Acc. Chem. Res.* **1982**, following paper in this issue). We are grateful to them for making their manuscript available to us prior to publication.

(2) Deceased May 21, 1976. This Account is dedicated to the memory of Dr. Parham.

(3) This author, now retired, served as principal investigator for the Parham project from 1976 until its termination in 1979.

(4) Gilman, H.; Jacoby, A. L. *J. Org. Chem.* **1938**, *3*, 108.
(5) Wittig, G.; Pockels, V.; Dröge, H. *Chem. Rev.* **1938**, *71*, 1903.
(6) Gilman, H.; Arntzen, C. E. *J. Am. Chem. Soc.* **1947**, *69*, 1537.
(7) Gilman, H.; Melstrom, D. S. *J. Am. Chem. Soc.* 1948, *70*, 4177.
(8) Hofferth, B. F.; *Iowa* State *J. Sci.* **1952**, *26*, 219.
(9) Köbrich, G.; Buck, P. *Chem. Ber.* **1970**, *103*, 1412.
(10) Parham, W. E.; Sayed, Y. A. *J. Org. Chem.* **1974**, *39*, 2053.
(11) Parham, W. E.; Jones, L. D. *J. Org. Chem.* **1976**, *41*, 2704.
(12) Boykin, D. W. Ph.D. Dissertation, Duke University, 1978.
(13) Parham, W. E.; Jones, L. D. *J. Org. Chem.* **1976**, *41*, 1187.
(14) Parham, W. E.; Jones, L. D.; Sayed, Y. A. *J. Org. Chem.* **1975**, *40*, 2394.
(15) Parham, W. E.; Jones, L. D.; Sayed, Y. A. *J. Org. Chem.* **1976**, *41*, 1184.
(16) Parham, W. E.; Bradsher, C. K.; Reames, D. C. *J. Org. Chem.* **1981**, *46*, 4804.
(17) Reames, D. C. Ph.D. Dissertation, Duke University, 1979.

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Table I
Yields As Measured by Reaction with Added Electrophilic Reagents

$ZC_6H_4Br + BuLi \rightarrow ZC_6H_4Li + BuBr$

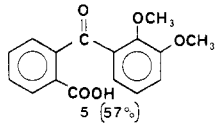
no.	Z	site Br	reagent	product	yield %	ref
1	COOLi[a]	*o*	$C_6H_5COOCH_3$	keto acid	75	10
2	COOLi[a]	*m*	$C_6H_5COOCH_3$	keto acid	61	10
3	COOLi[a]	*p*	$C_6H_5COOCH_3$	keto acid	64	10
4	$COOCH(CH_3)_2$	*o*	C_6H_5NCO	phthalimide	53	11
5	$COOC(CH_3)_3$	*o*	$(CH_3)_3SiCl$	silane	61	12
6	$COOC(CH_3)_3$	*m*	$(CH_3)_3SiCl$	silane	44	12
7	$COOC(CH_3)_3$	*p*	$(C_6H_5)_2CO$	tertiary alcohol	76	11
8	CN	*o*	cyclohexanone	iminophthalan	82	13
9	CN	*m*	$(C_6H_5)_2CO$	tertiary alcohol	86	13
10	CN	*p*	$(C_6H_5)_2CO$	tertiary alcohol	83	13
11	CH_2CH_2COOLi[a]	*p*	cyclohexanone	cyclohexene	67	14
12	$CH_2CH_2CONHLi$[a]	*o*	cyclohexanone	tertiary alcohol	40	14
13	$C(CH_3)_2CN$	*o*	$CH_3CH_2CH_2CH_2Br$	butylarene	74	13
14	CH_2Cl	*o*	cyclohexanone	phthalan	75	15
15	$CH(CH_3)Cl$	*o*	cyclohexanone	phthalan	65	16
16	$C(CH_3)_2Cl$	*o*	C_6H_5NCO	phalimidine	29	16
17	CH_2CH_2Br	*o*	cyclohexanone	isochroman	75	15
18	$CH_2CH_2CH_2Cl$	*o*	cyclohexanone	tertiary alcohol	64	15
19	$CH{=}N{-}OCH_3$	*o*	solid CO_2	acid	88	17

[a] By reaction of carboxylic acid with 2 equiv of butyllithium.

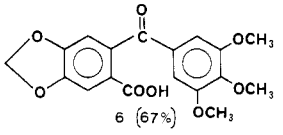
or the reactivity of the added electrophile is too low, the loss of the reagent by reaction (ether splitting)[18] with the tetrahydrofuran used as a solvent and halogen–lithium exchange catalyst can become important.

Reaction of Reagents Derived from Bromobenzoic Acids. In their seminal study, Gilman and Arntzen[6] found that at −75 °C the slow addition of 2 mol of butyllithium to *o*-bromobenzoic acid (**1**) in ether afforded first the salt (**2**) and then the dianion, lithium *o*-lithiobenzoate (**3**), which by carbonation was shown to have been present in 38% yield. Parham and Sayed[19] found that when the addition was carried out at −100 °C in THF, followed by 2 h at −75 °C, the desired dianion (**3**) was formed in much higher yield (Table I). Addition of water to the reaction mixture afforded benzoic acid in 83% yield.

Of more synthetic utility was the addition of the dianion **3** to the methyl esters of aromatic acids (including those of heterocyclic acids[20]) at −75 °C to produce keto acids analogous to **4** (Scheme I).[21] A more surprising discovery[22] was that the addition of the strong electrophile, benzoyl chloride, at −100 °C to the dianion **3** afforded *o*-benzoylbenzoic acid (**4**) in 62% yield. Several *o*-benzoylbenzoic acids, including some difficult to make by other means, have been prepared by the reaction of the appropriate aroyl chloride with dianion **3** or its congeners. These have included[22] a new intermediate (**5**) for the synthesis of alizarin dimethyl ether and a degradation product (**6**) of podophyllotoxin.[23]



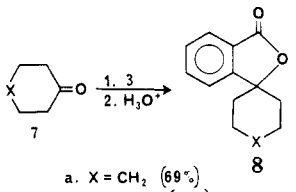
5 (57%)



6 (67%)

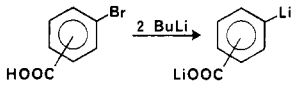
When a solution containing lithium *o*-lithiobenzoate (**3**) was allowed to warm up to −20 °C and to remain at the temperature for 5 h, acidification afforded the self-condensation product *o*-benzoylbenzoic acid (**4**) in 68% yield. Only a small quantity of anthraquinone (2.3%) was formed, and efforts to maximize the yield never produced more than 44%.

Another application of lithium *o*-lithiobenzoate (**3**) has been in the synthesis of spirolactones.[24,25] Reaction of **3** with cyclohexanone (**7a**) or 1-methyl-4-piperidone (**7b**), followed by heating with dilute acid, gave the desired spirolactone (**8a** and **8b**) in 69% and 72% yields, respectively.



a. X = CH_2 (69%)
b. X = CH_3N (72%)

Addition of 2 equiv of butyllithium to *m*-bromobenzoic acid (**9**) afforded lithium *m*-lithiobenzoate (**10**),

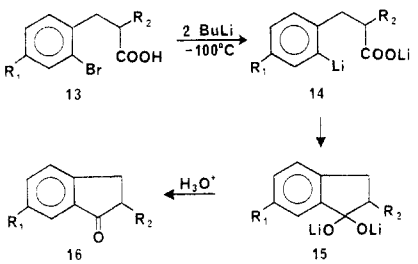


9 meta 10
11 para 12

which underwent self-condensation[19] or reaction with methyl esters[11] in good yield. Similar results were obtained starting with *p*-bromobenzoic acid (**11**), affording lithium *p*-lithiobenzoate (**12**).[19,26] The para dianion **12**

(18) Wakefield, B. J. "The Chemistry of Organolithium Compounds"; Pergamon: Oxford, 1974; p 198.
(19) Parham, W. E.; Sayed, Y. A. *J. Org. Chem.* **1974**, *39*, 2051.
(20) Parham, W. E.; Piccirilli, R. M. *J. Org. Chem.* **1976**, *41*, 1268.
(21) Cf.: Raynolds, P. W.; Manning, M. J.; Swenton, J. S. *Tetrahedron Lett.* **1977**, 2383 and Swenton, J. S.; Jackson, D. K.; Manning, M. J.; Raynolds, P. W. *J. Am. Chem. Soc.* **1978**, *100*, 6182.
(22) Parham, W. E.; Bradsher, C. K.; Edgar, K. J.; *J. Org. Chem.* **1981**, *46*, 1057.
(23) Professor V. Snieckus reports (private communications) that *o*-lithio-*N*,*N*-diethylbenzamide does not afford the *o*-benzoylbenzamide when allowed to react at −78 °C with either methyl benzoate or benzoyl chloride.
(24) Parham, W. E.; Egberg, D. C.; Sayed, Y. A.; Thraikill, R. W.; Keyser, G. E.; Neu, M.; Montgomery, W. C.; Jones, L. D. *J. Org. Chem.* **1976**, *41*, 2628.
(25) (a) Cf.: Bodem, G. D.; Leete, E. *J. Org. Chem.* **1979**, *44*, 4696. (b) Beak and Brown (Beak, P.; Brown, R. A. *J. Org. Chem.* **1977**, *44*, 1823, 4463) prepared related phthalans by reaction of ketones with reagents generated by metalation of aryl amides.
(26) A 62% yield of lithium *p*-lithiobenzoate was achieved by Gilman and Arntzen.[6]

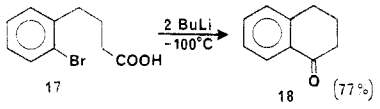
Scheme II



a. $R_1 = R_2 = H$
b. $R_1 = H$; $R_2 = o\text{-}BrC_6H_4CH_2$
c. $R_1 = CN$; $R_2 = H$

reacted with methyl benzoate,[10] as did the ortho (**3**) and meta (**10**) isomers. Self-condensation of **12** appeared to be slower than that of **3** or **10**, for a yield of only 40% of *p*-benzoylbenzoic acid was obtained under the conditions that produced over 60% of the ortho and meta isomers. The yield could be increased to 55–60% by increasing the proportion of hexane in the solvent, or lowered to zero by increasing the amount of tetrahydrofuran.

Reagents Derived from (Bromoaryl)alkanoic Acids[14]—The Parham Cycliacylation. If the carboxylate function is attached to an ortho side chain of a reagent, the possibility for intramolecular condensation (cyclization) arises. (*o*-Bromophenyl)acetic acid (like its para isomer) reacts with 2 equiv of butyllithium to produce no cyclic ketone but a mixture of products derived by lithium replacement of the carboxylate hydrogen, the methylene hydrogen, and/or the bromine atom. Better success was obtained when 3-(*o*-bromophenyl)propionic acid (**13a**) was allowed to react at −100 °C with 2 equiv of butyllithium; the yield of pure 1-indanone (**16a**) was 76% (Scheme II). A similar experiment using an *o*-bromobenzyl derivative (**13b**) of the phenylpropionic acid afforded the substituted indanone **16b** in 66% yield. In a discussion of the probable scope of the cyclization, Parham et al.[14] predicted that, unlike the Friedel–Crafts cyclization, the new reaction would not be inhibited by the presence of a meta-directing group. This proved correct, for when a 3-(*o*-bromophenyl)propionic acid bearing a cyano group para to the side chain (**13c**) was treated at −100 °C with 2 equiv of butyllithium, the cyanoindanone **16c** was obtained in 69% yield.[17,27] The predicted[14] cyclization of 4-(*o*-bromophenyl)butanoic acid (**17**) to tetralone **18** was carried out in 77% yield.[28,29] The



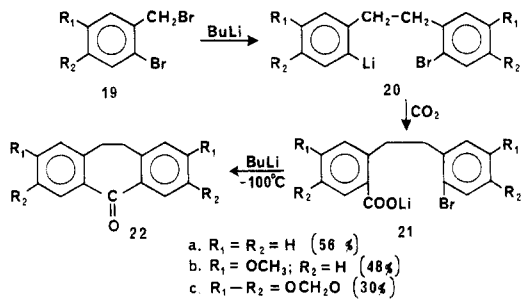
discovery[15] that the action of 1 equiv of butyllithium on *o*-bromobenzyl bromide (**19**) afforded good yields of 1-(2-lithiophenyl)-2-(2-bromophenyl)ethane (**20**) offered an opportunity to achieve a simple one-pot synthesis

(27) Since meta-directing groups do not inhibit cyclization, the possibility for a double cyclization could be considered.

(28) Jones, L. D. Ph.D. Dissertation, Duke University, 1976, p 8.; *Diss. Abstr., Int. B*, **1976**, *37*, 2857.

(29) It was later shown by Boatman et al. (Boatman, R. J.; Whitlock, B. J.; Whitlock, H. W., Jr. *J. Am. Chem. Soc.* **1977**, *99*, 4822; **1978**, *100*, 2935) that the preformed lithium salt of **17** could be cyclized in 73% yield by the action of *tert*-butyllithium. The same authors have made important application of the Parham cycliacylation in the preparation of anthracycline intermediates.

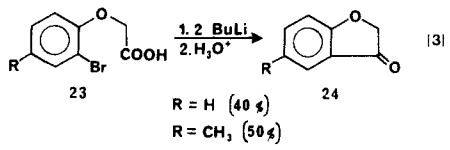
Scheme III



a. $R_1 = R_2 = H$ (56%)
b. $R_1 = OCH_3$; $R_2 = H$ (48%)
c. $R_1 - R_2 = OCH_2O$ (30%)

of dibenzosuberones (**22**) via the Parham cycliacylation (Scheme III).

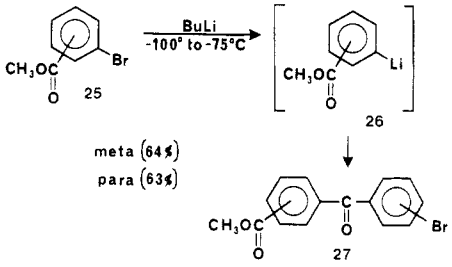
Although the new method of ring closure might likewise find extensive application in heterocyclic synthesis, the sole such example to date involves the synthesis of benzofuranones (**24**) (eq 3).[17] The low yields



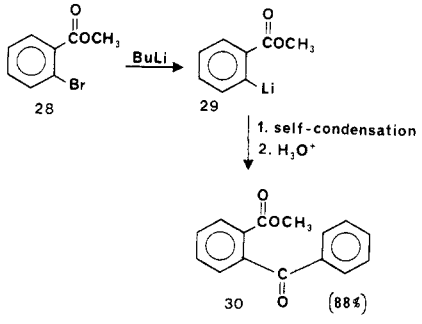
(3)

achieved may be due in part to the low stability[30] of these products.

Reagents Bearing an Ester Function. The carbonyl group of an ester is, in general, more reactive than that of a carboxylate ion, and it is not surprising that halogen–lithium exchange of methyl *m*- and *p*-bromobenzoates (**25**) to form **26** is swiftly followed by its reaction with the carbonyl group of the unreacted bromo ester (**25**) present, to yield the methyl ester (**27**) of a (bromobenzoyl)benzoic acid.

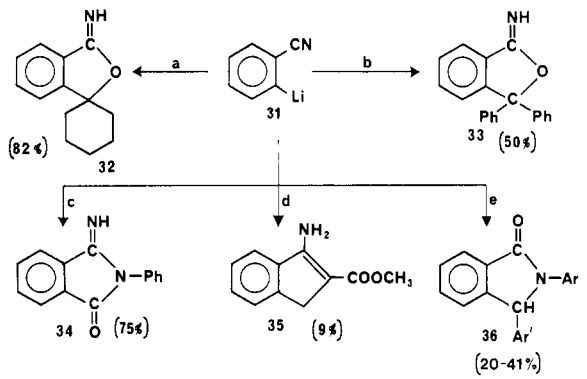


With 1 equiv of butyllithium under essentially the same conditions, the reaction of the ortho ester (**28**) takes a different course. For reasons which may involve interaction (chelation) of the ortho groups, or steric hindrance, the lithio reagent **29** does not attack unchanged bromo ester **28** but, instead, slowly undergoes self-condensation. Acidification of the mixture[31] af-



(30) Mustafa, A. In "The Chemistry of Heterocyclic Compounds", Weissberger, A. Taylor, E. C., Eds.; Wiley: New York, 1974, vol. 29.

Scheme IV

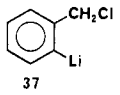


Reagents: a, cyclohexanone
b, benzophenone
c, phenylisocyanate
d, methyl acrylate
e, ArN=CH-Ar', then H_3O^+

fords methyl *o*-benzoylbenzoate (**30**) in 88% yield.

From the more hindered isopropyl *o*-bromobenzoate or *tert*-butyl bromobenzoates (any isomer), less reactive reagents have been prepared, permitting reactions with added electrophiles (Table I).

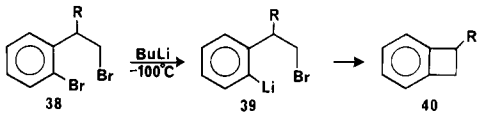
Reagents Bearing Nitrile Groups[13]—Cyclizations Requiring Added Electrophiles. Bromobenzonitriles undergo halogen–lithium exchange to afford reagents (e.g., **31**) that show little tendency to undergo self-condensation and usually react with added electrophiles. It the lithium atom of the reagent is ortho and the added electrophile creates a new anion which can attack the nitrile group, a new ring can result, as illustrated by the preparation of spiro[cyclohexane-1,1′[3*H*]isobenzofuran]-3′-imine (**32**). Other cyclizations involving added electrophiles are shown in Scheme IV. Of the cyclic products, the most interesting was that obtained by conjugate addition to methyl acrylate, but the yield of the cyclic product (**37**) was very poor. The



task of developing a useful annelation reaction from the conjugate addition of aryllithium reagents was difficult,[32] but it has now been achieved by two groups, using as substrates vinyl sulfone[33] or methyl 2-(trimethylsilyl)acrylate.[34] Slightly better yields of the isoindolone derivative **36** can be obtained by use of isopropyl *o*-lithiobenzoate instead of **31** in reaction with Schiff bases.[35]

(Bromophenyl)acetonitriles undergo selective hydrogen–lithium exchange of the methylene group,[36] and where the bromine is in the ortho position it has been demonstrated that the anion so derived can be readily monoalkylated by suitable halides.[37] As was recorded in Table I, 2-(*o*-bromophenyl)-2-methylpropionitrile with no acidic protons underwent halogen–lithium exchange readily.

Reagents with Halogenated Side Chains—The Parham Cyclialkylation. The discovery[15] that aryl bromides bearing halogenated side chains nearly all undergo halogen–lithium exchange preferentially at the aromatic halogen[38] has been of importance to organic synthesis. The aryllithium reagents (**38**) having the side

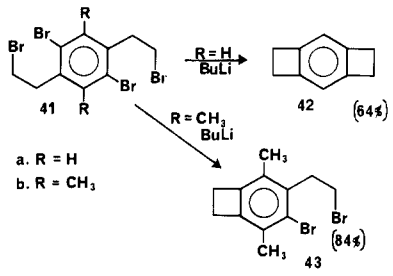


a. R = H (68%)
b. R = $PhCH_2$ (78%)
c. R = Bu (86%)

chain ortho to the lithium atom have been studied extensively because of their potential for cyclization, either directly (the Parham cyclialkylation) or after reaction with an added electrophile.

The simplest member of the series, *o*-lithiobenzyl chloride (**37**), does not cyclize directly but, on warming, dimerizes to afford 9,10-dihydroanthracene (43% yield). The simplest Parham cyclialkylation was that observed when 2-(2-bromophenyl)-1-bromoethane (**38a**) was treated at −100 °C with butyllithium and the mixture allowed to warm to 25 °C; benzocyclobutene (**40a**) was produced in 68% yield. This cyclization has proved to be a convenient nonpyrolytic route to benzocyclobutene and its derivatives. An obvious extension, the preparation of benzocyclobutenes bearing alkoxyl groups in the aryl ring, was achieved in good yield.[39,40] The recently described[37] extension of the synthesis to the preparation of 1-substituted benzocyclobutenes (e.g., **40b** and **40c**) may prove useful for the synthesis of intermediates for intramolecular cycloaddition.[41,42]

It has proved possible to prepare benzo[1,2:4,5]dicyclobutene (**42**) by a dual Parham cyclialkylation of **41a**.[43] An attempted extension to the related dimethyl



tetrabromide (**41b**) failed to give a dimethylbenzodicyclobutene but, instead, afforded a product with only a *single* cyclobutene ring (**43**).[44]

(31) There is no evidence concerning the nature of the anion present in the reaction mixture. An attempt at carbonation or bromination might be instructive.

(32) Compare K. J. Edgar, Ph.D. Dissertation, Duke University, 1979.

(33) Ponton, J.; Ponton, P.; Helquist, P.; Conrad, P. C.; Fuchs, P. L. *J. Org. Chem.* **1981**, *46*, 118.

(34) Narula, A. P. S.; Schuster, D. I. *Tetrahedron Lett.*, **1981**, 3707.

(35) Bradsher, C. K.; Hunt, D. A. *J. Org. Chem.* **1981**, *46*, 327.

(36) The aryl halogen of such anions is reluctant to undergo halogen–lithium exchange.

(37) Bradsher, C. K.; Edgar, K. J. *J. Org. Chem.* **1981**, *46*, 4600.

(38) The notable exception, *o*-bromobenzyl bromide, first exchanges the benzylic bromine (Scheme III).

(39) Brewer, P. D.; Tagat, J.; Hergrueter, C. A.; Helquist, P. *Tetrahedron Lett.* **1977**, 4373.

(40) Bradsher, C. K.; Hunt, D. A.; *Org. Prep. Proced. Int.* **1978**, *10*, 267.

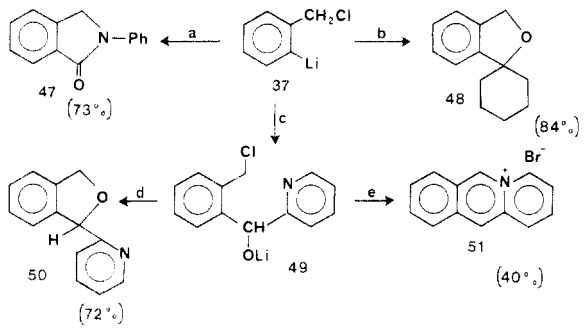
(41) It was explained[37] that the usual route to 1-substituted benzocyclobutenes involved the Bunnett cyclization[42] of *o*-halodihydrocinnamonitrile.

(42) Bunnett, J. F.; Skorcz, J. A. *J. Org. Chem.* **1973**, *29*, 73.

(43) Bradsher, C. K.; Hunt, D. A. *J. Org. Chem.* **1981**, *46*, 4600.

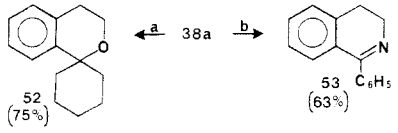
(44) A reasonable explanation for the failure of the remaining aryl halogen of **52** to exchange is that strain caused by the methyl groups induced carbanion formation by hydrogen–lithium exchange. It would have been instructive to carbonate the reaction mixture before hydrolysis.

Scheme V



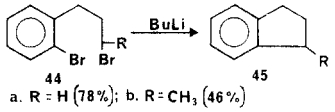
Reagents and conditions: a, C_6H_5NCO at -100°C to 25°C; b, cyclohexanone at -100°C to 25°C; c, picolinaldehyde at -100°C; d, from -100°C to 25°C; e, C_2H_5OH at -78°C, 80°C, HBr

Scheme VI



Reagents and conditions:
a, cyclohexanone, warm to 25°C
b, benzonitrile, warm to 25°C

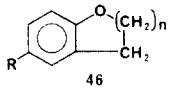
It was also demonstrated that 3-(2-bromophenyl)-1-bromopropane (**44a**) can be cyclized to indan (**45a**) in 78% yield. If the bromine was secondary, as in **44b**,



a. R = H (78%); b. R = CH_3 (46%)

cyclization was much slower, and only a 46% yield of 1-methylindan (**45b**) was obtained.[17]

While the extension of the new cyclialkylation method to larger carbocyclic ring systems remains to be tried, experiments with the more readily accessible 2,ω-dibromoaralkyl ethers indicate that rings having up to seven members may be formed readily (**46**).[45,46]



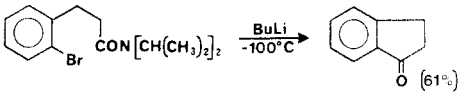
R = CH_3, H, n = 1-3
(69-80%)

Most ortho reagents with halogenated side chains can be made to react with certain substrates to create new anions, and these anions, often at temperatures well below the ambient, serve as nucleophiles to displace the halogen in the side chain, creating a heterocyclic system (Scheme V). For example, the reaction of *o*-lithiobenzyl chloride (**37**) with phenyl isocyanate must first produce the lithium salt of *o*-(chloromethyl)benzanilide, which, when allowed to warm to room temperature, cyclizes to produce *N*-phenylphthalimidine (**47**).[15] The addition of the same reagent to cyclohexanone leads to a phthalan (**48**), which must be generated by an internal Williamson synthesis. In the same way, the addition of picolinaldehyde to the reagent also leads to a phthalan (**50**). Evidence that the intermediate (**49**) has more than a transitory existence is provided by the observation that when it was quenched at −78 °C in ethanol, internal quaternization and dehydration provided a new route to acridizinium bromide (**51**).[47]

When the same general pattern of first creating a cyclizable anion is followed, the reagent **38a** generated from *o*-bromophenethyl bromide reacts with cyclohexanone to give, on cyclization, an isochroman[15] (**52**, Scheme VI). If the added electrophile was benzonitrile, the imine salt first formed lost lithium bromide to furnish 1-phenyl-3,4-dihydroisoquinoline (**53**).[48,49]

Other Cyclizations of the Parham Type. The Parham cyclialkylation and the Parham cycliacylation have in common that an electrophilic group attached to an *ortho* side chain of an aryl organolithium compound is attached by the anionic center. Reagents having compatible electrophilic groups other than haloalkyl groups or the carboxylate ion offer the possibility for additional cyclizations of the Parham type.

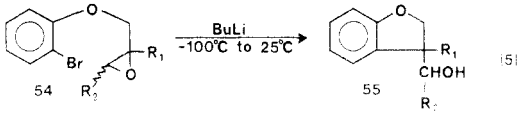
A little-studied variant of the cycliacylation reaction involves the use of the *N,N*-dialkylamide group instead of the carboxylate ion (eq 4).[14] The method has the



(4)

advantage of using only 1 equiv of butyllithium and avoids the "internal quenching"[50] that may occur with bromo carboxylic acids if the rate of halogen–lithium exchange is comparable with that of hydrogen–lithium exchange.[29,50,51]

At −100 °C the epoxide linkage is sufficiently unreactive to permit it to serve as the electrophilic group of a reagent, making possible another Parham-type cyclization (eq 5).[17,52] For convenience, the epoxides



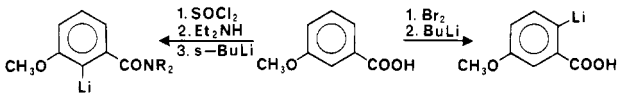
(5)

$R_1 = R_2 = H$ (64%)
$R_1 = CH_3$, $R_2 = H$ (34%)
$R_1 = H$, $R_2 = CH_3$ (79%)

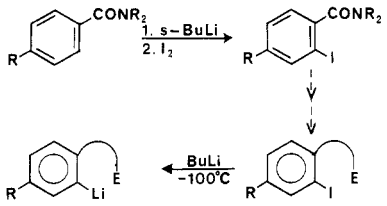
selected for study were derived from allyl ethers of *o*-bromophenol and its congeners. The epoxides **54** all cyclized to produce tetrahydrofuran derivatives **55** as the result of exo addition.[53] The yields were good except when access to the proximal end of the epoxide group was impeded by a substituent.

(45) Bradsher, C. K.; Reames, D. C. *J. Org. Chem.* **1981**, *46*, 1384.
(46) The eight-membered ring (**46**, *n* = 4) was not isolated in a state of purity, but IR–mass spectral analysis indicated the presence of a 20% yield.
(47) Bradsher, C. K.; Hunt, D. A. *J. Org. Chem.* **1980**, *45*, 4248.
(48) The earlier description of this reaction (with the better yield) was made by Hergrueter et al. (Hergrueter, C. A.; Brewer, P. D.; Tagat, J.; Helquist, P. *Tetrahedron Lett.* **1977**, 4145], in which they also described derivatives bearing alkoxy substitutents in the benzenoid ring.
(49) Parham, W. E.; Bradsher C. K.; Hunt, D. A. *J. Org. Chem.* **1978**, *43*, 1606.
(50) The phenomenon of "internal quenching" was described by: Stein, C. A.; Morton, T. H. *Tetrahedron Lett.* **1973**, 4933.
(51) Internal quenching of bromo acids may be avoided by addition of the butyllithium solution to a performed carboxylate salt (see ref 50 and 29).
(52) Bradsher, C. K.; Reames, D. C. *J. Org. Chem.* **1978**, **43**, 3800.
(53) Recently Dhawan et al. (Dhawan, K. L.; Gowland, B. D.; Durst, T. *J. Org. Chem.* **1980**, *45*, 922] have revealed that if the epoxide ring is first opened by treatment with anhydrous magnesium bromide, addition of butyllitium produces endo cyclization.

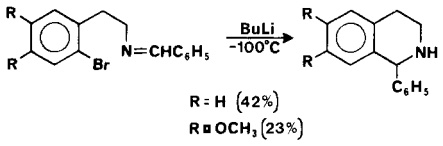
Scheme VII



Scheme VIII



One other type of side chain that has been used in a cyclization of the Parham type is the substituted aldimino group (Schiff base).[35] While the yields were poor (eq 6), no effort was made to optimize them.



(6)

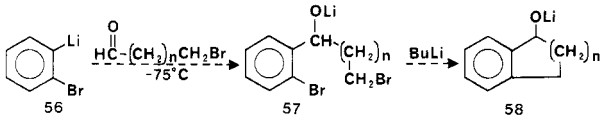
A Brief Summary and an Appraisal of Future Direction

Organolithium reagents bearing electrophilic groups that are passive in nature at low temperature may be prepared in a regiospecific manner from the appropriate aryl halide. Where the functional group is ortho to the halogen, the reagent formed by halogen–lithium exchange may react with an added (external) electrophile to give an anion capable of cyclization to produce a new heterocyclic ring. If the electrophilic group of the aryl halide is suitably positioned on an ortho alkyl side chain, direct cyclization may occur.

Most of the prototype bromobenzoic acids, nitriles, phenylalkanoic acids, phenylalkyl halides, etc., needed and not available by purchase could be prepared by straightforward methods. Alkoxy-substituted aryl halides bearing electrophilic groups were restricted to those which at some stage could be prepared by direct bromination. This approach is not as general as the direct lithiation method,[1] which always introduces lithium ortho to the dialkylamido group. Scheme VII shows how the two methods may be complementary; in this case either of the two possible *o*-lithio orientations are available from *m*-methoxybenzoic acid depending on the selection of the direct vs. the exchange method of orientation.

Should the goal of the research be to carry out a Parham cyclialkylation or cycliacylation, not yet achievable by the direct metalation method, one could first carry out a direct metalation (Scheme VIII) followed by iodination, elaboration of the amide side chain, and exchange.

The tedious task of building a side chain for cyclialkylation may be simplified by a method suggested by the recent observation[54] that at −110 °C the lithium exchange will produce good yields of *o*-lithiobromobenzene (**56**), which can be made to react efficiently



with a variety of electrophiles. If an ω-bromo aldehyde were used as the electrophile, the expected product would be the alkoxide **57**, which when treated with butyllithium would yield a benzocycloalkenol (**58**).

It is known[55] that 1,2-dibromocyclopentene also undergoes stepwise halogen–lithium exchange, and the resulting organolithium reagent could undergo a similar annelation reaction.[56]

The continued appearance of references to the preparation by halogen–lithium exchange of aromatic lithium reagents bearing electrophilic groups, as well as the imaginative uses to which these reagents have been put,[57] attests to the usefulness of the methods which Parham and his students have played so important a role in developing.

It has been a pleasure to work with the former students of W. E. Parham, who share with me a great enthusiasm for his discoveries. The names of those involved in the organolithium project are recorded in the references. In particular, I wish to thank two of them, Drs. Kevin J. Edgar and David C. Reames, for reading the manuscript. We are indebted to the Army Research Office for partial support of this project through Grants DAHC04-74-GD128 and DAAG29-77-G-0170.

(54) Chen, L. S.; Chen, G. *J. Organom. Chem.* **1980**, *193*, 283.
(55) Wittig, G.; Weinlich, J.; Wilson, R. W. *Chem. Ber.* **1965**, *98*, 458.
(56) It is well-established that bromoalkenes bearing electrophilic groups can undergo halogen–lithium exchange; e.g.: Köbrich, G.; Trapp, H.; Akhtar, A. *Chem. Ber.* **1968**, *101*, 2644; Köbrich, G.; Stöber, I. *Chem. Ber.* **1970**, *103*, 2744; Elbe, H.-L. Köbrich, G. *Tetrahedron Lett.* **1944**, 2557; Parham, W. E.; Boykin, D. W. *J. Org. Chem.* **1977**, *42*, 260; Boykin, D. W.; Parham, W. E. *J. Org. Chem.* **1979**, *44*, 424; Baker, W. R.; Coates, R. M. *J. Org. Chem.* **1979**, *44*, 1022; Caine, D.; Frobese, A. S. *Tetrahedron Lett.* **1978**, 5167.
(57) E.g.: Ziegler, F. E.; Fowler, K. W.; Kanfer, S. *J. Am. Chem. Soc.* **1978**, *98*, 8282; Newkome, Y. R.; Onishi, M. *J. Organomet. Chem.* **1980**, *198*, 225; also ref 21, 25, 29, 33, 34, 39, 48, 53.