Review

THE MECHANISM OF THE LITHIUM - HALOGEN INTERCHANGE REACTION: A REVIEW OF THE LITERATURE

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The exchange of halogen and lithium atoms in the metathesis reaction of an organic halide with an organolithium is known as the lithium-halogen interchange or, more generally, as metal-halogen interchange. The purpose of this review is to survey mechanistic studies of the interchange that have been reported in the fifty years since its discovery.

$$R-Li + R'-X \rightleftharpoons R-X + R'-Li$$

## I. Historical Introduction and Background Information

The reaction was first described in 1938 by Wittig and co-workers.[1] This initial report noted that treatment of 4,6-dibromo-1,3-dimethoxy-benzene with phenyllithium (PhLi) in diethyl ether resulted in a 95% yield of 4-bromo-1,3-dimethoxybenzene after hydrolysis with water (see Scheme 1). The authors concluded that the monobromide could only have been produced from an intermediate aryllithium compound.

Scheme 1

$$95\%$$
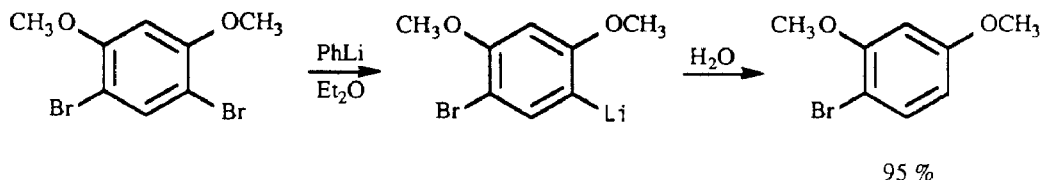
The metal-halogen interchange was undoubtedly observed, if not recognized as such, at least a decade before the publication by Wittig. Marvel, for example, reported in 1927[2] that treatment of m-bromotoluene with n-butyllithium (n-BuLi) for 4 days in petroleum ether gave toluene in 87% yield (Scheme 2). This observation was not, however, exploited and there may well be other examples of the metal-halogen interchange reaction in the early literature.

Scheme 2

$$87\%$$
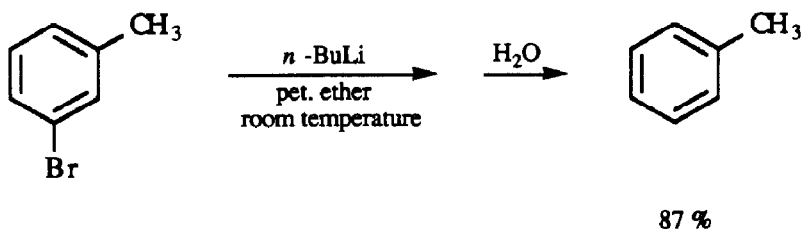
The bulk of the early studies of the metal-halogen interchange reaction were carried out by Henry Gilman and he has written two reviews which describe much of this pioneering work.[3-4] Gilman's first publication on the topic appeared in 1939.[5] This article reported that carbonation of a reaction mixture, prepared by the addition of o-bromoanisole in diethyl ether to an ethereal solution of n-BuLi, resulted in a 47% yield of o-methoxybenzoic acid (Scheme 3). It was recognized that the intermediate
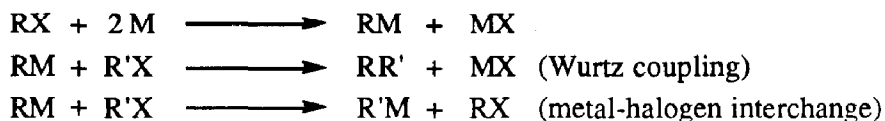
Scheme 3

47 %
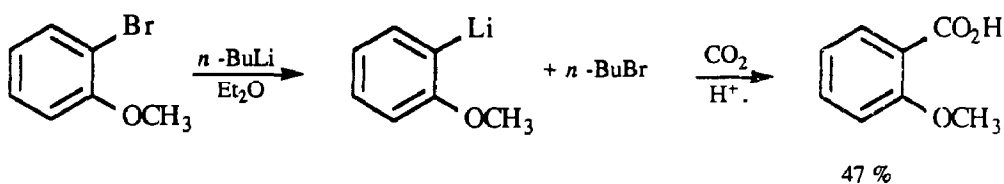
o-lithioanisole was derived from lithium-bromine exchange.[5] In one of Gilman's first reports, it was concluded that," . . . there is no present evidence (as of 1940) of any significant halogen-metal interconversion in reactions between alkyl halides and RLi compounds . . ."[6] Such evidence was however soon obtained. The initial observation that reactions between aryllithiums and alkyl halides were quite sluggish[7] undoubtedly led Gilman to employ aryl halides in a majority of his pioneering studies of the metal-halogen exchange reaction.[3,4] Some of the conclusions which derive from these early studies are as follows: (a) aryl fluorides and chlorides do not undergo interchange;[6] (b) the rates of interchange of aryl halides decrease in the order I>Br>Cl;[8] (c) interchange is a reversible process leading to an equilibrium mixture favoring the more stable organo-lithium[3,4,7]. These early observations remain a useful guide to understanding the interchange reaction.

Since its discovery, the metal-halogen interchange reaction has been widely used for the preparation of otherwise inaccessible organolithiums and the vast literature on this topic has been extensively reviewed[3,4,9-12].

These reviews, with a few exception[9,12], delt primarily with the synthetic utility of the reaction and, despite continued interest in the interchange as a synthetic method, the mechanism of the reaction remains something of an enigma. The lack of consensus as to mechanistic detail is attributable in large measure to the capricious behavior of organic halides when treated with organolithiums. Competing reactions are particularly troublesome in mechanistic studies and metal-halogen interchange is often accompanied by such side-reactions as β-elimination,[4,5,9-12] α-metallation,[13,14] reduction of the organohalide[15] and Wurtz-type coupling to produce symmetrical and "mixed" hydrocarbons.[9-12,16]

Discussion of the relationship (if any) between metal-halogen interchange and Wurtz-type coupling has a long history. The Wurtz reaction, which involves formation of alkanes by dimerization of alkyl halides over sodium metal, is one of the oldest "name reactions" in organic chemistry.[17,18] The name has come to be associated more generally with the formation of hydrocarbons via coupling of an organometallic compound with an organohalide. It has been postulated that organometallics are in fact intermediates in Wurtz-type reactions and, therefore, the mechanism of this coupling process and that of metal-halogen interchange may be closely related. Spencer and Price[19], for example, suggested in 1910 that organolithium compounds were produced as intermediates in the coupling of organohalides over lithium metal. It is of interest to note that this suggestion predates the first synthesis and isolation of an organolithium compound (prepared by metal-metal exchange from organomercurials and lithium metal) by Schlenk and Holtz in 1917[20]. It was not until 1930 that organolithiums were prepared directly from organohalides and lithium metal by Ziegler and Colonius[21].

Gilman and Jones[7] also believed that organometallics were intermediates in Wurtz-type processes. It was postulated that these reactive organometallics could interact with an organic halide to give either the coupling product or exchange products as shown in Scheme 4.

Scheme 4

RX + 2 M $\longrightarrow$ RM + MX

RM + R'X $\longrightarrow$ RR' + MX (Wurtz coupling)

RM + R'X $\longrightarrow$ R'M + RX (metal-halogen interchange)

In addition to the problem of side-product formation, investigation of the mechanism of metal-halogen interchange is further complicated by the fact that organolithium compounds do not exist as monomers. They, in fact, exist as aggregates whose degree of association may be affected by such factors as solvent, concentration and temperature.[9-12,22-25] The degree of association of some common organolithiums in the gas phase and in various solvents is given in Table 1. Two general trends can be deduced from the data presented in this table: (a) the degree of association is primarily dependent on steric interactions between alkyl groups; and, (b) the degree of association for a particular organolithium decreases upon changing from a hydrocarbon to a basic solvent.

It is known that lithium organics are electron deficient species[11,24] in that "there are more interatomic contacts than there are valence electron pairs available for bonding".[32] X-Ray analyses have shown that lithium is tetracoordinate in the majority of structures that have been studied.[33] Consequently, electron-donating solvents such as diethyl ether or THF coordinate strongly to lithium. Amines are commonly used as complexing agents for alkyllithiums,[33-39] with diamines such as tetramethylethylenediamine (TMEDA) being especially effective for this purpose.[33,34,36,37] Complexation with Lewis bases results in lower-order aggregates of organolithiums which have significantly higher levels of reactivity. In some instances reactivity is enhanced to the point where the lithium reagent is consumed through reaction with the additive or solvent[40-42]. Secondary and tertiary alkyllithiums, for example, have a maximum lifetime of about 1 hour in diethyl ether at room temperature and an even shorter lifetime in THF.[40]

Table 1

Association of Organolithium Compounds[a]

Alkyl Portion	Vapor	Hydrocarbon Solvent[b]	Basic Solvent[c]
CH_3	-	-	4
CH_3CH_2[d]	4,6[g]	6	-
$(CH_3)_2CH$[e]	-	4,6[h]	-
$CH_3CH_2CH_2CH_2$	-	6	4[i]
$(CH_3)_3C$	4	4	2[j]
Ph	-	-	2
$PhCH_2$[f]	-	-	1
$(CH_3)_3SiCH_2$	4	4,6[h]	-

a. Data obtained from reference 24 unless noted otherwise.

b. Values determined in benzene, cyclohexane or hexane.

c. Values determined in diethyl ether and/or THF.

d. Reference 26.

e. Reference 27.

f. Reference 28.

g. Both forms exist in the gas phase.

h. Exists as a tetramer at low concentrations and as a hexamer at high concentrations.

i. McGarrity and co-workers[29,30] believe that n-BuLi exists as an equilibrium mixture of tetrameric and hexameric forms in THF.

j. Schleyer and co-workers[25] have shown that t-BuLi exists as a dimer in diethyl ether and as a monomer in THF.

Not only do particular lithium organics show different degrees of association in different types of solvents, but to complicate the issue still further, organolithium compounds can also form mixed aggregates of varying stoichiometries with a variety of compounds.[24,33] It is known that

organolithium compounds can co-associate with other organolithiums[43] (produced in the metal-halogen exchange with an organohalide), with lithium halides[24,44-47] (these may be present if the organolithium reagent being used was made from an organohalide and lithium metal and/or they can be produced as a by-product of coupling between an organolithium and an organic halide), or with lithium alkoxides[26,30] (produced via the reaction of an organolithium with adventitious oxygen present during preparation of the organolithium reagent or during the interchange). Winkler and Winkler[45,46] believe that coordination with lithium halides results in a decrease in the reactivity of an organolithium, whereas McGarrity and co-workers[30] have presented evidence that association with lithium alkoxides increases the reactivity of organolithium reagents.

It is generally agreed that a lower degree of association results in a more reactive organolithium. It is, however, extremely difficult to identify the actual organolithium species that is responsible for the chemical transformation being investigated in a given study. Brown,[24] for example, has argued that dimers are the most reactive species in the majority of reactions involving organolithium reagents and McGarrity's group has provided recent evidence that this is so for the reactions of $\underline{n}$-BuLi with benzaldehyde at low temperature in THF solvent.[30] Brown has noted, however, that one can not exclude the possiblity that small concentrations of very reactive monomer may be responsible for the chemistry of these organometallics[24]. Indeed, studies of the addition of organolithiums to alkenes[48,49] or ketones[50] provide evidence that monomers are in fact   the reactive species and Andrews has shown that CH_3Li exists as a monomer at 15°K in an argon matrix.[51] Clearly then, any study which probes the reaction of an organolithium with a substrate should consider the fundamental question of the nature of the species ($\underline{i.e.}$ monomer, dimer, tetramer, etc.) that is responsible for the observed chemistry. Unfortunately, due to the inherent practical difficulties associated with obtaining such data for even the simplest of systems, most studies of the metal-halogen interchange reaction do not address the problem of relating organolithium association with observed reactivity.

At this juncture it is worth noting explicitly that organolithiums are depicted as monomeric species throughout this review. This convention is not meant to imply the actual structure of the reagents; rather, the use of RLi [or $(RLi)_n$] to represent an organolithium is adopted for the sake of pictoral clarity.
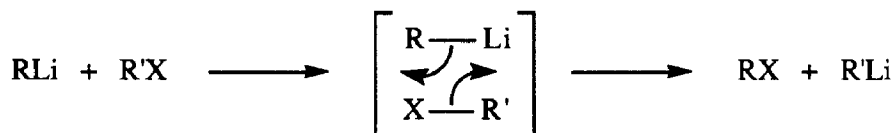
II. Mechanistic Schemes

The mechanism of the metal-halogen interchange has been explored by a number of research groups using a variety of experimental approaches. The results of these studies have, for the most part, been interpreted in terms of three principal mechanistic schemes: (1) the four-center transition state model; (2) radical-mediated mechanisms; (3) nucleophilic attack on halogen. It is instructive to consider these schemes, and the evidence for each, before proceeding to a discussion of detailed mechanistic studies.

A. Four-Center Transition State Model

This model, which was outlined in its most succinct form by Wakefield[9], involves "head-to-tail" association of RLi and RX followed by concerted if not entirely synchronous bond-breaking and bond-making as depicted in Scheme 5.

Scheme 5

$$\text{RLi} + \text{R'X} \longrightarrow \left[\begin{array}{c} \text{R} \rightharpoonup \text{Li} \\ \text{X} \!-\! \text{R'} \end{array} \right] \longrightarrow \text{RX} + \text{R'Li}$$
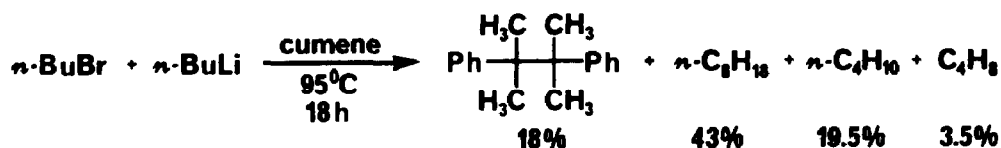
This formulation is more in the nature of a description of the reaction rather than a rigorous mechanistic pathway. Thus, although this model has been widely used to illustrate the interchange reaction, there is little,

if any, direct evidence that supports such a mechanism. Rogers and Houk[52], for example, have concluded that such a concerted exchange of lithium and halogen was a plausible model for the rate-limiting step in the lithium-bromine interchange of n-BuLi with substituted bromobenzenes but they note that their kinetic data do not demonstrate that the interchange is in fact a concerted process.

B. Radical-Mediated Mechanisms

In 1956, Bryce-Smith[53] demonstrated that radicals were generated in the reaction of n-BuLi with n-butyl bromide. He found that reaction of n-BuLi with n-butyl bromide in cumene at 95°C after 18 hours gave 2,3-dimethyl-2,3-diphenylbutane in 18% yield along with other products which are shown in Scheme 6. The only plausible way to account for the result, Bryce-Smith argued, is through the dimerization of two cumyl radicals generated from the cumene solvent via hydrogen atom abstraction by n-butyl radicals[53]. Although these results are consistent with the formation of radicals in the reaction of n-BuLi with 1-bromobutane, it is not at all clear that such intermediates are responsible for metal-halogen inter-change. Indeed, while Bryce-Smith has argued that these experiments demonstrate a radical component to Wurtz-type coupling (to give n-octane), he did not address the question of lithium-bromine exchange[53].

Scheme 6

$$n\text{-BuBr} + n\text{-BuLi} \xrightarrow[\substack{95^0\text{C} \\ 18\,\text{h}}]{\text{cumene}} \quad \underset{\substack{H_3C\ \ CH_3 \\ | \quad | \\ Ph \text{---}\!\!\!\!\text{---} Ph \\ | \quad | \\ H_3C\ \ CH_3 \\ 18\%}}{} \quad + \quad n\text{-}C_8H_{18} \quad + \quad n\text{-}C_4H_{10} \quad + \quad C_4H_8$$

18%   43%   19.5%   3.5%

It is generally agreed that radicals which may be produced in organo-metallic processes arise in most instances through a mechanism mediated by

single-electron transfer (SET) and a brief discussion of this mechanism as it pertains to metal-halogen interchange is therefore appropriate. Scheme 7 shows that SET from an organolithium compound to an organohalide produces a radical-cation (from the organolithium) and a radical-anion (from the organohalide) within the solvent cage. These short-lived[54-57] species can now follow one of two pathways: (a) loss of lithium cation and halide anion within the solvent cage results in two carbon-centered radicals which may undergo disproportionation and/or combination; (b) if, on the other

Scheme 7
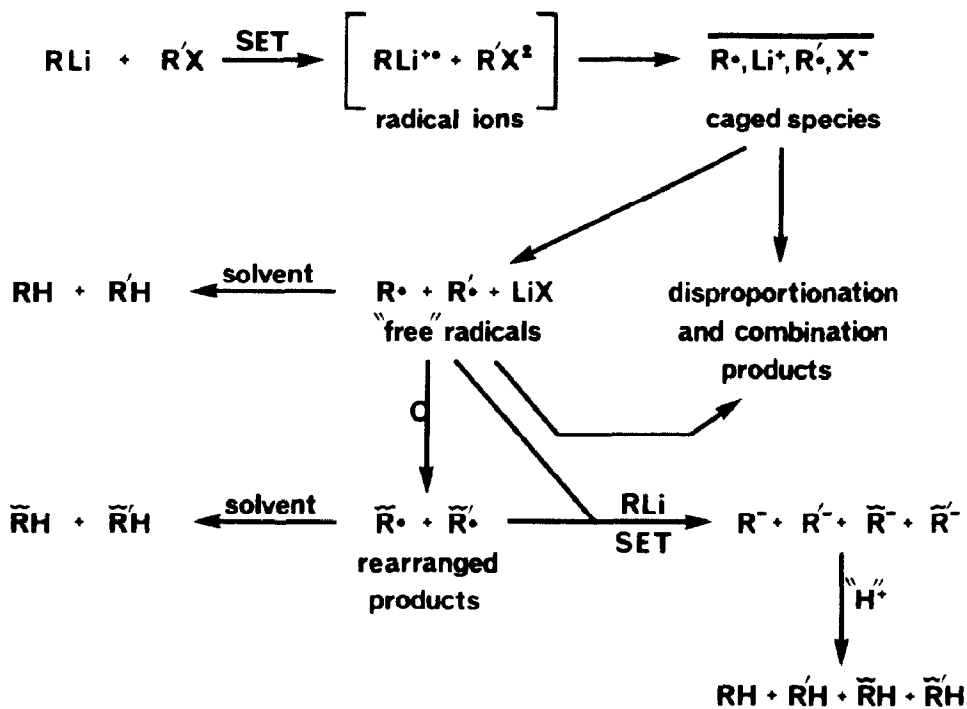
hand, the radical ions have sufficiently long lifetimes, they can diffuse from the solvent cage, and now upon loss of their attached lithium and halide ions, the resulting "free radicals" have a variety of pathways open to them. When such radicals contain certain structural characteristics

(see below), skeletal rearrangements may occur (if a particular rearrangement is extremely rapid, it can possibly take place within the solvent cage prior to coupling and/or disproportionation). Both the rearranged and unrearranged species may abstract a hydrogen atom from the solvent or be further reduced to carbanions by SET from another equivalent of the organolithium reagent. These newly produced lithium organics are then hydrolyzed by the addition of a suitable proton source or further functionalized by reaction with some other type of electrophile. It is also possible for free-radicals which are present in solution to undergo combination and disproportionation reactions, although such processes are much less likely to occur once these species have left the solvent cage.

Such a SET mediated mechanism provides an explanation for the observation of "dicumyl" in the study by Bryce-Smith[53] cited above. One would be hard pressed to think of a reasonable scheme in which this dimer originates from ionic or nucleophilic processes. Indeed, more recent studies, employing a variety of methods, have provided a great deal of direct evidence for the intermediacy of radicals in the reactions of organolithiums with organohalides. Some of these studies will now be described as they have a direct bearing on the question of possible radical intermediates in the metal-halogen interchange.

1. Spectroscopic Evidence

Electron-spin resonance (ESR) spectroscopy was used by Fisher in a 1969 study of the reactions of several alkyl halides with a variety of organolithiums[58]. Fisher concluded that radicals were generated as intermediates in the reaction of secondary and tertiary alkyllithiums with alkyl halides. No radicals were observed in reactions of primary alkyllithiums or phenyllithium with alkyl halides[58]. Russell and Lamson[59] also detected radicals by ESR spectroscopy in the reactions of n-BuLi or sec-BuLi with various alkyl bromides and iodides, but only when diethyl ether or TMEDA was present in the reaction mixture at a concentration that was approximately equal to that of the alkyllithium.

Although these ESR studies demonstrate that radicals may be generated in reactions of organolithiums with organohalides, it is not at all clear from such data that radicals are involved as intermediates in the metal-halogen interchange.

The technique of chemically induced dynamic nuclear polarization (CIDNP) has been used in a number of studies to probe the mechanism of the metal-halogen exchange.[60-67] Polarization of proton NMR signals has been observed in the spectra of the alkyl halides involved in the reaction (both the original halide and that formally produced in the interchange)[61-63], in the alkenes formed by elimination (Cf. Scheme 7)[60,63,66], and in dimeric products generated by Wurtz-type coupling[61,63]. At no time, has CIDNP been observed in the spectrum of the reactant or product alkyllithium[60-64,66,67] and CIDNP has not been observed in reactions of organolithiums with organohalides under conditions known[16] to give exclusive lithium-halogen exchange[66,67].

These CIDNP studies demonstrate that radicals may be produced when alkyl bromides and iodides are treated with alkyllithiums. It is, however, not clear from the results of such studies that radical intermediates are responsible for the interchange reaction. As noted above, CIDNP has never been observed for the alkyllithium produced via interchange and the polarization of the ^{1}H NMR signals for the halide molecules produced in the reactions may well be due to the well-established radical-mediated halogen-atom exchange (R-X + R$'\bullet$ → R$'$-X + R$\bullet$)[68].

2. Use of Radical Probes

A "radical probe" is a suitably structured species which, when converted to a radical in the course of a reaction, will undergo a characteristic intramolecular rearrangement. The most widely used of these radical probes are those based on the well-studied cyclization of a 5-hexen-1-yl radical to a cyclopentylmethyl radical (Scheme 8)[69-76] and the literature is replete with examples of the use of a variety of such probes in mechanistic studies.[71,72]
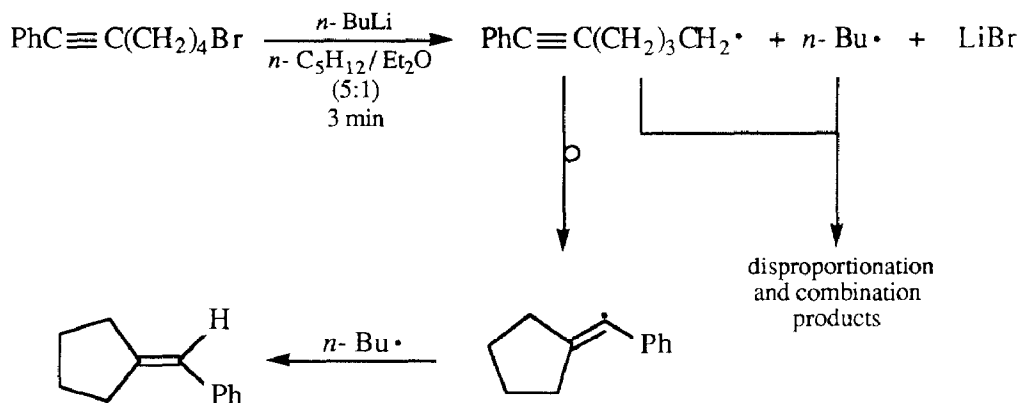
Alkyl halide radical probes have been used in a number of mechanistic studies of the lithium-halogen interchange.[77-87] A discussion of the more recent of these studied[79-87] will be deferred to a later section since interpretation of the results of these studies involves consideration of a variety of mechanistic schemes.

Scheme 8

Cyclizable probes were first[78] used by Harold Ward to study metal-halogen interchange in 1967.[77] Ward treated 6-bromo-1-phenyl-1-hexyne with n-BuLi in hexane/diethyl ether (5:1 by volume) at room temperature and discovered that a variety of products were produced upon hydrolysis with water (Scheme (9). The major product was found to be benzylidene-cyclopentane (60% yield), which, he reasoned, could have been formed from cyclization of 1-lithio-1-phenyl-1-hexyne (cf. ref. 78). If the lithio compound were responsible for the cyclization then quench with D_2O should have resulted in cyclized product with deuterium incorporation of almost 100%. Upon performing D_2O hydrolysis of the reaction mixture Ward found, however, that this product contained only 25% deuterium. In an additional experiment, n-BuLi in hexane and the starting alkynyl bromide were sealed in an NMR tube. A proton NMR spectrum, recorded before opening the tube, clearly showed the vinyl proton of the cyclic product. Addition of D_2O to the contents of the tube gave benzylidenecyclopentane containing approximately 11% deuterium. All of these results lend support to Ward's suggestion of a radical-mediated mechanism for the reaction (Scheme 9) and discount an ionic route as being the major pathway for the cyclization.

Scheme 9

$$PhC\equiv C(CH_2)_4Br \xrightarrow[\substack{n\text{-}C_5H_{12}/Et_2O \\ (5:1) \\ 3\ min}]{n\text{-}BuLi} PhC\equiv C(CH_2)_3CH_2\text{\textbullet} + n\text{-}Bu\text{\textbullet} + LiBr$$

disproportionation
and combination
products

As suggested by this discussion of Ward's investigation,[77] the use of radical probes in mechanistic studies of organometallic reactions is fraught with difficulties. It is well recognized that the intermediacy of radicals does not follow as a logical consequence of the simple observation of rearranged products from experiments employing radical probes.[72,85,86] The conclusion that a free radical is responsible for an observed isomerization is valid only to the extent that other plausible intermediates can be shown not to undergo rearrangement similar to that of the radical. This factor is especially important in mechanistic studies of the metal-halogen interchange for two reasons: (i) the product alkyllithium may be capable of a rearrangement that mimics that of the radical, and; (ii) to the extent that the organometallic is persistent, anionic rearrangement may be relatively slow and yet lead to non-negligible quantities of isomerized product. In this connection, it is to be noted that organometallic derivatives of the 5-hexenyl system are known to cyclize to cyclopentylmethyl organometallics.[88-92] In particular, 5-hexen-1-yllithium undergoes isomerization analogous to that of the 5-hexen-1-yl radical at a rate that is a strong function of temperature[85] (Scheme 10): at low temperature (ca -78°C), the alkenyllithium is indefinitely stable, but it undergoes rapid cyclization upon warming to higher temperatures (at 23°C, $t_{1/2}$ = 5.5 min)[85].

Scheme 10

The fact that organometallics can mimic the behavior of radicals generated from so-called radical probes demonstrates, as noted elsewhere,[72,85,86] that the simple observation of rearranged products is not sufficient evidence to establish the intermediacy of radicals in reactions that involve organometallic species. In order to establish that rearranged compounds which are found in a reaction product mixture were derived only from radicals, one must show that the corresponding carbanionic species does not undergo the same isomerization under the conditions of the study. When such control experiments are performed, the use of cyclizable radical probes can prove to be an extremely powerful mechanistic tool, since, through product analysis alone, one may identify those species which were derived from radicals in a complex reaction mixture. A number of recent studies of the mechanism of the metal-halogen interchange, which have used strategies based on radical probes,[79-87] must be interpreted in light of the behavior of organometallics derived from such probes.

C. Nucleophilic Mechanisms

The proposal that metal-halogen interchange could take place through nucleophilic attack of the organolithium on the halogen of the organic halide was first offered by Sunthankar and Gilman[93] in their 1951 study of the reactions of a variety of bromonaphthalenes with n-BuLi. This is an unusual mechanistic suggestion in that it involves a carbanion as the leaving group (see Scheme 11). More generally, one thinks of attack at carbon with subsequent loss of halogen as the normal pathway in a nucleo-

philic process. There are, however, many examples in the literature of
nucleophilic substitutions occurring at substituents bound to carbon and
Zefirov and Makhon'kov[94] have coined the term "X-philic" to describe this
newly recognized family of well-documented reactions.

Scheme 11

$$R-Li \; + \; X-R' \longrightarrow R-X \; + \; R'-Li$$

In their studies of the reactions of benzyl bromide and bromo-
triptycene (9,10-o-benzeno-9-bromo-10H-anthracene) with n-BuLi, Wittig and
Schöllkopf[95] postulated that such a mechanism may proceed with the rever-
sible formation of an intermediate "ate-complex" as shown in Scheme 12. As
a note of historical interest, such a structure, consisting of a complex
anion associated with an electropositive metal, was first named an "ate-
complex" by Wittig in 1958.[96]

Scheme 12

$$R-Li \; + \; R'-X \; \rightleftharpoons \; \left[R-\bar{X}-R' \quad Li^+ \right] \; \rightleftharpoons \; R-X \; + \; R'-Li$$
$$\text{"ate-complex"}$$
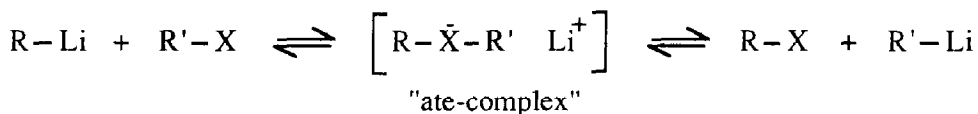
Since the pioneering work of Gilman and Wittig, a number of researchers
have suggested that metal-halogen interchange occurs through the nucleophilic
pathway outlined above and some reports have presented evidence for the
intermediacy of an "ate-complex" under special circumstance. These studies
will now be review in the order of their appearance in the literature.

Winkler and Winkler[45-46] carried out an elegant study of the reactions

of PhLi with a variety of substituted bromobenzenes and demonstrated that: (a) interchange was a clean, equilibrium-controlled process in all cases; (b) interchange using "salt-containing" PhLi (lithium halides present) followed reversible second-order kinetics, whereas those using "salt-free" PhLi did not; (c) use of "salt-free" PhLi led to larger rate constant values while the presence or absence of lithium halides had no effect on the value of the observed equilibrium constants; (d) reaction rates were increased when substituted bromobenzenes contained electron-withdrawing substituents; (e) reaction rates were increased upon changing solvent from diethyl ether to THF, but the corresponding equilibrium constants for the processes were virtually identical in both solvents; (f) excess negative charge developed in the transition state for the slow step of the reaction. The authors concluded that all of these results were consistent with a mechanism in which concerted exchange of lithium and halogen occurs via nucleophilic attack of a carbanion-like aryllithium on the bromine atom of the aryl halide.

In 1969 Johncock[97] studied the reaction of n-BuLi (as a solution in diethyl ether or pentane) with perfluoro-n-heptyl iodide at low temperatures and found evidence which supported "ate-complex" formation, although he did not recognize it as such. Johncock observed that 0.05 $\underline{M}$ solutions of the iodide in diethyl ether were opaque at -95°C. Treatment of the mixture with 1.0-1.5 equivalents of n-BuLi at this temperature reduced the opacity, although not completely. Addition of CO_2 at this point showed that metal-halogen interchange had occurred to the extent of 40-50%. When Johncock instead added acetaldehyde to the turbid reaction mixture and then carried out hydrolysis forty minutes later at -95°C, he obtained 1-(perfluoro-n-heptyl)-ethanol in only 22% yield. The main reaction product, 2-hexanol (formed from the addition of n-BuLi to acetaldehyde), was produced in a yield of 72%.

Johncock made the further observation that a heterogeneous mixture of n-BuLi and the perfluoro iodide became homogeneous when allowed to warm above -90°C. If the same mixture was prepared in the presence of acetal-

dehyde at -95°C and then allowed to warm above -90°C, reaction between perfluoro-n-heptyllithium and the acetaldehyde occurred very quickly and gave a 73% yield of 1-(perfluoro-n-heptyl)ethanol. Similar results were obtained when analogous experiments were performed using perfluoro-n-propyl iodide or perfluoroisopropyl iodide. Johncock concluded that both the cloudiness and the relatively low reactivity of reaction mixtures prepared at -95°C could be attributed to association of the perfluoroalkyl iodide with the perfluoroalkyllithium produced through metal-halogen interchange between n-BuLi and the iodide. If such an association indeed existed, then it quite possibly could have had the structure of the "ate-complex" (cf. Scheme 11) postulated by Wittig[95] as the intermediate in metal-halogen interchange. The negative charge that is formally centered on iodine would have been greatly dispersed by inductive stabilization through the many fluorine atoms which were present in Johncock's system.[97]

A kinetic study of the reactions of substituted bromobenzenes and n-BuLi in hexane solution was performed by Rogers and Houk[52] in 1982. This study concluded that the metal-halogen interchange most likely occurred through nucleophilic attack of n-BuLi on the bromine atom of the substrate (see Scheme 10) although, as noted above, the authors could not discount a mechanism which proceeded through a concerted four-centered transition state (see Scheme 5). These proposals were supported by the observation that the systems explored were found to be kinetically first-order in bromobenzene and first-order in n-BuLi. This result obviously excludes dissociation of alkyllithium aggregates into monomers as the rate-limiting step of the reaction for two reasons: (a) a fractional order in n-BuLi would have been expected as n-BuLi is known to be a hexamer in hexane; and, (b) bromobenzene would not appear in the rate expression.

An Arrhenius plot (ln k vs 1/T) of the data of Rogers and Houk[52] gave an activation energy for the exchange of 12 kcal mol^{-1}. Rogers and Houk therefore concluded that the interchange reactions did not involve a slow step which was diffusion-controlled as such processes were expected to have activation energies in the range of 2-5 kcal mol^{-1}. They also deduced that

radical pathways were not involved as no experiment gave coupling products in yields of greater that 5% and at no time was CIDNP observed by proton NMR in any reaction mixture.[52] The proposal that nucleophilic attack on halogen is the key step in the interchange was supported by the observation that Hammett plots indicated negative charge buildup in the transition state for the exchange.[52]

Reich and co-workers[98] recently reported the results of experiments which suggest the formation of "ate-complexes" in lithium-iodine exchange reactions. Evidence for such a conclusion was furnished through study of the coupling reaction between 0.2 M solutions of PhLi and 1-iodobutane in THF at -78°C. The yield of n-butylbenzene was found to be ⁻32% after a reaction time of 1 hour, but it successively decreased when identical experiments were carried out in the presence of increasingly greater amounts of iodobenzene. At an iodobenzene concentration of 1.2 M, the yield of coupling product was only about 7% after 1 hour. On the assumption that second-order kinetics were being followed it was determined that the addition of iodobenzene to the PhLi-1-iodobutane system reduced the observed rate of coupling by approximately 15%. It was concluded that the observed rate-lowering was due to intermediate production of a relatively unreactive "ate-complex" as shown in Scheme 13.
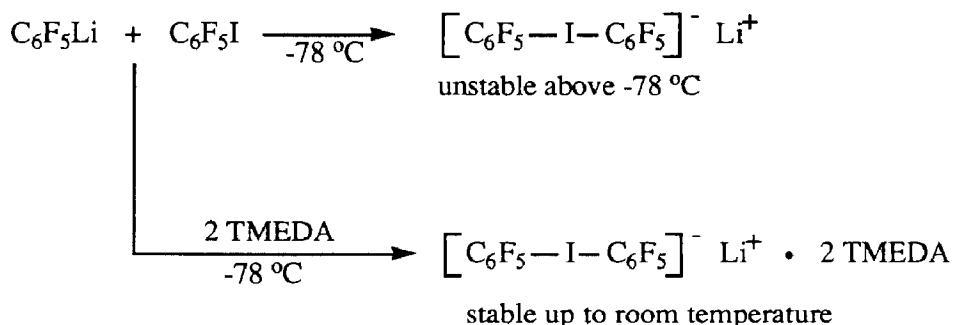
Scheme 13
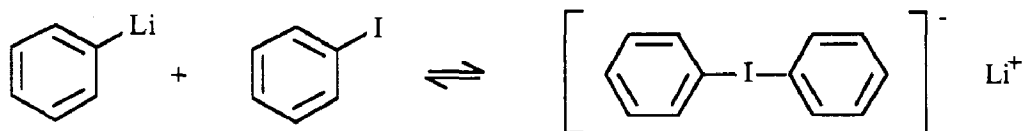
Reich and co-workers also added various quantities of hexamethyl-phosphoric triamide (HMPA) to the reaction mixture and found that this material resulted in an even greater reduction in the rate of coupling

between PhLi and n-butyl iodide than when iodobenzene was used as an additive. These results were interpreted in terms of preferential co-ordination of HMPA with the lithium cation of the "ate-complex" (Scheme 13) which was thought to be stronger than coordination to the lithium cation in PhLi itself.[98] A similar rate depression was seen in the production of phenyltrimethylsilane from PhLi and hexamethyldisiloxane in THF/HMPA at -78°C upon the addition of various quantities of iodobenzene and "ate-complex" formation was also given as the cause of these observations.[98]

In a truly elegant study of metal-halogen interchange, Farnham and Calabrese[99-100] recently reported the isolation and characterization of a hypervalent (10-I-2) iodine compound having the structure of Wittig's "ate-complex". Treatment of (pentafluorophenyl)lithium with penta-fluorophenyl iodide in diethyl ether/petroleum ether (1:1 by volume) at -78°C resulted in the formation of the unstable lithium bis(penta-fluorophenyl)iodinanide, which is shown in Scheme 14. This complex was isolated at -78°C, but was found to vigorously decompose at higher tem-peratures.

Scheme 14

$$C_6F_5Li \ + \ C_6F_5I \ \xrightarrow{-78\ ^{\circ}C} \ \left[C_6F_5-I-C_6F_5 \right]^- Li^+$$

unstable above -78 °C

$$\xrightarrow[-78\ ^{\circ}C]{2\ TMEDA} \ \left[C_6F_5-I-C_6F_5 \right]^- Li^+ \cdot 2\ TMEDA$$
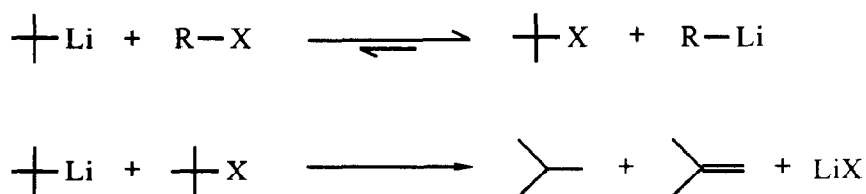
stable up to room temperature

Remarkably, when two equivalents of TMEDA were added to the above iodinanide salt at -78°C, a new "ate-complex" was isolated which was stable for short periods of time under an inert atmosphere at room temperature[99] (Scheme 14). This complex decomposed in solution at 25°C, but dissolution

in ether at 25°C followed by rapid cooling to -20 to -30°C resulted in a crystalline material whose structure was determined by x-ray crystallo-graphy[99]. The important structural features of this compound (Scheme 14) are: (a) the presence of a nearly linear C-I-C bond (<C-I-C=175°C); (b) the exceedingly long carbon-iodine bonds which are present; (c) the penta-fluorophenyl groups are apical ligands in a three-center, four-electron bonding arrangement; (d) the coordination of each lithium cation by two TMEDA molecules. Farnham and Calabrese further demonstrated that this complex reacts readily with electrophiles, releasing pentafluorophenyl iodide and delivering a nucleophilic C_6F_5 group. The unprecedented stability of this 10-I-2 complex is undoubtedly due to the stabilizing effects of the electron-withdrawing C_6F_5 units. Indeed, the authors were unable to isolate an "ate-complex" from the reaction of PhLi with iodoben-zene[99]. These observations would seem to lend support to the inter-pretation of Johncock's 1969 results[97] noted above.

III. Recent Mechanistic Studies

As noted above, a number of recent studies of the lithium-halogen interchange reaction have employed alkyl halides designed to function as radical probes.[79-87] These investigations have for the most part focused on the reaction of t-BuLi with primary (1°) or secondary (2°) alkyl bro-mides and iodides. The rationale for the use of t-BuLi in these studies (rather than, for example, n- or sec-BuLi) follows from two considerations: (1) the interchange equilibrium is favorable when 1° or 2° halides are treated with a 3° alkyllithium[16], and; (2) the interchange can be rendered completely irreversible through the use of 2 molar equivalents of t-BuLi since an equivalent of t-BuLi consumes the tert-butyl halide formally generated in the interchange[101-102] (Scheme 15). Although both isobutane and isobutylene have been identified as products of this reaction, the mechanism by which t-BuLi is consumed has not been determined[101-102].

Scheme 15

$$\text{\textbardbl}\!-\!Li \ + \ R\!-\!X \ \rightleftharpoons \ \text{\textbardbl}\!-\!X \ + \ R\!-\!Li$$

$$\text{\textbardbl}\!-\!Li \ + \ \text{\textbardbl}\!-\!X \ \longrightarrow \ \text{>}\!-\! \ + \ \text{>}\!=\! \ + \ LiX$$

It should be noted that the metal-halogen interchange can be an extremely rapid process. Bailey and co-workers have recently reported that t-BuLi undergoes exchange with a primary iodide more rapidly than it abstracts a proton from methanol[86]. For example, as illustrated in Scheme 16, treatment of a 0.1M solution of 6-iodo-1-hexene in n-pentane-diethyl ether (3:2 by volume) containing 2.0 molar equiv. of CH_3OH with 2.0 molar equiv of t-BuLi at -78°C leads to greater than 90% of the metal-halogen interchange product[86] (t-BuI was observed as a product in this reaction demonstrating that protonation of t-BuLi by CH_3OH is competitive with the formal dehydrohalogenation depicted in Scheme 15). The literature contains several other reports that bear on the question of the relative rates of proton abstraction and lithium-halogen interchange[103-106]. The results of these studies, involving competition between proton abstraction and interchange in molecules containing both an acidic proton (or deuterium) and a halogen atom, are inconclusive: arguments have been presented that both support[103-105] and refute[106] the contention that metal-halogen interchange may be more rapid than proton transfer.

Scheme 16
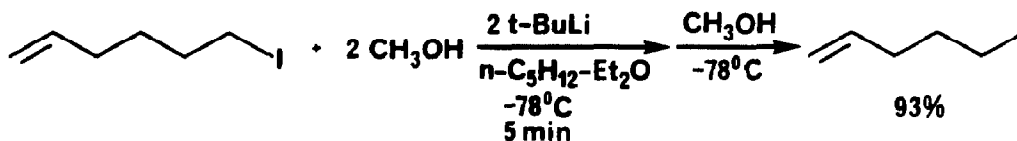
In 1984, Bailey, Gagnier and Patricia reported the results of an investigation of the reactions of t-BuLi with α,ω-dihaloalkanes.[84] It was found that addition of 2.0-2.2 molar equiv. of t-BuLi in pentane to a 0.1$\underline{M}$ solution of a 1,3-, 1,4-, or 1,5-diiodide in $\underline{n}$-pentane-diethyl ether (3:2 by volume) at -23°C resulted in nearly quantitative yields or 3-, 4-, and 5-membered carbocyclic rings.[84] For instance, as shown in Scheme 17, treatment of 1,5-diiodopentane with t-BuLi gave a 99% yield of cyclo-pentane. The mixed solvent system used in these experiments was that found by Applequist and O'Brien, in their classical studies of exchange equili-bria[16], to afford clean lithium-halogen interchange free from competing elimination reactions. This solvent mixture has been widely used by a number of research groups in mechanistic studies of the interchange. The t-BuLi most likely exists predominantly as a dimer in this solvent mixture (Table 1 and ref. 25).

Scheme 17
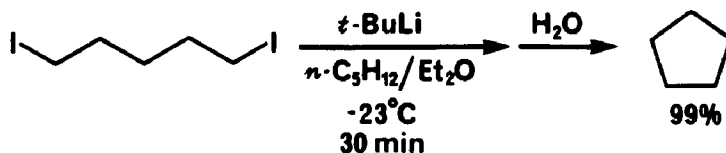
The following observations were made by Bailey and co-workers in their study of the reactions of t-BuLi with α,ω-dihalides:[84] (a) metal-halogen interchange (to give LiCH$_2$⌇⌇⌇CH$_2$X) followed by cyclization was the exclusive process observed in reactions of α,ω-dihaloalkanes with t-BuLi provided at least one halogen of the substrate was an iodine; (b) addition of t-BuLi to dibromides resulted in the formation of a complex mixture composed of cycloalkane, alkenes, products of Wurtz-type coupling, and quantities of parent alkane derived from formal reduction of the dibromide.

The disparate behavior of bromides and iodides in reactions with t-BuLi led to the suggestion that the identity of the halogen atom may have a profound effect on the mechanism of the interchange.[84]

The question of the mechanism of the exchange was further probed by investigation of the reactions of t-BuLi with 6-bromo- and 6-iodo-1-hexene under the conditions used in the dihalide studies.[84] It was found that methylcyclopentane was the major constituent of reaction mixtures produced from both the bromide and the iodide. As shown in Scheme 18, the cyclized hydrocarbon was formed in 85-95% yield from the 1° iodide and in 45-54% yield from the 1° bromide.[84] Unrearranged 1-hexene accounted for the bulk of the reaction mixture in both cases. The formation of rearranged product was attributed to rapid cyclization of the 5-hexen-1-yl radical (Scheme 8) and it was concluded that the interchange reactions proceeded via SET from the t-BuLi to the halides. On the basis of these conclusions, a unified SET mechanism for metal-halogen interchange and Wurtz coupling was formulated along the lines of that shown in Scheme 7. The halogen effect on the mechanism of the interchange was attributed to the intermediacy of alkyl radical-halide ion adducts with halogen dependent lifetimes.[84]

The demonstration that cyclized product results from reaction of t-BuLi with 6-halo-1-hexenes would seem to confirm that the interchange is mediated by SET. However, the authors noted that "ongoing studies indicate that an unknown proportion of the methylcyclopentane produced in these reactions was the result of slow but non-negligible cyclization of 6-lithio-1-hexene".[84] Despite this observation, it was concluded that the bulk of the observed rearrangement was the result of cyclization of a 5-hexenyl radical. Isomerization of 5-hexen-1-yllithium (Scheme 10) was discounted on the basis of literature data for analogous organometallics which suggested that an anionic cyclization would be too slow to account for the large proportion of methylcyclopentane observed in the study.[84]

A 1985 communication by Ashby, Pham and Park seemed to confirm that radical intermediates are generated in the lithium-halogen exchange.[80] These authors used three different alkyl halide radical probes to in-

Scheme 18

| X = Br | 45-54% | 25-30% |
| X = I | 85-95% | 5-10% |
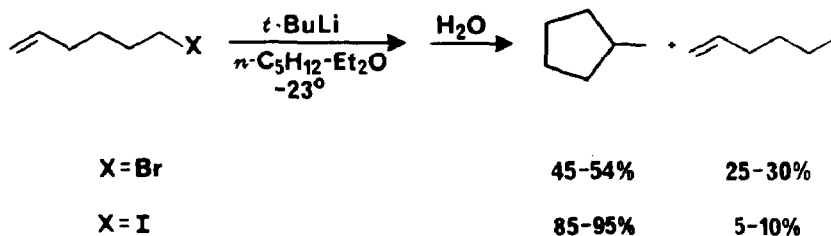
vestigate the interchange with t-BuLi in pentane/ether (4:1 by volume) at low temperature (-78°C or -130°C). In one set of experiments, reaction of either 6-bromo or 6-iodo-1-hexene with t-BuLi at -78°C or -130°C followed by quench with water was found to give 81% of 1-hexene and 19% of methylcyclopentane. These observations were interpreted in terms of cyclization of an intermediate 5-hexen-1-yl radical. The possibility that cyclized product arose from isomerization of 5-hexen-1-yllithium was excluded on the basis of the observation that the proportion of methylcyclopentane did not change when the hexenyllithium was allowed to stand at -130°C for four hours prior to quench with water.[80]

Ashby's group further explored the interchange using endo-5-(2'-bromomethyl)-2-norbornene, a bicyclic 1° bromide probe, and 6-bromo-1-heptene, a 2° bromide radical probe.[80] Both of these probes contain a 5-hexenyl unit. Each bromide was treated with t-BuLi in pentane/ether (4:1 by volume) at -78°C for periods ranging from 10 min to 24 hrs prior to addition of D_2O. In each instance a significant proportion of product was derived from cyclization of the probe. The authors concluded on the basis of these results, and experiments in the presence of additives such as TMEDA, HMPA, and 18-crown-6, that an SET-mediated mechanism was responsible for the interchange reaction between the bromides and t-BuLi.[80] The behavior of the chloride and iodide derivatives of these probes was not examined.

Soon after these papers appeared, Bailey's group reported that 5-hexen-1-yllithium cyclizes to cyclopentylmethyllithium (Scheme 10)[85] at a non-negligible rate under the conditions used in the mechanistic studies. The realization that a product organolithium can undergo fairly rapid isomerization at ambient temperatures analogous to the low-temperature cyclization of the 5-hexenyl radical was further reinforced by a 1985 report from Woolsey and co-workers [82] that the aryllithium generated at -78°C by metal-halogen interchange between n-BuLi and o-(3-butenyl)-bromobenzene undergoes rapid cyclization at +23°C. Thus, as noted in Section II.B.2, care must be exercised in interpretation of results from experiments that employ radical probes since the product organometallic may well mimic the behavior of the radical.[72,85,86] Indeed, the facile cyclization of 5-hexen-1-yllithiums at room temperature provides a convenient preparative route to functionalized carbocycles containing the cyclopentylmethyl moiety.[107]

In light of these findings, the mechanism of the interchange between 1° alkyl halides and t-BuLi was reinvestigated by Bailey's group.[86,87] The reaction of t-BuLi with 1° iodides and 1° bromides containing the 5-hexenyl unit was investigated at -78°C in pentane-ether (3:2 by volume). Reaction mixtures were stirred at -78°C for 5 min and quenched at -78°C by addition of an excess of anhydrous, oxygen-free methanol.[86,87] Because the 5-hexen-1-yllithiums produced in the exchange were known to be stable to cyclization under the conditions employed in these experiments[85], the formation of rearranged products could confidently be attributed to a radical-mediated cyclization. In the event, no products attributable to cyclization of 5-hexene-1-yl radicals were detected in reactions of the iodides with t-BuLi[86] but evidence for the intermediacy of radicals was obtained from reactions of the bromides with t-BuLi.[87]

These results confirmed the pronounced halogen effect on the mechanism of the lithium-halogen interchange which was first noted in the 1984 study.[84] Since there was no evidence for SET in the rapid low-temperature lithium-iodine exchange between a 1° iodide and t-BuLi, the authors noted

that the results were consistent with an interchange mechanism involving nucleophilic attack of the t-BuLi on the iodine of the halide.[87] This is shown pictorially in Scheme 19. The reaction may well be a concerted, if not entirely synchronous, process involving a 10-I-2 species as a transition state or the interchange may proceed via reversible formation of a intermediate complex (Cf. Section II.C.; Schemes 11 and 12). This mechanism for lithium-iodine interchange is consistent with the conclusions, discussed in Section II.C, drawn by Reich[98] and Farnham.[99]

Scheme 19
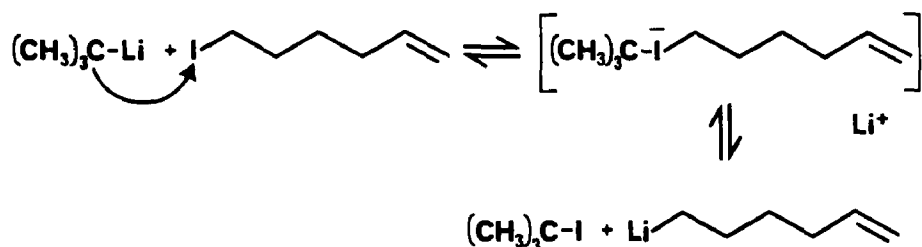

Evidence for the intermediacy of radicals in the lithium-bromine interchange was obtained from experiments involving reaction of t-BuLi with 1-bromo-6-methyl-5-heptene in pentane-ether (3:2 by volume) at -78°C.[87] Bailey and co-workers concluded that, under the conditions used in the study, at least 15% of the reaction proceeded via SET.[87] The fact that at least a portion of the lithium-bromine interchange proceeded via SET from the t-BuLi to the 1° bromide is consistent with the mechanistic conclusions drawn by Ward in his pioneering 1967 study[77] and by Ashby and co-workers in the study described above.[80] The fact that neither Winkler and Winkler[45,46] nor Rogers and Houk[52] detected radical intermediates in their investigations of the lithium-bromine exchange of aryl bromides (Section II.C) suggests that the mechanism of the interchange may not be the same for alkyl bromides and aryl bromides.

These mechanistic results were somewhat unexpected insofar as it was the 1° bromides, rather than the more easily reduced 1° iodides, that were

found to undergo interchange at least partially via SET. The authors noted that although the reduction potentials of the substrates suggest that SET to R-I would be more facile than to R-Br, the more easily reduced halide is also the one that is most susceptible to nucleophilic attack[94] by t-BuLi.[87]

Radical intermediates in the lithium-bromine interchange were also detected by Newcomb, Williams, and Crumpacker in a 1985 study[79] that employed a novel mechanistic probe for radical intermediates. The 2,2-dimethyl-3-buten-1-yl radical, shown in Scheme 20, undergoes rapid rearrangement, via a 2,2-dimethylcyclopropylcarbinyl intermediate, to the more stable 2-methyl-4-penten-1-yl radical with a rate constant of 5.0×10^6 sec^{-1} at 25°C.[108] This rearrangement is approximately an order of magnitude faster than the cyclization of the 5-hexen-1-yl radical.[69-76] Moreover, Newcomb's probe offers several advantages relative to 5-hexen-1-yl based systems for the investigation of reactions involving strongly basic reagents: (a) an organometallic derived from the probe will not undergo an analogous rearrangement;[108] (b) the precursor halide, being neopentyl-like, is resistant to substitution reactions, and; (c) E_2 elimination reactions will not complicate product analysis.

Scheme 20
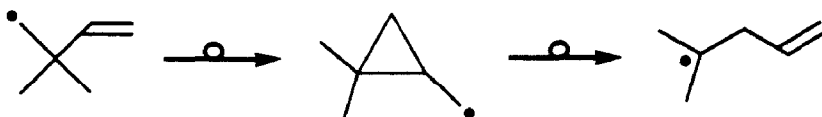
Treatment of 4-bromo-3,3-dimethyl-1-butene with t-BuLi in n-pentane-diethyl ether (3:2 by volume) at -23°C gave a complex product mixture that contained a 13% yield of the rearranged product, 4-methyl-1-pentene.[79] Although other products generated in the reaction were not identified, Newcomb and co-workers concluded that at least 13% of the reaction proceeded by an SET path.[79] This result is a good agreement with those of

noted above from low-temperature studies of lithium-bromine interchange in substrates containing the 5-hexen-l-yl probe. Unfortunately, Newcomb's study did not extend to investigation of lithium-iodine exchange.

A 1987 paper by Ashby and Pham[81] amplified the results communicated in their earlier report[80] on the mechanism of the interchange and extended the studies to include investigation of the reaction under a variety of experimental conditions using a variety of radical probes based on the 5-hexenyl system. At -78°C the reaction of 1° alkyl iodides containing a 5-hexenyl unit with t-BuLi in a solution of n-pentane-diethyl ether (4:1 by volume) afforded no evidence for the intermediacy of radicals.[81] Radical-derived products were, however, observed under the these conditions in reactions of t-BuLi with the analogous 1° bromides. These observations are fully in accord with those discussed above: there seems to be no evidence for radical intermediates in the interchange between t-BuLi and 1° alkyl iodides in pentane-ether mixtures at -78°C[81,86] but SET is responsible for at least a portion of the interchange between t-BuLi and 1° alkyl bromides under these conditions.[77,79-81,84,87]

Ashby and Pham extended their study of the lithium-iodine interchange between t-BuLi 1° iodides in a series of experiments in which the exchange was performed at higher temperatures in a pentane-ether mixture (4:1 by volume).[81] Rearranged products were observed when endo-5-(2'-iodoethyl)--2-norbornene was treated with t-BuLi at -45°C, -23°C, and 0°C. The amount of cyclized product increased with an increase in temperature as would be expected if the initially formed 1° lithium were undergoing addition to the double bond. In an attempt to assess the extent to which anionic cyclization contributed to the formation of rearranged product, reaction mixtures were aged at the temperature used for the interchange. The proportion of rearranged product remained fairly constant for reactions performed at -45°C (3.3% rearrangement after 30 min, 4.0% rearrangement after 1h) and -23°C (5.5% rearrangement after 5 min, 5.2% rearrangement after 48 h) but it changed dramatically at 0°C (5% rearrangement after 5 min, 30% rearrangement after 35 min).[81] The constancy of the proportion of
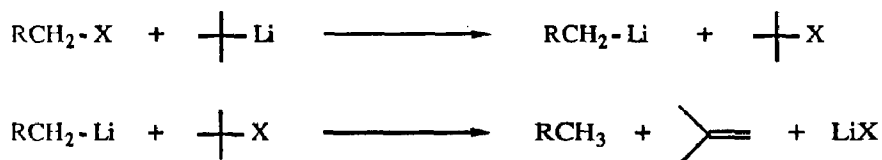
cyclized product at -45°C and -23°C was taken as an indication that anionic cyclization was not responsible for the observed rearrangement at these temperatures and SET was invo ked to account for at least a proportion of the interchange.[81] The observation that anionic cyclization does indeed occur at an appreciable rate at 0°C, coupled with the facts that the interchange reaction is an exothermic process[86] and no evidence for SET is found in reactions conducted at -78°C, suggests an alternative explanation for the results. Thus, local heating during the addition of t-BuLi to solutions of the iodide at -45°C and -23°C might account for the formation of small quantities of cyclized product. The known rates of rearrangement of 5-hexen-1- yllithium to cyclopentylmethyllithium at -45°C and -23°C are not inconsistent with the formation of ca. 3-5% in such experiments (i.e., approx. 2-3% cyclization in 5 min. at -23°C).[85] Unfortunately, the kinetics of the cyclization of the organolithium derived from the bicyclic probe are not known. Consequently, the observation of rearranged products in experiments using this probe is open to interpretation.

The effect of solvent on the mechanism of the lithium-iodine interchange was investigated by Ashby and Pham[81] in a series of experiments in which the 1° iodide probe was allowed to react with t-BuLi in pure n-pentane at -78°C and at -23°C. Since the degree of association of t-BuLi is predominantly dimeric in the pentane-diethyl ether solvent system [25] and predominantly tetrameric in pure pentane (Table 1), the aggregate structure of the organolithium is effectively a function of solvent and it is of interest to determine if such changes affect the mechanism of the interchange reaction. It was found that the lithium-iodine exchange was much slower in pure pentane than in a solvent system containing ether; only 10% of the iodide underwent exchange after 30 min at -78°C. Here again, a higher proportion of cyclized product was observed in reactions run at higher temperatures.

In these experiments and others, Ashby and Pham noted that a portion of the halide substrate was reduced to a hydrocarbon by incorporation of a hydrogen (or deuterium) from the t-BuLi (or t-BuLi -d_9) used in the inter-

change.[81] They attributed this reduction to the abstraction of a hydrogen

atom from the t-BuLi reagent by an intermediate radical generated in the

course of the interchange.[81] Bailey and co-workers have also reported that

organolithiums generated via lithium-iodine exchange between a 1° R-I and

t-BuLi contain a small but non-negligible amount of hydrocarbon formally

derived from reduction of the halide and experiments using t-BuLi-d$_9$

confirmed that the hydrocarbon product incorporated deuterium from the

t-BuLi.[107] However, unlike Ashby and Pham,[81] Bailey and co-workers did not

invoke radical intermediates to account for this result. Rather, by

analogy with the behavior of t-BuLi in the presence of t-BuX (Scheme 15),

they attributed reduction of the iodide to an elimination reaction (Scheme

21) between the RLi and the t-BuI generated in the interchange to give RH

and $CH_2=C(CH_3)_2$.[107]

Scheme 21

$$RCH_2\text{-}X \quad + \quad \overset{|}{\underset{|}{-}}Li \quad \longrightarrow \quad RCH_2\text{-}Li \quad + \quad \overset{|}{\underset{|}{-}}X$$

$$RCH_2\text{-}Li \quad + \quad \overset{|}{\underset{|}{-}}X \quad \longrightarrow \quad RCH_3 \quad + \quad \rangle\!\!=\!\!= \quad + \quad LiX$$

The lithium-halogen interchange between secondary alkyl halides and

t-BuLi has been systematically investigated by Ashby's group in experiments

using the 6-halo-1-heptenes as radical probes[80,81] and Bailey's group has

reported the outcome of the exchange reaction between t-BuLi and 6-iodo-1-hep-

tene.[107] In each of these studies mechanistic information was provided by

the proportion of cis and trans isomers of 1,2-dimethylcyclopentane pro-

duced upon hydrolysis of the reaction mixtures. This is a consequence of

the fact that radical-mediated cyclization can be distinguished from

isomerization of an intermediate alkenyllithium on the basis of the stereo-

chemistry of the product. The secondary 6-hepten-2-yl radical is known to

cyclize with a distinct preference for the cis-sterochemistry[70,72,74,76]
and there are reports of cis/trans ratios in the range of 2.3[70-72] to 4.9[89]
for this isomerization. In contrast to the behavior of the secondary
radical, the cyclization of the organolithium derived from a 6-halo-1-hep-
tene has been reported by Drozd and co-workers to give predominantly the
trans-isomer (cis/trans = 0.2).[90] A similar propensity for formation of
the trans-isomer upon cyclization of organometallic derivatives of the
6-hepten-2-yl system has been reported for the Grignard reagent (cis/trans
< 0.1[92]) and the organosodium (cis/trans < 1).[89] Thus, the relative
proportions of cis- and trans-1,2-dimethylcyclopentane produced in react-
ions that employ the 6-halo-1-heptene probe are diagnostic of mechanism:
radical-mediated processes give high cis/trans ratios while isomerization
of an organometallic intermediate leads to cis/trans ratios that are less
than unity. It is of interest in this connection to note that the 2°
6-hepten-2-yl organometallics apparently undergo cyclization much more
rapidly than do the 1° 5-hexen-1-yl organometallics.[89-92,107] This rate
enhancement is most likely a consequence of the favorable transformation of
a 2° carbon-metal bond in the open chain compound into a 1° carbon-metal
bond in the cyclized product. Although there are no quantitative data on
the rate of cyclization of 2° alkenyllithiums, Bailey and co-workers have
reported that the cyclization of 6-hepten-2-yllithium (the 2° alkenyllithium
derived from 6-iodo-1-heptene) is so facile that it is apparently complete
within a few minutes at -78°C.[107] This view is, however, not shared by
Ashby and Pham who have concluded that the cyclization of the 2° 6-hepten-2-
yllithium is slower than that of the 1° 5-hexen-1-yllithium.[81]

Ashby and Pham studied the reactions of 6-bromo- and 6-iodo-1-heptene
with t-BuLi at -78°C in both pentane-ether (4:1 by volume) and in pure
pentane.[81] Experiments were also conducted in the presence of a Lewis base
such as HMPA, TMEDA, and 18-crown-6 in an effort to assess the effect of
coordination of the lithium atom on the outcome of the reactions. Reactions
were conducted by either adding the t-BuLi to a solution of the halide
(arbitrarily termed "normal addition") or by adding a solution of the

halide to the organolithium ("inverse addition"). Not unexpectedly[16], the reactions of the 2° halides with t-BuLi did not lead to clean lithium-halogen exchange. Both the bromide and the iodide reacted with t-BuLi to give 1-heptene and cis- and trans-1,2-dimethylcyclopentane as well as substantial quantities (ca. 30-40%) of other, uncharacterized hydrocarbons formed by elimination and Wurtz-type coupling.[81]

Reactions that employed 6-bromo-1-heptene produced a preponderance of the cis-isomer of 1,2-dimethylcyclopentane (cis/trans > 4) in both pentane-ether solution and in pure pentane.[81] The mode of addition of the reagents (normal vs inverse) had no substantial effect upon the relative proportions of cyclized products. On this basis, Ashby and Pham concluded that the 2° bromide reacts with t-BuLi via an SET pathway.[81]

The outcome of reactions between t-BuLi and 6-iodo-1-heptene was found to be strongly dependent on both the solvent and the relative concentrations of the reactants. Addition of a pentane solution of t-BuLi to 0.1M solutions of the 2° iodide in pentane-ether (normal addition) afforded a low yield (ca. 12%) of 1,2-dimethylcyclopentanes having a cis/trans ratio of ca. 1.7. Much higher proportions of the cis-isomer, characteristic of cyclization of the 2° radical, were generated in reactions conducted in pure pentane (cis/trans = 3.3-4.0).[81] The cis/trans ratio was, however, found to be a strong function of the relative concentrations of t-BuLi and the halide. When the relative concentration of t-BuLi was kept high, either by inverse addition of the halide to excess t-BuLi or by rapid addition (5 sec) of excess organolithium to the halide solution, the cyclized product was found to be almost exclusively the trans-isomer (cis/trans = 0.05-0.03).[81] These results were interpreted by Ashby and Pham in terms of cyclization of 6-hepten-2-yllithium generated via a heterolytic lithium-iodine interchange. Analogous results have been reported by Bailey and co-workers.[107] It would seem therefore, as noted by Ashby and Pham,[81] that the mechanism of the lithium-iodine interchange between a 2° alkyl iodide and t-BuLi may be finely balanced between two scenarios: nucleophilic attack of the organolithium on the halide

(Schemes 11 and 12) and SET from RLi to generate radical intermediates (Scheme 7). Seemingly minor variation in experimental conditions can apparently influence the mechanistic pathway followed in reactions of 2° alkyl iodides with t-BuLi.[81,107]

Miscellaneous Studies

Two specific types of organohalide substrates have been extensively studied in terms of their reactions with a variety of organolithium compounds. These substrates contain a halogen atom which is bound either to a cyclopropyl or a vinyl backbone. Structural units such as these are found in many organic molecules and their importance to a synthetic chemist is obvious. Indeed, the great amount of work that has been devoted to the study of the metal-halogen interchange of vinyl- and cyclopropyl halides has been carried out in an attempt to perform the transformation with total stereospecificity. This goal has been realized in both of these systems. A brief overview of the seminal work on this topic is presented below.

A. Cyclopropyl Systems

Much of the pioneering work on the metal-halogen interchange between organolithium compounds and cyclopropyl halides has been performed by Walborsky and his group.[109-111] In an early paper, Walborsky and Impastato[109] treated (+)-(S)-1-bromo-2,2-diphenylcyclopropane, in a solution of benzene/petroleum ether (1:1 by volume), with a solution of n-BuLi in diethyl ether at 6°C and upon methanolysis obtained (-)-(R)-1-methyl-2,2-diphenylcyclopropane in 43% yield with 60% net retention of configuration (Scheme 22).

Five years later, in 1964, Walborsky, Impastato and Young[110] published the results of a more thorough study of the cyclopropyl system described above. Their findings were as follows: (a) use of pure diethyl ether or a mixture of petroleum ether and dimethoxyethane as solvent increased the

Scheme 22
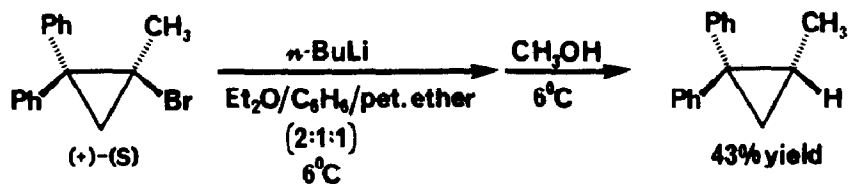
yield of 1-methyl-2,2-diphenylcyclopropane to 61-73%, but improved the stereospecificity of the reaction only slightly; (b) varying reaction time (from 10 to 30 minutes) or temperature (from -3 to +35°C) had litle effect upon the yield or optical purity of the product; (c) quench of the intermediate cyclopropyllithium compound with bromine, iodine or solid carbon dioxide resulted in products which completely retained the configuration of the starting bromide.

Freeman and Hutchinson[112] developed conditions in which metal-halogen exchange between alkyllithiums and various cyclopropyl bromides would proceed with almost no loss of stereochemical integrity. The authors treated syn-7-bromonorcarane with n-BuLi (hexane) in THF at -78°C and found that subsequent addition of an excess of ethylene dibromide (EDB) at the same temperature gave 99+% of the starting syn-bromide as depicted in Scheme 23 (before addition of EDB, the reaction mixture was warmed to 0°C for 5 minutes and analysis of an aliquot showed that all of the starting bromide was consumed). The reaction was also found to proceed stereospecifically when anti-7-bromonorcarane was treated with n-BuLi and EDB under exactly the same conditions as those used for the syn-isomer. When n-BuLi was added to each of the above bromides in THF at -15°C (in separate experiments) followed 1 minute later by addition of D_2O, both lithium-bromine exchange and addition of the electrophile were again discovered to have taken place with complete retention of configuration. No mechanistic interpretation was given for these results.
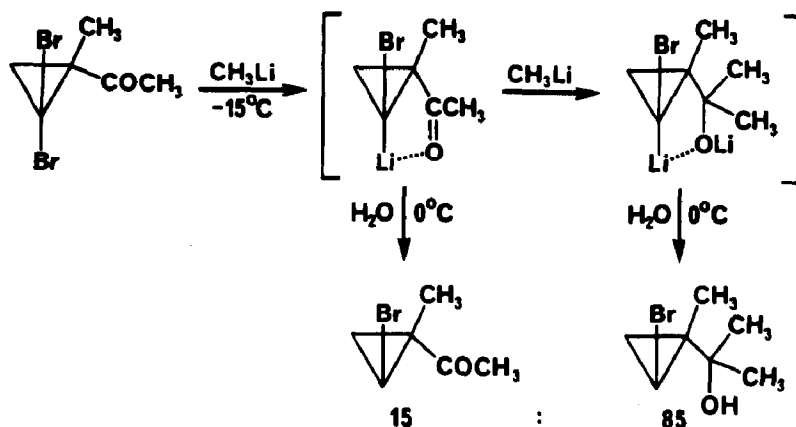
Scheme 23
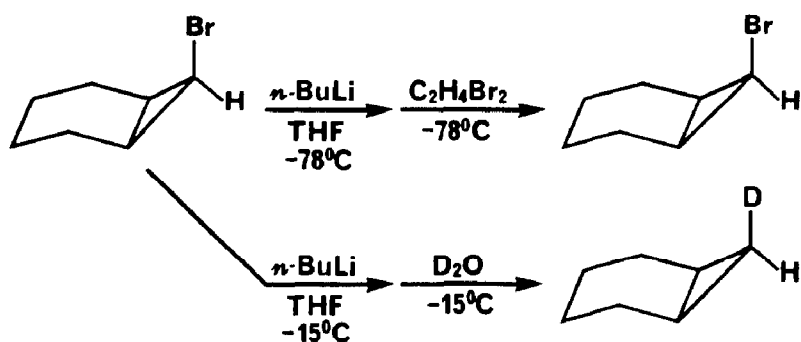
As an aside, Freeman and Hutchinson further demonstrated that metal-halo-
gen interchange with a non-cyclopropyl secondary bromide could also occur
in a stereospecific manner.[112] For example, they reacted syn-7-bromonorbornene
with t-BuLi in a solution of THF and pentane (10:1 by volume) at 50°C and
found that D_2O quench resulted in a mixture of syn- and anti-7-deuterio-
norbornenes in a ratio of at least 20 to 1.

Recently, Paquette and co-workers[113] provided evidence that gem-di-
bromocyclopropanes react with alkyllithium compounds by a pathway that may
involve carbenoid intermediates. As illustrated in Scheme 24, treatment of
the tetrabromide with 2.3 equivalents of methyllithium (CH_3Li) in diethyl
ether at 0°C, followed by stirring at room temperature for 3 hours and
hydrolysis with H_2O, gave the hexacycloolefin in a yield of 59%. This, in
fact, turns out to be a general procedure and Paquette has reported many
more examples of similar cyclizations in a variety of systems.

Scheme 24
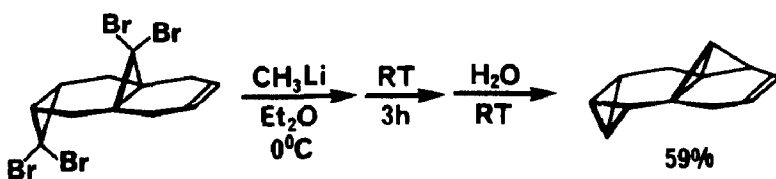
Barlet[114] has demonstrated that metal-halogen interchange could be restricted to the removal of only one bromine in gem-dibromocyclopropanes when other functionality exists in the molecule to stabilize the intermediate α-bromocyclopropyllithium compound.

Scheme 25

As shown in Scheme 25, addition of excess CH_3Li to an ethereal solution of 1,1-dibromo-2-carbomethoxy-2-methylcyclopropane at -15°C led to lithium-bromine exchange. The reaction mixture was warmed to 0°C over a 4-5 hr period and then hydrolyzed with H_2O to give a 75% yield of the alcohol and ketone pictured in the Scheme in a ratio of 85:15, respectively. Barlet proposed that the selective replacement of the bromine located cis to the CO_2CH_3 group was a consequence of stabilization of the resulting lithio derivative by complexation with an adjacent oxygen. Sydnes and Skattebol[115] drew similar conclusions from studies of the same system.

B. <u>Vinyl Systems</u>

The first vinyllithium compound was prepared in 1937 by George Wright[116] through the interaction of β-bromostyrene with lithium metal at room tempera-

ture in "Grignard-dried" diethyl ether. Carbonation of this reaction mixture gave a 25-30% yield of a 4-to-1 mixture of trans-cinnamic acid and phenylpropiolic acid. These products were obtained regardless of whether Wright started with the cis- or trans-vinyl bromide (Scheme 26).

Scheme 26
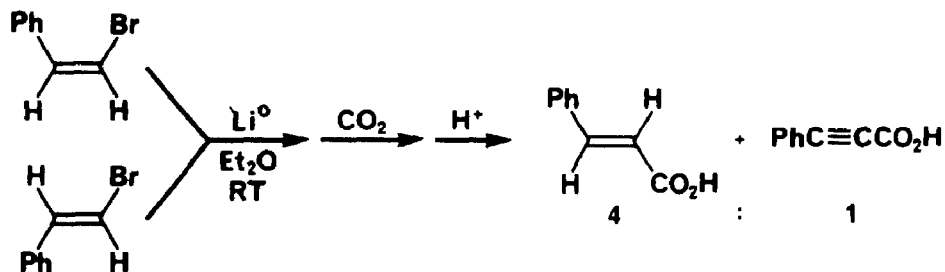
This early report highlights a common problem which has plagued many chemists in their studies of the metal-halogen interchange between vinyl halides and organolithium compounds: the reaction can proceed with formation of significant quantities of unwanted alkyne. A study by Curtin and Flynn[117] is representative. Treatment of various 1,1-diphenyl-2-halo-ethylenes with n-BuLi in diethyl ether at -35°C, followed by reaction with CO_2 and hydrolysis produced various mixtures of β-phenylcinnamic acid and diphenylacetylene as shown in Scheme 27.

The authors postulated that the alkyne forms through initial abstraction of the vinyl proton to give an α-halovinyllithium. Phenyl migration then occurs, with loss of halogen as the final step in the

Scheme 27
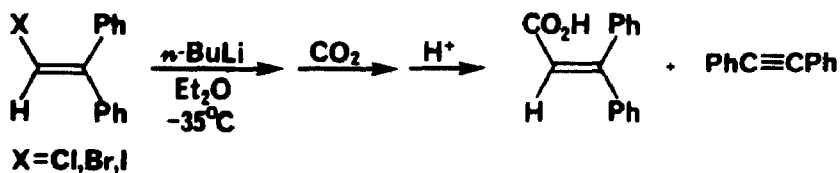
mechanism. When 1,1-dibromo-2,2-diphenylethylene was used as a substrate, only diphenylacetylene could be isolated as a reaction product. On the basis of many experiments utilizing a variety of vinyl chlorides, bromides and iodides, Curtin and Flynn concluded that the relative rate of metal-halogen interchange with n-BuLi decreases in the order I>Br>Cl and that the relative rate of α-metallation decreases in the order Cl>Br>I.

In later work with similar systems Curtin[118-119] made the following additional discoveries: (a) the reaction proceeded by way of a carbenoid mechanism when the vinyl moiety was placed in an exocyclic position so that rearrangements could not occur[118] (see Scheme 28); (b) the racemization of vinyllithium compounds is promoted through use of ethereal solvents (especially THF) and relatively high reaction temperatures (0°C to room temperature).

Scheme 28
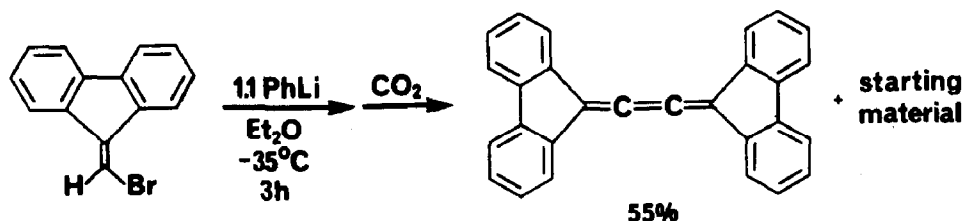
A large number of papers[111,120] published since Curtin's pioneering studies, have been concerned with the reactions of organolithiums with vinyl halides. One report in particular, by Neumann and Seebach,[120(f)] demonstrated that exclusive lithium-halogen exchange could be accomplished in such systems under appropriate conditions. Thus, addition of two equivalents of t-BuLi (in pentane) to a solution of a terminal vinyl bromide (many such substrates were used) in the Trapp-solvent mixture[121] (THF/diethyl ether/pentane in a ratio of 4:1:1) at -120°C resulted in an essentially quantitative yield of the desired vinyllithium compound. All reactions went to completion with full retention of configuration; no α-metallation and no rearrangement to acetylenic substances was observed.

To avoid alkyne formation, the reaction solutions were maintained at a temperature below -110°C. It was found that once interchange was complete, the mixtures could be warmed to room temperature (racemization was not observed in this process) for further reaction with a variety of electrophiles.

Lau and Schlosser[122] showed that when an ethoxy group was situated in a configuration that was cis- to either a hydrogen or bromine atom in a terminal olefin, reaction with n-BuLi occurs to give primarily metallation in the first case (ethoxy cis- to H) and interchange in the second (ethoxy cis- to Br). The authors treated an ethereal solution of (Z)-1-bromo-2-ethoxyethylene with n-BuLi (in hexane) at -80°C and then, 24 hours later, added benzaldehyde to the reaction mixture at the same temperature. Hydrolysis with water at 25°C resulted in an 84% yield of (Z)-3-ethoxy-1-phenyl-2-propen-1-ol. In another reaction, addition of n-BuLi to (E)-1-bromo-2-ethoxyethane was followed by treatment with pivaldehyde and hydrolysis under the conditions described above to give a 58% yield of (E)-1-ethoxy-2-bromo-4,4-dimethyl-1-penten-3-ol. It is obvious from these experiments that the site of attack of the n-BuLi is totally controlled by the positioning of the ethoxy substituent. Lau and Schlosser attributed such selective reactivity to the oxygen's ability to coordinate and stabilize only that intermediate vinyllithium which forms cis to the ethoxy function. In a more recent study, Meyers and Spohn[123] investigated reactions between alkyllithium compounds and alkoxy-substituted vinyl bromides and presented results and conclusions which were totally consistent with those of Lau and Schlosser.[122] Much of this work has been recently reviewed.[13]

Acknowledgment

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