FMC

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Metal-Halogen Exchange Metalations (M↔X) of Aryl and Heteroaryl Ring Systems Using Alkyllithiums

FROM THE EDITOR

The world's largest producer of lithium products, FMC Lithium Division, is pleased to bring you the fifth issue of the "Lithium Link" newsletter.

This issue's feature article highlights the use of organolithiums in metal-halogen exchange metalations (M↔X) of aromatic and heteroaromatic ring systems. This methodology is extensively reported in the literature and is also practiced on an industrial scale (see Figs 23 and 24). The author is Professor Don Slocum. You'll find more information about Professor Slocum at the end of the article.

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In the two previous newsletters, attention focused on lithium-hydrogen exchange metalation reactions (Li↔H) of aromatic and heteroaromatic substrates using organolithiums as strong bases. As shown in those feature articles, the utility of Li↔H methodologies is dependent on the substrates possessing *ortho*-directing metalating groups (DMGs). When a substrate containing appropriate DMG is not applicable, lithiation via metal-halogen exchange (M↔X) provides an alternative for preparing a desired product. The regiospecificity offered by M↔X, of particular importance in heterocyclic chemistry, is its most unique feature. In the last decade, it has become the method of choice for the preparation of several sophisticated macrocycles and natural products.

A number of reviews on the topic are available, but none of very recent vintage that would be useful to the preparative chemist. Those to be found in Wakefield[1] and by Jones and Gilman[2] are the most comprehensive but are somewhat dated. Others by Parham and Bradsher[3] (reactive substituents) and Bailey and Patricia[4] (mechanism) provide focussed examinations. Short overviews on the topic can be

ABBREVIATIONS

acac .....acetylacetonate
M↔H ....metal-hydrogen (or proton) exchange
M↔X ....metal-halogen exchange
***n*-BuLi ....normal-Butyllithium**
PCC .....pyridinium chlorochromate
pyr .....pyridine
***sec*-BuLi ..secondary-Butyllithium**
***t*-BuLi .....tertiary-Butyllithium**
TFA .....trifluoroacetic acid
TMEDA ...tetramethylethylenediamine
TMS .....trimethylsilyl

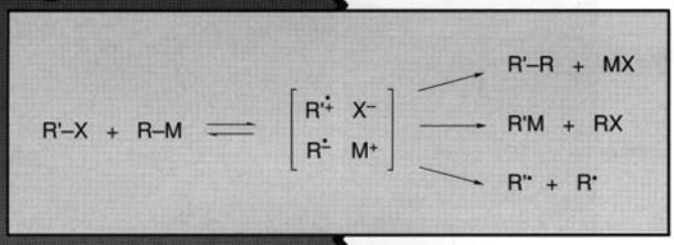
found in Wakefield[5] and Wardell.[6] A useful summary of a number of procedures can be found in the monograph by Brandsma and Verkruijsse.[7]

MECHANISM

Various mechanisms have been considered for the M↔X exchange.[4] The reaction appears to be an equilibrium involving a concerted S_N2 displacement, a single electron transfer (SET), or an intermediate called an "ate-complex." Under some conditions, second-order kinetics have been observed. Separate studies have demonstrated both stereochemical inversion and retention. Relatively recent studies, some of which are described below, argue against the once common description of the reaction as taking place through a four-center intermediate.[1,4]

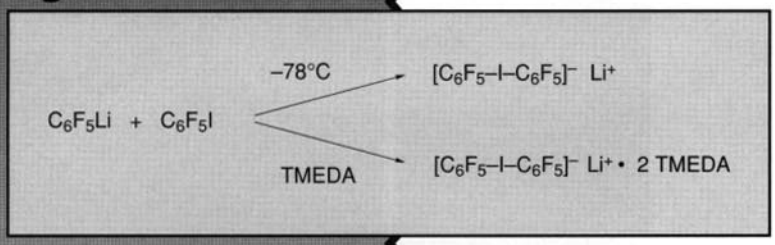
In support of the SET mechanism,[8] a number of coupling products have been found (Fig. 1). In addition, for certain systems, chemically induced dynamic nuclear polarization (CIDNP) signals have been observed, such signals being indicative of radical character in the intermediate(s).

Fig. 1



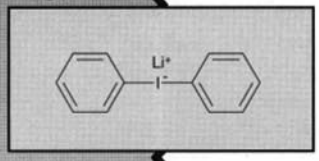
There is support for the "ate-complex" intermediate; such a complex has been isolated in one case. For the equilibrium of pentafluorophenyllithium with pentafluorophenyliodide, the unstable complex was observed at -78°C; addition of two equivalents of TMEDA, however, resulted in formation of a stabilized "ate-complex" (Fig. 2) which was isolated and characterized by X-ray spectroscopy.[9]

Fig. 2



Solution NMR evidence continues to be gathered in favor of the "ate-complex" mechanism. The "ate-species," (Fig. 3) has been observed as a discreet solvent-separated ion pair and it was demonstrated to serve as a phenyl anion donor.[10] Evidence in favor of the linear intermediate demanded by such a structure has been published.[11]

Fig. 3



As mentioned above, M↔X exchange complements metalation and directed metalation for the synthesis of substituted aromatic compounds. The process is in effect a reversible equilibrium with the formation of the more stable anion serving as the driving force. It seems likely that an "ate-complex" serves as an intermediate at least in those equilibria involving aryl systems. The use of *n*-BuLi or *t*-BuLi appears to be advantageous; however, in the case of *t*-BuLi, two equivalents are generally required. The second equivalent of *t*-BuLi reacts with the byproduct *t*-butyl bromide to form LiBr which in some cases may improve the subsequent reaction of the lithiated substrate and electrophile.

Note: Because of the high volatility of pentane which is the solvent for commercially available *t*-BuLi, a new formulation in heptane is now available for laboratory and pilot use. The less volatile heptane results in a safer and easier to handle *t*-BuLi solution.

Aryl bromides and iodides best undergo the exchange, whereas aryl chlorides do not participate in M↔X exchange promoted by alkyllithiums. However, several successful examples of exchange with "activated" aryl chlorides are known. A claim that M↔X exchange with *n*-BuLi can take place faster than ionization of a relatively acidic alcohol proton[12] has, for the time being, been refuted.[13]

ARENES

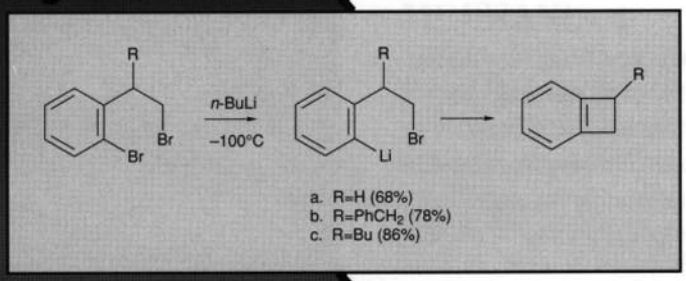
The original observations of Jones and Gilman[2] that the M↔X exchange of aryl halides could be extended to aryl-bearing substituents, which are sensitive to alkyllithium reagents, were not of significant synthetic impact due to the relatively low yields reported. The low yields undoubtedly resulted from not performing the reactions at much lower temperatures. In fact, twenty years later, Kobrich and Buck[14] observed that *o*-lithio nitrobenzene could be prepared in nearly quantitative yield from *o*-bromonitrobenzene at -100°C. Additional examples of systems with high yields under low-temperature conditions are included in Table 1. Further discussion of this technique can be found in the review by Parham and Bradsher.[3] Of course, extremely low temperatures, although accessible in the laboratory, are expensive in industrial applications. However, several companies already have pilot- and plant-scale low temperature capabilities (> -80°C) in place and efforts are underway to improve the economics of low temperature processes. Higher temperatures may be possible by limiting or eliminating the use of Lewis bases as shown by the preparation of phenyllithium (see first entry, Table 1). The economics of this approach must be balanced against the limited solubility of lithiated aryl substrates. Of course, limited solubility may be necessary to prevent alkylation by the butyl bromide byproduct, which may have to be separated from the lithiated substrate.

Table 1 - Substituted Lithiobenzenes by M↔X Exchange

SUBSTRATE	ORGANOLITHIUM REAGENT (SOLVENT)	°C	PRODUCT	REFERENCE
C_6H_5Br	*n*-Bu (toluene)	50	C_6H_5Li	15
p-BrC_6H_4OMe	Ph (Et_2O)	0	*p*-LiC_6H_4OMe	16
p-$IC_6H_4CO_2H$	Ph (Et_2O)	-75	*p*-$LiC_6H_4CO_2Li$	17
o-$BrC_6H_4NO_2$	Ph (THF)	-100	*o*-$LiC_6H_4NO_2$	14
p-BrC_6H_4Cl	*n*-Bu (Et_2O)	25	*p*-ClC_6H_4Li	18
o-BrC_6H_4CN	*n*-Bu (THF)	-78	*o*-LiC_6H_4CN	19
2,5-$Br_2C_6H_3NMe_2$	*n*-Bu (THF)	-100	2-Li-5-$BrC_6H_3NMe_2$	20
2,6-$(O_2N)_2C_6H_3Br$	*n*-Bu (THF)	-100	2,6-$(O_2N)_2C_6H_3Li$	21

A useful technique pioneered by Parham and Bradsher[3] is a series of cyclizations known as "Parham Cyclizations." Cyclialkylations (Fig. 4) and cycliacylations (Fig. 5), as well as other cyclizations, have been accomplished. These reactions are also best carried out at low temperatures.

Fig. 4



Fused bromoarene systems have in a few instances been subjected to M↔X exchange to produce the organolithium intermediate with good-to-excellent yields (Table 2). An exception is the lithio derivative from 2-bromophenanthrene which was generated at only 37% based on the yield of the product isolated.[24]

Fig. 5

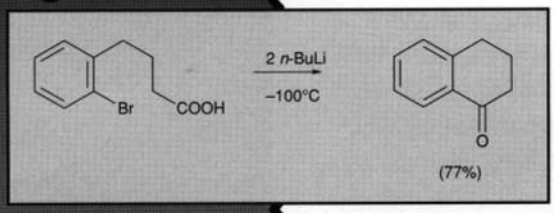


Table 2 - Lithioarenes by the M↔X Exchange

SUBSTRATE	ORGANOLITHIUM REAGENT (SOLVENT)	PRODUCT	REFERENCE
1-Bromonaphthalene	*n*-Pr (Et_2O)	1-$LiC_{10}H_7$	22
2-Bromonaphthalene	*n*-Bu (Et_2O)	2-$LiC_{10}H_7$	23
2-Bromophenanthrene	*n*-Bu (Et_2O)	2-$LiC_{14}H_9$	24
9-Bromophenanthrene	*n*-Bu (Et_2O)	9-$LiC_{14}H_9$	25
1-Bromopyrene	Ph (Et_2O)	1-$LiC_{16}H_{11}$	26

Activated aryl chlorides also undergo M↔X exchange. While the actual activation mechanism is unclear, certain perhalobenzenes which contain chlorine undergo the reaction quite readily (Table 3). Perhalobenzenes which contain a bromo or iodo substituent undergo exchange at the site of the bromine or iodine atom. Interestingly, C_6Br_6 affords a much lower yield (17%) of the lithio-perhaloarene[27] than does C_6Cl_6 (Table 3).

Table 3 - Haloarenes by X↔ M Exchange

SUBSTRATE	ORGANOLITHIUM REAGENT (SOLVENT)	°C	PRODUCT	REFERENCE
C_6F_5Cl	*n*-Bu (Et_2O)	-70	C_6F_5Li	28
1,3-$Cl_2C_6F_4$	*n*-Bu (Et_2O)	-70	3-ClC_6F_4Li	29
1,2-$Br_2C_6F_4$	*n*-Bu (Et_2O)	-70	1,2-$Li_2C_6F_4$	30
C_6Cl_6	*n*-Bu	-78	C_6Cl_5Li	31
C_6Cl_6	*t*-Bu	-125	C_6Li_6	32

Perlithiobenzene, C_6Li_6, was isolated in 53% yield,[32] a significant achievement. Dilithiobenzene has, in the instance of the 1,4-analog, been prepared by the M↔X exchange.[33] The 1,2-isomer has been prepared by the halogen-mercury exchange (a significantly underexploited reaction) followed by treatment with *n*-BuLi (Fig. 6).[34]

Fig. 6

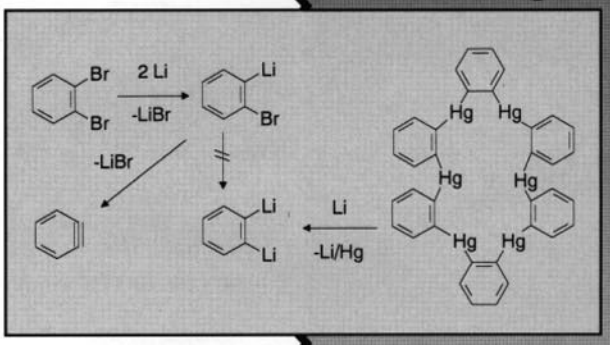


Fig. 7

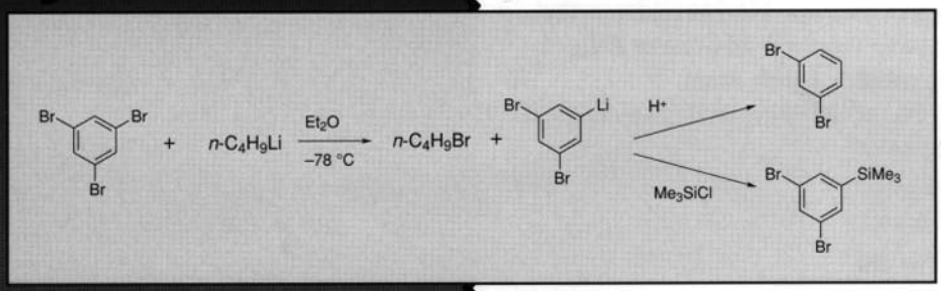


Fig. 8

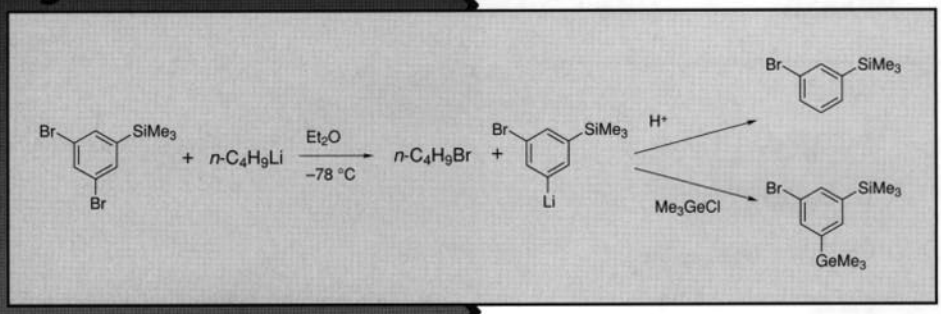
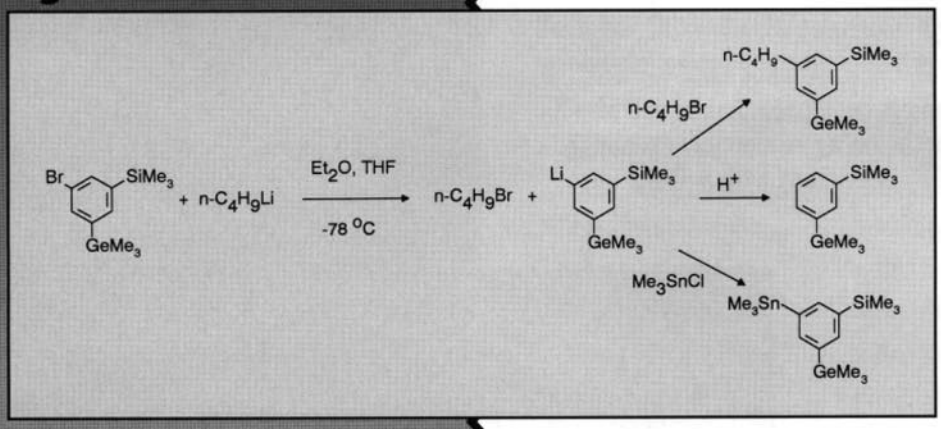


Fig. 9



C. Tamborski, who pioneered much of the earlier work on polyhaloarenes, illustrated the power of the M↔X exchange by the preparation of a series of 1,3,5-trisubstituted benzenes as illustrated in equations 7, 8, and 9.[35]

HETEROCYCLES

The M↔X exchange is particularly useful for the preparation of organolithio intermediates of reducible heterocycles, such as pyridine. Organolithium reagents tend to add to the electron-deficient π-system in such molecules when metalation (M↔H exchange) is attempted. Another potentially useful set of intermediate lithio compounds are those generated at the position(s) not favored by electrophilic substitution in the respective heterocycles. Thus, the 3-lithio intermediates in the monoheteroatom 5-membered ring heterocycles lead to products that complement those prepared at the 2-position by electrophilic substitution techniques or by metalation. A different situation exists for the simple benzo derivatives of the 5-membered ring heterocycles. Papers describing preparation of the 3-lithio derivatives via M↔X exchange have been published. However, the 3-position in such heterocycles is also the one favored by electrophilic substitution. A summary of information regarding a number of these intermediates can be found in Table 4.

Table 4 - Lithioheterocycles by the M↔X Exchange

SUBSTRATE	ORGANOLITHIUM REAGENT (SOLVENT)	°C	PRODUCT	REFERENCE
Single-ring Heterocycles				
3-Bromopyrrole	*n*-Bu (THF)	-23	3-LiC_4H_3NX[a]	36
3-Bromofuran	*n*-Bu (Et_2O)	-70	3-LiC_4H_3O	37
3-Bromothiophene	*n*-Bu (Et_2O)	-70	3-LiC_4H_3S	38,7
2-Bromopyridine	*n*-Bu (Et_2O)	-70	2-LiC_5H_4N	39
3-Bromopyridine	*n*-Bu (Et_2O)	-35	3-LiC_5H_4N	40,7
Fused-ring Heterocycles				
3-Iodoindole	*t*-Bu (THF)	-100	3-LiC_8H_5NY[b]	41
3-Bromobenzothiophene	*n*-Bu (Et_2O)	-70	3-LiC_8H_5S	42
3-Bromoquinoline	*n*-Bu (THF)	-100	3-LiC_9H_6N	7

[a]X is protecting group -Si(i-Pr)$_3$; [b]Y is protecting group -O_2SPh

MACROCYCLE SYNTHESES

More sophisticated uses of the M↔X exchange are rapidly emerging. Cram et al.[43,44] have demonstrated the potential use of the reaction in the synthesis of several spherands and cavitands (Figs. 10 and 11). Interestingly, the decision to use the two-step processes, generation of the dibromo intermediate followed by M↔X exchange rather than a double directed metalation, must have been based on the low yields afforded by methoxy-directed metalations.

The initial step in the formation of a macrocyclic polyketone[45] was the addition/oxidation sequence shown in Fig. 12. The dilithio intermediate was generated by the M↔X exchange on the corresponding dibromo compound. Remarkably, the polyketone generated undergoes spontaneous isomerization to a spirobicyclic polyketal.

Fig. 10

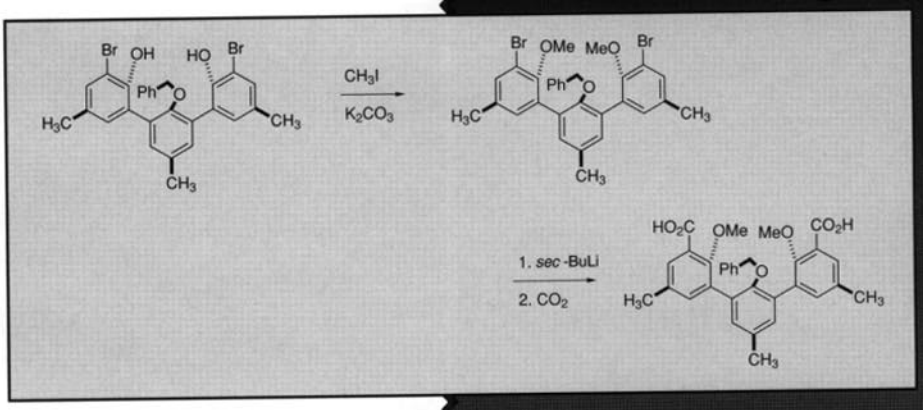


Fig. 11

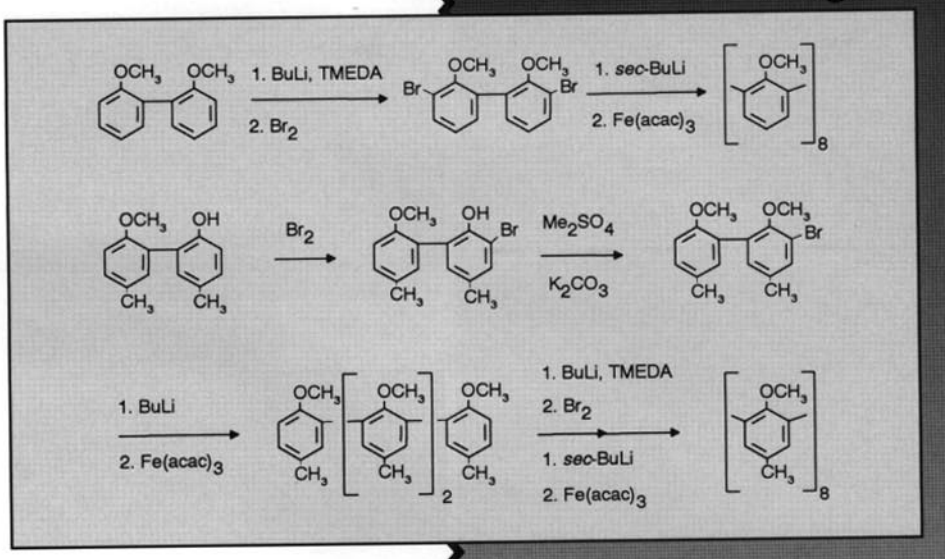


Fig. 12

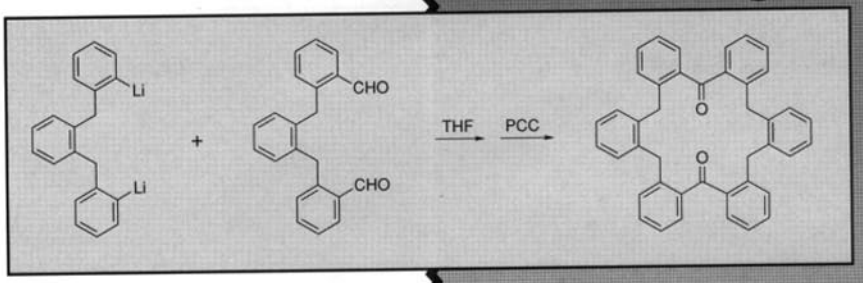


Fig. 13

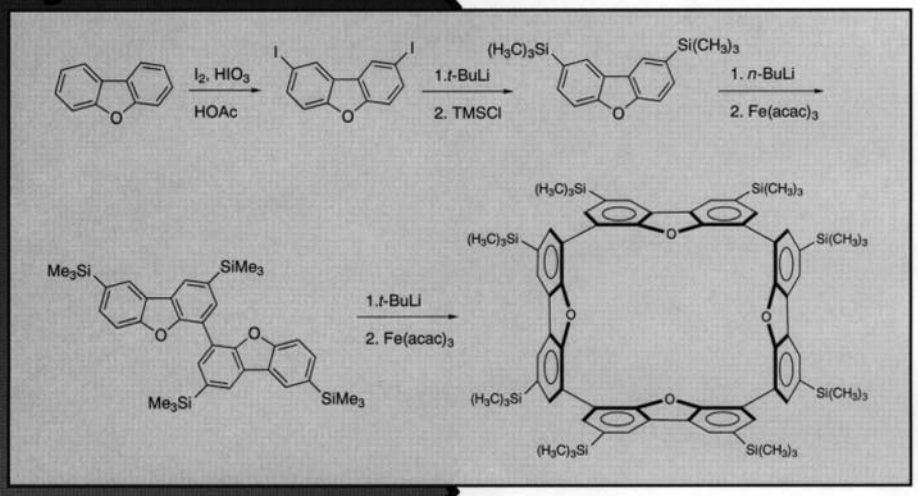


Fig. 14

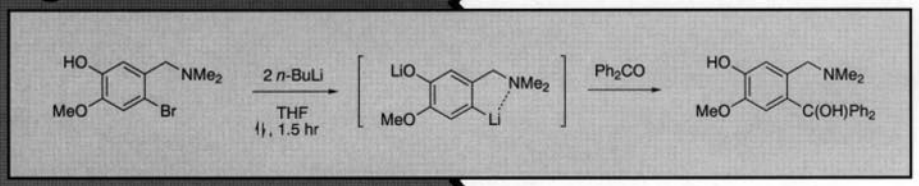


Fig. 15

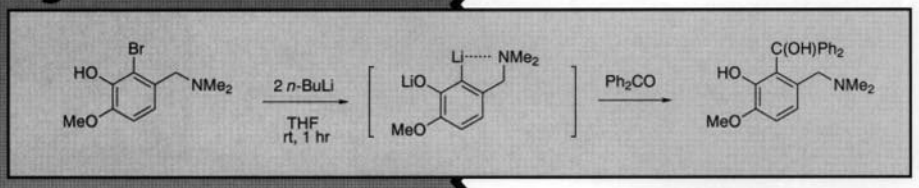
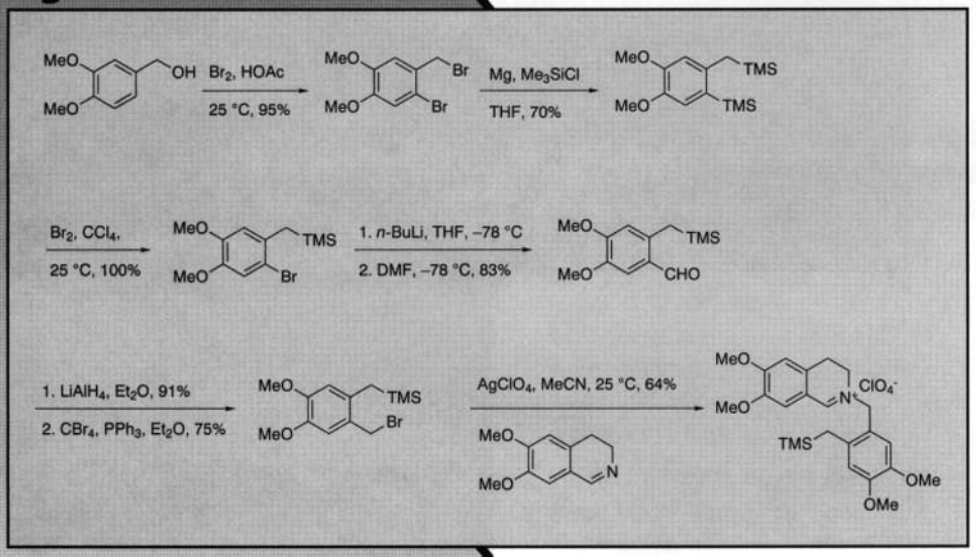


Fig. 16



In more recent work, Cram et al.[46] have extended their macrocycle syntheses to the use of fused ring heterocycles (Fig. 13). One M↔X exchange and, in essence, two directed metalation reactions are featured in this synthesis.

NATURAL PRODUCT SYNTHESIS

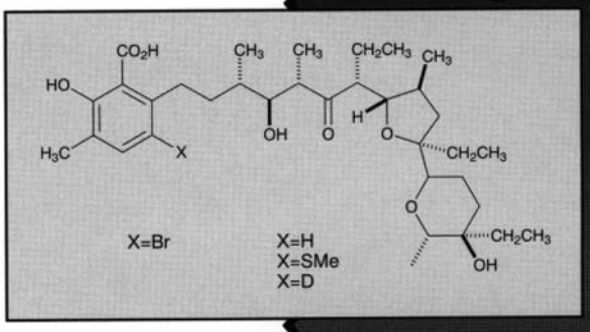
For regiospecific syntheses of a variety of natural products containing highly substituted aromatic rings, the M↔X exchange has found increasing use. Often the decision to use the M↔X exchange is mitigated by the possibility of more than one site of metalation afforded by the directed metalation reaction.

Syntheses of N,N-dimethylvanillylamine and N,N-dimethylisovanillylamine illustrate this point (Figs. 14 and 15).[47] The two isomeric bromo compounds were prepared by different routes. Directed metalation of 3-hydroxy-4-methoxydimethylbenzylamine would have afforded a mixture of both lithio-intermediates from which a mixture of both products would have been generated. Presumably, the difficulty of separating such a mixture precluded this strategy.

In the synthesis of protoberine alkaloids,[48] a unique series of selective reactions involving several bromine-containing intermediates, including one M↔X exchange, was used (Fig. 16). Of particular interest is the strategy of creating the aliphatic/aromatic di-TMS product which was selectively converted to the aryl bromide by aryl desilylation.

Polylithiated derivatives of salicylic and oligosalicylic acids can be generated by M↔X exchange.[49] Treatment of 5-bromosalicylic acid with *t*-BuLi at -90°C afforded the O,O,C-trilithio derivative from which a variety of substituted salicylic acids were prepared. Identical treatment of 5-iodosalicylic acid lead exclusively to recovery of the deiodinated product. To test the procedure, the base-sensitive salicylic acid, 5-bromolasalocid A (Fig. 17) was subjected to the same conditions as above and treated with D_2O. The approximately 50% of the deuteriated product (40% recovery) exhibited total retention of structural and stereochemical integrity.

Fig. 17



A noteworthy example of the use of M↔X exchange in natural product precursor synthesis is the development of a general route for synthesis of substituted phthalides.[50] Intramolecular trapping of the adjacent carbamate functionality by the lithio intermediate affords a Parham-type cyclization product (Fig. 18). Application of this lactonization procedure to the total synthesis of aristocularines has been accomplished (Fig. 19).[51]

Fig. 18

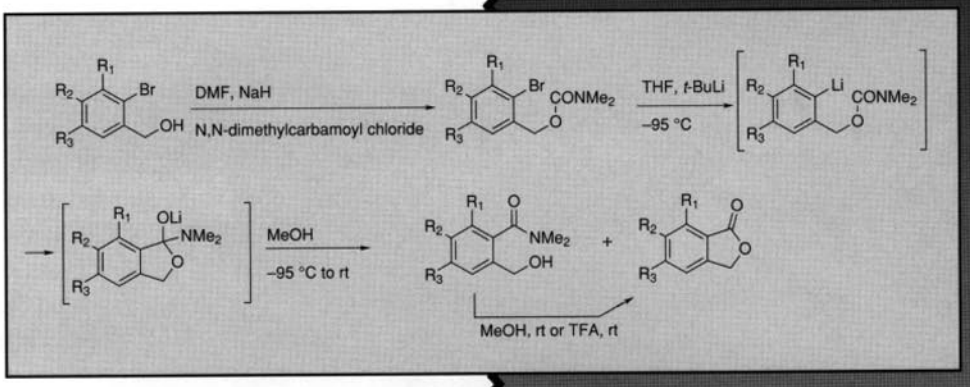


Fig. 19

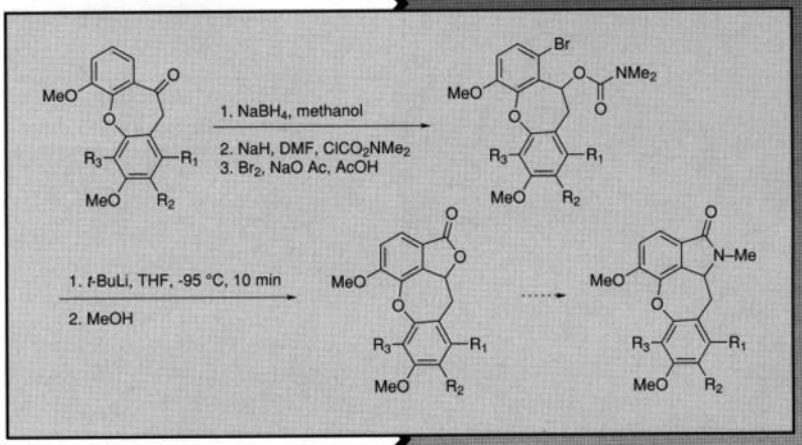


Fig. 20

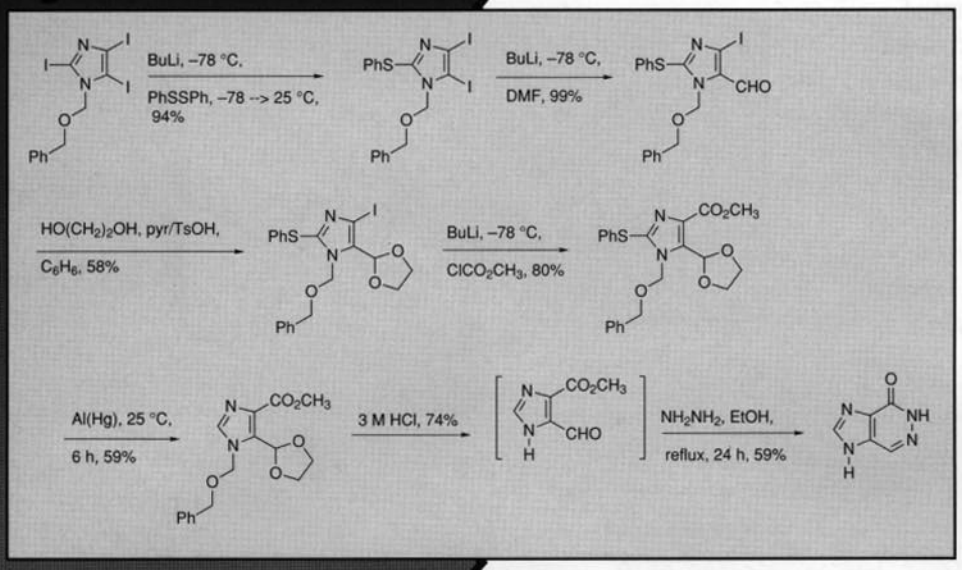


Fig. 21

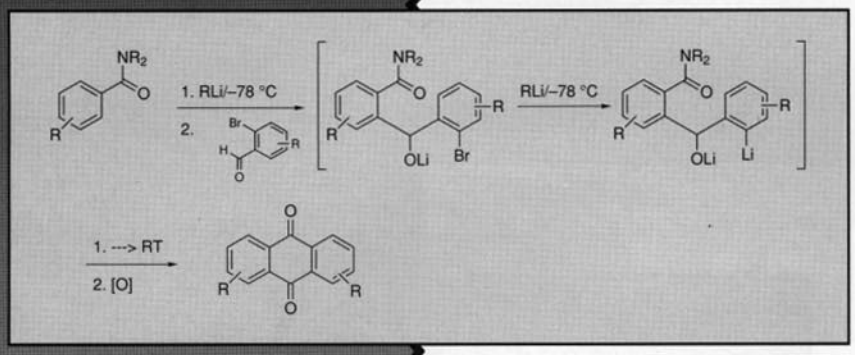


Fig. 22

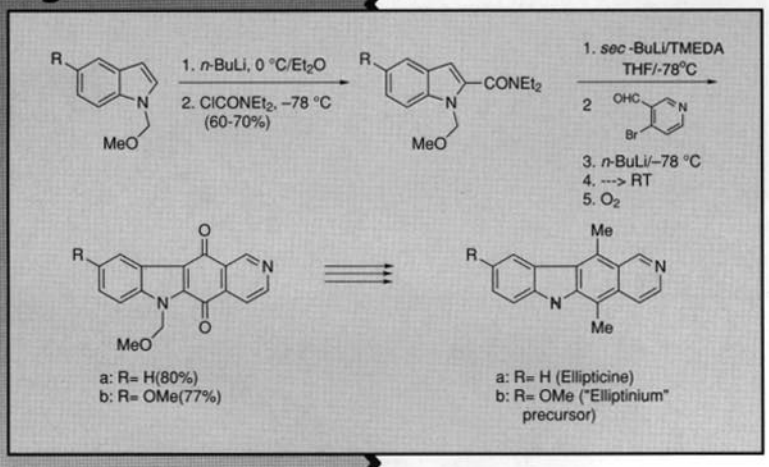
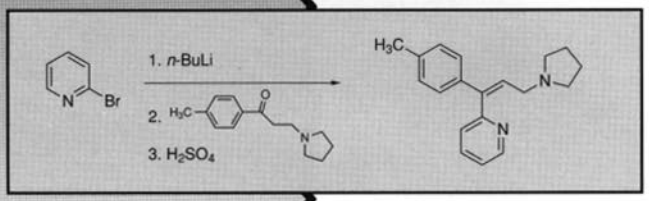


Fig. 23



A recent paper entitled "Multifunctionalization of Imidazole via Sequential Halogen-Metal Exchange: A New Route to Purine-Ring Analogs" illustrates the power of the M↔X exchange to assist in the preparation of analogs of known bioactive species.[52] Treatment of 1-[(benzyloxy)methyl-2,4,5-triiodoimidazole sequentially with *n*-BuLi, TMSCl, *n*-BuLi, $Me_2NN(Me)CHO$, *n*-BuLi and $(MeOCO)_2O$ gave the N-protected-4-(methoxycarbonyl)-imidazole-5-carboxaldehyde in a remarkable overall yield of 25%. A separate route to this compound featuring three sequential M↔X exchanges is illustrated (Fig. 20). This compound was only two steps removed from the desired product. Of paramount concern during such syntheses is the generation of a less or least favored anion of the imidazole system. This strategy has potential application in other systems.

In an elegant variation on the Parham-cyclization, a tandem M↔H/M↔X exchange procedure has been developed for the synthesis of a number of specifically substituted anthraquinones (Figs. 21 and 22).[53,54] An intervening step, linking the arene containing the functional group to a second arene containing the requisite bromine atom, is effected before M↔X exchange.

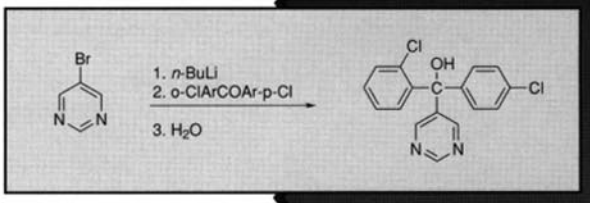
CONCLUSION

M↔X exchange can be used on an industrial scale. For instance, Burroughs Wellcome Co. manufactures triprolidine[55] (Fig. 23) and Dow Elanco prepares fenarimol[56] (Fig. 24) via low temperature processes.

Large-scale use of M↔X exchange will increase as more is understood about this method, especially concerning:

- temperature optimization,
- use of continuous reaction schemes (kinetics),
- effect of limiting Lewis bases,
- outlets for the byproduct butyl bromide (i.e., in BuLi production),
- availability of brominated substrates.

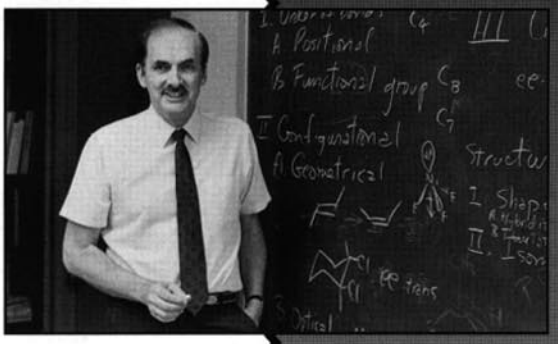
Fig. 24



These challenges are offered to the chemists and engineers considering lithium methodologies.

More About the Author of the Feature Article

Professor Don W. Slocum currently serves as the Chemistry Department Chairman at the University of Western Kentucky. In addition to his teaching duties, he leads a research group of undergraduate students. The major area of interest for his group is in directed metalation of aromatic systems. Over the past few years, the results of their research have been reported at ACS meetings, as well as to pharmaceutical companies.



Future Feature Articles

Upcoming issues of Lithium Link will feature:

• "Metal-Halogen Exchange Involving Aliphatic Substrates Using Organolithiums" by Professor William Bailey of University of Connecticut. Professor Bailey has published extensively in this area. Scheduled to appear in the Spring 1994 issue, this article will complement this issue's topic.

• "Assaying Commercial Organolithiums." An accurate assay method is very important when it is critical to know the concentration of organolithiums such as butyllithium, methyllithium, lithium diisopropylamide, and others. This article will review some of the methods as well as recommend one which can be used for assaying most of the commercially available organolithiums.

• "Organolithiums in the Synthesis of Lactams." In recent years, lactams have been prepared as possible candidates for antibiotics. This article will present the diverse use of organolithiums in synthesis of important ring systems, especially β-lactams.

• "Preparation of Alkenes and Alkynes via Organolithium Methodologies." Several methods are available for multiple bond preparation, ranging from olefination and dehydrohalogenation to simple addition reactions involving vinyllithium or alkynyllithium derivatives.

Note: If you have some information of interest regarding these topics that you would like to share with our readers, please contact us so that we may include it in these upcoming issues.

Feature Articles from Previous Lithium Link Newsletters:

"Focus on *t*-Butyldimethylchlorosilane (TBSCl)" Spring 1991. (photocopy only)

"Chirals and Carbanions" Fall 1991. (photocopy only)

"Ring and Lateral Metalation of Aryl Substrates Using Strong Base Systems" Spring 1992.

"Ring and Lateral Metalation of Heteroaryl Substrates Using Strong Base Systems" Spring 1993.

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secondary(***sec***)-**Butyllithium (SBL),** (12 wt%) in cyclohexane, or heptane

tertiary(***t***)-**Butyllithium (TBL),** (18-22 wt%) in pentane

Lithium diisopropylamide (LDA-9505), 2 M (26 wt%), nonpyrophoric

Lithium hexamethyldisilazide (LHS), 1.3 M (25 wt%) in THF or 1 M (21 wt%) in THF/cyclohexane

Methyllithium (MeLi-9307), 1.1 M (3 wt%) in THF/cumene, nonpyrophoric

Dibutylmagnesium (DBM), 0.7 M (14 wt%) in heptane

***t*-Butyldimethylsilyl chloride (TBSCl),** solid 98%, $(CH_3)_3CSi(CH_3)_2Cl$

***t*-Butyldimethylsilyl chloride (TBSCl),** 3 M (50 wt%) in toluene

Lithium *t*-Butoxide (LTB), 2 M (18 wt%) in THF, $LiOC(CH_3)_3$

Lithium methoxide (LM), 2.2 M (10 wt%) in methanol, $LiOCH_3$

DEVELOPMENTAL PRODUCTS

(Pilot Quantities - typical concentrations)

***n*-Hexyllithium (NHL),** 2.8 M (35 wt%) in hexane, $CH_3CH_2CH_2CH_2CH_2CH_2Li$

Di-*t*-butylsilane (DTBS), bp 128°C, 98%, $(t\text{-Butyl})_2SiH_2$

***n*-Butyllithium**, 2.2 M (17 wt%) in Toluene

RESEARCH PRODUCTS

(Laboratory quantities - typical concentrations)

2-Ethylhexyllithium (EHL), 2 M in heptane, $CH_3CH_2CH_2CH_2CH(Et)CH_2Li$

***n*-Octyllithium (NOL),** 2 M in heptane, $CH_3CH_2CH_2CH_2CH_2CH_2CH_2CH_2Li$

***t*-Butyllithium (TBL),** 1.8 M in **HEPTANE**. This product in heptane is safer to handle than the current commercial formulation in pentane.

***t*-Butyldiphenylsilyl chloride (BPS),** liquid 97%, $(CH_3)_3CSiPh_2Cl$, liquid

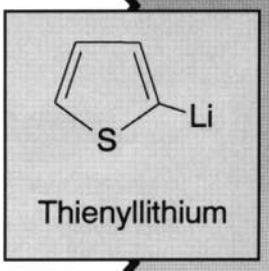
***t*-Butyltrichlorosilane (BTC),** waxy solid 97%, $(CH_3)_3CSiCl_3$

Di-*t*-butyldichlorosilane (BDC), liquid 97%, $[(CH_3)_3C]_2SiCl_2$

Lithium methoxide (LMS), solid >97%, $LiOCH_3$

Lithium *t*-butoxide (LTB), solid >97%, solid, $LiOC(CH_3)_3$

Thienyllithium (TLT), 1.5 to 2 M in THF/heptane



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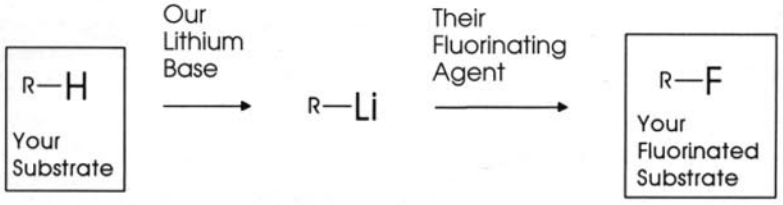

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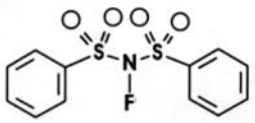

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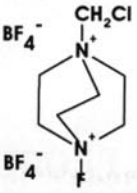

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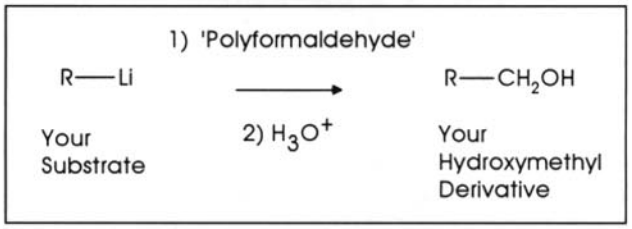

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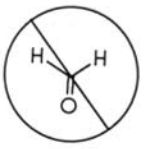

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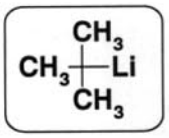

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