FMC
LITHIUM LINK™
Spring 1992

Ring and Lateral Metalation of Aryl Substrates Using Strong Base Systems

INTRODUCTION

Metalated aromatic and heteroaromatic ring systems can be readily prepared via metal-halogen exchange (M↔X) or metal-hydrogen exchange (M↔H) using alkyllithiums. Isomers of butyllithium are always used directly in metal-halogen exchange. Whereas in metal-hydrogen exchange, butyllithiums may be used directly or indirectly, which means they are used in presence of, or first reacted with, various "modifiers". These "modifiers" may be sodium, lithium, or potassium alkoxides, inorganic salts (e.g., LiX, or MgX_2) and/or amines (e.g., tetramethylethylenediamine (TMEDA), diisopropylamine, or tetramethylpiperidine). There are extensive examples of both metalation types.[1,2,3,4,5,6,7,8] These produce useful nucleophiles which can be reacted with various electrophiles (Fig 1). Although these metalations are used extensively on the laboratory scale, the ultimate usefulness of metalation methods is measured by the extent to which they are used on a large scale.

The major portion of this issue will focus on metal-hydrogen exchange (Fig 1A, 1B). There is an abundance of information reported for this type, especially involving ring systems having the so-called "Directed Metalation Group(s)" (DMG).[3] In spite of the numerous M↔H methodologies for ring systems involving DMGs, limited (and only recent) applications have been observed on the pilot scale.[9] Increased awareness of the utility of DMG methodologies for aryl substrates may encourage metalation use at the bench and on an industrial scale.

FROM THE EDITOR

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

This bi-annual newsletter focuses on one of the fastest growing segments of our business, the use of lithium-based products in organic synthesis.

This issue's feature article highlights the use of organolithiums for directed metalation of aromatic ring systems. This topic was recently reviewed by Professor Vic Sneickus (see reference 3). His excellent review is the basis and springboard for this article and future articles in ring and lateral metalation of aromatic substrates.

We are making available a limited number of reprints of his review article. The article covers in detail much of what his lab has accomplished over the past several years. If you would like a copy of the reprint, please indicate your request on the enclosed reply card. Request will be filled on a first-come, first-serve basis until supplies are exhausted.

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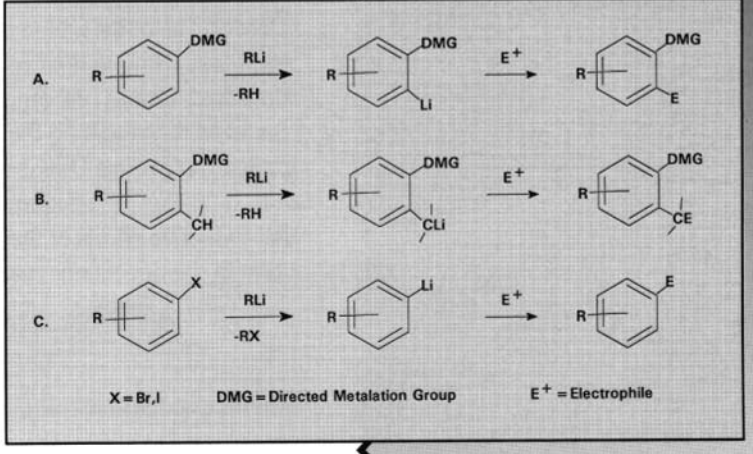
Fig. 1



Large scale application of M↔H of heteroaromatic substrates[10,11,12] and the M↔X methods for aryl (Fig 1C) and heteroaromatic[13,14] substrates are already being practiced. The methodologies for these substrates will be addressed separately in future issues.

METALATION VIA METAL-HYDROGEN EXCHANGE (M↔H)

The first part of this discussion covers ring metalation of aryl substrates followed by a second section dealing with lateral metalation of aryl substrates. Also given are the various electrophiles that can be intermolecularly reacted with the phenyl- and benzyllithium derivatives resulting from described metalations. Because cyclization represents a novel outcome of an intramolecular nucleophile/electrophile reaction involving a metalated substrate, it is covered separately in the final section.
To cover all types of nucleophiles and electrophiles is well beyond the limits of this newsletter. We hope that enough information is given so the reader can apply these concepts to his or her work.

Directed Ring Metalation of Aryl Substrates

Regiospecific M↔H of aromatic compounds is directed and activated by an *ortho* substituent. The *ortho* group always contains a heteroatom(s) which can interact with the cation of the approaching base and/or inductively increase the acidity of the *ortho* hydrogen to be abstracted. A general hypothesis which explains how all *ortho* groups participate is not available, but evidence to support prevailing hypotheses is given.[3,15]

The *ortho*-directed metalation group (DMG) exerts its effect by close coordination of the organolithium (RLi) with the heteroatom of the DMG.[3,16] Coordination of an electron pair of the heteroatom of certain DMGs with the lithium cation of the RLi maximizes the electron-withdrawing inductive effect of the DMG. Thus subsequent attack of the R^- of the RLi at the *ortho* hydrogen is facilitated (Fig 1A). The ability of *ortho* DMGs to precomplex with butyllithium is further evidenced in the M↔H of six-membered heteroaromatic rings containing C=N bonds,[17] which normally undergo addition reactions.

Various theoretical and NMR data suggest that both kinetic and thermodynamic factors facilitate *ortho* lithiation of aromatic compounds with appropriate DMGs.[15]

Ortho-directed metalation groups (DMGs) have varying degrees of effectiveness. In Table 1, three classes of DMGs are listed according to their ability to direct *ortho* metalation (DoM).[3] The order within each class of the strong, moderate, and the weak DMGs is not a listing according to their relative abilities; this is better summarized in Scheme 1.[3] Using these three classes one can predict the favored site of metalation if two DMGs of different classes were present on the same ring system. In Table 1, Professor Snieckus has also graded the various DMGs according to their proven effectiveness in synthetic applications by using "+" assignments. The pKa's were included in the original table to show that inductive effects of the DMG can not be used to understand the role that the DMG plays in the direct *ortho* metalation (DoM) process.[18]

In Table 1, the -OMe DMG is listed as being "+++ or well proven,"[6] although it is only a moderate director. In an effort to understand more about the DoM process, various crystal,[61,62,63,64] solution NMR,[63,64,15] and theoretical[65,15] studies of *ortho*-lithiated aryl-OMe compounds have been reported. Depending on the temperature, the ethereal solvents and additives present, and the reaction times, dimetalation of *o*- and *p*-dimethoxybenzenes with *n*-BuLi/TMEDA[66] produces useful dianions (Fig 2). Yet a strong base system such as 2:1 *t*-BuLi:*t*-BuOLi[65] which appeared to be less reluctant to cleave THF[67] can cause undesirable *O*-demethylation.

Fig. 2

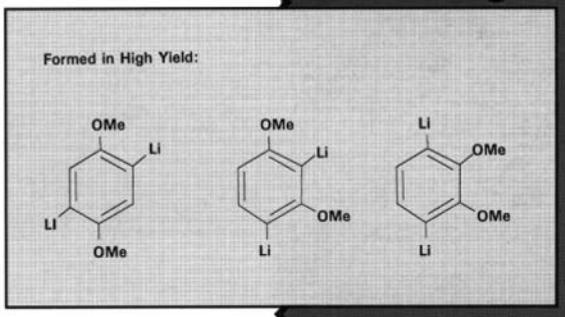
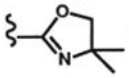
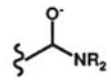
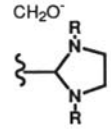
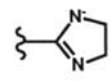


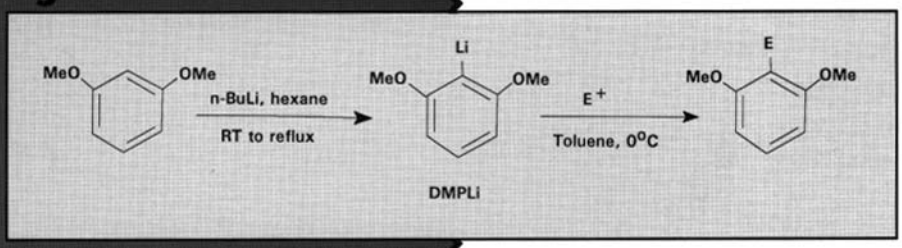
Table 1 - DMGs in Synthesis: Qualitative Evaluation

Z (pKa) Carbon Based[a]	Synthetic Utility[b]	Ref	Z (pKa) Heteroatom Based[a]	Synthetic Utility[b]	Ref
Strong					
CON^-R	+++	6, 19f	N^-COR (≥40.5)	++	20
CSN^-R	++	21	N^-CO_2R	+++	22
$CONR_2$ (37.8)	+++	19a-e	$OCONR_2$ (37.2)	++	23
$CONR_2$ (31.1)[24]	++	24	$OPO(NR)_2$	+	25
CON(R)CH(Z)TMS	+	26, 27	OCH_2OMe	+++	28, 29
Z = H, TMS			tetramer	+	30
 (38.1)	+++	19g	OTHP (40.0)	20, 23	6
			OPh (38.5)	+	32
			SO_3R	+	33
CH=NR	++	31	SO_2N^-R	+	6
$(CH_2)_nNR_2$ (≥40.3) n=1,2	+	6	SO_2NR_2 (38.2)	+	6
$CH(OH)CH_2NR_2$	+	6	SO_3^-	+	34
CN (38.1)	+	37	SO_2t-Bu	+	35
			SO*t*-Bu	+	36
Moderate					
CF_3	+	6	NR_2 (≥40.3)	+	6
			N≡C	++	38
	++	39	OMe (39.0)	+++	6
			OMe (33.0)[24]	+	24
			$OCH=CH_2$	+	40
			$OPO(OR)_2$	+	41
			$O(CH_2)_2X$ X = OMe, NR_2	+	42
			F	+	43
			Cl	?	44
			$PO(NR)_2$	+	45
			$PS(Ph)NR_2$	+	46
Weak					
$C(OTMS)=CH_2$	+	6	O^- (≥40.5)	+	47
$CH(OR)_2$	+	48	S^-	+	49
CH_2O^-	++	50			
	+	51			
	+	52			
$C≡C^-$	+	53			
Ph	+	54			

a) pKa data in parenthesis are given in ref. 18

b) +++ = well proven/extensively applied
++ = promising/requires studies in scope
+ = inadequately tested/new/limited use

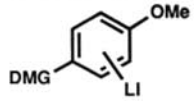
Fig. 3



Among the different conditions under which 1,3-dimethoxybenzene may be metalated, it was found that sparingly soluble 2,6-dimethoxyphenyllithium (DMPLi) could be prepared in high yield in hexane alone at room temperature (Fig 3).[68] Although only a moderate DMG, the DoM power of 1,3-DMG substitution is well illustrated. (See also Fig 18 for additional examples of 1,3-substituted aryl substrates as well as a cyclic acetal, -OCF_2O-).

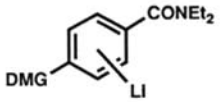
Scheme 1 - Relative Directing Abilities of *ortho* Metalation Groups

Intramolecular Competition:

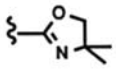


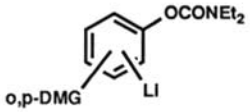
n-BuLi/various conditions
Slocum and Jennings 1976 — **ref 55**

DMG = SO_2NR_2, SO_2N^-R, CON^-R, CH_2NR_2 > OMe > $CH_2CH_2NR_2$, NR_2, CF_3, F



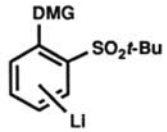
s-BuLi/TMEDA/THF/-78°C
Beak and Brown 1979, 1982, 1983 — **ref 56, 57, 58**

DMG = $CON^-R \geq CONR_2$ >  > SO_2NR_2, SO_2N^-R, CH_2NR_2, OMe, Cl



s-BuLi/TMEDA/THF/-78°C
Miah and Snieckus 1984 — **ref 59**

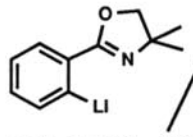
DMG = $OCONEt_2$ >> $CONEt_2$ >> OMOM > OMe, Cl

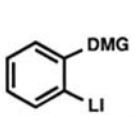


n-BuLi/THF/-78°C
Iwao *et al* 1989 — **ref 35, 36**

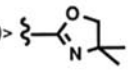
DMG = $OCONEt_2$ (*t*-BuLi) > SO_2t-Bu > $CONEt_2$, OMOM, ^-N*t*-BOC

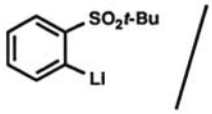
Intermolecular Competition:

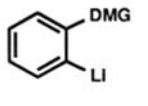




n-BuLi/THF/-45°C
Meyers and Lutomski 1979 — **ref 60**

DMG = SO_2NR_2 > $CONR_2$ (*s*-BuLi)>  > CON^-R (HMPA)



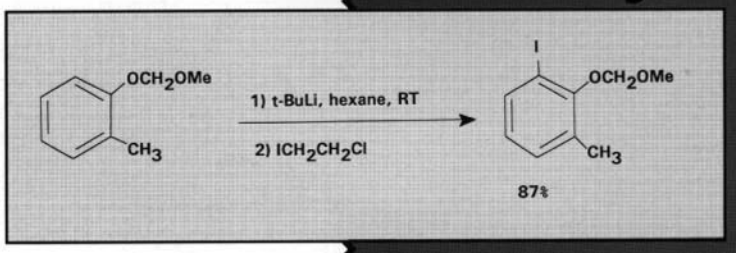


n-BuLi/THF/-78°C
Iwao *et al* 1989 — **ref 35, 36**

DMG = SO_2*t*-Bu > $CON(i\text{-}Pr)_2$, $OCON(i\text{-}Pr)_2$, OMOM > ^-N*t*-BOC (*t*-BuLi)

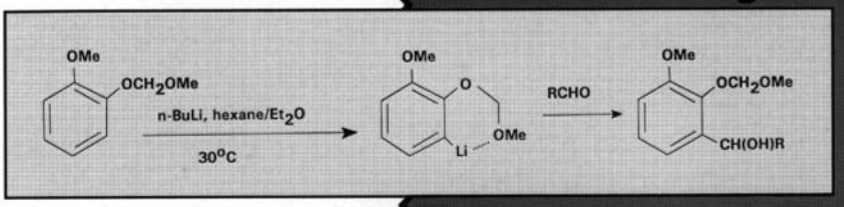
A strong ethereal DMG, $-OCH_2OCH_3$ (or -OMOM), is possibly more effective because the *ortho*-lithiated aryl[69] (Fig 4A[28], 4B[29]) (and naphthyl[70]) species is often insoluble and precipitates from solution as was the case for DMPLi above. Although -OMOM has demonstrated utility, the preparation of this DMG from chloromethyl methyl ether, a known, regulated carcinogen, is prohibitive beyond laboratory scale.

Fig. 4A



Interestingly the DMG, $-CH_2OCH_2CH_2OCH_3$ or OMEM, underwent substantial rearrangement and to a lesser degree cleavage during an attempt to condense its *ortho*-lithiated species with cyclohexanone.[71]

Fig. 4B



In methodologies where the DMG is a protected functionality that must be selectively deprotected in a subsequent step, several other nonethereal OH protective groups are available. These DMGs, including $OC(O)NR_2$,[3,72] OTHP[6,73] and $OP(O)NR_2$,[74] are easier to cleave than $-OCH_3$ ethers. Although similar to the OMEM, the 2-(trimethylsilyl)ethoxymethoxy (OSEM) DMG is useful for allowing selective cleavage under mild conditions but requires prohibitive reagents for large-scale application (Fig 5).[75]

Of course, initial protection of phenol[47] or benzyl[50,76] alcohol (even naphthol[77,78]) is avoided by formation of the corresponding phenoxide[47] or benzyloxide[50,76] anion DMG (Fig 6). This route obviously saves the protection and deprotection steps - if one can overcome such problems as low solubility of the dianion and selective reactivity of the electrophile with the carbanionic site.

Fig. 5

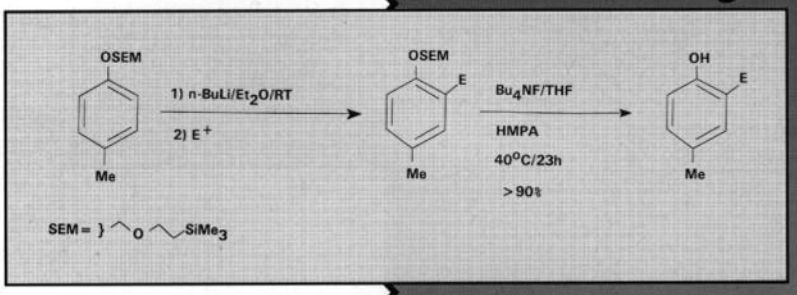


Fig. 6

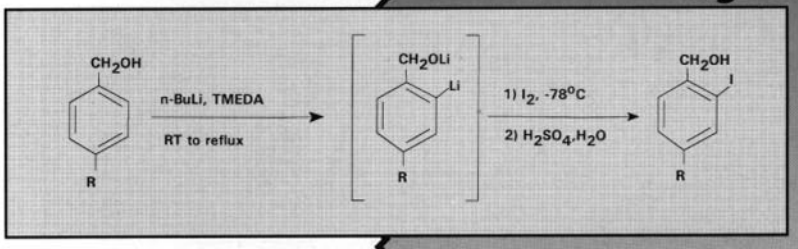
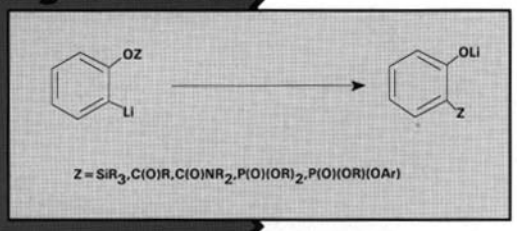
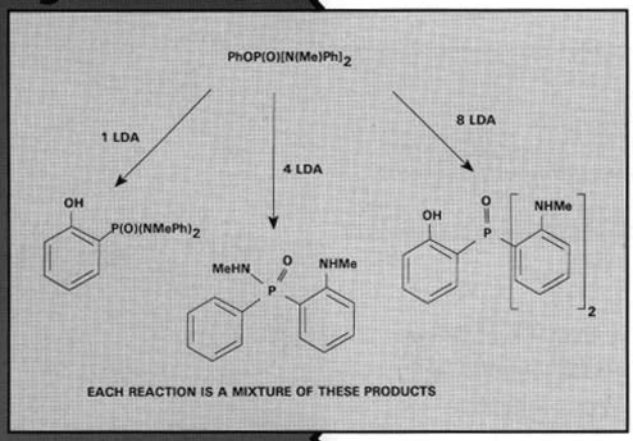


Fig. 7



A second alternative for avoiding at least a separate deprotection step is initially to protect the phenolic or benzylic oxygen with a group which migrates to the *ortho* position during the metalation step. Induced migration from oxygen to an *ortho*-lithiated aromatic carbon has been demonstrated for electrophilic groups Z such as R_3Si,[78,80] C(O)R,[81] $C(O)NR_2$,[82], $P(O)(OR)_2$ and P(O)(OR)(OAr) (Fig 7). The latter two moieties undergo single[83] and double migration[84].

Fig. 8

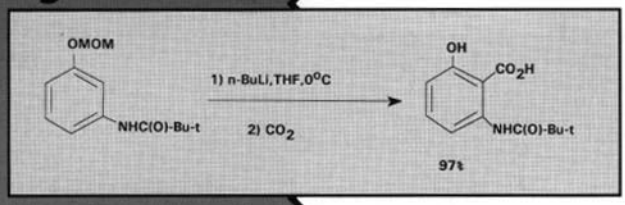


Similarly, various phosphoramidates undergo fission of a P-N bond and formation of a P-C bond after O→C migrations (if possible) have occurred (Fig 8).[85] The extent of migration is dependent on the amount of LDA used. Efforts to selectively prepare any of these products were not successful.

In addition to DMGs containing the aryl-P foundation listed in Table 1, $-P(O)Ph_2$[86] and $-P(S)(NEt_2)_2$[87] have been reported.

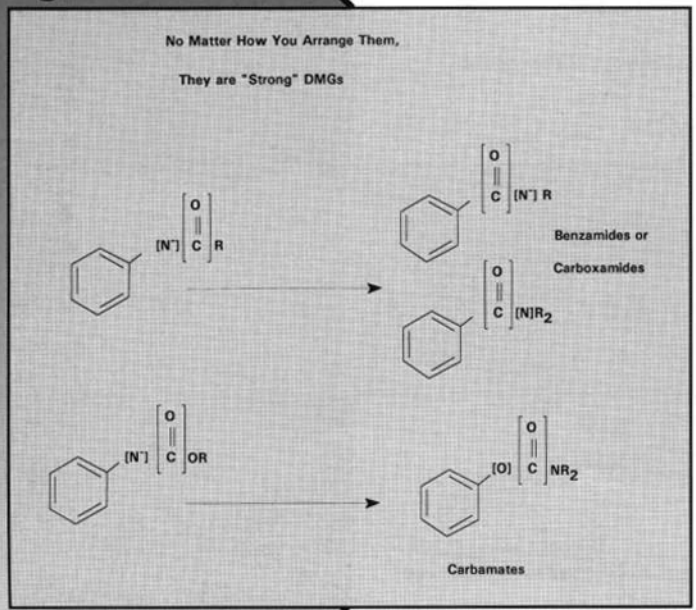
Based on Table 1, the synthetic utility of amines such as $-NMe_2$[6,88] and $-CH_2NMe_2$[31,88,89] is apparently of limited use.[6,90] It also appears that the Lewis base property of nitrogen, thought to participate in the DoM process, is enhanced by being on an α-carbon. (However, in one instance a ring tautomer resulted from DMF formylation of an *ortho*-lithiated N,N-dimethyl-α-(*m*-methoxyphenyl)ethylamine.[91]) Also because of the vast difference in the hierarchy between the "strong" oxazolinyl moiety,[19g,60] and "weak" 2-imidazolyl anion[52] or protected 2-pyrroyl,[51] it appears that planarity and neutral charge are important DMG features for cyclic amines.

Fig. 9



As was the case discussed earlier for the protected phenol, masked or protected amines in the DMG form of $-N^-C(O)R$ (Fig 9)[20] or $-N^-C(O)OR$[22] are considerably more useful DMGs.

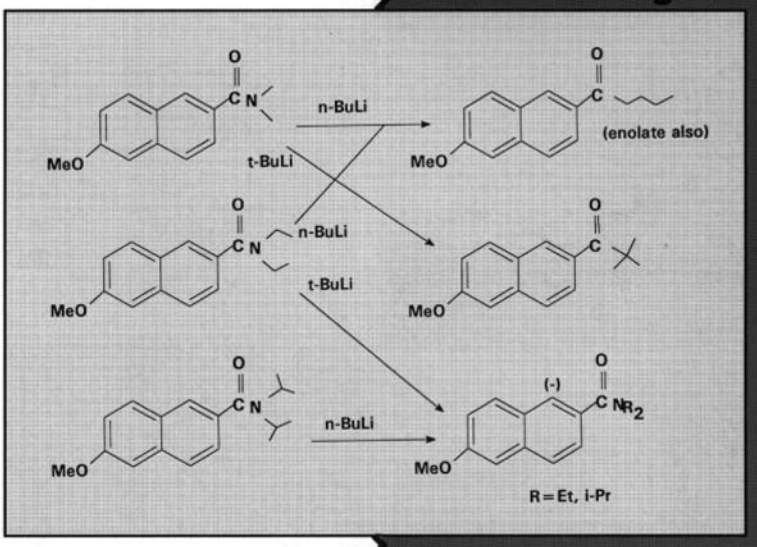
Fig. 10



Yet in terms of a "strong" DMG containing a nitrogen, simple reversal of the DMG atoms (namely the N and C=O) affords benzamides (Fig 10) which have been demonstrated as synthetically useful DMGs.[3]

The steric factors of both the butyllithium and the dialkyl substitution of tertiary amides of aryl[56] and naphthyl[92] substrates determine the success of the desired lithiation. *n*-Butyllithium required employment of the N,N-diisopropylnaphthalene carboxamide DMG, while *t*-butyllithium also worked with N,N-diethylnaphthalene carboxamide (Fig 11).

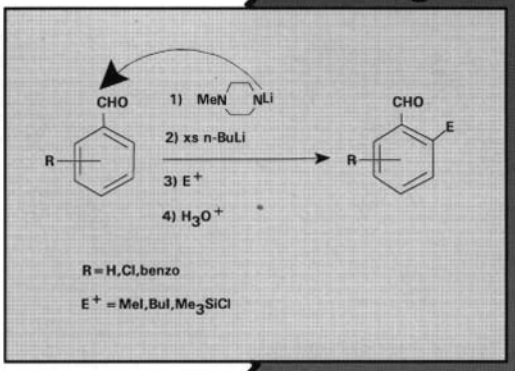
Fig. 11



The base system normally employed for these symmetrical benzamide substrates is *sec*-BuLi/TMEDA[6,58] in THF at <-78°C . This same base system has also been used for unsymmetrical N-tert-butyl-N-methyl benzamide.[93] More recently, in an extensive base-system study involving the tertiary amide DMG, the *LICKOR* base (*t*-BuLi/KOBu-*t*) was found to be superior to the several strong base systems.[94]

Because amides (-$CONEt_2$) are not easily hydrolyzed and require an additional reduction step to yield an aldehyde, a novel approach was developed using the aldehyde directly. Here, *ortho* functionalization to an aldehyde moiety was achieved by prior *in situ* protection with lithium N-methylpiperidide (Fig 12). After the addition of the organoamide to the aldehyde, the resulting adduct acts as an *ortho* DMG for the subsequent lithiation with butyllithium.[95]

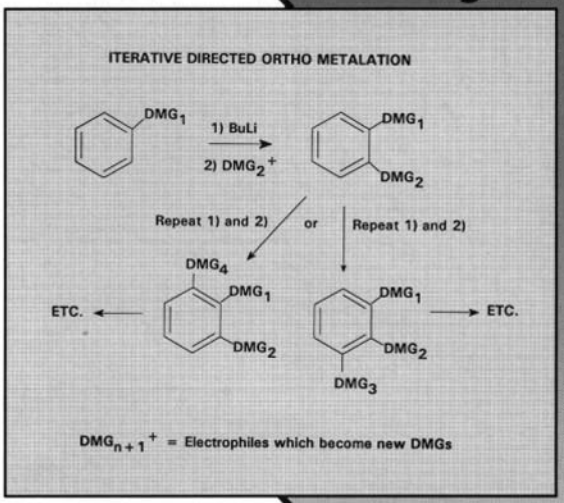
Fig. 12



Attempted ring lithiation of *ortho*-alkoxy aromatic aldehydes and ketones which were similarly protected *in situ* via organoamides resulted in *O*-dealkylation using *n*-BuLi.[96]

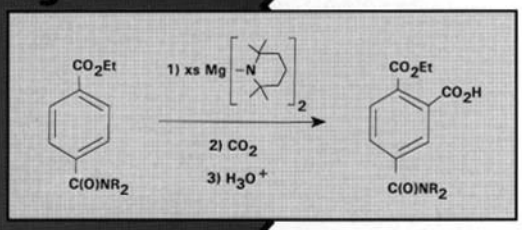
The use of **iterative DoM** processes has been explored to a limited extent using benzamides[97] and carbamates[59] as starting materials. The potentially valuable process allows "one-pot" syntheses of polysubstituted aryl derivatives. The iterative DoM process is a series of metalation, electrophile reaction sequences in which the newly created DMG_{n+1} may also direct the next metalation (Fig 13).

Fig. 13



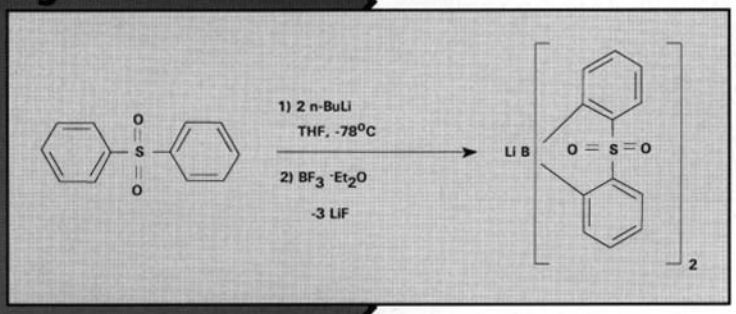
Finally (with regard to benzamides), note that benzoate ester, which is not listed in Table 1, was shown to be a stronger DMG than -C(O)NR_2 when excess, sterically-hindered magnesium organoamide was used as the base system (Fig 14).[98]

Fig. 14



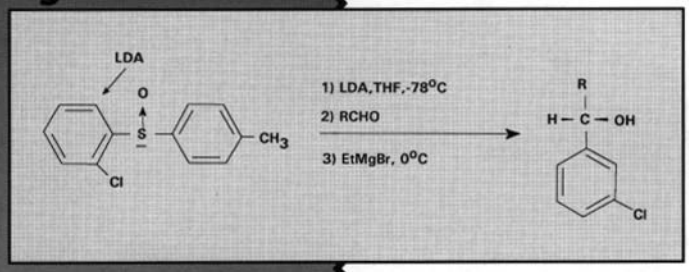
Several "strong" DMGs containing at least an -SO- moiety are indicated in Table 1, but in comparison to benzamides they received only a "+" in synthetic utility. However, among the limited reports involving these groups, a few interesting applications have been cited. Dimetalation of diarylsulfones is easily accomplished with *n*-BuLi.[99] The resulting dianions can be reacted with $BF_3{\cdot}Et_2O$ to give boron compounds which are part of toner compositions for copiers (Fig 15).[99b]

Fig. 15



Metalation of unsymmetrical diarylsulfoxides with LDA proved useful for the preparation of optically active sulfoxides, including the separation of diastereomers (Fig 16).[100] In this scheme and depending on the halogen present, *n*-butyllithium 1) caused racemization of the diarylsulfoxide adducts regardless of halogen, 2) participated in metal-halogen exchange when Br or I, or 3) cleaved the sulfoxide when Cl or Br. The pure sulfoxides adducts were desulfinylated with Grignards or organolithiums to give optically active arylcarbinols.

Fig. 16



Fluorine and chlorine are weak DMGs and require low temperatures to prevent unwanted benzyene formation. For example, *sec*-butyllithium in THF at -105°C insures stability of the *ortho*-lithiated C-1 substrates to be used as nucleophiles in Michael addition reactions.[101,102]

In spite of -Cl and -F being only "weak" DMGs, they sufficiently compete with -OMe DMG, making it difficult to control regiospecific metalations when both are present on the same substrate.[101,102] However regiospecific methods of preparing *ortho*-lithiated -F or -Cl substrates have been developed. One method involves the use of the "anti" DMG, -OTBS group (Fig 17A),[103] instead of the -OMe, while the other employs (tricarbonyl)chromium(0) complexes (Fig 17B).[104]

Fig. 17A

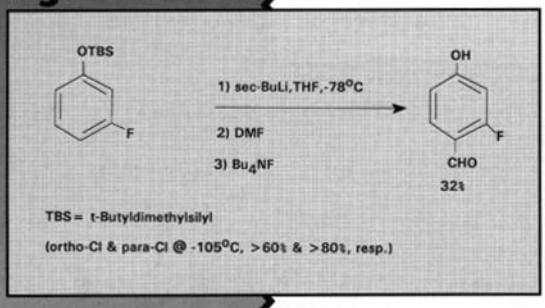
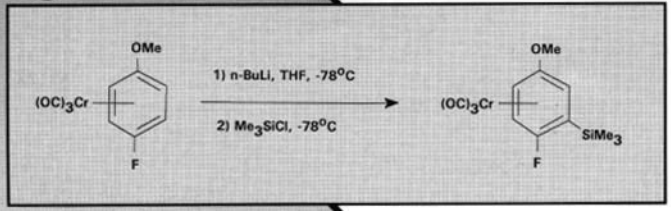
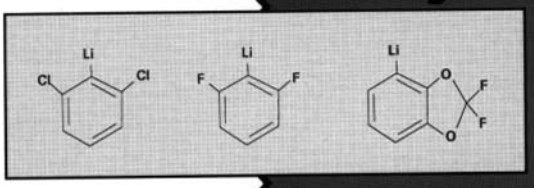


Fig. 17B



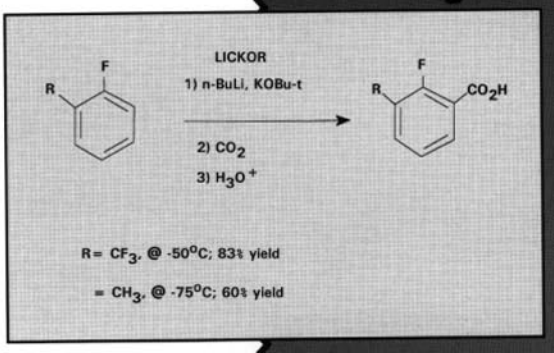
As would be expected, 1,3-substituted aromatics such as 1,3-dichloro-[105] and 1,3-difluorobenzenes[106] are suitable for preparation of the corresponding 2,6-dihalophenyllithium intermediates (Fig 18). Also a unique 4-lithio-2,2-difluoro-1,3-1,3-benzodioxole is a efficiently prepared and can be reacted with various electrophiles to provide a useful route to intermediates for microbiocides (Fig 18).[107]

Fig. 18



Using the LICKOR superbase (from butyllithium) at -50°C followed by carboxylation, various *ortho*-fluorobenzoic acids were cleanly prepared from fluoro- and trimethylfluorobenzene[108a] and fluorotoluene isomers (Fig 19).[108b]

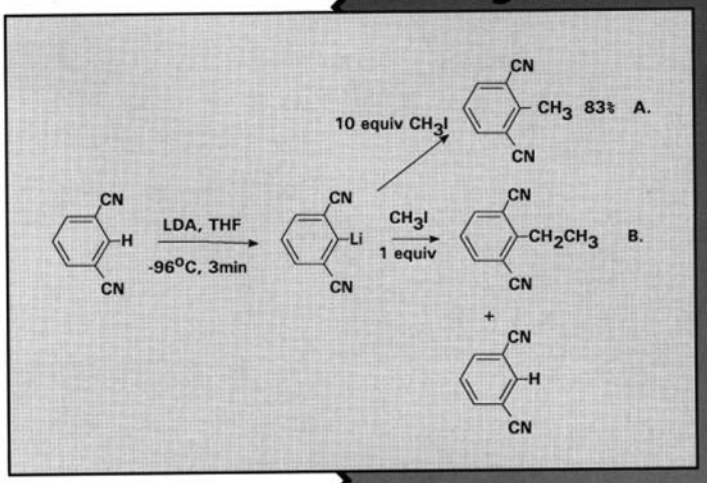
Fig. 19



Of the few aryl ring metalations involving LDA, DoM of isophthalonitrile is very facile (Fig 20A).[109] Although the resulting 2,6-(CN)$_2$arylLi (DCALi) successfully reacted with different electrophiles, ethylation was the main product when one equivalent of methyl iodide was employed (Fig 20B).

By using excess methyl iodide, the rate of ring methylation competed sufficiently with metalation of the methylated product by DCALi. This problematic occurrence is always favored when the initial electrophile/nucleophile reaction is slow compared to the M↔H equilibration of adduct and initial anion.

Fig. 20A & B



Lateral Metalation of Aryl Substrates

The above example illustrates the thermodynamic acidity of benzylic protons compared to aryl protons. It also shows that LDA is a useful base for lateral metalation. For example, lithiation involving the lateral methyl group can also be accomplished with LDA instead of *sec*-BuLi (Fig 21).[110]

Fig. 21

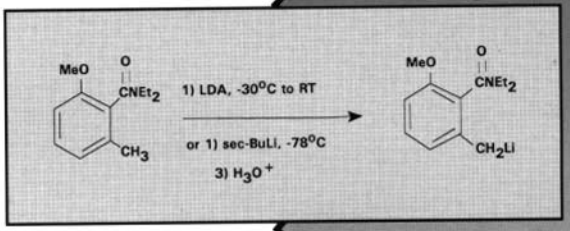
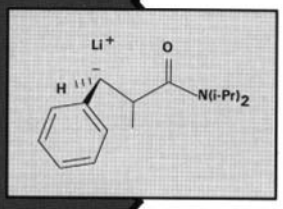


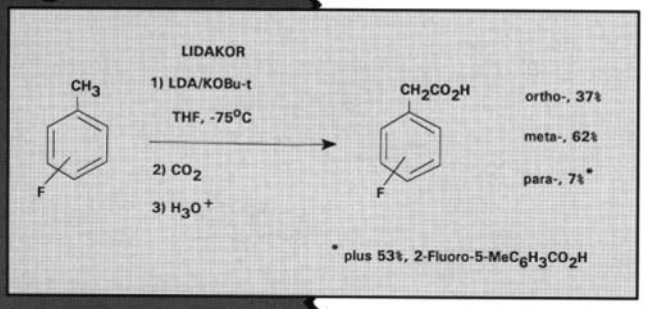
Fig. 22



Using NMR chemical shift data, Beak and coworkers propose a non-ring "DMG" or complex induced proximity effect for the β-lithiations of carboxamides of the type in Fig 22.[111]

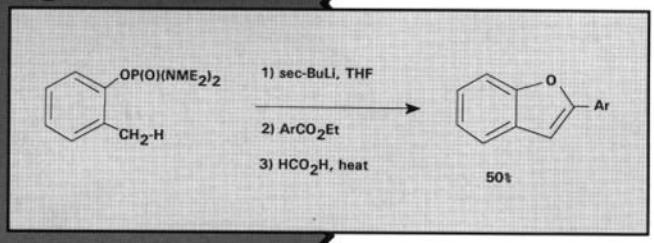
Because of the greater acidity of benzylic protons, several base systems have been identified for simple alkylbenzenes. Interestingly, 2-ethylhexyllithium/potassium *t*-pentyloxide (1:3 ratio) was the most efficient base system for benzylic metalation (100%) of toluene.[112] (See last page for availability of 2-ethylhexyllithium, which was also used with the same alkoxide to successfully dimetalate phenol.) The same study showed that M↔H of benzylic protons of *o*- and *m*-cresol could be achieved with 1:2:2 ratio of KOBu-*t*:*n*-BuLi:TMEDA and 2:2:2 ratio of KOBu-*t*:*n*-BuLi:TMEDA, respectively.[112]

Fig. 23



The same DMG hierarchy also applies to M↔H at *ortho* lateral methyl groups (Fig 1B) as shown in Table 1. Lateral metalation of fluorotoluene is selectively achieved with LDA/KOBu-*t* (LIDAKOR) (Fig 23).[108] Intermediates useful for 2-arylbenzofurans are prepared from phosphoramidates with *sec*-BuLi and benzoate esters (Fig 24).[114]

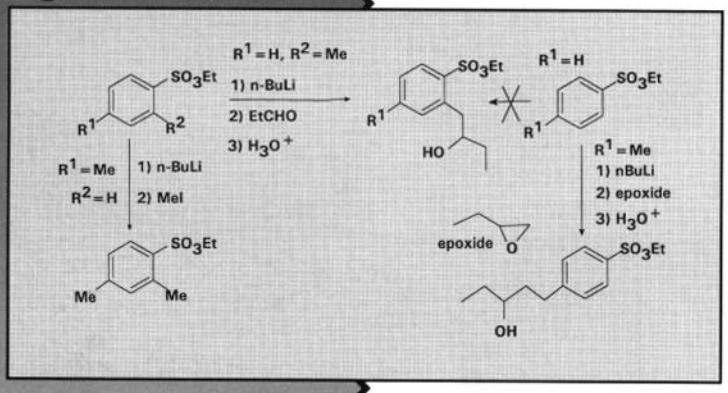
Fig. 24



Benzylic anions were obtained by lateral regiospecific lithiations of ethyl 2-methyl-, 2,4-dimethyl- and 4-methyl-benzenesulphonates (Fig 25).[115] The thermodynamically stable 4-tolyl anion was formed from the kinetically favored 2-lithoarylSO$_3$Et by warming the reaction to room temperature.

Asymmetric lateral alkylation of tetrahydroisoquinolines (Fig 26) which employed a chiral auxiliary after lithiation with *t*-BuLi gave high enantiomeric excess (>95%).[116]

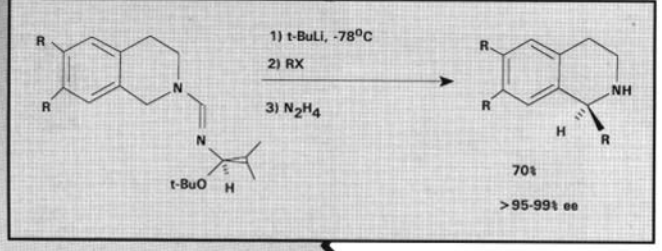
Fig. 25



Cyclization

Snieckus and co-workers have reported several syntheses of natural products which involve cyclization steps. For preparation of certain key intermediates, it was found that trans-metalation of the lithiated intermediate with $MgBr_2$ was required prior to the subsequent condensation with aliphatic aldehydes (Fig 27A). Apparently the lithiated arylLi acts as a base and abstracts the α-proton from the electrophilic aliphatic aldehyde. However, transmetalation to the more selective, magnesiated anion was also necessary for the electrophile, allyl bromide.[117]

Fig. 26



To produce a similar intermediate (Fig 27B), lithiated carbanions of silyated N,N-dialkylbenzamides were reacted directly with aromatic aldehydes.[118]

Biaryl and *m*-teraryl amides treated with LDA or *t*-butyllithium (0°C to RT for 12 hrs) underwent directed remote metalation to give fluorenones via anionic Friedel-Crafts mechanism (Fig 28).[119] If the 3 position (*ortho* to the amide DMG) is not blocked with an aryl group, LDA is the required base to smoothly afford the desired fluorenone. If *t*-butyllithium is used instead of LDA, the 3-lithio derivative is produced.

Remote directed metalation also caused biaryl *o*-carbamates (again 3-substituted) to undergo ring-to-ring carbamoyl transfer to give useful biaryl amides (Fig 29).[120] The resulting biaryl amide could be further transformed into dibenzo[*b*,*d*]pyranones from which fluorenones could also be prepared (Fig 29).

In the literature, most intramolecular cyclizations involving lithium anions occur adjacent to C-lithiated ring systems. To a lesser degree, cyclizations can also be mediated through lateral metalated anions. In Fig 30, a phenanthrene derivative is prepared in high yield via 1) remote metalation/carbamoyl transfer, 2) methylation of the exposed -OH, 3) remote lateral metalation/condensation with the new amide from step 1 (cyclization).[121]

Intramolecular cyclizations of lithiated lateral methyl groups in anionic cycloadditions have been reported.[122] Intermolecular cycloaddition[123] and addition[124] reactions also occur involving benzyne intermediates prepared from appropriate haloaromatic substrates and butyllithium or LDA.

CONCLUDING REMARKS

We have seen numerous examples of directed ring and lateral metalations of aryl substrates. Obviously there is still much to do in terms of understanding and developing DMGs which can be easily formed especially for large-scale applications. Readily available and safe starting materials are a must. Fortunately organolithiums already meet those requirements.

In Table 2, various conditions for achieving *ortho* directed ring metalations are shown. Those familiar with this methodology are aware of the low temperature and inert atmosphere requirements. Although these conditions are relatively expensive, these costs should be offset by the advantageous selectivity, yield, and flexibility of the DoM process.

Efforts to understand the conditions which allow these reactions at higher temperatures are part of an ongoing research effort in our laboratory and elsewhere. Many times the low temperature requirement is due to competitive cleavage of the solvent of choice, THF.[125] Just as we have found that the strongly basic organolithiums, LDA and MeLi, could be stabilized in solution form, it should be possible

Fig. 27A & B

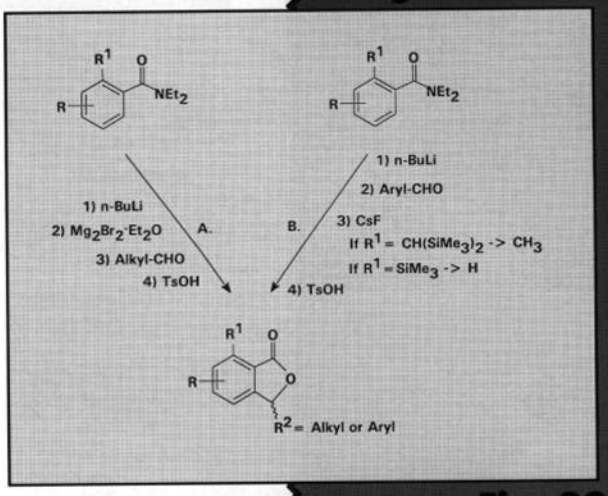


Fig. 28

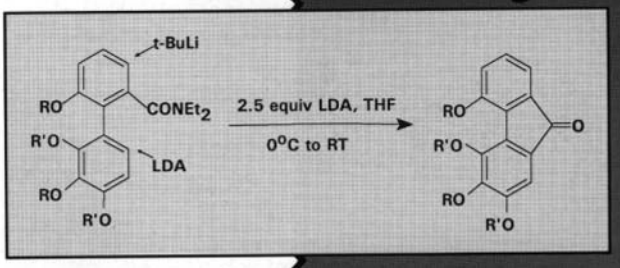


Fig. 29

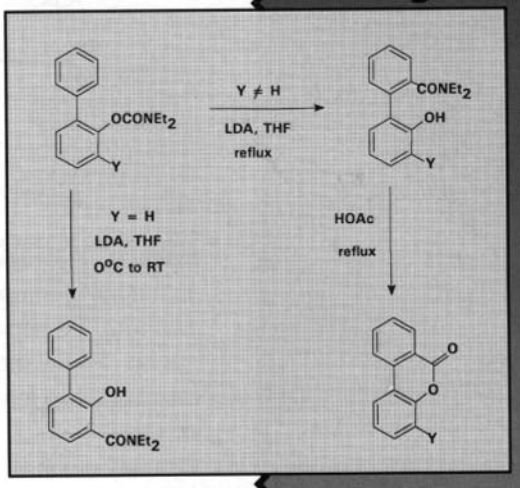


Fig. 30

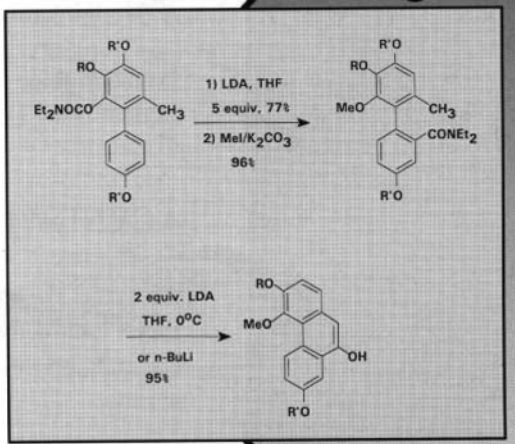
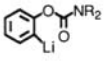


Table 2 - Practical Aspects of the DMG Reaction

Ortho Lithiated Species	Base	Typical Conditions Solvent	Additive	Temp, °C	Ref
		Carbon-Based Groups			
	*n*-BuLi	THF or Et_2O	none or TMEDA	-78 to reflux	6
	*n*-BuLi or *s*-BuLi	THF or Et_2O	none	-45 to 0	19g
	*s*-BuLi	THF	TMEDA	-78	57
	*n*-BuLi or LDA	THF	none	-78	125
	*n*-BuLi	THF	none	-78 to -20	39
	*n*-BuLi	n-hexane	TMEDA	reflux	50
		Heteroatom-Based Groups			
	*n*-BuLi[a] *t*-BuLi[b]	THF THF	none none	0 -20	20 22
	*s*-BuLi	THF	TMEDA	-78	23
	*n*-BuCor *t*-BuLi	Et_2O	none	0 to +25	28
	*n*-BuLi	THF	none	-10 to +25	6
	*n*-BuLi	Et_2O	none	-50	43

[a]R = *t*-Bu., [b]R = O-*t*-Bu.

to minimize competitive cleavage of THF by limiting amount present in the reaction medium. Perhaps an alternative ether, which is more resistant to cleavage, will be just as useful. *t*-Butyl methyl ether (MTBE), which has the added benefits of peroxide formation resistance and lower water solubility, may be the answer.

In many of the article's examples, the "modifier" TMEDA was used on an equivalent basis with butyllithium to promote metalation. It has been shown that for the DMG, -OMe, 0.1 equivalents of TMEDA is enough to facilitate the desired metalation.[126]

There are going to be tradeoffs for these new approaches, but the balance will lean in favor of using DoM on the large scale.

ACKNOWLEDGEMENTS

We would like to thank the American Chemical Society for granting permission to use Tables 1 and 4, and Scheme 7 from the Snieckus review article.[3] Also the Snieckus group was quite helpful in providing modified, camera ready copies of the respective tables and scheme.

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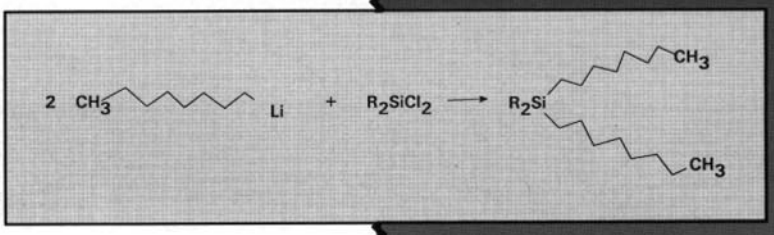
Di-*n*-octylsilane derivative



In reference 112 of the feature article, 2-ethylhexyllithium in the presence of a potassium *t*-alkoxide was reportedly the only base system to give quantitative formation of benzyllithium via metalation of toluene.

Also, we can use these alkyllithiums, for example, to make di-*n*-octylsilane derivatives.

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-2-Ethylhexyllithium (EHL), 2 M in heptane. 125ml = $75.00. **$CH_3$-$CH_2$-$CH_2$-$CH_2$-CH(Et)-$CH_2$-Li**

-*n*-Octyllithium (NOL), 2 M in heptane. 125 ml = $75.00. **$CH_3$-$CH_2$-$CH_2$-$CH_2$-$CH_2$-$CH_2$-$CH_2$-$CH_2$-Li**

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