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LITHIUM LINK™

Ring and Lateral Metalation of Heteroaromatic Substrates Using Strong Base Systems

INTRODUCTION

Because of their possible use in new pharmaceutical, agrichemical, polymer and materials applications, there is intense interest and effort directed toward preparing new heteroaromatic compounds. Preparation of this class of compounds is facilitated by a number of methodologies involving organolithiums both as reactants and reagents. In our last issue, the use of *ortho*-directed metalation groups (DMG) to regiospecifically functionalize aryl substrates via lithiation with strong base systems was amply discussed.[1] In fact it was shown that several heteroaromatic rings themselves were excellent DMGs. As one would expect, DMGs for aryl substrates are also useful in modifying heteroaromatic compounds via these organolithium methodologies; however, the heteroatom(s) in the ring system itself provide additional influence on the thermodynamic and kinetic proton acidities at various substrate site(s) susceptible to lithiation. Also, the presence of the heteroatom(s) in the ring system provides additional reaction pathways (both desirable and undesirable). For example, the organolithium may add to the heteroaromatic substrate itself, or the lithiated substrate may undergo ring opening. In comparison to aryl substrates, regiospecific lithiation of heteroaromatic substrates appears to be more affected by changes in solvent, temperature and time of reaction. Reactions of the lithiated heteroaromatic substrates with various electrophiles are variable and sometimes unpredictable.

FROM THE EDITOR

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

This issue's feature article highlights the use of organolithiums in directed metalations of heteroaromatic systems. It is beyond the scope of this newsletter to include an in-depth review of this topic, but for those readers who desire more information in this important area it is highly recommended that you contact Professor Victor Snieckus. He has presented a short course at several pharmaceutical companies entitled, "Methods and Strategies in Heteroaromatic Metalation." He can be reached at:

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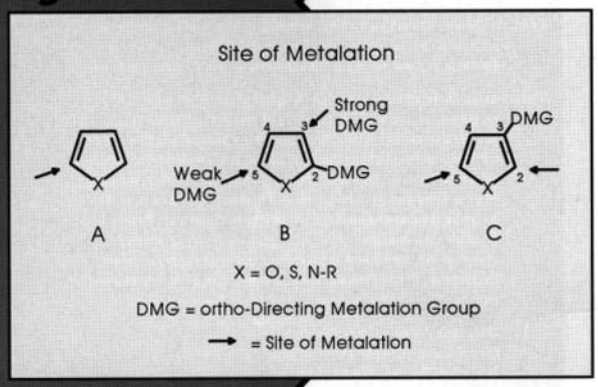
ABBREVIATIONS

***n*-BuLi**	***normal* Butyllithium**
***sec*-BuLi**	***secondary* Butyllithium**
***t*-BuLi**	***tertiary* Butyllithium**
DME	**Dimethoxyethane**
DMG	**Directed metalation group**
E⁺	**Electrophile**
HMPA	**Hexamethylphosphoramide**
LDA	**Lithium diisopropylamide**
LHS	**Lithium hexamethyldisilazide**
LNMP	**Lithium N-methylpiperazide**
LTMDA	**Lithium Dimethylaminoethyl-methylamide**
LTMP	**Lithium 2,2,6,6-tetramethylpiperidide**
SEM	**[2-(Trimethylsilyl)ethoxy]methyl**
TBS	***t*-Butyldimethylsilyl**
TES	**Triethylsilyl**
TMS	**Trimethylsilyl**
TMEDA	**Tetramethylethylenediamine**
Ts	***p*-Toluenesulfonyl**

Although there are interesting reactions involving organolithiums and certain classes of "heteroaromatic" rings that contain Te,[2] Se,[3] P,[4] Si,[4] or several S atoms,[5] this article will focus on major classes of heteroaromatic substrates for which information is abundant. Several classes of five-membered heteroaromatic substrates which include those fused with a benzene ring (i.e., benzofuran) are discussed. For each class, different DMGs, electrophiles, and base systems are shown. Also included are examples of 1) lateral metalation (lithiation of pendant methyl groups) of heteroaromatic substrates, 2) ring opening and, 3) preparation of heteroaromatic substrates via cyclization.

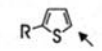
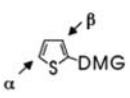
Fig. 1



FIVE-MEMBERED HETEROAROMATIC SUBSTRATES CONTAINING ONE HETEROATOM

In Fig. 1, unsubstituted substrates (1A) are metalated at the C-2 position because in part of the inductive influence of the 1-heteroatom. For 2-substituted substrates, a strong 2-DMG is

Table 1 - Metalation of Thiophene Substrates

	Substrate	(R or DMG), Base, Conditions, Comments, or (Yield)	Ref.
1		A n-BuLi, THF, hexane, -10° to -25°C	8
		B MeLi, THF, cumene, RT	9
2		A (SO_2NH-t-Bu), n-BuLi or LDA; E^+ dependent	10
		B (-C(OH) = $W(CO)_5$), LDA/THF, -70°C, 30 min	11
		C (CO_2H), 2 LDA, THF, -78°C	12
		D -(Me), n-BuLi,THF, 0°C, 10 min	13
		E (Ph), n-BuLi; $ZnCl_2$; Pd, 2, 5-dibromothiophene	14
		F (2-pyridyl), n-BuLi, THF, -20°C	15
		G (4-pyrimidyl), LDA, THF, -78°C	16
3		A 2 n-BuLi, TMEDA, hexane, 40°C to reflux 30 min	17
4		A ((cis)-C=C-ArCO_2Li-2), LDA, Et_2O, RT	18
		B ($CONEt_2$), cyclization	19
		C (C≡CH) KOt-Bu, 2 n-BuLi; $MgBr_2$, Et_2O, I_2	20
		D (CO_2H), 2 LDA/THF, -78°C	12
		E (OAr), PhLi, Et_2O, 0°C	21
		F (NHCOR, R = t-Bu, CF_3), 2 n-BuLi, -20°C	22
5		A (-SMe), LDA, -78°C (slowly)	23
		B (Br), LDA, -80°C, 'Halogen Dance'	24
6		A (2-imidazolino) β 2.5 n-BuLi, THF, -78°C, 2h (98%)	25
		B (2-imidazolino) α 2.2 LDA, THF, -78°C, 2h (78%)	25
		C (2-oxazolino) β LDA, Et_2O, -78°C, PhHCO, (100%)	26
		D (2-oxazolino) α LDA, THF, 0°C; MeOD (82%)	26

Taken in part from a short course entitled "Methods and Strategies in Heteroaromatic Metalation" by Professor Victor Snieckus.

required to cause metalation at the C-3 position (Fig. 1B). On the other hand, if a weak 2-DMG is employed, lithiation at the C-5 position is achieved.

Thiophene

Of the heteroaromatic substrates in Fig. 1, thiophene is most easily metalated.[6] Thienyllithium in Fig. 1A is quite stable even in THF and is actually sold commercially.[7]

Table 1 provides examples of lithiation of various substituted thiophenes.

For C-2 substituted thiophenes, LDA is often used for lithiation of the C-5 position. In Fig. 2, lithiation of 2-iodothiophene is achieved with LDA at moderately low temperatures. The resulting 2-iodo-5-substituted thiophene is useful in Sonogashira alkyne coupling.[27]

The secondary carboxamido functionality, C(=O)NH-*t*-Bu, is an excellent 2-DMG for directing 3-lithiations. In Fig. 3, two equivalents of *n*-BuLi achieved 3-lithiation even at O°C in THF (-10°C for DME) and the resulting 3-thienyllithium could be reacted with a host of electrophiles (E^+).[28]

Although a weaker 2-DMG, N,N-diethylcarboxamide provides, as shown in Fig. 4, two routes for functionalization of C-3 and C-5 positions[29] via 1) a step-wise approach involving monoanions (upper route), or 2) a dianion as shown by the lower route of Fig. 4.

Although hydrolysis of the C(=O)NH-*t*-Bu group (which is distantly an aldehyde) has been demonstrated, the use of lithium organoamides to protect aldehydes *in situ* continues to be a novel and facile approach for preparing substituted heteroaromatic carboxaldehydes. In Fig. 5, LNMP or LTMDA/adducts allow further 3- or 5-lithiation and subsequent methylation. Interestingly, the LTMDA adduct (or lithium α-amino-alkoxide) provides the better *ortho*-DMG, while LNMP was always used to metalate at the C-5 position.

The combination of LDA and *n*-BuLi for the lithiation of 3-thiophene-carboxaldehyde was required to overcome the relative acidities of C-2 protons of thiophene (5A) and diisopropylamine.[30]

Fig. 2

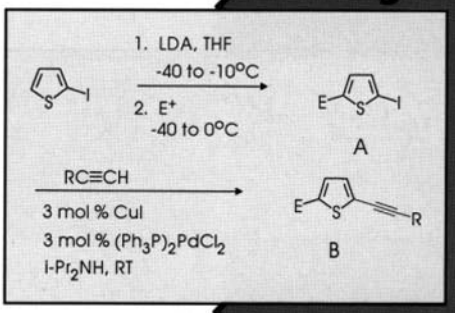


Fig. 3

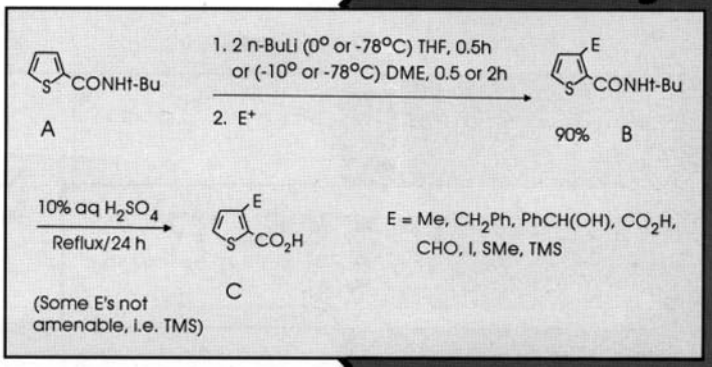


Fig. 4

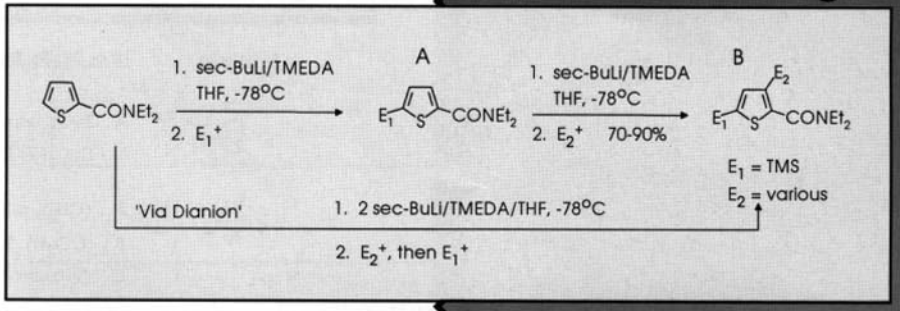


Fig. 5

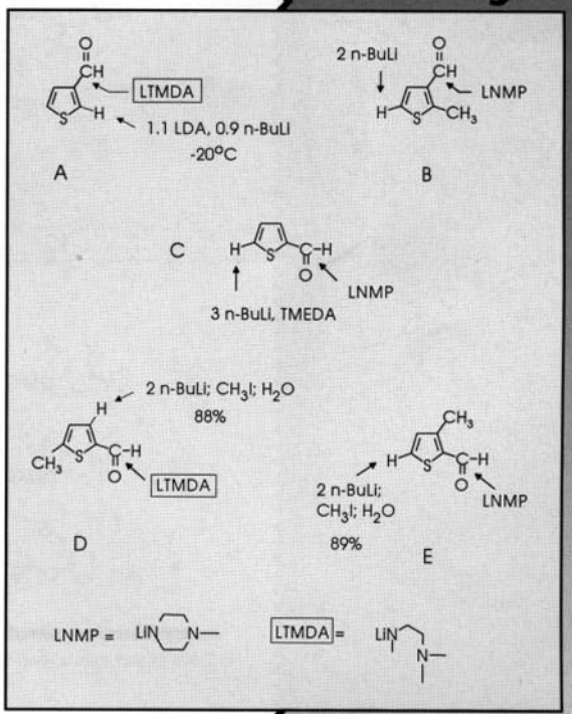
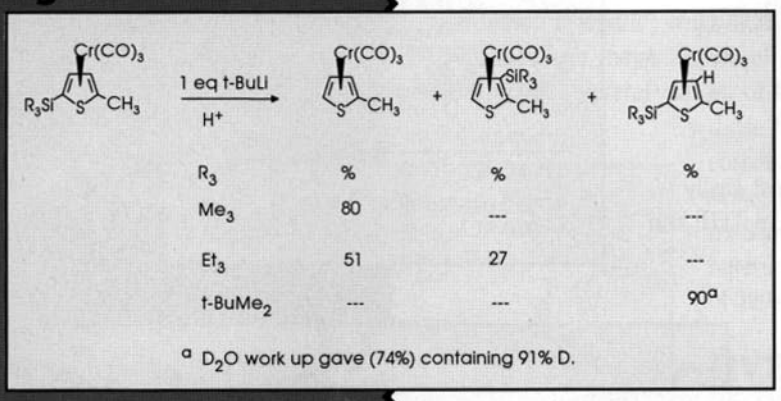


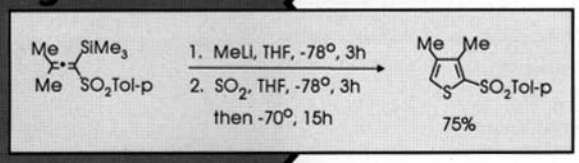
Fig. 6



A 2,5-disubstituted-thienyl Cr(0) complex (Fig. 6) was used to achieve good β-lithiation on the basis of employing the combined steric hindrance of the stable TBS group and *t*-BuLi itself. Although deuterium incorporation was good, the chemical yield was moderate (74%).[31]

Cyclization reactions involving organolithiums to form benzothiophene,[32] benzosulfolene,[33] or thiophenes[34] are available. For example in Fig. 7, a thiophene derivative is prepared from an allene, methyllithium and SO_2.[35]

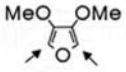
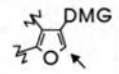
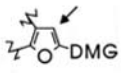
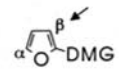
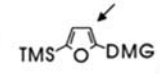
Fig. 7



Furan

Numerous examples of various 2- and 3-metalations of furan substrates are shown in Table 2.

Table 2 - Metalation of Furan Substrates

	Substrate	(R or DMG), Base, Condition, Electrophile, or (Yield)	Ref.
1		A $ZnCl_2$; vinyl and aryltriflates; Pd-Cat. cross coupling	36
		B CuI, THF; $C_5H_5N^+CO_2Et$ Cl^- ; O_2; 2 or 4-addition	37
2		A (CH_3), n-BuLi, TMEDA, 0°C; Me_2S_2 (53%)	38
		B (CO_2H), 2 LDA, THF, -78°C, various E^+	39
		C (2-oxazolino), 2 LDA, THF, TMEDA, -78°C, TMSCl (88%)	40
3		A 2 n-BuLi, 2 KOt-Bu, TMEDA, Pentane, -25° to -5°C	17
4		A 3 n-BuLi/TMEDA, RT, Me_2S_2 (80%)	38
5		A (CO_2H), 2 LDA, -78°C, various E^+	39, 41
		B (CO_2H), benzofuran, 2 LDA, THF; TMSCl, (98%)	42
6		A (cyclic -C_8-OH), 2 n-BuLi; TMSCl, (82%)	43
		B (fused -Cl-C_5H_3N), t-BuLi, -70°C, E^+	44
		C (2, 3-dialkyl), n-BuLi, THF, -5°C	45
7		A (CO_2H), benzofuran, 2 LDA, -90°C ring opening	42
		B (CO_2H), 5-MeO-benzofuran, LDA, -90°C	42
8		A (2-oxazolino) n-BuLi, DME, -78°C β:α = 9.5:1	46
9		A (2-oxazolino), sec-BuLi, THF, -78°C	40

Taken in part from a short course entitled "Methods and Strategies in Heteroaromatic Metalation" by Professor Victor Snieckus.

In Fig. 8, transmetalation of 2-furyllithium with zinc bromide improved the selectivity of this anion for the addition to an aldehyde.[47]

In Fig. 9, the stability of a TBS-ether, which is part of the E^+, is required for the alkylation step as well as the subsequent 5-lithiation with *n*-BuLi/TMEDA at -23°C.[48]

In Fig. 10, 2-silylation, shown in Eq. 1, is achieved in good yield with *n*-BuLi followed by XCl where X=TMS or TBS. Note that the 2-TBS group remained intact during subsequent lithiation, functionalization with E^+, and oxidation.[49] Oxidation of substituted furans[50,51] and thiophenes[52] (Fig. 10, Eq. 2) provides unique routes to useful intermediates.

Using a TBS group to block the C-2 position of a furan (or thiophene) having 3-CO_2H[53] or 3-CH_2OH[54] substituents provides a route to 4-substituted furans (11D). In Fig. 11, the best method for preparing the intermediate of 11B was via 11A (not 11C) and involved monoanion formation followed by O→C migration.[53]

When employing ethyl ether at room temperature for 2-lithiations, the TBS group did not undergo O→C migration from 3-CH_2OTBS or 3-CH_2CH_2OTBS to the 2-lithio position.[51]

Fig. 8

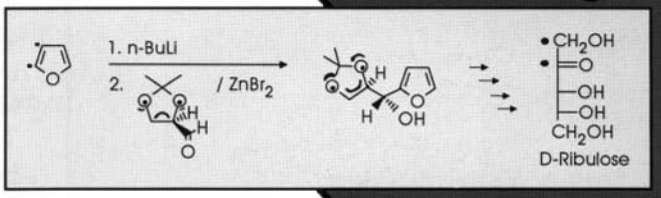


Fig. 9

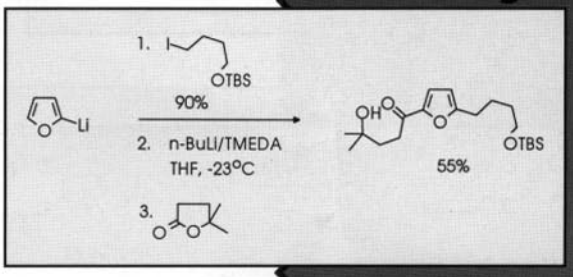


Fig. 10

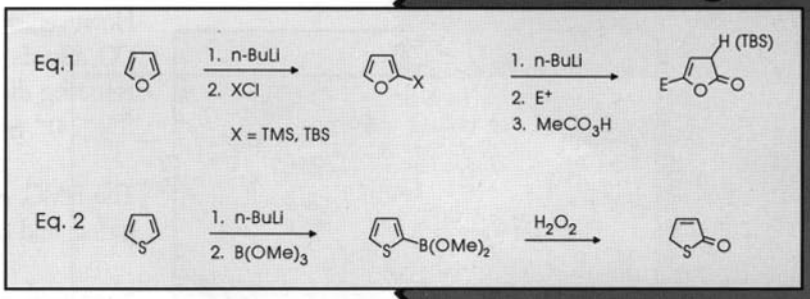


Fig. 11

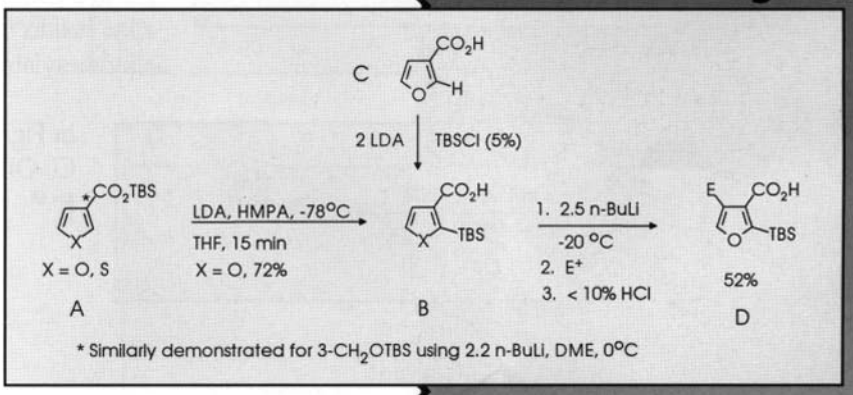
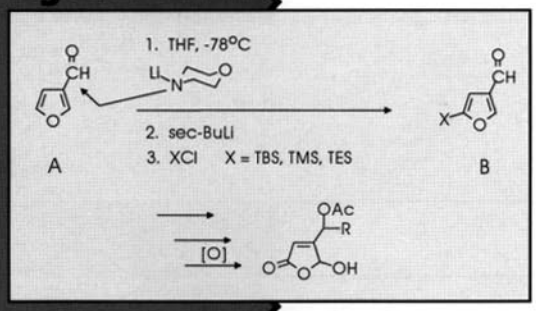


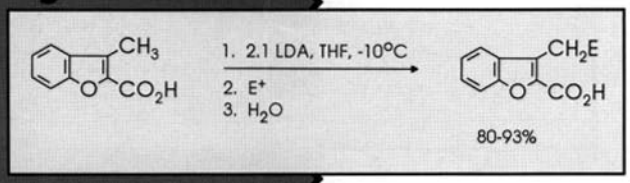
Fig. 12



As seen in the preceding thiophene section, *in situ* protection of an aldehyde is quite useful. In a patented procedure 5-lithiation of 3-furaldehydes was possible after the addition of lithium morpholidide to the aldehyde (Fig. 12).[55]

The lithiated carboxylic group is a useful DMG[12,39,41] for developing synthetic strategies. In Fig. 13, lateral lithiation is also facilitated by the 2-CO_2Li DMG.[42]

Fig. 13

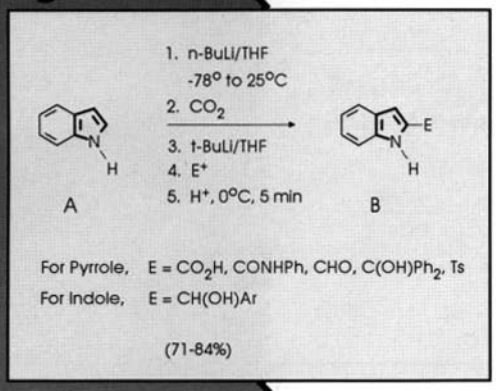


Preparation of 2,3-[56] and 2,5-[57] disubstituted furans can be accomplished via cyclization. Preparation of benzofuran via cyclization of lithium intermediates are rare.[58] Benzofuran ring systems can be opened with 2 equivalents of organolithiums to produce useful intermediates.[59]

Pyrrole and Indole

Although indole can be 2-lithiated directly, formation of the corresponding dianion of pyrrole has not been reported. However, *in situ* protection of N-lithio-pyrrole[60] and -indole[61] with CO_2 affords an adduct suitable for 2-lithiation with *t*-BuLi. The resulting dianion can be reacted with several types of electrophiles (Fig. 14).

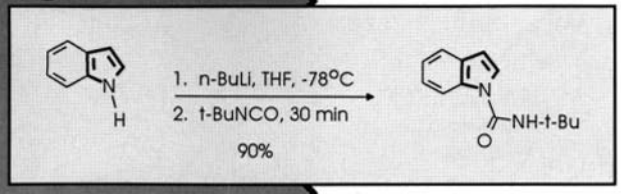
Fig. 14



The DMG, -C(=O)NH-t-Bu, is an excellent N-DMG for pyrrole and indole and can be prepared via *n*-BuLi and *t*-BuN=C=O (Fig. 15).[62]

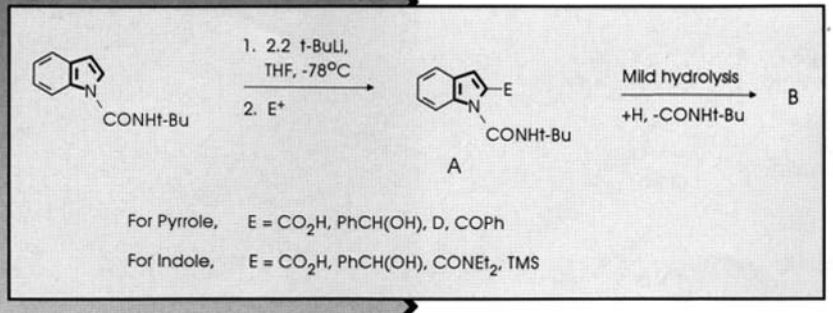
N-protection with LHS/dimethyl carbonate has been shown to be useful for 2-methylindole,[63] while N-lithiation of 2,3-dimethylindole led to 3-alkylation when the resulting anion was reacted with an alkyl halide.[64] Efficient N-alkylation was achieved with *n*-BuLi and alkylmesylates.[65]

Fig. 15



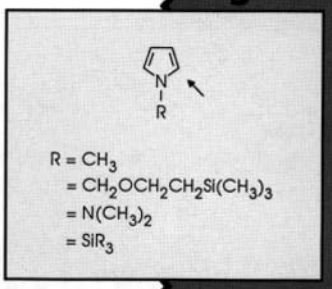
In Fig. 16, pyrrole and indole N-protected with C(=O)NH-*t*-Bu are easily 2-lithiated and reacted with various E^+.[62]

Fig. 16



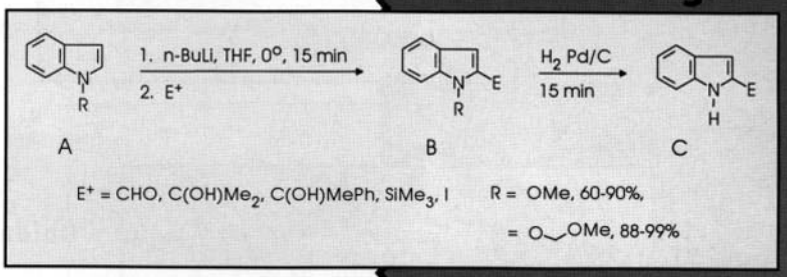
Some success for other N-DMGs for pyrrole in Fig. 17 for directing 2-lithiation has been demonstrated for 1) SEM with *n*-BuLi in DME at -15°C,[66] or *t*-BuLi in hexane at -10°C,[67] 2) -NMe_2 using *n*-BuLi in THF,[68] 3) -CH_3,[69] and 4) trimethyl and triethylsilyl groups which undergo cleavage and/or N→C migration[70] in the presence of BuLi. Cleavage of N-DMG, -SO_2Ph, was observed.[71]

Fig. 17



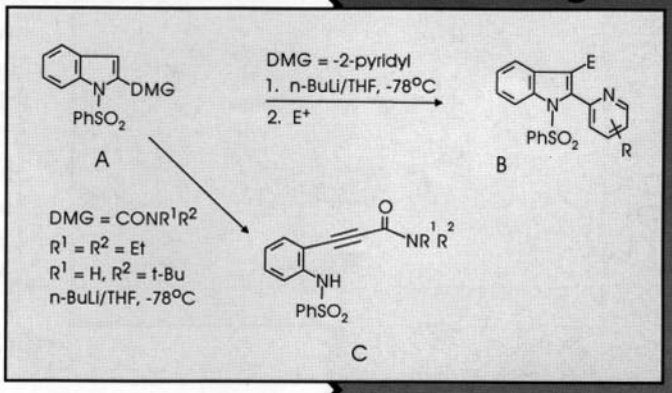
Indole, N-protected with -OMe or -OCH_2OMe (which can be removed via hydrogenation to give 18C) provides a convenient route to 2-substituted indoles 18B and 18C in Fig. 18.[72]

Fig. 18



In Fig. 19, N-protected-2-DMG indoles provide 3-substituted indoles[73] (19B) or acetylenic derivatives (19C) resulting from ring opening.[74] Other N-protected-2-substituted indoles, having 2-CHO,[75] 2-borate,[76] or 2-(1,3-dithian-2-yl)[77] groups, led to functionalization at the 3-position.

Fig. 19



Also, N-protected-3-DMG indoles, where the DMGs are 3-I,[78] 3-CO_2H,[79] 3-COR,[80] 3-CHO,[30] 3-CH_2OH,[81] 3-CH(C=N-*t*-Bu),[82] or 3-CH_2NMe_2 (Fig. 20A),[83] afforded 2-lithiation and subsequent functionalization with electrophiles. In Fig. 20, bulky N-protection provided by the triisopropylsilyl group prevented 2-lithiation with sterically hindered *t*-BuLi, but yielded instead 5-lithiation and moderate-to-good yields with E^+.[83]

Fig. 20

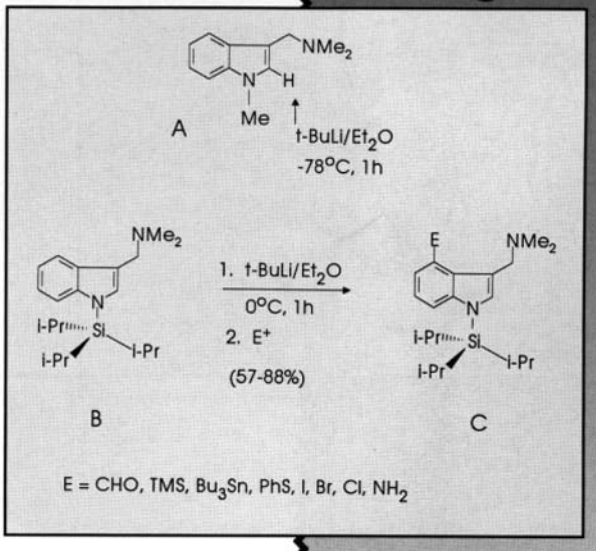
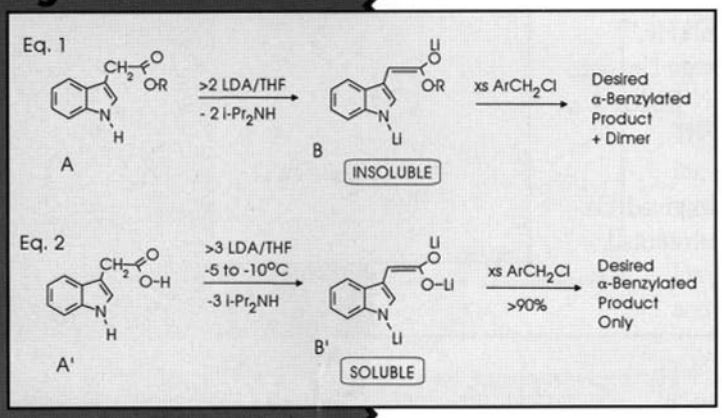


Fig. 21



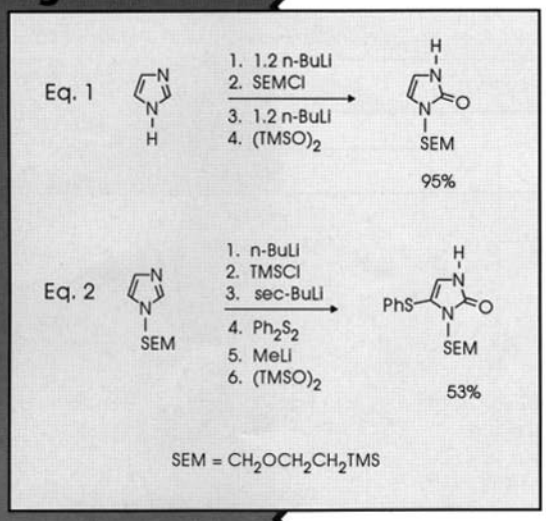
Lateral metalation of indole at the C-2[84] and C-3[85] positions has been reported. In Fig. 21, the formation of the insoluble dianion (21B), prepared from the ester (21A) using LDA, resulted in poor benzylation (Fig. 21, Eq. 1). However in Eq. 2, switching to the acid 21A' resulted in the formation of a soluble trianion 21B' which was easily benzylated.[86] The phenomenon of alternating solubilities of multianionic species is becoming a useful tool in optimization of reactions.[87]

Finally, cyclization reactions to form indole derivatives are common.[88]

FIVE-MEMBERED HETEROAROMATIC SUBSTRATES CONTAINING 1,3-HETEROATOMS

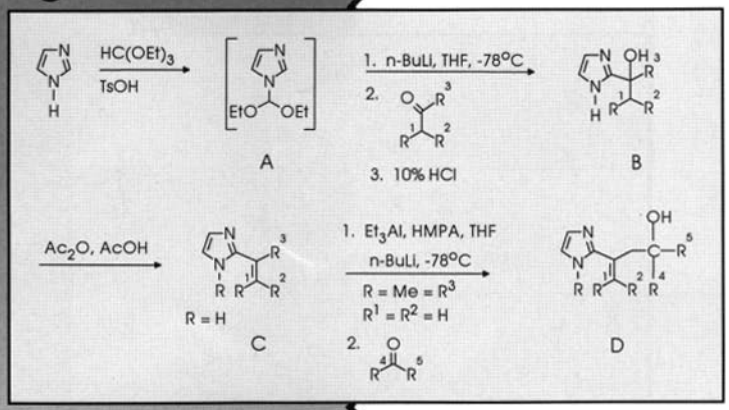
Imidazoles

Fig. 22



In comparison to pyrrole, imidazole substrates offer more versatility in their utility with organolithiums. Fig. 22 shows two "one pot" syntheses. In Fig. 22, Eq. 1, the imidazole is first N-protected with SEM, followed by 2-lithiation and reaction with bis-trimethylsilyl peroxide $(TMSO)_2$. In Fig. 22, Eq. 2, N-SEM-protected imidazole undergoes 2-lithiation and 2-silylation with TMSCl, followed by 5-lithiation and 5-sulphenylation. The selective desilylation of TMS is achieved with MeLi leaving a 2-lithio-derivative for reaction with $(TMSO)_2$.[89]

Fig. 23

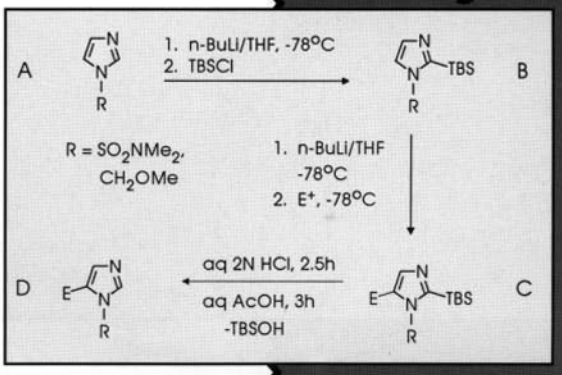


In Fig. 23, *in situ* N-protection is achieved with $-CH(OEt)_2$. The resulting N-1,1-diethoxymethylimidazole[90] is then 2-lithiated and condensed with ketones. Dehydration of 23B leads to a useful monomer (23C) for polymerization. Further elaboration at R^3 is also possible via a complex lithium organoaluminate to give 23D.[91]

Although not prepared *in situ* prior to 2-lithiation, other N-protected imidazoles with $-CH_3$,[92] $-CH(CH_3)OEt$,[93] $-CH_2OMe$,[94] and $-CH_2Ar$-F-4,[95] lend themselves to C-2 functionalization.

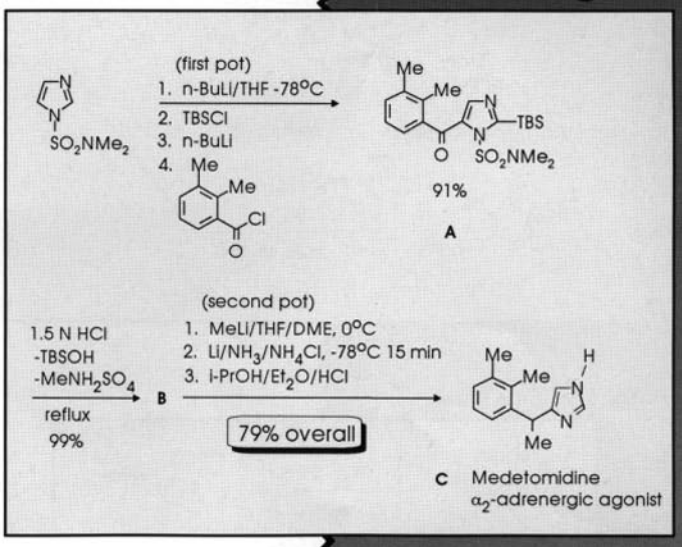
By temporarily blocking C-2 with TBS, 5-substituted imidazoles can be prepared. In Fig. 24, imidazole, N-protected with $-SO_2NMe_2$ or $-CH_2OMe$, can be 2-lithiated with n-BuLi followed by 2-silylation with TBSCl to produce substrates suitable for 5-lithiation. Removal of TBS is easily achieved with 2N HCl.[96]

Fig. 24



In Fig. 25, a "first pot" methodology was also demonstrated in the high yield for the preparation of intermediate 25A for Medetomidine.[97] After removal of $-SO_2NMe_2$ and TBS groups with HCl (25A to 25B), a "second pot" tandem addition-reduction protocol[98] with MeLi, followed by reduction with lithium metal led to Medetomidine (25C).

Fig. 25



Lateral metalation of 2-methylimidazoles[99] has been reported, but instances of accompanying 5-lithiation may be troublesome.[100] Conversely, 2-methylbenzimidazoles, with or without N-protection, are suitable for lateral metalation.[101]

Oxazoles, Thiazoles, and Isoxazoles

Because 2-lithiation is easily achieved for 26A, where X = O or S, useful synthetic schemes have been developed for these substrates and their derivatives.[102] However, if a 2-methyl group is present (26B), lithiation occurs at both the 2-lateral methyl group and C-5. Lateral lithiation of 2-methyl is possible if C-5 is substituted with an R or DMG. In general, 5-lithiation of 26D can be achieved if a strong 4-DMG is present. However, if a weak 4-DMG or R group such as a 4-methyl group is present, 2-lateral lithiation is achieved with *n*-BuLi.[103]

Fig. 26

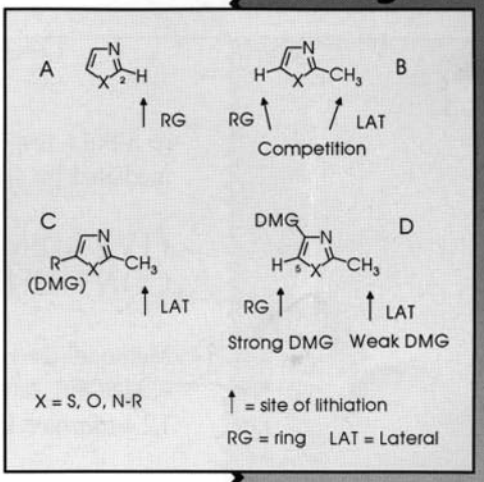


Fig. 27

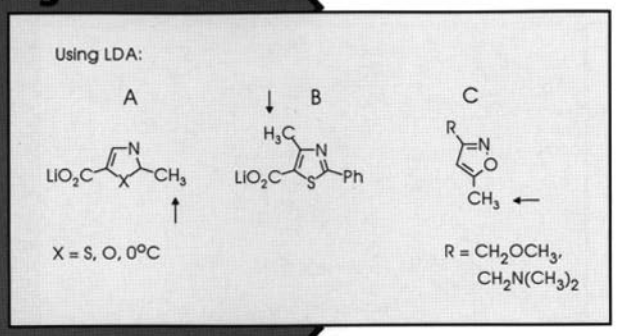


Fig. 28

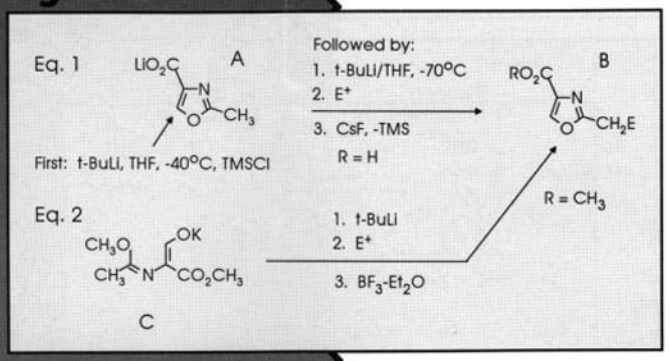
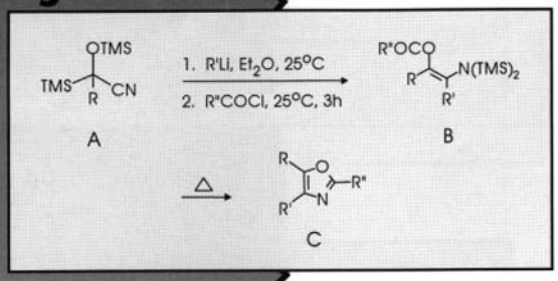


Fig. 29



LDA is the commonly used base for lateral lithiation. In Fig. 27, substrate 27A undergoes lateral metalation at 0°C in spite of the presence of the strong 5-DMG, CO_2Li, which can induce lateral 4-lithiation if C-2 is blocked, such as in 27B.[104]

Lateral lithiation has been demonstrated for the 2-methyl-4,5-disubstituted oxazoles,[105] and 3-methyl-5-substituted isoxazole, 27C.[106]

Strong DMGs, such as 4-CO_2Li[107] or 4-CO_2-*t*-Bu[108] will direct 5-lithiation. Temporary silylation of C-5 with *t*-BuLi/TMSCl will allow further lateral metalation with *t*-BuLi and provide 27B (Eq. 1).[107] An alternate pathway to prepare 27B is via cyclization in Fig. 27, Eq 2.[109]

Other cyclizations to prepare substituted oxazoles[110] have been reported, such as shown in Fig. 29.[111]

In terms of lithiation procedures, the difficult-to-prepare 2,4-disubstituted thiazoles were prepared via a novel lithiation/E^+ sequence followed by ring opening of a fused triazole ring.[112]

FIVE-MEMBERED HETEROAROMATIC SUBSTRATES CONTAINING 1,2-HETEROATOMS

There are few examples of metalation involving five-membered heteroaromatic substrates, namely pyrazoles and isoxazoles. Pyrazoles, having N-Ts,[113] N-SEM,[114] N-SO_2NMe_2,[115] N-phenyl[116] and N-CH_2OH[117] (prepared *in situ* from $(CH_2O)_n$, see diazine section and Refs. 168, 169) were C-lithiated. While 5-lateral lithiation[118] and 4-lithiation[119] of isoxazoles is possible, 3- or 5-lithiation of isoxazoles with LDA or *n*-BuLi, respectively, lead to ring opening.[120] As always there are cyclizations mediated by lithium to prepare these substrates such as pyrazoles.[121]

FIVE-MEMBERED HETEROAROMATIC SUBSTRATES CONTAINING THREE OR FOUR NITROGENS

Methodologies for lithiation of 1,2,3- and 1,2,4-triazoles using N-protection by -$CMe(OEt)_2$ have been reported.[122] Another useful N-protection group for 1,2,4-triazoles is -$CH_2N(CH_2)_4$ or 1-pyrrolidinomethyl.[123]

In the entire class of triazoles, the most extensively studied substrate is the benzotriazole (Bt) shown in Fig. 30 involved in N-lateral metalations. Numerous schemes (30A,[124] B,[125] C,[126] D,[127] E,[124] F,[128] G,[129] H[130]) are briefly shown where all, or a portion of Bt, either becomes part of the final product or was just used as a carrier of an acyl anion equivalent.

Similar methodologies were reported for lateral alkylation of pyrazoles[131] or 5-phenyl tetrazoles.[132]

SIX-MEMBERED HETEROAROMATIC SUBSTRATES

Pyridine and Quinoline

Just like the preceding 5-membered heteroaromatic substrates, pyridine and quinoline substrates (and other 6-membered substrates), organolithiums can be used as strong bases to facilitate ring or lateral metalation. But, 6-membered heteroaromatic substrates also participate in nucleophilic addition with organolithiums. In spite of this propensity, which has also been shown to have synthetic utility, several DMG's are quite effective in promoting regiospecific lithiation.

Attempts to regiospecifically metalate pyridine itself at the C-2 and C-4 positions with *n*-BuLi/KOt-Bu have met with partial success (90%) at -100°C.[133]

In Fig. 31, the strong DMG, -NH(C=O)-*t*-Bu, not only inhibits any unwanted addition but promotes avenues to 3- and 4-E-substituted pyridine derivatives (31A, B and C). Note how both the 4-DMG and 2-DMG substrates yield different 3-E-substituted products 31A and 31B. Lateral metalation of these substrates (where E=Me) with *n*-BuLi provides two azaindoles isomers 31D.[134] Similar methods for the preparation of naphthyridines were also reported.[135]

In addition to the formation of 4-E-substituted pyridine derivatives (Fig. 32A), the 3-DMG (-OC(=O)NEt_2 or carbamate), of 32A directs 2-lithiation yielding 32B.[136]

Fig. 30

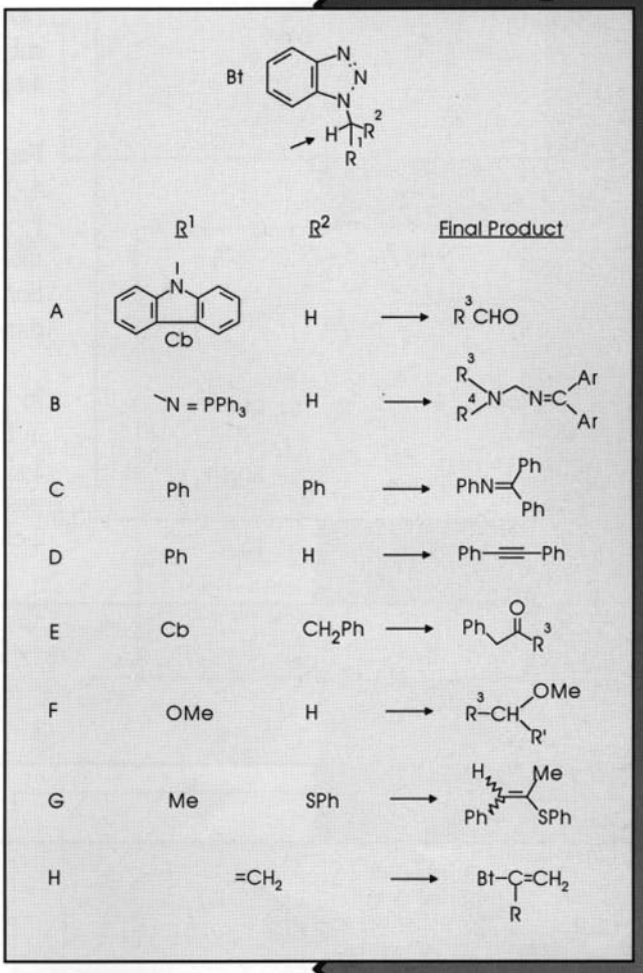


Fig. 31

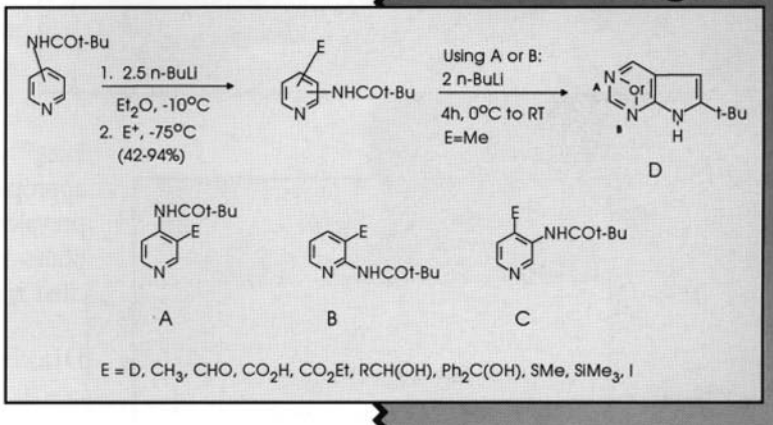


Fig. 32

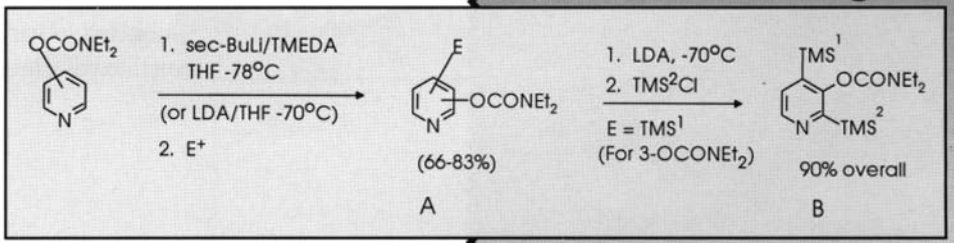
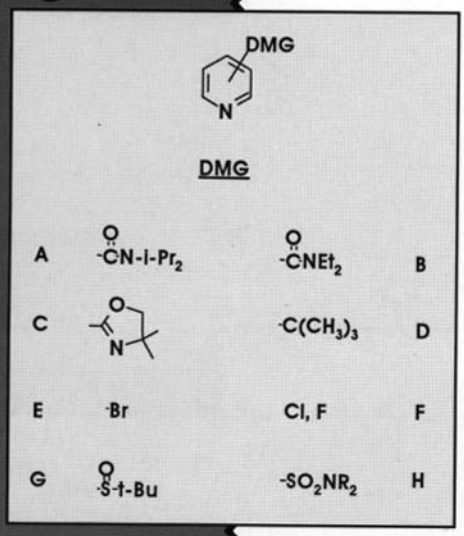


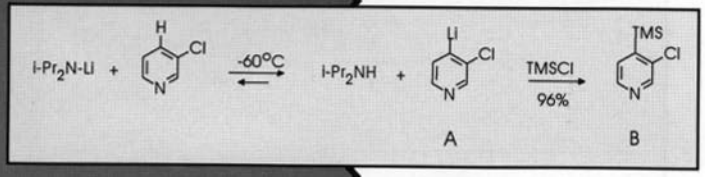
Fig. 33



In Fig. 33, DMG-pyridine substrates 33B,[137] 33G,[138] 33H,[139] require LDA for lithiation. Substrate 33A[140] requires *n*-BuLi or LTMP and substrate 33C[141] uses methyllithium to achieve lithiation. The 4-*t*-butyl group 33D caused 2-lithiation with LTMP.[142]

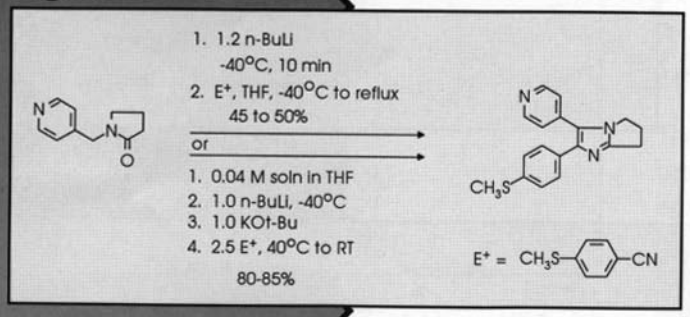
For halo-pyridines, the relative acidity of protons in pyridine is 4>3>2 and the stability of the resulting lithio-halo-pyridines is F>>Cl>Br>I.[143] *ortho*-Lithiations of bromopyridines may produce the desired lithio-pyridines[143,144] or can result in pyridyne formation[145] (which may desirable[146]) or undergo troublesome "halogen dance."[145]

Fig. 34



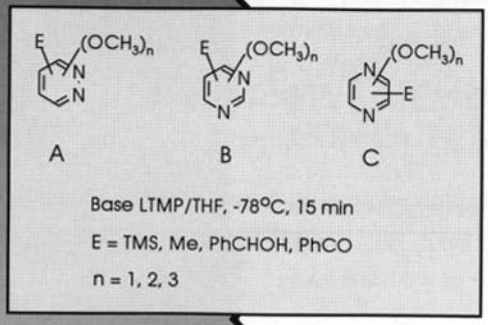
In Fig. 34, the regioselective 4-lithiation (34A) is achieved with LDA in the presence of TMSCl to give 34B.[147] The resulting 34B can be 2-silylated with LDA/TMSCl. 2-Lithiation of 3-chloropyridine is possible with *n*-BuLi/TMEDA.[147] Also 3-lithiation of 2-fluoro-,[148] 2-chloro-[149,150] or 4-chloropyridine[150] has also been demonstrated with LDA.

Fig. 35



Examples of lateral metalation of pyridine derivatives are abundant and usually straightforward. For instance, various 2- and 3-methylpyridines undergo lithiation using *n*-BuLi/THF at -20°C[151] (or LDA/THF at -10° to 0°C)[152] and -10°C,[153] respectively. Lateral lithiation of 4-alkylpyridines can be problematic.[154] Lateral lithiation of pyridines having a 2-CH_2SiR_3[155] or 2-CH_2Me (as a Cr complex)[156] has been demonstrated. In Fig. 35, the overall yield of 4-lateral lithiation and subsequent reaction with E^+, 4-(methylthio)-benzonitrile, was significantly improved by transmetalation of *in situ* formed 4-lithiomethylpyridine with KO-*t*-Bu prior to reaction with the E^+.[157]

Fig. 36



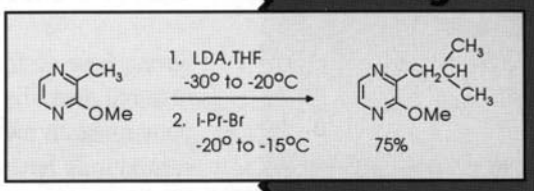
Using lithium methodologies, pyridine derivatives may be prepared via cyclocondensation,[158] while quinolines[159] or quinazolinone[160] may be prepared by cyclization of appropriately *ortho*-substituted aryl derivatives. Because of the prevalence of addition reactions involving carbanionic nucleophiles with pyridine[161] or quinoline[162] substrates, a few recently cited references are included.

Diazines

Lithiation of diazines (and pyrazine 1-oxides)[163] is accomplished with LTMP in THF at -70°C. Various disubstituted diazines containing either -Cl,[164] -OMe[165] or both[166] have been lithiated and subjected to various E^+. In Fig. 36, several mono-, di-, and trimethoxydiazines were readily functionalized.[165]

LDA is used to achieve lateral lithiation/alkylation of pyrazines (Fig. 37) as intermediates for perfumes and flavorings.[167]

Fig. 37



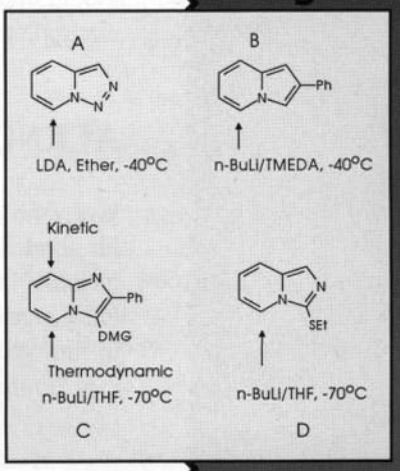
Lateral lithiated methylpyridazines[168] were condensed with formaldehyde generated from α-polyoxymethylene.[169]

Finally LDA can be used to prepare 4-lithio-5-bromopyrimidine which suggests that hetaryne formation is much slower than the reaction with 1) carbonyl-containing E⁺s or 2) unmetalated substrates.[170]

Miscellaneous Masked Pyridine Substrates

Triazolopyridines (Fig. 38A) readily undergo 7-lithiation/7-E⁺ sequences.[171] The resulting 7-E-substituted (38A) can then be ring-opened to form 2,6-disubstituted pyridines. Regioselective lithiation of 2-phenylindolizine (38B) results from treatment with *n*-BuLi/TMEDA at -40°C (-78°C is too low) for 2 hours.[172] The anion at C-5 of 38B gives high yields when reacted with various E⁺. To insure that the only the thermodynamic anion of 38C is formed, the reaction medium was allowed to equilibrate to 0°C before reaction with MeI and Me_2S_3.[173] Lithiated 38D was reacted with either benzonitrile (which gave cyclized products)[174] or MeI.[175] In the latter case the EtS-group was removed with Raney Ni.

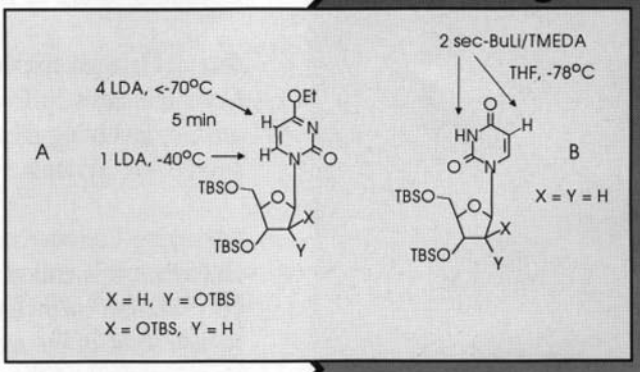
Fig. 38



NUCLEOSIDES

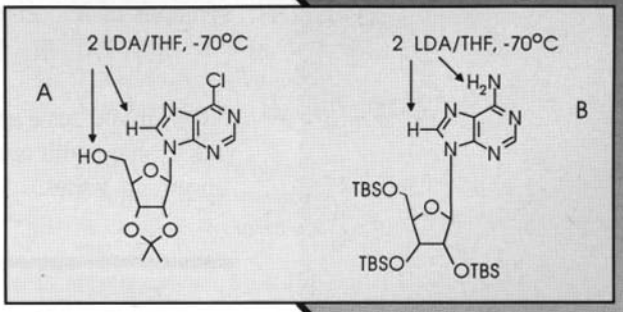
Certain nucleosides are suitable substrates for metalation. The laboratory of Miyasaka has prepared various substituted nucleosides via lithiated intermediates. In Fig. 39A, the C-5 position is metalated under kinetic conditions (4 equivalents of LDA) to provide a useful nucleophile.[176] Although the thermodynamic site C-6 could be selectively metalated, the resulting anion provided a poor nucleophile. The EtO group at C-4 of 39A was subsequently displaced with ammonia to give the 4-amino derivative. Methods for 6-lithiation were successful for a closely related derivative of 39B[177] (not shown), while selective 5-lithiation of 39B resulted in only modest yields when the 5-lithio-anion was reacted with E⁺.[178]

Fig. 39



In Fig. 40A, 8-substituted purine nucleosides were prepared via 8-lithiation/8-E⁺ sequence. The 5-chloro group of 40A was readily replaced with amino-, mercapto-, and hydrogen.[179] The 5-amino-derivative, 40B, could also be metalated directly to prepare new 8-substituted-5-amino derivatives.[180]

Fig. 40



CONCLUDING REMARKS

Strong base systems for the metalation of heteroaromatic substrates are a growing research area; the examples presented in this article should provide a good start for your research involving heteroaromatic substrates. The search is not only for new compounds having targeted applications, but for methodologies suitable for scale-up. Methodologies using organolithiums will only improve as more is learned about modification of the reactivity and selectivity of the base systems, lithiated substrates, electrophiles and choice of appropriate DMGs.

ACKNOWLEDGEMENTS

We want to thank Professor Victor Snieckus for liberally providing information from his short course "Methods and Strategies in Heteroaromatic Metalation" that was included in this article. As mentioned in his course work material, we also want to encourage our readers who are actively involved in this type of research to forward on to him your results (published or unpublished) for possible inclusion in this course. (See "From the Editor," page 1.)

Future Feature Articles

Upcoming issues of Lithium Link will feature:

"Metal-Halogen Exchange Involving Aryl, Heteroaryl and Other Substrates Using Organolithiums." This article will complement both this and previous issues' feature articles, involving metal-proton exchange of aryl and heteroaryl substrates with strong base systems.

"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.

"The Role of Organolithiums in the Synthesis of Lactams." In recent years considerable effort has been targeted towards the preparation of lactams as possible candidates for antibiotics. This article will present the diverse use of organolithiums in synthesis of important ring systems, especially β-lactams.

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.

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Organometallics Product List

COMMERCIAL PRODUCTS

normal**(n)-Butyllithium** (15, 24, and 86 wt%) in various hydrocarbon solvents

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

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

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

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

t-Butyldimethylchlorosilane (TBSCl), 98% as solid, or 50 wt% in **toluene**

DEVELOPMENTAL PRODUCTS
(Pilot quantities - typical concentrations)

n-Hexyllithium (NHL), 2.8 M (35 wt%) in hexane, CH_3-CH_2-CH_2-CH_2-CH_2-CH_2-Li

Di-t-butylsilane (DTBS), bp 128°C, 98%, **(t-Butyl)$_2$SiH$_2$**

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

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

Lithium methoxide, 2.2 M (10 wt%) in methanol, **LiOCH$_3$**

RESEARCH PRODUCTS
(Laboratory quantities - typical concentrations)

2-Ethylhexyllithium (EHL), 2 M in heptane, CH_3-CH_2-CH_2-CH_2-CH(Et)-CH_2-Li

n-Octyllithium (NOL), 2 M in heptane, CH_3-CH_2-CH_2-CH_2-CH_2-CH_2-CH_2-CH_2-Li

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

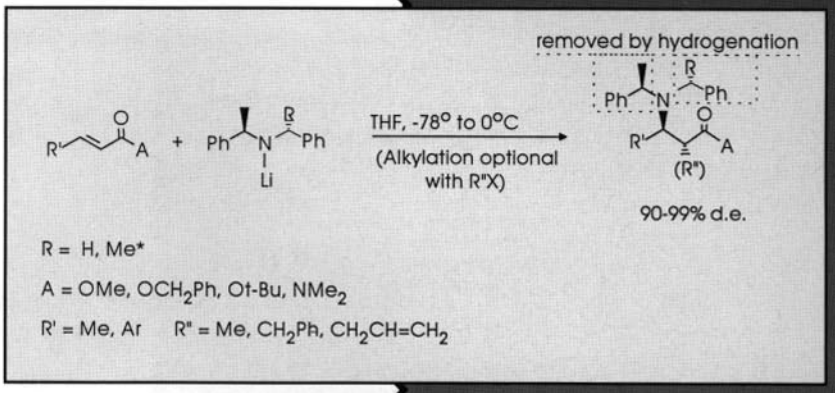
t-Butyldiphenylsilyl Chloride, 97%, **(CH$_3$)$_3$CSiPh$_2$Cl**

t-Butyltrichlorosilane, 97%, **(CH$_3$)$_3$CSiCl$_3$**

Di-t-butyldichlorosilane, 97%, **[(CH$_3$)$_3$C]$_2$SiCl$_2$**

Chiral Lithium Organoamide Technology Available

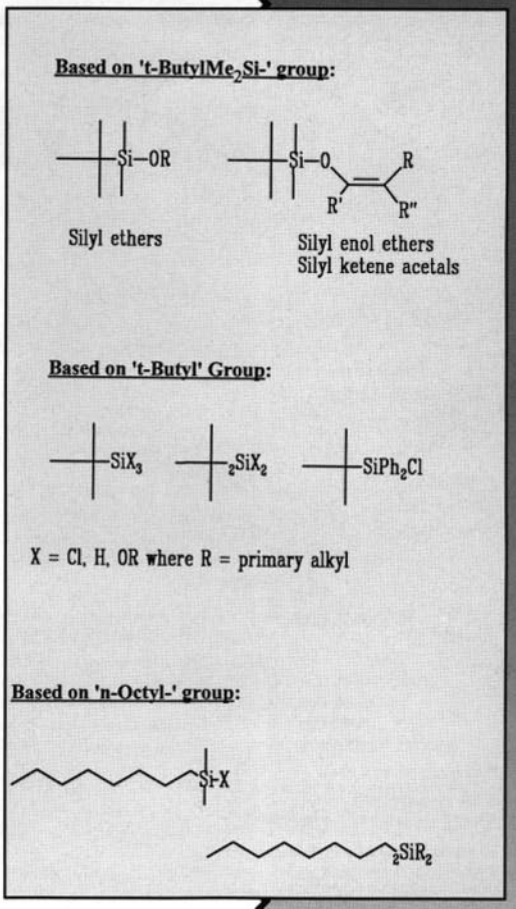
*These amines are commercially available. For more information and scaleup, contact us or Dr. Mario Polywka or Dr. Stephen G. Davies, Oxford Asymmetry Limited, 57 Milton Park, Abingdon, Oxfordshire, OX14 4RX, U.K.
Telephone: 44 235 861561
Fax: 44 235 863139



Silicon-Lithium Link New Product Ideas

Because of our customer's increased interest in silicon products and our knowledge gained in the manufacture of TBSCl, we are exploring new product possibilities as shown on the right.

Give us a call to discuss your particular application. In the USA, 1-800-362-2549.



Customer Support

Smaller Product Bottles for Laboratory Use

We are also offering our organometallic solutions in 125 ml bottles as well as our typical 500 ml containers. Smaller containers reduce contamination and waste.

Consultations and Presentations

Our chemists and engineers are available for customer visits and confidential consultations aimed at specific customer needs. Also available are presentations ranging from general reviews of the utility of our products in organic synthesis to safety, storage and handling procedures.

Literature

"Organometallics in Organic Synthesis." This comprehensive brochure includes extensive utility references as well as a complete description of our organometallic products.

"Butyllithium: Guidelines For Safe Handling." This new brochure is a must for those customers who are considering handling butyllithium contained in cylinders.

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.

Call us toll-free in the USA for more information:

1-800-362-2548

FMC

LITHIUMLINKSpring 1993

Lithium Division
449 North Cox Road
Gastonia, NC 28054

What's Inside?

Visit our exhibit booth:

- **March 29 to 31 at the National ACS meeting in Denver.**
- **June 22 to 24 at ChemSpec Europe '93 in Basal, Switzerland.**
- **August 23 to 25 at the National ACS meeting in Chicago.**

Meet one of our representatives:

- **March 26 to 27 at the Organosilicon Symposium 1993 in Indianapolis, IN.**
- **May 6 to 7 at Chiral USA '93 in Washington, DC.**
- **July 12 to 16 at Organic Reactions and Mechanisms meeting of the Gordon Research Conference.**
- **September 19 to 23 at OMCOS VII in Kobe, Japan.**