# Directed lithiation of simple aromatics and heterocycles for synthesis of substituted derivatives

**Gamal A. El-Hiti,*[a] Keith Smith,*[b] Amany S. Hegazy,[b]**
**Mohammed B. Alshammari,[c] and Ali M. Masmali [a]**

[a] *Cornea Research Chair, Department of Optometry, College of Applied Medical Sciences,*
*King Saud University, P.O. Box 10219, Riyadh 11433, Saudi Arabia*
[b] *School of Chemistry, Cardiff University, Main Building, Park Place,*
*Cardiff, CF10 3AT, UK*
[c] *Chemistry Department, College of Sciences and Humanities,*
*Salman bin Abdulaziz University, P.O. Box 83, Al-Kharij 11942, Saudi Arabia*

*E-mail: gelhiti@ksu.edu.sa, smithk13@cardiff.ac.uk*

**Dedicated to Professor Manfred Schlosser to mark the scientific achievements within his career**

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## Abstract

Directed lithiation of substituted aromatics and heterocycles containing a directing metalating group with alkyllithium in anhydrous tetrahydrofuran or diethyl ether at low temperature provides the corresponding lithium intermediates. Reaction of the lithium reagents obtained *in situ* with various electrophiles gives the corresponding substituted derivatives in high yields. The process has been applied for various derivatives and has proven to be a convenient method for modification of ring systems. This brief review highlights the importance of directing metalating groups in directed lithiation of simple aromatic compounds and some common heterocycles as a tool for regioselective substitution.

**Keywords**: Lithium reagents, directed lithiation, lithium intermediates, electrophiles, substituted aromatics, heterocycles, synthesis

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## 1. Introduction

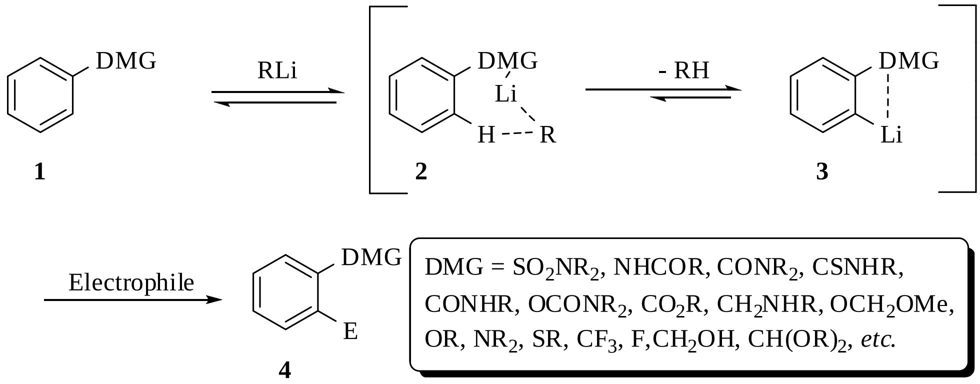
Electrophilic aromatic substitution reactions are commonly used for the synthesis of various types of valuable chemicals. However, industry still often relies on technologies developed many years ago for the production of such chemicals. Consequently, many current industrial processes suffer serious disadvantages, including the use of large quantities of mineral or Lewis acids as activators, which could generate large quantities of toxic and corrosive waste by-products during the work-up. They also frequently involve use of stoichiometric quantities of toxic reagents and/or produce mixtures of regioisomers that require separation.[1-3]

Recently, many efforts have been made to develop cleaner and environmentally friendlier processes for the production of single isomeric products. Solids such as zeolites can play an important role in the development of greener organic syntheses for the production of *para*-isomers through their abilities to act as heterogeneous catalysts.[4-12] While zeolites offer routes to *para*-substituted products *via* shape selectivity, organolithiums play an important role for the clean production of *ortho*-products. Various substituted aromatics and heterocycles undergo lithiation *ortho* to a directing metalating group to produce useful intermediates for the synthesis of *ortho*-disubstituted derivatives.[13-41]

Synthesis of isomerically pure *ortho*-disubstituted aromatics is a significant goal in synthetic chemistry, but simple aromatic electrophilic substitution reactions often produce mixtures of isomers.[42] *ortho*-Lithiation followed by reaction with an electrophile is one of the most efficient alternatives. Directed transition metal catalyzed C-H bond activation and functionalization is an alternative approach to *ortho*-substituted systems.[43-47]

The reactions of substituted aromatics with lithium reagents usually take place at low temperatures, in practice at –78 °C in the presence of anhydrous solvent. Diethyl ether ($Et_2O$) is easily dried, has an appropriate boiling point and a low enough freezing point and therefore it is one of the most commonly used solvents for lithiation reactions.[18] Moreover, most lithium reagents are soluble in diethyl ether and do not cleave the ether too rapidly. Also, tetrahydrofuran (THF) is widely used as an alternative to diethyl ether when a more strongly Lewis–basic solvent is required.[18]

Directed *ortho*-lithiation of an aromatic compound **1** involves removal of a proton from a site *ortho* to a directing metalating group (DMG) that incorporates a heteroatom, usually oxygen, nitrogen or sulfur. The base, normally an alkyllithium, leads to the production of *ortho*-lithiated species **3** *via* initial coordination of the lithium species to the DMG (**2**, Scheme 1). Reaction of **3** with electrophiles produces the corresponding *ortho*-disubstituted products **4**.[18-41] It appears that the complexation between the DMG and the lithium reagent prior to lithiation serves to bring the lithium reagent into closer proximity with the *ortho* proton, which is then selectively removed.[48,49]

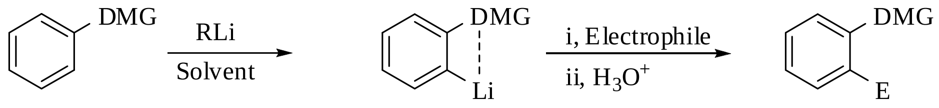


**Scheme 1.** Directed lithiation of substituted aromatics **1** followed by reactions with electrophiles.

Successful deprotonation requires the DMG to be a good coordinating site for the lithium reagent and at the same time a poor electrophilic site for attack by the lithium reagent. Strong directing metalating groups that encourage *ortho*-lithiation include $SO_2NR_2$, NHCOR, $CONR_2$, CSNHR, CONHR, $OCONR_2$, $CO_2R$, $CH_2NHR$, $OCH_2OMe$. Moderate DMGs include OR, $NR_2$, SR, $CF_3$ and F, while weak DMGs include $CH_2OH$ and $CH(OR)_2$.[50] Along with others, we have shown that use of organolithium intermediates is an important strategy for the synthesis of regiospecifically substituted aromatics and heterocycles.[51-80]

## 2. Directed lithiation of benzenoid compounds

Directed lithiation of substituted benzenes **1**, having various DMGs, with a lithium reagent produces lithium intermediates **3**, which react with electrophiles to produce the corresponding substituted benzenes **4** (Scheme 2).[23,24] For example, double lithiation of *N*-pivaloylaniline, on nitrogen and on the carbon at position 2, by use of two molar equivalents of *n*-butyllithium (*n*-BuLi) at 0 °C in anhydrous THF (Scheme 2, **1**; DMG = NHCOBu$^t$) produces a dilithium intermediate *in-situ*, which reacts with electrophiles to give the corresponding *ortho*-substituted derivatives (DMG = NHCO$^t$Bu) in high yields.[81] Some examples of substituted benzenes **1** that have been subjected to directed lithiation reactions, along with the relevant reaction conditions, are shown in Table 1.



**1** **3** **4**

DMG = NHCO$^t$Bu, NHCO$_2$$^t$Bu, NHCONMe$_2$, CH$_2$NHCO$^t$Bu, CH$_2$NHCONMe$_2$, CH$_2$CH$_2$NHCO$^t$Bu, CH$_2$CH$_2$NHCONMe$_2$, CH$_2$CH$_2$NHCO$_2$$^t$Bu, CONHMe, CONHPh, CONEt$_2$, CON$^i$Pr$_2$, CON(Me)$^t$Bu, OCONEt$_2$, CH$_2$NEt$_2$, OTHP, DHDPO, 1*H*-tetrazol-5-yl, OMe, SH, CF$_3$, F

**Scheme 2**. Directed lithiation of substituted benzenes **1.**

**Table 1.** Examples of substituted benzenes **1** lithiated according to Scheme 2

| DMG | Reaction conditions | | | Reference |
|---|---|---|---|---|
| | RLi | Solvent | T (°C) | |
| NHCO$^t$Bu | *n*-BuLi | THF | 0 | 81 |
| NHCO$_2$$^t$Bu | *t*-BuLi | THF | –20 | 82,83 |
| NHCONMe$_2$ | *n*-BuLi | THF | –78 | 84 |
| CH$_2$NHCO$^t$Bu | *t*-BuLi | THF | –78 | 73 |
| CH$_2$NHCO$^t$Bu | *n*-BuLi | THF | 0 | 85 |
| CH$_2$NHCONMe$_2$ | *t*-BuLi | THF | –78 | 73 |
| CH$_2$NHCONMe$_2$ | *sec*-BuLi | THF | –50 | 86 |
| CH$_2$CH$_2$NHCO$^t$Bu | *n*-BuLi | THF | –20 to 0 | 87 |
| CH$_2$CH$_2$NHCONMe$_2$ | *n*-BuLi | THF | –20 to 0 | 88 |
| CH$_2$CH$_2$NHCO$_2$$^t$Bu | *n*-BuLi | THF | –20 to 0 | 88 |
| CONHMe | *n*-BuLi | THF | –78 | 89 |
| CONHPh | *n*-BuLi | THF | –78 | 89 |
| CONEt$_2$ | *sec*-BuLi | THF/TMEDA[a] | –78 | 90,91 |

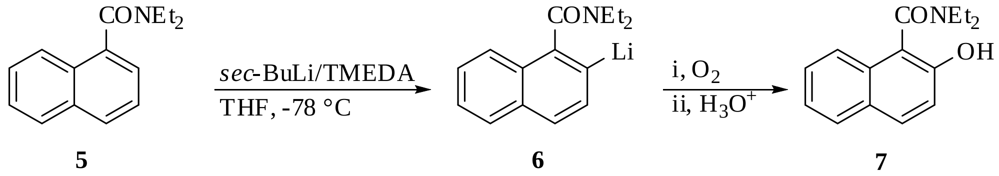
**Table 1 (continued)**

| | | | | |
|---|---|---|---|---|
| CON$^i$Pr$_2$ | *sec*-BuLi | THF | –78 | 92 |
| CON$^i$Pr$_2$ | *n*-BuLi | THF | –78 | 93 |
| CON(Me)$^t$Bu | *sec*-BuLi | THF/TMEDA[a] | –78 | 94 |
| OCONEt$_2$ | *sec*-BuLi | THF/TMEDA[a] | –78 | 95 |
| CH$_2$NEt$_2$ | *t*-BuLi/ZnCl$_2$ | THF/Et$_2$O (1:1) | –78 to 0 | 96 |
| OTHP[b] | *n*-BuLi | THF/TMEDA[a] | –20 to –10 | 97 |
| DHDPO[c] | *i*-PrLi | THF/DMPU[d] | –98 to –40 | 75 |
| 1*H*-tetrazol-5-yl | *sec*-BuLi | THF | –78 | 98 |
| OMe | *t*-BuLi | THF | –78 | 99 |
| OMe | *n*-BuLi | THF | –75 | 100 |
| OMe | *n*-BuLi | THF/TMEDA[a] | –108 to –78 | 101 |
| OMe | *n*-BuLi | THF/KO$^t$Bu | –95 | 102 |
| SH | *n*-BuLi | cyclohexane/TMEDA[a] | 0 to 25 | 103,104 |
| SH | *n*-BuLi | TMEDA[a] | 20 | 105 |
| CF$_3$ | LTMP[e] | THF | –75 | 106 |
| F | *n*-BuLi | Et$_2$O | –50 | 107 |

[a] TMEDA is *N,N,N′,N′*-tetramethylethylenediamine. [b] OTHP is *O*-tetrahydropyranyl. [c] DHDPO is 4,5-dihydro-4,5-diphenyloxazol-2-yl. [d] DMPU is *N,N′*-dimethylpropyleneurea (1,3-dimethyltetrahydropyrimidin-2(1*H*)-one). [e] LTMP is lithium 2,2,6,6-tetramethylpiperidide

## 3. Directed lithiation of naphthalenes

Directed lithiation of substituted naphthalenes having DMGs has received limited attention compared to benzene derivatives.[108-115] However, there are some useful reports. For example, *N,N*-diethyl-1-naphthoamide (**5**) has been lithiated with *sec*-BuLi in the presence of *N,N,N',N'*-tetramethylethylenediamine (TMEDA) at –78 °C in THF. The lithium intermediate **6** thus obtained has been reacted with oxygen to give 2-hydroxy-*N,N*-diethyl-1-naphthoamide (**7**; Scheme 3).[108,109] Similarly, lithiation and substitution of *N,N*-diethyl-2-naphthoamide produced the corresponding 1-substituted *N,N*-diethyl-2-naphthamides.[108]



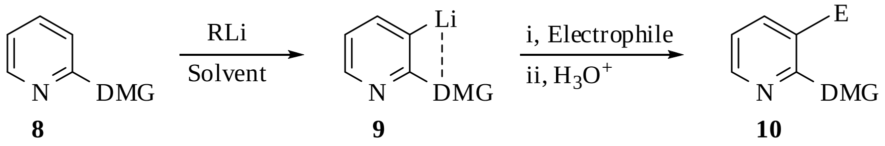
**Scheme 3.** Directed lithiation of *N,N*-diethyl-1-naphthoamide (**5**).

## 4. Directed lithiation of heterocycles

Many valuable bioorganic and pharmaceutical compounds contain a heterocyclic base unit, the synthesis of which is therefore extremely important. Use of organolithium intermediates is an efficient process for *ortho*-functionalization of π-deficient heteroaromatics such as pyridine, quinoline, isoquinoline and diazines.[58] In many cases, the lithiation reaction requires use of less nucleophilic lithium reagents such as lithium diisopropylamide (LDA) and lithium 2,2,6,6-tetramethylpiperidide (LTMP) to avoid nucleophilic addition of alkyllithiums to the azomethine (C=N) bond, even at low temperature.

### 4.1 Directed lithiation of pyridines

**4.1.1 Directed lithiation of 2-substituted pyridines.** Directed lithiation of pyridines **8** containing a DMG at the C-2 position takes place at the 3-position to provide the corresponding lithium intermediates **9** (Scheme 4).[116-138] Reactions of **9** with electrophiles provide the corresponding substituted derivatives **10** (Scheme 4). For example, successful C-3 lithiation of 2-(pivaloylamino)pyridine (Scheme 3; DMG = NHCO$^t$Bu) took place with *n*-BuLi in THF at 0 °C.[116,117] Some examples of 2-substituted pyridines **8** that have been subjected to directed lithiation, along with the appropriate reaction conditions, are shown in Table 2.



DMG = NHCO$^t$Bu, CONHPh, CONEt$_2$, CON*i*Pr$_2$, SO$^t$Bu, SOAr, CO$_2$H, OCH$_2$OEt, OMe, F, Cl

**Scheme 4.** Directed lithiation of substituted pyridines **8.**

**Table 2.** Examples of 2-substituted pyridines **8** lithiated according to Scheme 4

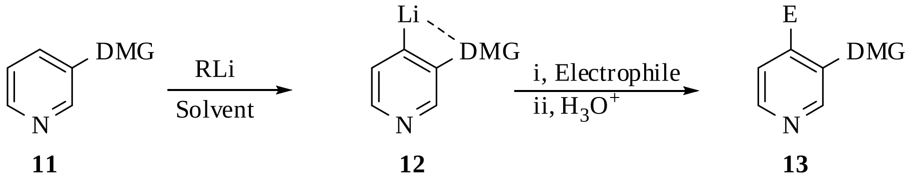
| DMG | RLi | Solvent | T (°C) | Reference |
|---|---|---|---|---|
| NHCO$^t$Bu | *n*-BuLi | THF | 0 | 116,117 |
| CONHPh | *n*-BuLi | THF | –78 | 118 |
| CONHPh | LDA | THF | –78 | 119 |
| CONEt$_2$ | *sec*-BuLi | THF | –78 | 120 |
| CONEt$_2$ | LDA | Et$_2$O | –78 | 121 |
| CON$^i$Pr$_2$ | *n*-BuLi | THF | –78 | 122 |
| CON$^i$Pr$_2$ | LDA | Et$_2$O | –78 | 123 |

**Table 2 (continued)**

| DMG | RLi | Solvent | T (°C) | Reference |
|---|---|---|---|---|
| $\mathrm{CON}^i\mathrm{Pr}_2$ | *sec*-BuLi | THF/TMEDA | –78 | 124 |
| $\mathrm{SO}^t\mathrm{Bu}$ | LDA | THF | –78 | 125 |
| SOAr | LDA | THF | –78 | 126,127 |
| $CO_2H$ | *n*-BuLi/LTMP | THF | –75 to 0 | 128,129 |
| $OCH_2OEt$ | *n*-BuLi | THF | –10 | 130,131 |
| OMe | *n*-BuLi/LDMAE[a] | hexane | 0 | 132 |
| F | LDA | THF | –75 | 133 |
| F | PhLi/DIA[b] | THF | –50 | 134 |
| F | *n*-BuLi/$^t$BuOK | THF | –75 | 135 |
| Cl | *n*-BuLi or LDA | THF | –80 | 136 |
| Cl | LDA | THF | –85 | 137 |
| Cl | PhLi/DIA[b] | THF | –40 | 134 |
| Cl | LTMP | THF | –78 | 138 |

[a] LDMAE is lithium 2-dimethylaminoethanolate. [b] DIA is diisopropylamine.

**4.1.2 Directed lithiation of 3-substituted pyridines.** Directed lithiation of 3-substituted pyridines **11** with various lithium reagents takes place predominately at C-4 to give the corresponding lithium intermediates **12** (Scheme 5). Reactions of **12** with electrophiles produce the corresponding substituted pyridines **13**.[121,123,128,129,135,139-159] Some examples of 3-substituted pyridines **11** that have been subjected to directed lithiation, along with the appropriate reaction conditions, are recorded in Table 3.



DMG = $SO_2NH^t$Bu, $NHCO^t$Bu, $NHCO_2{}^t$Bu, $CH_2NHCO^t$Bu, $CH_2NHCO_2{}^t$Bu, $CH_2NHCONMe_2$, $CONEt_2$, CON*i*$Pr_2$, $OCSNEt_2$, SOAr, $CO_2H$, OMe, OEt, F, Br, Cl

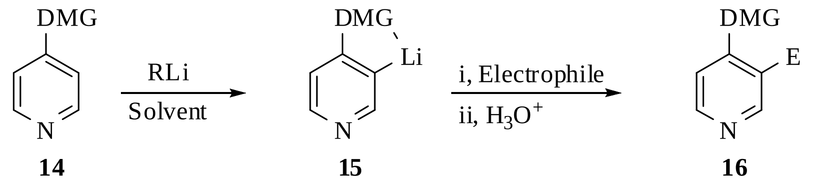
**Scheme 5.** Directed lithiation of 3-substituted pyridines **11.**

**Table 3.** Examples of 3-substituted pyridines **11** lithiated according to Scheme 5

| DMG | RLi | Solvent | T (°C) | Reference |
|---|---|---|---|---|
| $SO_2NH^tBu$ | *t*-BuLi | THF | –78 | 139 |
| $NHCO^tBu$ | *n*-BuLi | $THF/Et_2O/TMEDA$ | –70 to –30 | 140 |
| $NHCO^tBu$ | *n*-BuLi | THF/TMEDA | –25 | 141,142 |
| $NHCO_2{}^tBu$ | *n*-BuLi | THF | –20 | 142 |
| $NHCO_2{}^tBu$ | *n*-BuLi | $Et_2O/TMEDA$ | –10 | 143 |
| $CH_2NHCO^tBu$ | *t*-BuLi | THF | –78 | 144 |
| $CH_2NHCO_2{}^tBu$ | *t*-BuLi | THF | –78 | 144 |
| $CH_2NHCONMe_2$ | *t*-BuLi | THF | –78 | 144 |
| $CONEt_2$ | LDA | $Et_2O$ | –78 | 121 |
| $CONEt_2$ | LDA | THF | –78 | 145 |
| $CONEt_2$ | *t*-BuLi | THF/TMEDA | –80 | 146 |
| $CON^iPr_2$ | LDA | $Et_2O$ | –78 | 123 |
| $CON^iPr_2$ | LTMP | THF/TMEDA | –80 | 146–148 |
| $OCSNEt_2$ | LTMP | THF | –78 | 149 |
| SOAr | LDA | THF | –75 | 150 |
| $CO_2H$ | *n*-BuLi/LTMP | THF | –50 | 128 |
| $CO_2H$ | *n*-BuLi/LTMP | THF | –75 | 129 |
| OMe | *n*-BuLi | THF | 0 | 151 |
| OEt | MeLi | $THF/Et_2O$ | RT | 152 |
| F | *n*-BuLi/*t*-BuOK | THF | –75 | 135 |
| F | *n*-BuLi | THF | –75 | 153 |
| F | *n*-BuLi | THF | –78 | 154,155 |
| Br | LDA | THF | –78 | 156,157 |
| Cl | LDA | THF | –78 | 158,159 |

### 4.1.3 Directed lithiation of 4-substituted pyridines.

Directed lithiation of 4-substituted pyridines **14** takes place at C-3 to produce the corresponding 3-lithio intermediates **15** which on reactions with electrophiles give the corresponding 3,4-disubstituted pyridines (**16**; Scheme 6).[116,118,121,123,128,129,159-163] Some examples of 4-substituted pyridines **14** that have been subjected to directed lithiation, along with the appropriate reaction conditions, are shown in Table 4.



DMG = NHCO$^t$Bu, CONEt$_2$, CON$^i$Pr$_2$, CONHPh, CO$_2$H, CH(OEt)$_2$, OMe, Br, Cl

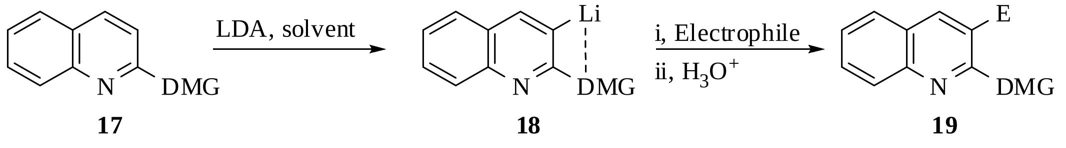
**Scheme 6.** Directed lithiation of 4-subtituted pyridines **14.**

**Table 4.** Examples of 4-substituted pyridines **14** lithiated according to Scheme 6

| DMG | RLi | Solvent | T (°C) | Reference |
|---|---|---|---|---|
| NHCO$^t$Bu | *n*-BuLi | THF | 0 | 116,160 |
| CONEt$_2$ | LDA | Et$_2$O | –78 | 121 |
| CON$^i$Pr$_2$ | LDA | Et$_2$O | –78 | 123 |
| CONHPh | *n*-BuLi | THF | –78 | 118 |
| CO$_2$H | *n*-BuLi/LTMP | THF | –50 to –25 | 128 |
| CO$_2$H | *n*-BuLi/LTMP | THF | –75 to –25 | 129 |
| CH(OEt)$_2$ | LDA | THF | –78 | 161 |
| OMe | PhLi | THF | 0 | 162 |
| Br | LDA | THF | –78 | 163 |
| Cl | *n*-BuLi | Et$_2$O/TMEDA | –70 | 159 |
| Cl | LDA | THF | –70 | 159 |

### 4.2 Directed *ortho*-lithiation of quinolines

Directed lithiation of various substituted quinolines has been achieved by the use of less nucleophilic lithium reagents at low temperatures.[164-173] For example, directed lithiation of 2-substituted quinolines **17** with LDA gives the corresponding lithium reagents **18** which on reactions with electrophiles produce the corresponding 2,3-disubstuited quinolines **19** (Scheme 7) in moderate to very good yields.[166-169] Some examples of 2-substituted quinolines **17** that have been subjected to directed lithiation, along with the appropriate reaction conditions, are shown in Table 5. Similarly, directed lithiation of 3-fluoroquinolines was achieved at the C-4 position by the use of LDA in THF or a THF/hexane mixture at low temperatures.[135,170,171]



DMG = NHCO$^t$Bu, OCONEt$_2$, CO$_2$H, OR, Cl

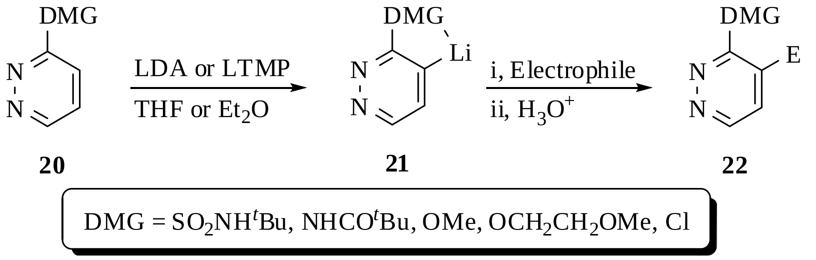
**Scheme 7.** Directed lithiation of 2-substituted quinolines **17.**

**Table 5.** Examples of 2-substituted quinolines **17** lithiated according to Scheme 7

| DMG | RLi | Solvent | T (°C) | Reference |
|---|---|---|---|---|
| NHCO$^t$Bu | *n*-BuLi | $Et_2O$ | –78 | 165 |
| $OCONMe_2$ | LDA | THF | –78 | 166,167 |
| $OCONEt_2$ | LDA | THF | –78 | 166,167 |
| $CO_2H$ | LTMP | THF | –50 to –25 | 169 |
| OMe | *n*-BuLi | $Et_2O$ | 0 | 168 |
| OMe | LTMP | THF | –78 | 169 |
| OEt | *n*-BuLi | $Et_2O$ | 0 | 168 |
| F | LDA | THF or THF/hexane | –78 | 135,170,171 |
| Cl | LDA | THF/hexane | –75 | 172 |
| $CF_3$ | LDA | THF/hexane | –75 | 173 |

### 4.3 Directed *ortho*-lithiation of diazines

**4.3.1 Directed *ortho*-lithiation of 1,2-diazines.** Directed lithiation of pyridazines **20**, containing a DMG at the C-3 position, has been achieved with LDA or LTMP to give the corresponding 4-lithio intermediates **21**, which react with electrophiles to give 3,4-disubstituted pyridazines **22** (Scheme 8).[150,174-180] Some examples of 3-substituted pyridazines **20** that have been subjected to directed lithiation, along with the appropriate reaction conditions, are shown in Table 6.

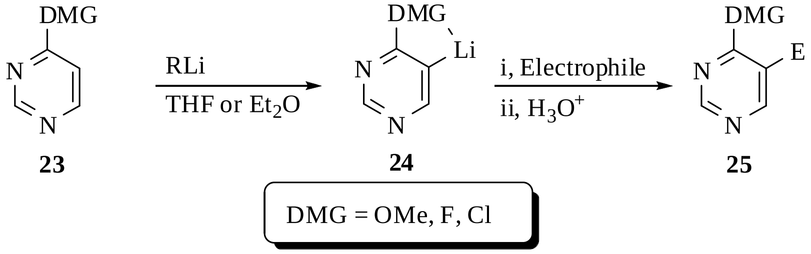


**Scheme 8.** Directed lithiation of pyridazines **20.**

**Table 6.** Examples of 3-substituted pyridazines **20** lithiated according to Scheme 8

| DMG | Lithium reagent | Solvent | T (°C) | Reference |
|---|---|---|---|---|
| $SO_2NH^tBu$ | LTMP | THF | –75 | 174 |
| NHCO$^t$Bu | LDA or LTMP | THF | –78 | 175 |
| OMe | LTMP | THF | –78 | 176 |
| OMe | LDA or LTMP | THF | –75 | 150 |
| $OCH_2CH_2OMe$ | LTMP | THF | –75 | 175 |
| Cl | LDA or LTMP | THF or $Et_2O$ | –100 to 0 | 177–180 |

**4.3.2 Directed *ortho*-lithiation of 1,3-diazines.** Directed lithiation of 4-substituted pyrimidines **23** takes place mainly at C-5 to give the corresponding 5-lithio intermediates **24**, which on reactions with electrophiles give the corresponding 4,5-disubstituted pyrimidines **25** (Scheme 9; Table 7).[136,176,177,181-188]

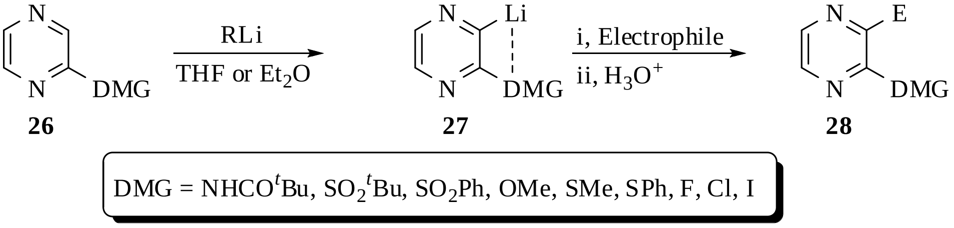


**Scheme 9.** Directed lithiation of 4-substituted pyrimidines **23.**

**Table 7.** Examples of 4-substituted pyrimidines **23** lithiated according to Scheme 9

| DMG | Lithium reagent | Solvent | T (°C) | Reference |
|---|---|---|---|---|
| OMe | LDA | $Et_2O$ | 0 | 181 |
| OMe | LTMP | THF | –78 to –70 | 176,182–184 |
| F | LDA | THF or $Et_2O$ | –70 | 185 |
| Cl | *n*-BuLi | THF | –75 | 176 |
| Cl | LDA | $Et_2O$ | –80 | 186 |
| Cl | LDA | THF | –70 | 136, 187 |
| Cl | LDA or LTMP | THF | –78 | 188 |

**4.3.3 Directed *ortho*-lithiation of 1,4-diazines.** Directed lithiation of 2-substituted pyrazines **26** takes place at the 3-position (Scheme 10).[174,184,189-196] Some examples of 2-substituted pyrazines **26** that have been subjected to such directed lithiation, along with the appropriate reaction conditions, are shown in Table 8. For example, directed lithiation of 2-(pivaloylamino)pyrazine (Scheme 10, DMG = $NHCO^tBu$) was successful by the use of alkyllithiums in THF or $Et_2O$ as solvent to give the corresponding organolithium intermediate **27** (DMG = $NHCO^tBu$), which on reactions with electrophiles produced the corresponding 2,3-disusbstituted pyrazines.[189]



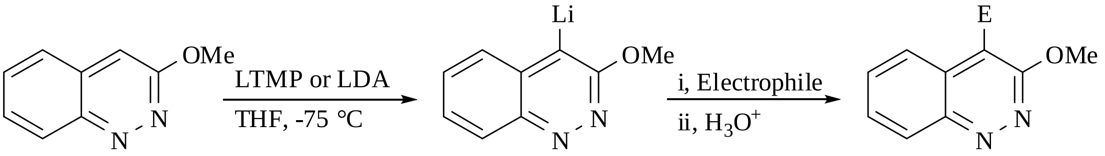
**Scheme 10.** Directed lithiation of 2-substituted pyrazines **26.**

**Table 8.** Examples of 2-substituted pyrazines **26** lithiated according to Scheme 10

| DMG | RLi | Solvent | T (°C) | Reference |
|---|---|---|---|---|
| $NHCO^tBu$ | R = *n*-Bu, *t*-Bu or LTMP | THF or $Et_2O$ | –70 to 20 | 189 |
| $SO_2{}^tBu$ | LDA or LTMP | THF | –75 | 174 |
| $SO_2Ph$ | LDA | THF | –75 | 190 |
| OMe | LDA or LTMP | THF | –78 to 0 | 191–193 |
| SMe | LTMP | THF | –75 | 190 |
| SPh | LTMP | THF | –78 | 191 |
| F | LTMP | THF | –75 | 184,194 |
| Cl | LTMP | THF | –70 | 195 |
| I | LTMP | THF | –78 | 196 |

## 4.4 Directed *ortho*-lithiation of cinnolines

3-Substituted cinnolines (OMe, Cl) have been lithiated with LTMP or LDA at C-4, while the 4-substituted analogues have been lithiated at C-3.[196] For example, 3-methoxycinnoline (**29**) has been lithiated at C-4 by use of LTMP or LDA in THF at -75 °C to give the lithium reagent **30** which reacted with various electrophiles to give the corresponding 4-substituted 3-methoxycinnolines **31** (Scheme 11) in high yields.[196]

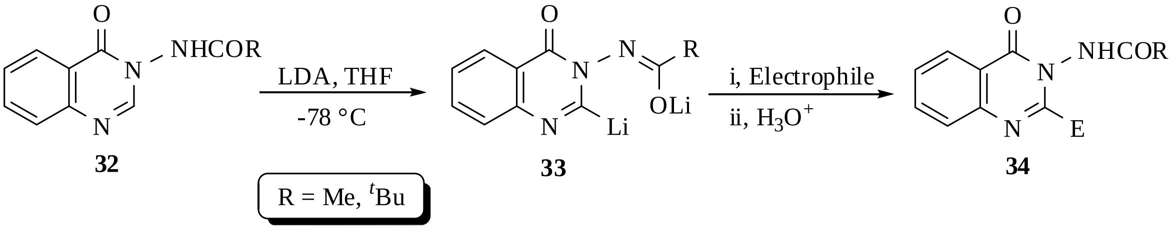


**29** **30** **31**

**Scheme 11.** Directed lithiation of 3-methoxycinnoline **29.**

## 4.5 Directed *ortho*-lithiation of 3*H*-quinazolin-4-ones

Directed lithiation of 3*H*-quinazolin-4-ones has been investigated.[197-200] For example, directed lithiation of 3-acylamino-3*H*-quinazolinones **32** was successful by the use of LDA in THF at -78 °C to give the dilithium reagents **33** (Scheme 12). Reactions of **33** with electrophiles gave the corresponding 2-substituted 3-acylamino-3*H*-quinazolinones **34** in very good yields.[197] By contrast, reactions of **32** with alkyllithiums led to the production of 1,2-addition products in excellent yields.[197]

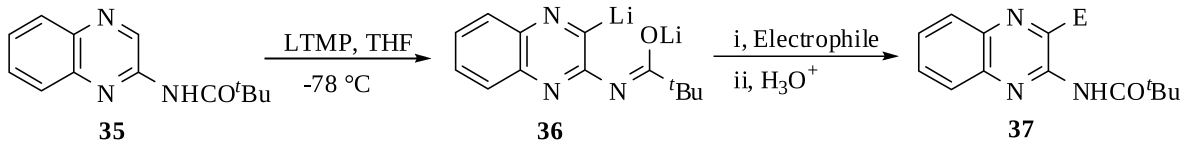


**32** **33** **34**

**Scheme 12.** Directed lithiation of 3-acylamino-3*H*-quinazolinones **32.**

### 4.6 Directed *ortho*-lithiation of quinoxalines

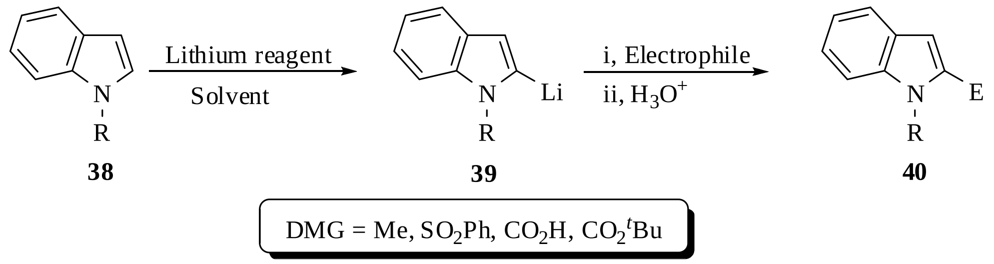
Directed lithiation of 2-(pivaloylamino)quinoxaline (**35**) with LTMP in THF at -78 °C was regioselective at position 3 to give dilithium reagent **36** (Scheme 13).[191,200,201] Reactions of **36** with electrophiles produced the corresponding *ortho*-substituted derivatives **37** in modest yields.[201]



**Scheme 13.** Directed lithiation of 2-(pivaloylamino)quinoxaline (**35**).

### 4.7 Directed *ortho*-lithiation of other heterocycles

Directed lithiation of various other heterocycles has also been investigated.[202-225] In some cases the ring heteroatom is sufficient to direct the lithiation to a site adjacent to the heteroatom, although the presence of a DMG may assist also. For example, directed lithiation of *N*-protected indoles **38** led to the production of 2-substituted *N*-protected indoles **40** (Scheme 14).[203-207] Some examples of protected indoles **38** that have been subjected to directed lithiation, along with the appropriate reaction conditions, are recorded in Table 9.

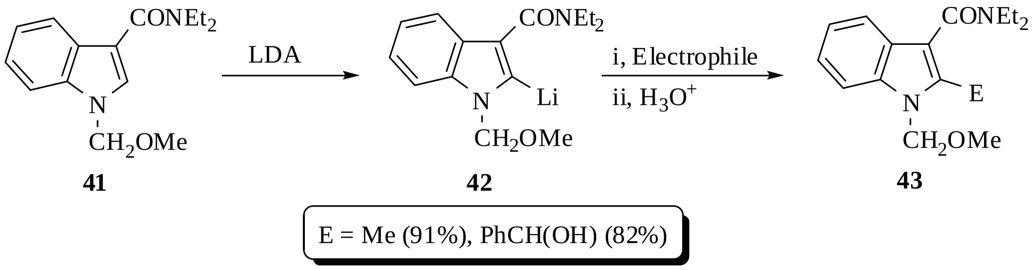


**Scheme 14.** Directed lithiation of *N*-protected indoles **38.**

**Table 9.** Examples of *N*-substituted indoles **38** lithiated according to Scheme 14

| R | Lithium reagent | Solvent | T (°C) | Reference |
|---|---|---|---|---|
| Me | *n*-BuLi | $Et_2O$ | reflux | 204 |
| Me | *t*-BuLi | THF | –120 to –78 | 205 |
| $SO_2Ph$ | MeLi | THF | 0 | 203 |
| $SO_2Ph$ | *n*-BuLi | $Et_2O$ | reflux | 206 |
| $SO_2Ph$ | *t*-BuLi | THF | 0 | 206 |
| $SO_2Ph$ | *t*-BuLi | THF | –120 to –78 | 205 |
| $CO_2H$ | *t*-BuLi | THF | –70 | 207 |
| $CO_2H$ | *t*-BuLi | THF | –120 to –78 | 205 |
| $CO_2{}^tBu$ | *t*-BuLi | THF | –78 | 203 |
| $CO_2{}^tBu$ | *t*-BuLi | THF | –120 to –78 | 205 |

Lithiation of *N,N*-diethyl-1-(methoxymethyl)-1*H*-indole-3-carboxamide (**41**) with LDA gave the corresponding 2-lithio reagent **42,** which on reaction with iodomethane and benzaldehyde gave the corresponding 2-substituted derivatives **43** (Scheme 15) in 91 and 82% yields, respectively.[214] Lithiation of *N*-protected indole-3-carboxylic acid behaved in similar manner.[214]

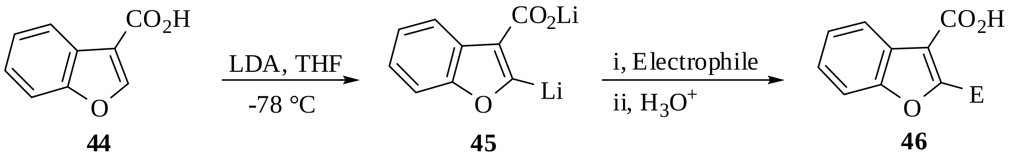


**41** **42** **43**

E = Me (91%), PhCH(OH) (82%)

**Scheme 15.** Lithiation of *N,N*-diethyl-1-(methoxymethyl)-1*H*-indole-3-carboxamide (**41**).

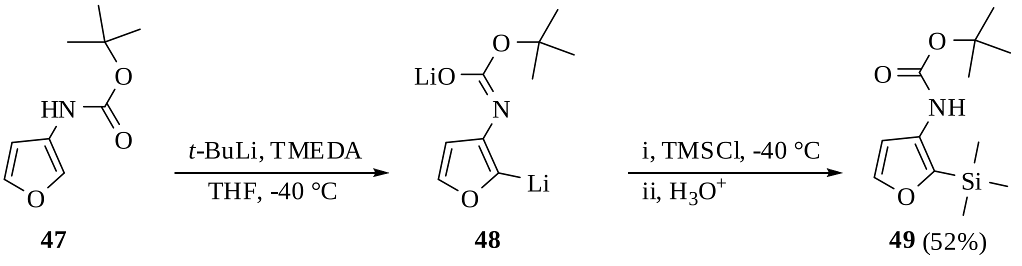
Lithiation of benzofuran-3-carboxylic acid (**44**) with LDA in THF at –78 °C gave the corresponding 2-lithio reagent **45**, which on reaction with various electrophiles gave the corresponding 2-substituted derivatives **46** (Scheme 16) in 75–100% yields.[215,216] Lithiation of benzofuran-2-carboxylic acid took place at the 3-position.[216]



**44** **45** **46**

**Scheme 16.** Lithiation of benzofuran-3-carboxylic acid (**44**).

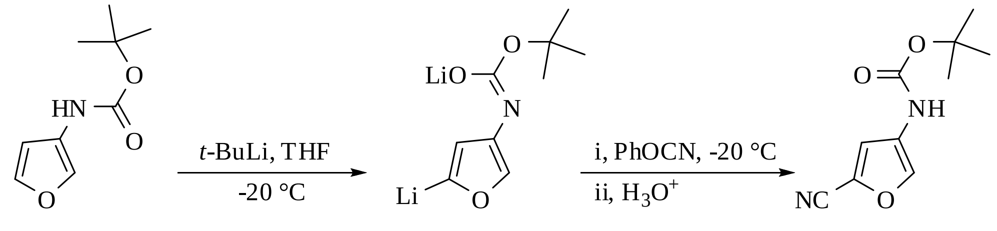
*ortho*-Lithiation of 3-(*tert*-butoxycarbonylamino)furan (**47**) with *t*-BuLi (2.5 equivalents) in the presence of TMEDA (2.5 equivalents) in THF at –40 °C took place regioselectively at the C-2 position to provide the corresponding 2-lithio reagent **48**, which with trimethylsilyl chloride gave 3-(*tert*-butoxycarbonylamino)-2-(trimethylsilyl)furan (**49**) in 52% yield (Scheme 17).[218]



**47** **48** **49** (52%)

**Scheme 17.** Regioslective lithiation of 3-(*N*-*tert*-butoxycarbonyl)furan (**47**) at the C-2 position.

In contrast, lithiation of **47** with *t*-BuLi (2.0 equivalents) in the absence of TMEDA in THF at –20 °C, followed by cyanation, took place at the C-5 position to give 5-substituted derivative **51** in 71% yield *via* formation of lithium reagent **50** (Scheme 18).[219,220]



**47** **50** **51** (71%)

**Scheme 18.** Regioslective lithiation of 3-(*N*-*tert*-butoxycarbonyl)furan (**47**) at the C-5 position.

## 5. Conclusion

Directed lithiation of various aromatics and heterocycles by lithium reagents at low temperatures and reactions of the lithium reagents thus obtained with electrophiles produces the corresponding *ortho*-substituted derivatives that might be difficult to prepare by other means.

## 6. Acknowledgements

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## Authors' Biographies

**Professor Gamal A. El-Hiti**

Gamal A. El-Hiti was born in Egypt. He received his BSc and MSc degrees from Tanta University, Egypt. He received his PhD degree from Tanta University in 1996 including two years at Swansea University, UK (Professor K. Smith). Lecturer (1996), Associate Professor (2001) and Professor (2006-2013), Tanta University (was on sabbatical leave to the UK; 1993-1995, 1998-1999 and 2002-2013). Academic Visitor, Swansea University (1998-1999). Lecturer and Research Officer, Swansea University (2002-2007). Research Fellow, Research Associate and Teacher in Organic Chemistry, Cardiff University (2007-2013). Technical Director of CatCelt Limited since 2006. His research interests are primarily in the development of novel organic synthetic methods, especially ones that are “greener” than traditionally, and synthesis of compounds with interesting properties. Particular current research projects involve use of zeolites and solid-supported reagents and catalysts to gain selectivity in organic reactions; lithiation reactions, which have been used to devise novel heterocyclic ring syntheses and to introduce selectivity into aromatic and heterocyclic substitution reactions; heterocyclic chemistry; design and synthesis of novel compounds with interesting chemiluminescent properties and chemistry of tears. He is currently a Professor of Organic Chemistry, since 2013, at King Saud University, College of Applied Medical Sciences, Department of Optometry, Saudi Arabia.

**Professor Keith Smith**

Keith Smith received his PhD degree from Manchester University in 1971 (Professor A. Pelter). Royal Society European Exchange Fellow, ETH Zürich (1971-1972; Professor A. Eschenmoser, chlorophyll derivatives). Lecturer, Swansea University (1972-1980). Visiting Research Associate, Purdue University West Lafayette IN USA (1978-1979; Professor H. C. Brown). Senior Lecturer and Reader Swansea University (1980-1988) and promoted to personal chair (1988). Head of Chemistry Department (1990-1993; 2001-2007). Professor of Organic Chemistry, Cardiff University (2007-2013). Managing Director of CatCelt Ltd since 2006. He is currently an Emeritus Professor, since 2013, at Cardiff University, UK.

**Dr Amany S. Hegazy**

Amany S. Hegazy was born in Egypt. She received her B.Sc. degree in Chemistry from Tanta University, Egypt. She received her MPhil degree from Swansea University, UK, in 2006 and her Ph.D. degree from Cardiff University, UK, in 2009. She carried out her postgraduate studies under the supervision of Professor Keith Smith. Her research focused on the green synthetic methods of heterocycles and aromatics *via* use of organolithium reagents as intermediates in organic synthesis.

**Dr Mohammed B. Alshammari**

Mohammed B. Alshammari was born in Saudi Arabia. He received his B.Sc. and M.Sc. degrees in Chemistry from King Saud University, Saudi Arabia. He received his Ph.D. degree from Cardiff University, UK, in 2013 under the supervision of Professor Keith Smith. His research is focused on the use of organolithium reagents as intermediates in organic synthesis. Currently, he is working as Assistant Professor of Organic Chemistry at Salman bin Abdulaziz University, Saudi Arabia.

**Dr Ali M. Masmali**

Ali M. Masmali was born in Saudi Arabia. He received his B.Sc. degree in Optometry from King Saud University, Saudi Arabia, in 2002. He received his Ph.D. degree from Cardiff University, UK in 2010 under the supervision of Professor Paul Murphy and Professor Christine Purslow. His research is focused on the development of tear ferning test protocols and a new grading scale. Currently, he is working as Assistant Professor of Optometry at King Saud University, Saudi Arabia.