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

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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 alkylthium 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 \textit{ortho} to a directing metalating group to produce useful intermediates for the synthesis of ortho-disubstituted derivatives.\(^13\)\(^-\)\(^41\)

Synthesis of isomerically pure \textit{ortho}-disubstituted aromatics is a significant goal in synthetic chemistry, but simple aromatic electrophilic substitution reactions often produce mixtures of isomers.\(^42\) \textit{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 (Et₂O) 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](image_url)

**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 SO₂NR₂, NHCOR, CONR₂, CSNHR, CONHR, OCONR₂, CO₂R, CH₂NHR, OCH₂OMe, OR, NR₂, SR, CF₃ and F, while weak DMGs include CH₂OH 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).\textsuperscript{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\textsuperscript{t}) produces a dilithium intermediate in-situ, which reacts with electrophiles to give the corresponding ortho-substituted derivatives (DMG = NHCOBu) in high yields.\textsuperscript{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.

![Scheme 2. Directed lithiation of substituted benzenes 1.](image)

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

<table>
<thead>
<tr>
<th>DMG</th>
<th>RLi</th>
<th>Solvent</th>
<th>T (°C)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>NHCOBu</td>
<td>n-BuLi</td>
<td>THF</td>
<td>0</td>
<td>81</td>
</tr>
<tr>
<td>NHCO\textsubscript{2}Bu</td>
<td>t-BuLi</td>
<td>THF</td>
<td>–20</td>
<td>82,83</td>
</tr>
<tr>
<td>NHCONMe\textsubscript{2}</td>
<td>n-BuLi</td>
<td>THF</td>
<td>–78</td>
<td>84</td>
</tr>
<tr>
<td>CH\textsubscript{2}NHCOBu</td>
<td>t-BuLi</td>
<td>THF</td>
<td>–78</td>
<td>73</td>
</tr>
<tr>
<td>CH\textsubscript{2}NHCONMe\textsubscript{2}</td>
<td>n-BuLi</td>
<td>THF</td>
<td>0</td>
<td>85</td>
</tr>
<tr>
<td>CH\textsubscript{2}NHCONMe\textsubscript{2}</td>
<td>t-BuLi</td>
<td>THF</td>
<td>–78</td>
<td>73</td>
</tr>
<tr>
<td>CH\textsubscript{2}NHCONMe\textsubscript{2}</td>
<td>sec-BuLi</td>
<td>THF</td>
<td>–50</td>
<td>86</td>
</tr>
<tr>
<td>CH\textsubscript{2}CH\textsubscript{2}NHCO\textsubscript{2}Bu</td>
<td>n-BuLi</td>
<td>THF</td>
<td>–20 to 0</td>
<td>87</td>
</tr>
<tr>
<td>CH\textsubscript{2}CH\textsubscript{2}NHCONMe\textsubscript{2}</td>
<td>n-BuLi</td>
<td>THF</td>
<td>–20 to 0</td>
<td>88</td>
</tr>
<tr>
<td>CH\textsubscript{2}CH\textsubscript{2}NHCO\textsubscript{2}Bu</td>
<td>n-BuLi</td>
<td>THF</td>
<td>–20 to 0</td>
<td>88</td>
</tr>
<tr>
<td>CONHMe</td>
<td>n-BuLi</td>
<td>THF</td>
<td>–78</td>
<td>89</td>
</tr>
<tr>
<td>CONHPh</td>
<td>n-BuLi</td>
<td>THF</td>
<td>–78</td>
<td>89</td>
</tr>
<tr>
<td>CONEt\textsubscript{2}</td>
<td>sec-BuLi</td>
<td>THF/TMEDA\textsuperscript{a}</td>
<td>–78</td>
<td>90,91</td>
</tr>
</tbody>
</table>
Table 1 (continued)

<table>
<thead>
<tr>
<th>Reaction</th>
<th>Reactants</th>
<th>Conditions</th>
<th>Products</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\text{CON}^\prime\text{Pr}_2$</td>
<td>$\text{sec-BuLi}$</td>
<td>THF</td>
<td>$-78$</td>
</tr>
<tr>
<td>$\text{CON}^\prime\text{Pr}_2$</td>
<td>$\text{n-BuLi}$</td>
<td>THF</td>
<td>$-78$</td>
</tr>
<tr>
<td>$\text{CON(Me)/Bu}$</td>
<td>$\text{sec-BuLi}$</td>
<td>THF/TMEDA$^a$</td>
<td>$-78$</td>
</tr>
<tr>
<td>$\text{OCONe}t_2$</td>
<td>$\text{sec-BuLi}$</td>
<td>THF/TMEDA$^a$</td>
<td>$-78$</td>
</tr>
<tr>
<td>$\text{CH}_2\text{N}e_t_2$</td>
<td>$\text{t-BuLi/ZnCl}_2$</td>
<td>THF/Et$_2$O (1:1)</td>
<td>$-78$ to $0$</td>
</tr>
<tr>
<td>$\text{OTH}_p^b$</td>
<td>$\text{n-BuLi}$</td>
<td>THF/TMEDA$^a$</td>
<td>$-20$ to $-10$</td>
</tr>
<tr>
<td>$\text{DHDPO}^c$</td>
<td>$\text{i-PrLi}$</td>
<td>THF/DMPU$^d$</td>
<td>$-98$ to $-40$</td>
</tr>
<tr>
<td>$1\text{H}$-tetrazol-5-yl</td>
<td>$\text{sec-BuLi}$</td>
<td>THF</td>
<td>$-78$</td>
</tr>
<tr>
<td>$\text{OMe}$</td>
<td>$\text{t-BuLi}$</td>
<td>THF</td>
<td>$-78$</td>
</tr>
<tr>
<td>$\text{OMe}$</td>
<td>$\text{n-BuLi}$</td>
<td>THF</td>
<td>$-75$</td>
</tr>
<tr>
<td>$\text{OMe}$</td>
<td>$\text{n-BuLi}$</td>
<td>THF/TMEDA$^a$</td>
<td>$-108$ to $-78$</td>
</tr>
<tr>
<td>$\text{OMe}$</td>
<td>$\text{n-BuLi}$</td>
<td>THF/KO$^t$Bu</td>
<td>$-95$</td>
</tr>
<tr>
<td>$\text{SH}$</td>
<td>$\text{n-BuLi}$</td>
<td>cyclohexane/TMEDA$^a$</td>
<td>0 to 25</td>
</tr>
<tr>
<td>$\text{SH}$</td>
<td>$\text{n-BuLi}$</td>
<td>TMEDA$^a$</td>
<td>20</td>
</tr>
<tr>
<td>$\text{CF}_3$</td>
<td>LTMP$^e$</td>
<td>THF</td>
<td>$-75$</td>
</tr>
<tr>
<td>$\text{F}$</td>
<td>$\text{n-BuLi}$</td>
<td>Et$_2$O</td>
<td>$-50$</td>
</tr>
</tbody>
</table>

$^a$ TMEDA is $N,N,N',N'$-tetramethylethylenediamine. $^b$ OTHP is O-tetrahydropyran. $^c$ DHDPO is 4,5-dihydro-4,5-diphenyl-oxazol-2-yl. $^d$ DMPU is $N,N'$-dimethylpropyleneurea (1,3-dimethyltetrahydropyrimidin-2(1H)-one). $^e$ LTMP is lithium 2,2,6,6-tetramethyldipiperidine

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 $\text{sec-BuLi}$ in the presence of $N,N,N',N'$-tetramethylethylenediamine (TMEDA) at $-78 \, ^\circ\text{C}$ 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).](image-url)
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 \(\pi\)-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 alkylolithiums 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\(\text{tBu}\)) 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.

![Scheme 4. Directed lithiation of substituted pyridines 8.](image)

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

<table>
<thead>
<tr>
<th>DMG</th>
<th>RLi</th>
<th>Solvent</th>
<th>(T (\degree\text{C}))</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>NHCO(\text{tBu})</td>
<td>(n)-BuLi</td>
<td>THF</td>
<td>0</td>
<td>116,117</td>
</tr>
<tr>
<td>CONHPh</td>
<td>(n)-BuLi</td>
<td>THF</td>
<td>–78</td>
<td>118</td>
</tr>
<tr>
<td>CONHPh</td>
<td>LDA</td>
<td>THF</td>
<td>–78</td>
<td>119</td>
</tr>
<tr>
<td>CON(\text{Et}_2)</td>
<td>(\text{sec-BuLi})</td>
<td>THF</td>
<td>–78</td>
<td>120</td>
</tr>
<tr>
<td>CON(\text{Et}_2)</td>
<td>LDA</td>
<td>Et(\text{2O})</td>
<td>–78</td>
<td>121</td>
</tr>
<tr>
<td>CON(\text{Pr}_2)</td>
<td>(n)-BuLi</td>
<td>THF</td>
<td>–78</td>
<td>122</td>
</tr>
<tr>
<td>CON(\text{Pr}_2)</td>
<td>LDA</td>
<td>Et(\text{2O})</td>
<td>–78</td>
<td>123</td>
</tr>
</tbody>
</table>
4.1.2 Directed lithiation of 3-substituted pyridines. Directed lithiation of 3-substituted pyridines 11 with various lithium reagents takes place predominantly at C-4 to give the corresponding lithium intermediates 12 (Scheme 5). Reactions of 12 with electrophiles produce the corresponding substituted pyridines 13. 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.

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

<table>
<thead>
<tr>
<th>DMG</th>
<th>RLi</th>
<th>Solvent</th>
<th>T (°C)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>SO₂NHᵗBu</td>
<td>t-BuLi</td>
<td>THF</td>
<td>−78</td>
<td>139</td>
</tr>
<tr>
<td>NHCOᵗBu</td>
<td>n-BuLi</td>
<td>THF/Et₂O/TMEDA</td>
<td>−70 to −30</td>
<td>140</td>
</tr>
<tr>
<td>NHCOᵗBu</td>
<td>n-BuLi</td>
<td>THF/TMEDA</td>
<td>−25</td>
<td>141,142</td>
</tr>
<tr>
<td>NHCO₂ᵗBu</td>
<td>n-BuLi</td>
<td>THF</td>
<td>−20</td>
<td>142</td>
</tr>
<tr>
<td>NHCO₂ᵗBu</td>
<td>n-BuLi</td>
<td>Et₂O/TMEDA</td>
<td>−10</td>
<td>143</td>
</tr>
<tr>
<td>CH₂NHCΟᵗBu</td>
<td>t-BuLi</td>
<td>THF</td>
<td>−78</td>
<td>144</td>
</tr>
<tr>
<td>CH₂NHCΟ₂ᵗBu</td>
<td>t-BuLi</td>
<td>THF</td>
<td>−78</td>
<td>144</td>
</tr>
<tr>
<td>CH₂NHCΟNMe₂</td>
<td>t-BuLi</td>
<td>THF</td>
<td>−78</td>
<td>144</td>
</tr>
<tr>
<td>CONEt₂</td>
<td>LDA</td>
<td>Et₂O</td>
<td>−78</td>
<td>121</td>
</tr>
<tr>
<td>CONEt₂</td>
<td>LDA</td>
<td>THF</td>
<td>−78</td>
<td>145</td>
</tr>
<tr>
<td>CONEt₂</td>
<td>t-BuLi</td>
<td>THF/TMEDA</td>
<td>−80</td>
<td>146</td>
</tr>
<tr>
<td>CON’Pr₂</td>
<td>LDA</td>
<td>Et₂O</td>
<td>−78</td>
<td>123</td>
</tr>
<tr>
<td>CON’Pr₂</td>
<td>LTMP</td>
<td>THF/TMEDA</td>
<td>−80</td>
<td>146–148</td>
</tr>
<tr>
<td>OCSNEt₂</td>
<td>LTMP</td>
<td>THF</td>
<td>−78</td>
<td>149</td>
</tr>
<tr>
<td>SOAr</td>
<td>LDA</td>
<td>THF</td>
<td>−75</td>
<td>150</td>
</tr>
<tr>
<td>CO₂H</td>
<td>n-BuLi/LTMP</td>
<td>THF</td>
<td>−50</td>
<td>128</td>
</tr>
<tr>
<td>CO₂H</td>
<td>n-BuLi/LTMP</td>
<td>THF</td>
<td>−75</td>
<td>129</td>
</tr>
<tr>
<td>OMe</td>
<td>n-BuLi</td>
<td>THF</td>
<td>0</td>
<td>151</td>
</tr>
<tr>
<td>OEt</td>
<td>MeLi</td>
<td>THF/Et₂O</td>
<td>RT</td>
<td>152</td>
</tr>
<tr>
<td>F</td>
<td>n-BuLi/t-BuOK</td>
<td>THF</td>
<td>−75</td>
<td>135</td>
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<tr>
<td>F</td>
<td>n-BuLi</td>
<td>THF</td>
<td>−75</td>
<td>153</td>
</tr>
<tr>
<td>F</td>
<td>n-BuLi</td>
<td>THF</td>
<td>−78</td>
<td>154,155</td>
</tr>
<tr>
<td>Br</td>
<td>LDA</td>
<td>THF</td>
<td>−78</td>
<td>156,157</td>
</tr>
<tr>
<td>Cl</td>
<td>LDA</td>
<td>THF</td>
<td>−78</td>
<td>158,159</td>
</tr>
</tbody>
</table>

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). 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.
Scheme 6. Directed lithiation of 4-substituted pyridines 14.

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

<table>
<thead>
<tr>
<th>DMG</th>
<th>RLi</th>
<th>Solvent</th>
<th>T (°C)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>NHCO'Bu</td>
<td>n-BuLi</td>
<td>THF</td>
<td>0</td>
<td>116,160</td>
</tr>
<tr>
<td>CONEt₂</td>
<td>LDA</td>
<td>Et₂O</td>
<td>–78</td>
<td>121</td>
</tr>
<tr>
<td>CONPr₂</td>
<td>LDA</td>
<td>Et₂O</td>
<td>–78</td>
<td>123</td>
</tr>
<tr>
<td>CONHPh</td>
<td>n-BuLi</td>
<td>THF</td>
<td>–78</td>
<td>118</td>
</tr>
<tr>
<td>CO₂H</td>
<td>n-BuLi/LTMP</td>
<td>THF</td>
<td>–50 to –25</td>
<td>128</td>
</tr>
<tr>
<td>CO₂H</td>
<td>n-BuLi/LTMP</td>
<td>THF</td>
<td>–75 to –25</td>
<td>129</td>
</tr>
<tr>
<td>CH(OEt)₂</td>
<td>LDA</td>
<td>THF</td>
<td>–78</td>
<td>161</td>
</tr>
<tr>
<td>OMe</td>
<td>PhLi</td>
<td>THF</td>
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<td>162</td>
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<tr>
<td>Br</td>
<td>LDA</td>
<td>THF</td>
<td>–78</td>
<td>163</td>
</tr>
<tr>
<td>Cl</td>
<td>n-BuLi</td>
<td>Et₂O/TMEDA</td>
<td>–70</td>
<td>159</td>
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<tr>
<td>Cl</td>
<td>LDA</td>
<td>THF</td>
<td>–70</td>
<td>159</td>
</tr>
</tbody>
</table>

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-disubstituted 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

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

<table>
<thead>
<tr>
<th>DMG</th>
<th>RLi</th>
<th>Solvent</th>
<th>T (°C)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>NHCO₂Bu</td>
<td>n-BuLi</td>
<td>Et₂O</td>
<td>−78</td>
<td>165</td>
</tr>
<tr>
<td>OCONMe₂</td>
<td>LDA</td>
<td>THF</td>
<td>−78</td>
<td>166,167</td>
</tr>
<tr>
<td>OCONEt₂</td>
<td>LDA</td>
<td>THF</td>
<td>−78</td>
<td>166,167</td>
</tr>
<tr>
<td>CO₂H</td>
<td>LTMP</td>
<td>THF</td>
<td>−50 to −25</td>
<td>169</td>
</tr>
<tr>
<td>OMe</td>
<td>n-BuLi</td>
<td>Et₂O</td>
<td>0</td>
<td>168</td>
</tr>
<tr>
<td>OMe</td>
<td>LTMP</td>
<td>THF</td>
<td>−78</td>
<td>169</td>
</tr>
<tr>
<td>OEt</td>
<td>n-BuLi</td>
<td>Et₂O</td>
<td>0</td>
<td>168</td>
</tr>
<tr>
<td>F</td>
<td>LDA</td>
<td>THF or THF/hexane</td>
<td>−78</td>
<td>135,170,171</td>
</tr>
<tr>
<td>Cl</td>
<td>LDA</td>
<td>THF/hexane</td>
<td>−75</td>
<td>172</td>
</tr>
<tr>
<td>CF₃</td>
<td>LDA</td>
<td>THF/hexane</td>
<td>−75</td>
<td>173</td>
</tr>
</tbody>
</table>

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.](image)

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

<table>
<thead>
<tr>
<th>DMG</th>
<th>Lithium reagent</th>
<th>Solvent</th>
<th>T (°C)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>SO₂NH'Bu</td>
<td>LTMP</td>
<td>THF</td>
<td>−75</td>
<td>174</td>
</tr>
<tr>
<td>NHCO₂Bu</td>
<td>LDA or LTMP</td>
<td>THF</td>
<td>−78</td>
<td>175</td>
</tr>
<tr>
<td>OMe</td>
<td>LTMP</td>
<td>THF</td>
<td>−78</td>
<td>176</td>
</tr>
<tr>
<td>OMe</td>
<td>LDA or LTMP</td>
<td>THF</td>
<td>−75</td>
<td>150</td>
</tr>
<tr>
<td>OCH₂CH₂OMe</td>
<td>LTMP</td>
<td>THF</td>
<td>−75</td>
<td>175</td>
</tr>
<tr>
<td>Cl</td>
<td>LDA or LTMP</td>
<td>THF or Et₂O</td>
<td>−100 to 0</td>
<td>177–180</td>
</tr>
</tbody>
</table>
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.](image)

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

<table>
<thead>
<tr>
<th>DMG</th>
<th>Lithium reagent</th>
<th>Solvent</th>
<th>T (°C)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>OMe</td>
<td>LDA</td>
<td>Et₂O</td>
<td>0</td>
<td>181</td>
</tr>
<tr>
<td>OMe</td>
<td>LTMP</td>
<td>THF</td>
<td>–78 to –70</td>
<td>176,182–184</td>
</tr>
<tr>
<td>F</td>
<td>LDA</td>
<td>THF or Et₂O</td>
<td>–70</td>
<td>185</td>
</tr>
<tr>
<td>Cl</td>
<td>n-BuLi</td>
<td>THF</td>
<td>–75</td>
<td>176</td>
</tr>
<tr>
<td>Cl</td>
<td>LDA</td>
<td>Et₂O</td>
<td>–80</td>
<td>186</td>
</tr>
<tr>
<td>Cl</td>
<td>LDA</td>
<td>THF</td>
<td>–70</td>
<td>136, 187</td>
</tr>
<tr>
<td>Cl</td>
<td>LDA or LTMP</td>
<td>THF</td>
<td>–78</td>
<td>188</td>
</tr>
</tbody>
</table>

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 = NHCO₂Bu) was successful by the use of alkyllithiums in THF or Et₂O as solvent to give the corresponding organolithium intermediate 27 (DMG = NHCO₂Bu), which on reactions with electrophiles produced the corresponding 2,3-disubstituted pyrazines.189

![Scheme 10. Directed lithiation of 2-substituted pyrazines 26.](image)
Table 8. Examples of 2-substituted pyrazines 26 lithiated according to Scheme 10

<table>
<thead>
<tr>
<th>DMG</th>
<th>RLi</th>
<th>Solvent</th>
<th>T (°C)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>NHCOO'Bu</td>
<td>R = n-Bu, t-Bu or LTMP</td>
<td>THF or Et₂O</td>
<td>-70 to 20</td>
<td>189</td>
</tr>
<tr>
<td>SO₂'Bu</td>
<td>LDA or LTMP</td>
<td>THF</td>
<td>-75</td>
<td>174</td>
</tr>
<tr>
<td>SO₂Ph</td>
<td>LDA</td>
<td>THF</td>
<td>-75</td>
<td>190</td>
</tr>
<tr>
<td>OMe</td>
<td>LDA or LTMP</td>
<td>THF</td>
<td>-78 to 0</td>
<td>191–193</td>
</tr>
<tr>
<td>SMe</td>
<td>LTMP</td>
<td>THF</td>
<td>-75</td>
<td>190</td>
</tr>
<tr>
<td>SPh</td>
<td>LTMP</td>
<td>THF</td>
<td>-78</td>
<td>191</td>
</tr>
<tr>
<td>Cl</td>
<td>LTMP</td>
<td>THF</td>
<td>-70</td>
<td>184,194</td>
</tr>
<tr>
<td>F</td>
<td>LTMP</td>
<td>THF</td>
<td>-75</td>
<td>195</td>
</tr>
</tbody>
</table>

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

![Scheme 11. Directed lithiation of 3-methoxycinnoline 29.](image)

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

Directed lithiation of 3H-quinazolin-4-ones has been investigated.¹⁹⁷–²⁰⁰ For example, directed lithiation of 3-acylamino-3H-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-3H-quinazolinones 34 in very good yields.¹⁹⁷ By contrast, reactions of 32 with alkylolithiums led to the production of 1,2-addition products in excellent yields.¹⁹⁷

![Scheme 12. Directed lithiation of 3-acylamino-3H-quinazolinones 32.](image)
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). Reactions of 36 with electrophiles produced the corresponding ortho-substituted derivatives 37 in modest yields.

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. 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). 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

<table>
<thead>
<tr>
<th>R</th>
<th>Lithium reagent</th>
<th>Solvent</th>
<th>T (°C)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Me</td>
<td>n-BuLi</td>
<td>Et₂O</td>
<td>reflux</td>
<td>204</td>
</tr>
<tr>
<td>Me</td>
<td>t-BuLi</td>
<td>THF</td>
<td>-120 to -78</td>
<td>205</td>
</tr>
<tr>
<td>SO₂Ph</td>
<td>MeLi</td>
<td>THF</td>
<td>0</td>
<td>203</td>
</tr>
<tr>
<td>SO₂Ph</td>
<td>n-BuLi</td>
<td>Et₂O</td>
<td>reflux</td>
<td>206</td>
</tr>
<tr>
<td>SO₂Ph</td>
<td>t-BuLi</td>
<td>THF</td>
<td>0</td>
<td>206</td>
</tr>
<tr>
<td>SO₂Ph</td>
<td>t-BuLi</td>
<td>THF</td>
<td>-120 to -78</td>
<td>205</td>
</tr>
<tr>
<td>CO₂H</td>
<td>t-BuLi</td>
<td>THF</td>
<td>-70</td>
<td>207</td>
</tr>
<tr>
<td>CO₂H</td>
<td>t-BuLi</td>
<td>THF</td>
<td>-120 to -78</td>
<td>205</td>
</tr>
<tr>
<td>CO₂t-Bu</td>
<td>t-BuLi</td>
<td>THF</td>
<td>-78</td>
<td>203</td>
</tr>
<tr>
<td>CO₂t-Bu</td>
<td>t-BuLi</td>
<td>THF</td>
<td>-120 to -78</td>
<td>205</td>
</tr>
</tbody>
</table>
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.\(^{214}\)

\[
\begin{align*}
\text{LDA} & \quad \text{LDA, THF} \\
\text{E = Me (91%), PhCH(OH) (82%)}
\end{align*}
\]

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.\(^{216}\)

\[
\begin{align*}
\text{LDA, THF} & \quad \text{i, Electrophile} \\
\text{LDA, THF} & \quad \text{i, Electrophile} \\
\text{E = Me (91%), PhCH(OH) (82%)} & \quad \text{i, Electrophile}
\end{align*}
\]

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

\textit{ortho}-Lithiation of 3-(\(\text{N-}\)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-(\(\text{N-}\)tert-butoxycarbonylamino)-2-(trimethylsilyl)furan (49) in 52% yield (Scheme 17).\(^{218}\)

\[
\begin{align*}
\text{t-BuLi, TMEDA} & \quad \text{i, TMSCl, -40 °C} \\
\text{O} & \quad \text{NH}
\end{align*}
\]

Scheme 17. Regioslective lithiation of 3-(\(\text{N-}\)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).

![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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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**


**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
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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.