

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 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

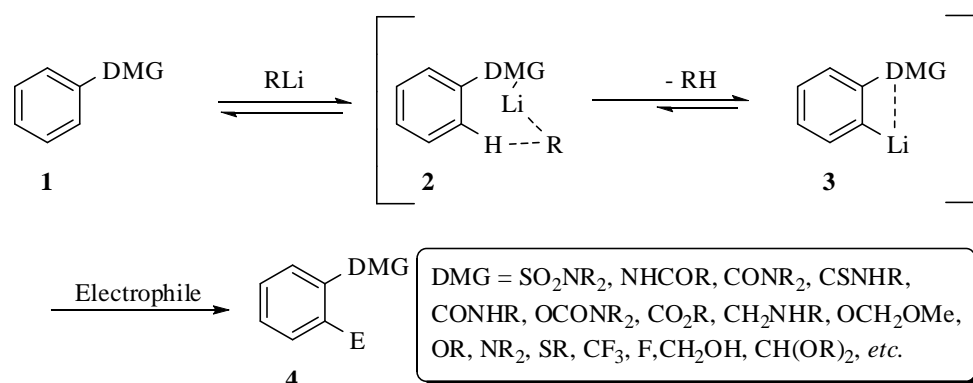
Recently, many efforts have been made to develop cleaner and environmentally friendlier processes for the production of single isomeric products. Solids such as zeolites can play an important role in the development of greener organic syntheses for the production of *para*-isomers through their abilities 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 $-78\text{ }^{\circ}\text{C}$ 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}

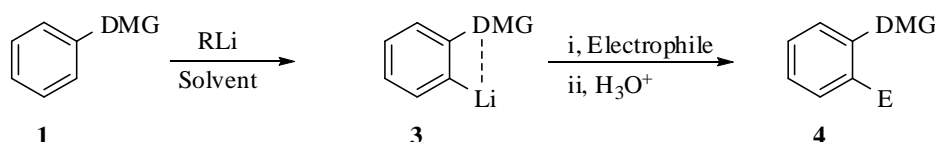


Scheme 1. Directed lithiation of substituted aromatics **1** followed by reactions with electrophiles.

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 $\text{CH}(\text{OR})_2$.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 = NHCOCu^t) produces a dilithium intermediate *in-situ*, which reacts with electrophiles to give the corresponding *ortho*-substituted derivatives (DMG = NHCOCu^t) 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.



DMG = NHCOCu^t, NHCOCu^tBu, NHCONMe₂, CH₂NHCOCu^t, CH₂NHCONMe₂, CH₂CH₂NHCOCu^t, CH₂CH₂NHCONMe₂, CH₂CH₂NHCOCu^tBu, CONHMe, CONHPh, CONEt₂, CON^tPr₂, CON(Me)^tBu, OCONEt₂, CH₂NEt₂, OTHP, DHDPO, 1*H*-tetrazol-5-yl, OMe, SH, CF₃, 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)	
NHCOCu ^t Bu	<i>n</i> -BuLi	THF	0	81
NHCOCu ^t Bu	<i>t</i> -BuLi	THF	-20	82,83
NHCONMe ₂	<i>n</i> -BuLi	THF	-78	84
CH ₂ NHCOCu ^t Bu	<i>t</i> -BuLi	THF	-78	73
CH ₂ NHCOCu ^t Bu	<i>n</i> -BuLi	THF	0	85
CH ₂ NHCONMe ₂	<i>t</i> -BuLi	THF	-78	73
CH ₂ NHCONMe ₂	<i>sec</i> -BuLi	THF	-50	86
CH ₂ CH ₂ NHCOCu ^t Bu	<i>n</i> -BuLi	THF	-20 to 0	87
CH ₂ CH ₂ NHCONMe ₂	<i>n</i> -BuLi	THF	-20 to 0	88
CH ₂ CH ₂ NHCOCu ^t Bu	<i>n</i> -BuLi	THF	-20 to 0	88
CONHMe	<i>n</i> -BuLi	THF	-78	89
CONHPh	<i>n</i> -BuLi	THF	-78	89
CONEt ₂	<i>sec</i> -BuLi	THF/TMEDA ^a	-78	90,91

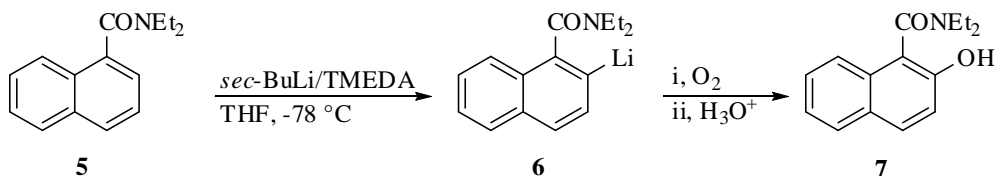
Table 1 (continued)

CON ^{<i>i</i>} Pr ₂	<i>sec</i> -BuLi	THF	-78	92
CON ^{<i>i</i>} Pr ₂	<i>n</i> -BuLi	THF	-78	93
CON(Me) ^{<i>t</i>} Bu	<i>sec</i> -BuLi	THF/TMEDA ^{<i>a</i>}	-78	94
OCONEt ₂	<i>sec</i> -BuLi	THF/TMEDA ^{<i>a</i>}	-78	95
CH ₂ NEt ₂	<i>t</i> -BuLi/ZnCl ₂	THF/Et ₂ O (1:1)	-78 to 0	96
OTHP ^{<i>b</i>}	<i>n</i> -BuLi	THF/TMEDA ^{<i>a</i>}	-20 to -10	97
DHDPO ^{<i>c</i>}	<i>i</i> -PrLi	THF/DMPU ^{<i>d</i>}	-98 to -40	75
1 <i>H</i> -tetrazol-5-yl	<i>sec</i> -BuLi	THF	-78	98
OMe	<i>t</i> -BuLi	THF	-78	99
OMe	<i>n</i> -BuLi	THF	-75	100
OMe	<i>n</i> -BuLi	THF/TMEDA ^{<i>a</i>}	-108 to -78	101
OMe	<i>n</i> -BuLi	THF/KO ^{<i>t</i>} Bu	-95	102
SH	<i>n</i> -BuLi	cyclohexane/TMEDA ^{<i>a</i>}	0 to 25	103,104
SH	<i>n</i> -BuLi	TMEDA ^{<i>a</i>}	20	105
CF ₃	LTMP ^{<i>e</i>}	THF	-75	106
F	<i>n</i> -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



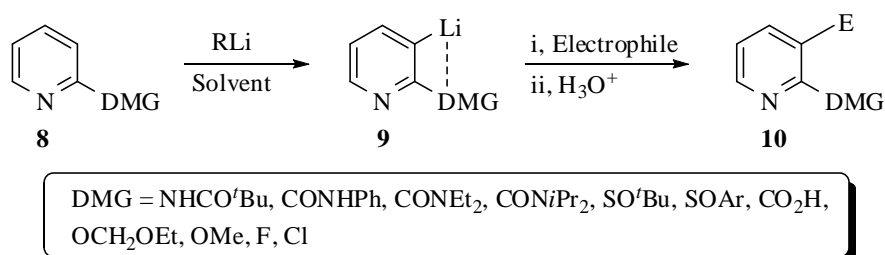
Scheme 3. Directed lithiation of *N,N*-diethyl-1-naphthoamide (**5**).

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^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**.

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

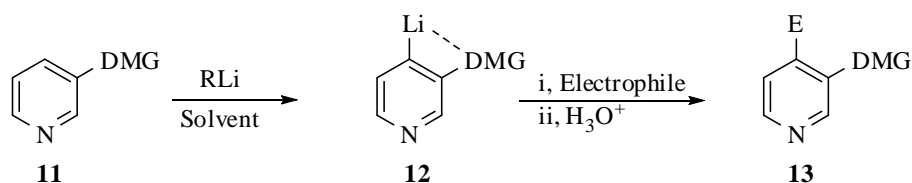
DMG	RLi	Solvent	T (°C)	Reference
NHCO ^t Bu	<i>n</i> -BuLi	THF	0	116,117
CONHPh	<i>n</i> -BuLi	THF	-78	118
CONHPh	LDA	THF	-78	119
CONEt ₂	<i>sec</i> -BuLi	THF	-78	120
CONEt ₂	LDA	Et ₂ O	-78	121
CON ⁱ Pr ₂	<i>n</i> -BuLi	THF	-78	122
CON ⁱ Pr ₂	LDA	Et ₂ O	-78	123

Table 2 (continued)

DMG	RLi	Solvent	T (°C)	Reference
CON ⁱ Pr ₂	<i>sec</i> -BuLi	THF/TMEDA	-78	124
SO ^t Bu	LDA	THF	-78	125
SOAr	LDA	THF	-78	126,127
CO ₂ H	<i>n</i> -BuLi/LTMP	THF	-75 to 0	128,129
OCH ₂ OEt	<i>n</i> -BuLi	THF	-10	130,131
OMe	<i>n</i> -BuLi/LDMAE ^a	hexane	0	132
F	LDA	THF	-75	133
F	PhLi/DIA ^b	THF	-50	134
F	<i>n</i> -BuLi/ ^t BuOK	THF	-75	135
Cl	<i>n</i> -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.



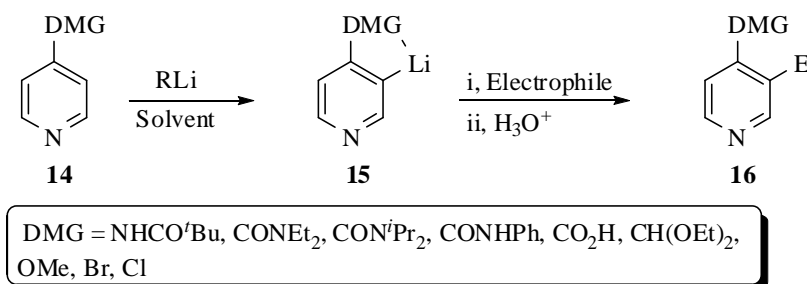
DMG = SO₂NH^tBu, NHCO^tBu, NHCO₂^tBu, CH₂NHCO^tBu, CH₂NHCO₂^tBu, CH₂NHCONMe₂, CONEt₂, CONⁱPr₂, OCSNEt₂, SOAr, CO₂H, OMe, OEt, F, Br, Cl

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 ₂ NH ^t Bu	<i>t</i> -BuLi	THF	-78	139
NHCO ^t Bu	<i>n</i> -BuLi	THF/Et ₂ O/TMEDA	-70 to -30	140
NHCO ^t Bu	<i>n</i> -BuLi	THF/TMEDA	-25	141,142
NHCO ₂ ^t Bu	<i>n</i> -BuLi	THF	-20	142
NHCO ₂ ^t Bu	<i>n</i> -BuLi	Et ₂ O/TMEDA	-10	143
CH ₂ NHCO ^t Bu	<i>t</i> -BuLi	THF	-78	144
CH ₂ NHCO ₂ ^t Bu	<i>t</i> -BuLi	THF	-78	144
CH ₂ NHCONMe ₂	<i>t</i> -BuLi	THF	-78	144
CONEt ₂	LDA	Et ₂ O	-78	121
CONEt ₂	LDA	THF	-78	145
CONEt ₂	<i>t</i> -BuLi	THF/TMEDA	-80	146
CON ⁱ Pr ₂	LDA	Et ₂ O	-78	123
CON ⁱ Pr ₂	LTMP	THF/TMEDA	-80	146-148
OCSNEt ₂	LTMP	THF	-78	149
SOAr	LDA	THF	-75	150
CO ₂ H	<i>n</i> -BuLi/LTMP	THF	-50	128
CO ₂ H	<i>n</i> -BuLi/LTMP	THF	-75	129
OMe	<i>n</i> -BuLi	THF	0	151
OEt	MeLi	THF/Et ₂ O	RT	152
F	<i>n</i> -BuLi/ <i>t</i> -BuOK	THF	-75	135
F	<i>n</i> -BuLi	THF	-75	153
F	<i>n</i> -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.



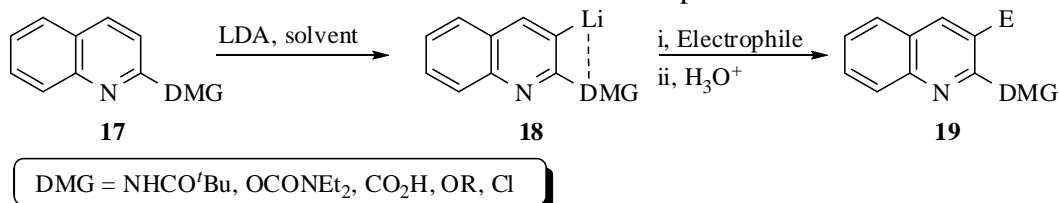
Scheme 6. Directed lithiation of 4-substituted pyridines **14**.

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

DMG	RLi	Solvent	T (°C)	Reference
NHCO ^t Bu	<i>n</i> -BuLi	THF	0	116,160
CONEt ₂	LDA	Et ₂ O	-78	121
CON ^t Pr ₂	LDA	Et ₂ O	-78	123
CONHPh	<i>n</i> -BuLi	THF	-78	118
CO ₂ H	<i>n</i> -BuLi/LTMP	THF	-50 to -25	128
CO ₂ H	<i>n</i> -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	<i>n</i> -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-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}



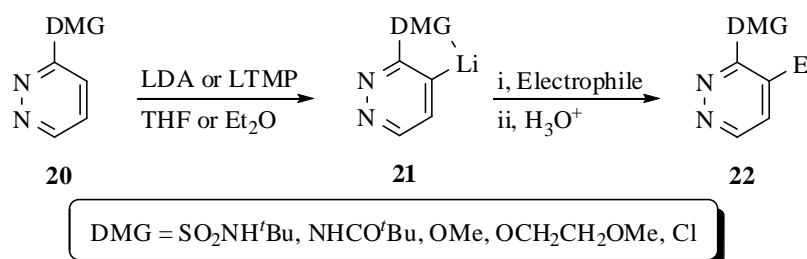
Scheme 7. Directed lithiation of 2-substituted quinolines **17**.

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

DMG	RLi	Solvent	T (°C)	Reference
NHCO ^t Bu	<i>n</i> -BuLi	Et ₂ O	-78	165
OCONMe ₂	LDA	THF	-78	166,167
OCONEt ₂	LDA	THF	-78	166,167
CO ₂ H	LTMP	THF	-50 to -25	169
OMe	<i>n</i> -BuLi	Et ₂ O	0	168
OMe	LTMP	THF	-78	169
OEt	<i>n</i> -BuLi	Et ₂ O	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

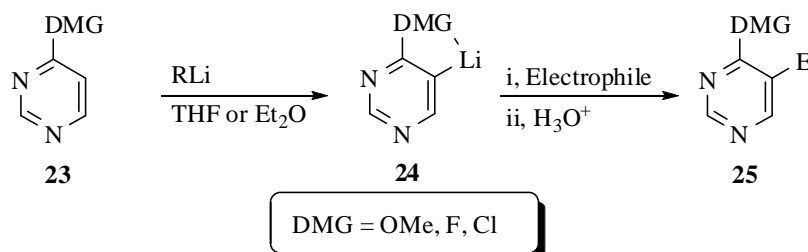
4.3 Directed *ortho*-lithiation of diazines

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 ₂ NH ^t Bu	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 ₂ CH ₂ OMe	LTMP	THF	-75	175
Cl	LDA or LTMP	THF or Et ₂ O	-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}

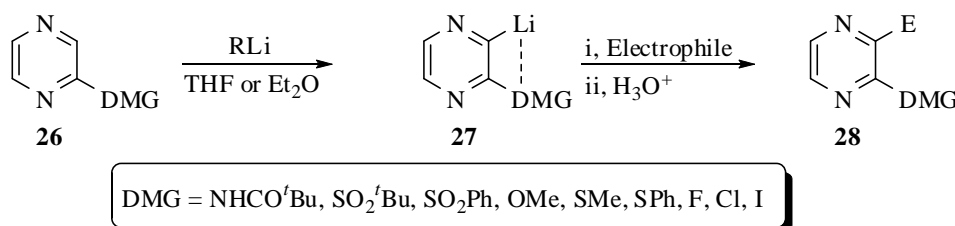


Scheme 9. Directed lithiation of 4-substituted pyrimidines **23**.

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

DMG	Lithium reagent	Solvent	T (°C)	Reference
OMe	LDA	Et ₂ O	0	181
OMe	LTMP	THF	-78 to -70	176,182-184
F	LDA	THF or Et ₂ O	-70	185
Cl	<i>n</i> -BuLi	THF	-75	176
Cl	LDA	Et ₂ O	-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 alkylolithiums in THF or Et₂O as solvent to give the corresponding organolithium intermediate **27** (DMG = NHCO^tBu), which on reactions with electrophiles produced the corresponding 2,3-disubstituted pyrazines.¹⁸⁹



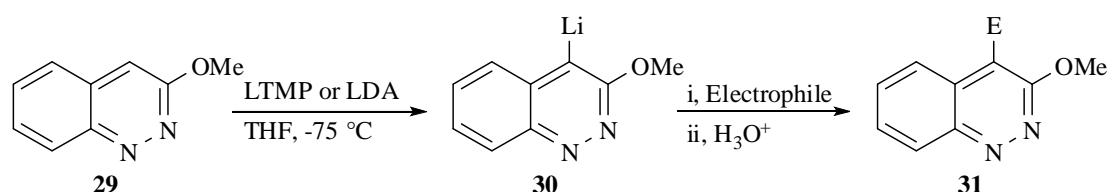
Scheme 10. Directed lithiation of 2-substituted pyrazines **26**.

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

DMG	RLi	Solvent	T (°C)	Reference
NHCO ^t Bu	R = <i>n</i> -Bu, <i>t</i> -Bu or LTMP	THF or Et ₂ O	-70 to 20	189
SO ₂ ^t Bu	LDA or LTMP	THF	-75	174
SO ₂ Ph	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

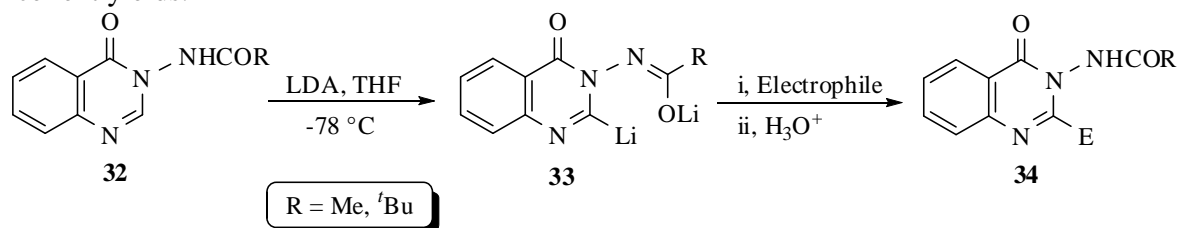
4.4 Directed *ortho*-lithiation of cinnolines

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

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

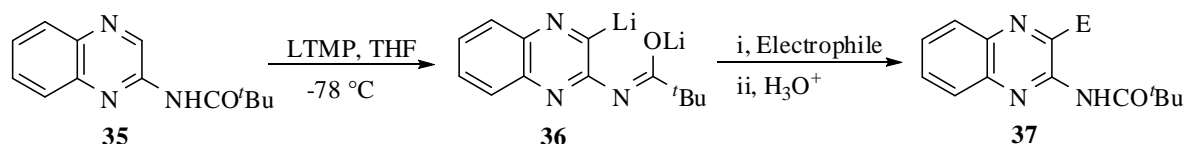
4.5 Directed *ortho*-lithiation of 3*H*-quinazolin-4-ones

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 alkylolithiums led to the production of 1,2-addition products in excellent yields.¹⁹⁷

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

4.6 Directed *ortho*-lithiation of quinoxalines

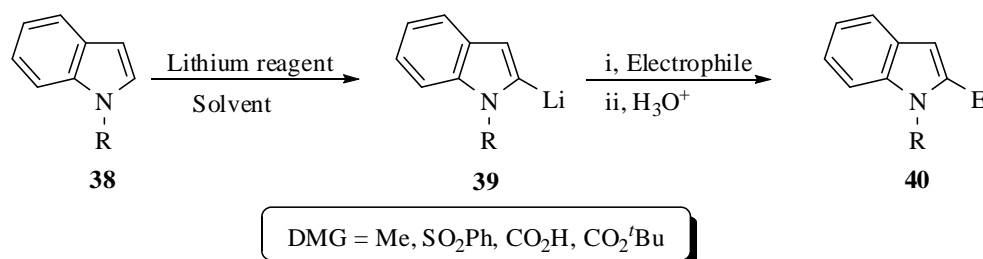
Directed lithiation of 2-(pivaloylamino)quinoxaline (**35**) with LTMP in THF at $-78\text{ }^{\circ}\text{C}$ was regioselective at position 3 to give dilithium reagent **36** (Scheme 13).^{191,200,201} Reactions of **36** with electrophiles produced the corresponding *ortho*-substituted derivatives **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.

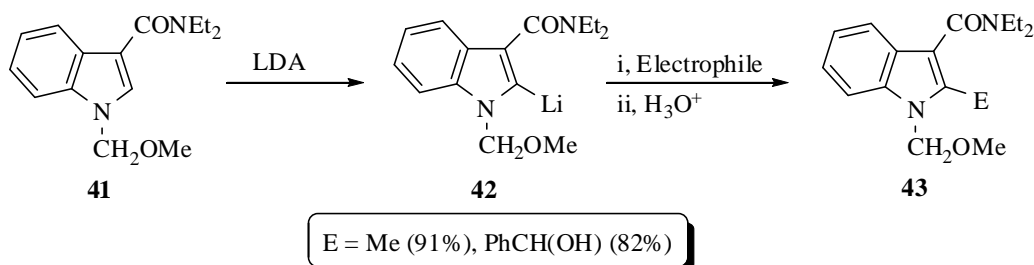


Scheme 14. Directed lithiation of *N*-protected indoles **38**.

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

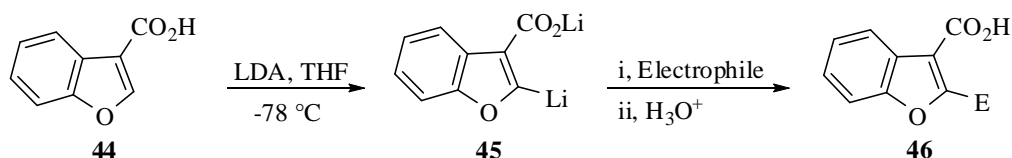
R	Lithium reagent	Solvent	T ($^{\circ}\text{C}$)	Reference
Me	<i>n</i> -BuLi	Et_2O	reflux	204
Me	<i>t</i> -BuLi	THF	-120 to -78	205
SO_2Ph	MeLi	THF	0	203
SO_2Ph	<i>n</i> -BuLi	Et_2O	reflux	206
SO_2Ph	<i>t</i> -BuLi	THF	0	206
SO_2Ph	<i>t</i> -BuLi	THF	-120 to -78	205
CO_2H	<i>t</i> -BuLi	THF	-70	207
CO_2H	<i>t</i> -BuLi	THF	-120 to -78	205
CO_2^tBu	<i>t</i> -BuLi	THF	-78	203
CO_2^tBu	<i>t</i> -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



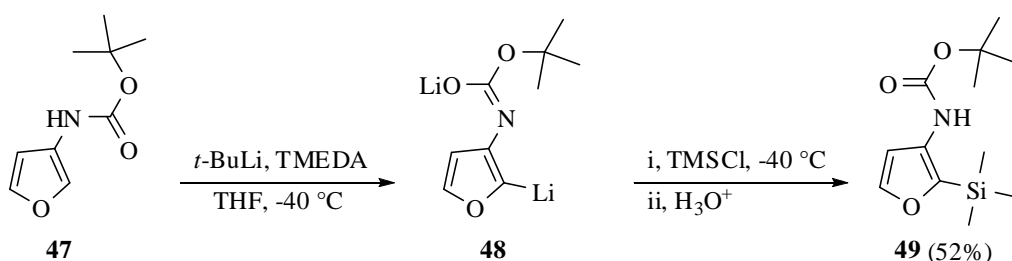
Scheme 15. Lithiation of *N,N*-diethyl-1-(methoxymethyl)-1*H*-indole-3-carboxamide (**41**).

Lithiation of benzofuran-3-carboxylic acid (**44**) with LDA in THF at $-78\text{ }^{\circ}\text{C}$ 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



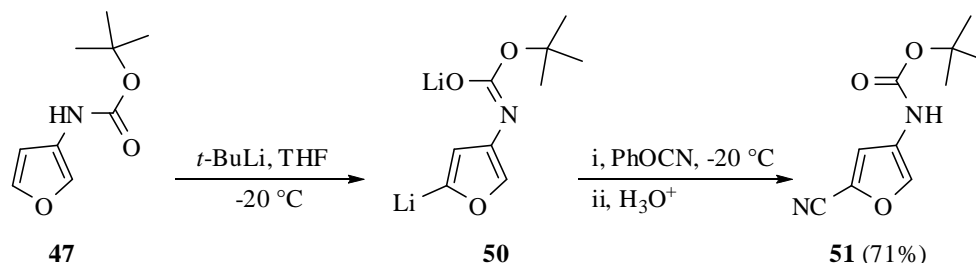
Scheme 16. Lithiation of benzofuran-3-carboxylic acid (**44**).

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 $-40\text{ }^{\circ}\text{C}$ 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



Scheme 17. Regioselective 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 $-20\text{ }^{\circ}\text{C}$, 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}



Scheme 18. Regioselective 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.

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