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DIRECTED LITHIATION AND SUBSTITUTION OF PYRIDINE DERIVATIVES

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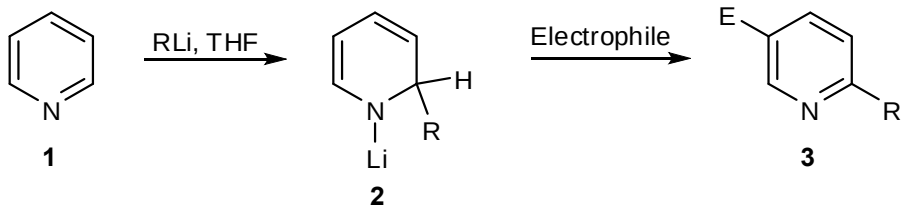
Abstract – Directed lithiation of substituted pyridines containing a directing metalating group (DMG) with a lithium reagent in anhydrous solvent at low temperature gives the corresponding lithium intermediates *in-situ*, which on reactions with electrophiles produce the corresponding substituted derivatives. The method is simple, general, convenient and often high yielding.

CONTENTS

1. INTRODUCTION

Pyridine derivatives are interesting compounds[1] that have a broad range of biological activities.[2,3] Therefore, it is not surprising that a range of substituted pyridine derivatives continue to be synthesised. One useful approach for the synthesis of substituted pyridines involves lithiation followed by treatment with an appropriate electrophile.[4-7] However, reactions of the parent heterocycle, pyridine (**1**), with organolithium reagents (RLi) usually result in addition to the C=N bond of the ring. For example, reaction

of pyridine with PhLi gives 1-lithio-2-phenyl-1,2-dihydropyridine (**2**; R = Ph; Scheme 1).[4,5] When the intermediate **2** (R = Ph) was isolated and allowed to react with iodomethane in tetrahydrofuran (THF) at 0 °C it gave 5-methyl-2-phenylpyridine (**3**; E = Me; R = Ph) in 34% yield[5] due to electrophilic attack of iodomethane on **2** (R = Ph) followed by aromatization. Similar results were obtained when other electrophiles (iodobenzene, benzyl chloride, bromine) were used to give the corresponding 2,5-disubstituted pyridines (R = Ph).[5]



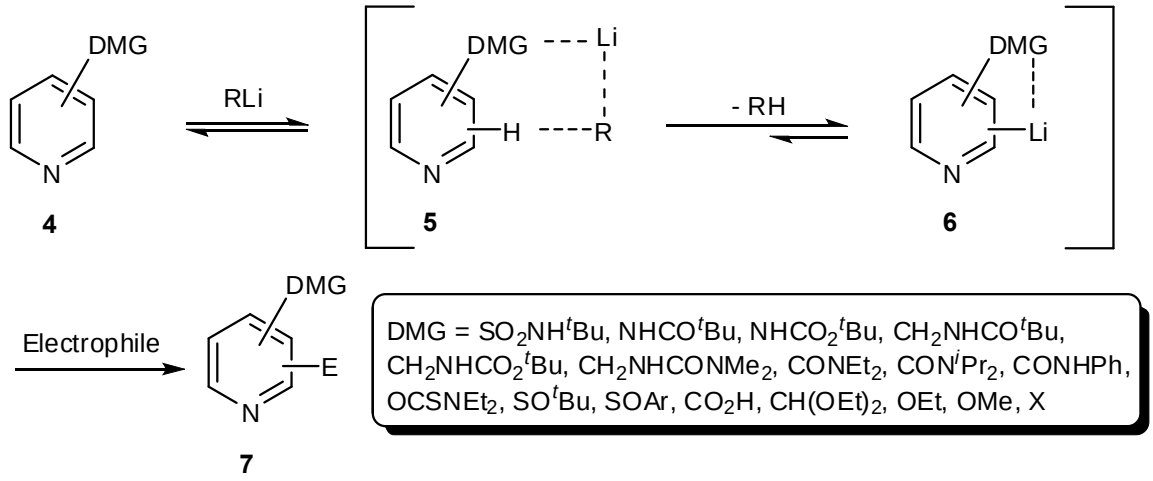
Scheme 1. Addition of organolithium reagents to pyridine (**1**)[4–7]

When the reactions described in Scheme 1 were carried out without isolation of the lithium intermediates 2,5-disubstituted pyridines **3** were obtained in lower yields along with other substituted products.[5-7]

The situation is somewhat different for many substituted pyridines. In such cases, organolithium intermediates can often be generated cleanly and used for the efficient production of *ortho*-disubstituted aromatic products in a simple and convenient process involving directed metalation.[8–21] The reactions of the substituted pyridines with lithium reagents usually take place at low temperatures in anhydrous ether (Et_2O) or THF. When addition of lithium reagent to the C=N bond of the pyridine ring remains a problem, it can often be avoided by use of a hindered lithiating reagent such as lithium diisopropylamide (LDA) or lithium 2,2,6,6-tetramethylpiperidide (LTMP) at low temperature. If all such variations are unsuccessful, an alternative approach is to use bromine-lithium exchange or some similar exchange reaction rather than direct lithiation, but this requires prior synthesis of the appropriately substituted derivative and this is beyond the scope of this review, which concentrates on direct lithiation (*i.e.* hydrogen-lithium exchange).

Directed lithiation of pyridine derivatives **4** possessing a directing metalating group (DMG) involves removal of a proton from a site *ortho* to the DMG by means of a lithiating reagent, which gives the *ortho*-lithium species **6** through initial coordination of the base to the DMG (**5**, Scheme 2). Reaction of **6** with electrophiles gives the corresponding substituted pyridines **7**.[16] The complexation between the reagent and the DMG prior to lithiation brings the lithium reagent into closer proximity to the proton in adjacent position, which is then selectively removed.[22,23] The DMG should be a poor electrophilic site for

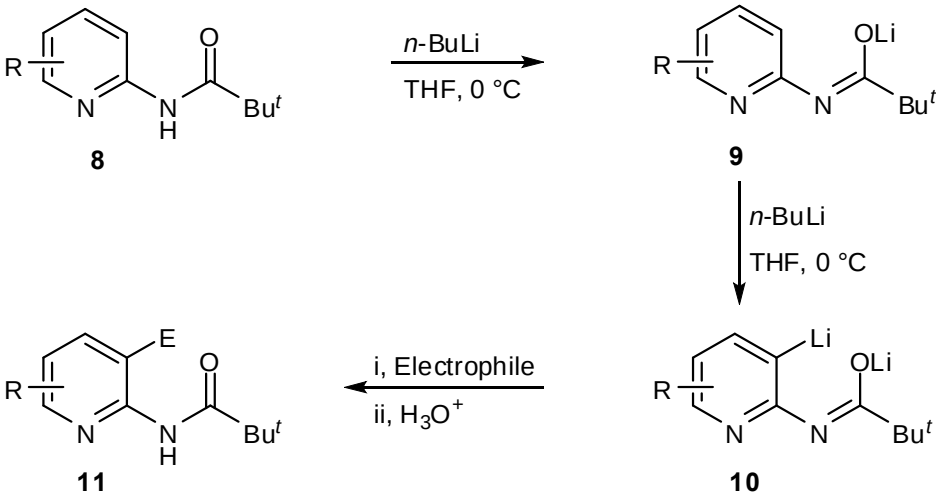
attack by the lithium reagent and at the same time a good coordinating site for the lithium reagent. Strong DMGs that encourage *ortho*-lithiation include SO_2NR_2, NHCOR, $CONR_2$, CSNHR, CONHR, $OCONR_2$, CO_2R, CH_2NHR, OCH_2OMe. Moderate DMGs include OR, NR_2, SR, CF_3 and F, while weak DMGs include CH_2OH and $CH(OR)_2$.[24]



Scheme 2. Directed lithiation and substitution of substituted pyridines **4**

2. DIRECTED LITHIATION AND SUBSTITUTION OF 2-SUBSTITUTED PYRIDINES

Directed lithiation of pyridines containing a DMG at the C-2 (α) position takes place at the 3-position to provide the corresponding lithium intermediates, which on further reactions with electrophiles give the corresponding substituted derivatives.[25–47] For example, C-3 lithiation of 2-(pivaloylamino)pyridines (**8**, Scheme 3) has been achieved with *n*-BuLi (2.2 mole equivalents) in anhydrous THF at 0 or –50 °C to monolithium intermediates **9** and then dilithium reagents **10**, which on reactions with electrophiles gave corresponding substituted pyridines **11** (Scheme 3) in 40–94% yields (Table 1).[25,26]



Scheme 3. Directed lithiation and substitution of 2-(pivaloylamino)pyridines **8**[25,26]

Table 1. Lithiation and substitution of **8** according to Scheme 3[25,26]

R	Electrophile	E	Yield (%)[a]
H	D_2O	D	87
H	MeI	Me	72
H	Me_3SiCl	Me_3Si	86
H	Me_2NCHO	CHO	54
H	$(MeS)_2$	MeS	67
H	$EtCO_2Cl$	CO_2Et	65
H	PhCHO	PhCH(OH)	63
H	$(^iPr_2NCS_2)_2$	$SCSN^iPr_2$	73
4-Me	$(MeS)_2$	MeS	40 (74)[b]
5-Me	$(MeS)_2$	MeS	94
6-Me	$(MeS)_2$	MeS	59 (74)[b]
5-Cl	$(MeS)_2$	MeS	86[c]
6-Cl	$(MeS)_2$	MeS	78[d]

[a] Standard conditions involve *n*-BuLi, THF, 0 °C; [b] Figures in parentheses are for reactions involving *t*-butyllithium (*t*-BuLi), –78 °C, Et_2O; [c] *t*-BuLi, –78 °C, THF; [d] *n*-BuLi, –20 °C, THF.

Carbonylation of **10** (R = H) with carbon monoxide at 0 °C gave 3-*tert*-butyl-7-azadioxindole (**12**; Figure in 62% yield following cyclization and rearrangement of the initial carbon monoxide adduct.[20]

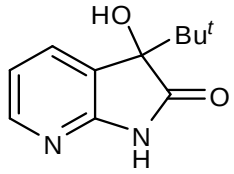


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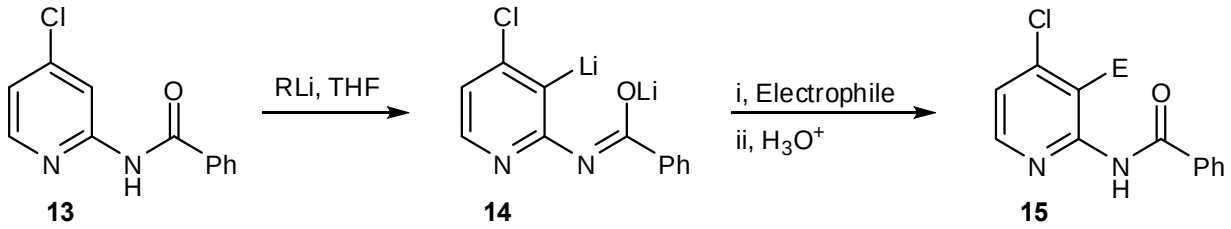
Figure 1. Structure of 3-*tert*-butyl-7-azadioxindole (**12**)[20]

Lithiation of 6-fluoro-2-(pivaloylamino)pyridine with *n*-BuLi (two mole equivalents) at –78 to 0 °C in followed by reaction with dimethyl disulfide gave a mixture of products due to substitution at the (45%) and the 5-position (30%).[25] However, when *t*-BuLi was used at –78 °C in Et_2O, substitution took place exclusively at the 3-position to give 6-fluoro-3-methylthio-2-(pivaloylamino)pyridine in 70%

Lithiation of 2-(benzoylamino)-4-chloropyridine (**13**) with two mole equivalents of LDA in THF at –78 produced the 3-lithio reagent **14**, which on reactions with electrophiles gave the corresponding 2,3,4-trisubstituted pyridines (**15**; Scheme 4 and Table 2).[27] Lithiation of **13** was also successful with *n*-BuLi (2.1 mole equivalents) at –20 to –78 °C.[28]

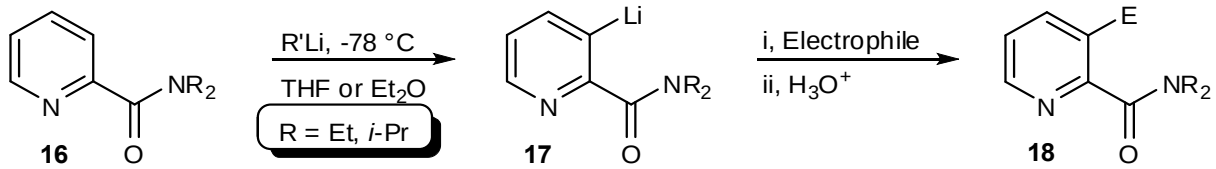


Scheme 4. Directed lithiation and substitution of 2-(benzoylamino)-4-chloropyridine (**13**)[27,28]

Table 2. Lithiation and substitution of **13** according to Scheme 4[27,28]

RLi	Electrophile	E	Yield (%)
LDA	MeI	Me	67
LDA	Bu_3SnCl	Bu_3Sn	84
LDA	Me_3SnCl	Me_3Sn	87
LDA	I_2	I	88
LDA	CO_2	CO_2H	42
n-BuLi	Me_3SnCl	Me_3Sn	48
n-BuLi	MeI	Me	65
n-BuLi	Me_2NCHO	CHO	19

Directed lithiation of *N,N*-dialkylpicolinamides **16** (Scheme 5) with 1.1 mole equivalents of *sec*-butyllithium (*sec*-BuLi) or LDA in THF or Et_2O at –78 °C, followed by reactions with electrophiles, gave the corresponding 2,3-disubstituted derivatives **18** (Table 3) *via* lithium intermediates **17**.[29–31]

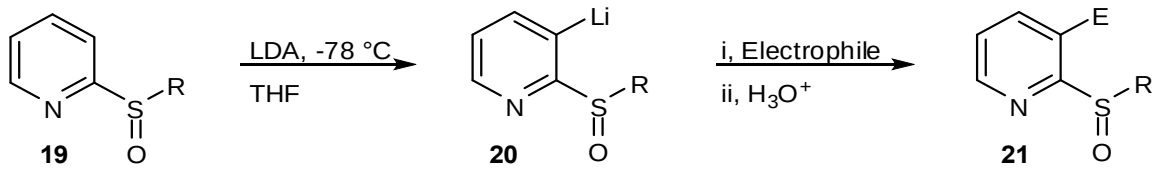


Scheme 5. Directed lithiation and substitution of *N,N*-dialkylpicolinamides **16**[29–31]

Table 3. Lithiation and substitution of **16** according to Scheme 5[29–31]

R	R′Li	Electrophile	E	Yield (%)
Et	*sec*-BuLi	MeI	Me	53
Et	*sec*-BuLi	PhCHO	PhCH(OH)	50
i-Pr	LDA	MeOD	D	55
i-Pr	LDA	Ph_2CO	$Ph_2C(OH)$	81
i-Pr	LDA	Me_2NCHO	CHO	35
i-Pr	LDA	$PhCONMe_2$	COPh	52

Directed lithiation and substitution of 2-(substituted sulfinyl)pyridines **19** was successful with LDA (one mole equivalent) in THF at –78 °C to give the corresponding substituted derivatives **21** (Scheme 6) in 20–93% yields (Table 4).[32–35]

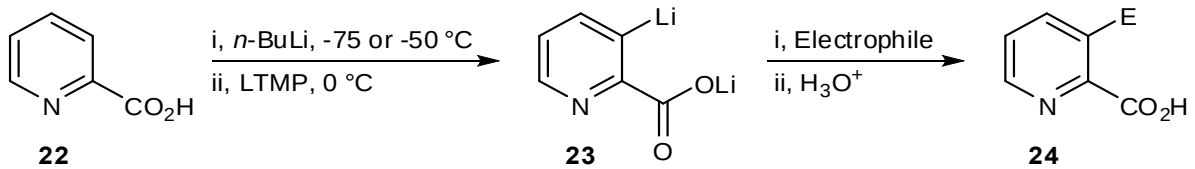


Scheme 6. Directed lithiation and substitution of **19**[32–35]

Table 4. Lithiation and substitution of **19** according to Scheme 6[32–35]

R	Electrophile	E	Yield (%)
t-Bu	MeOD	D	75
t-Bu	MeI	Me	82
t-Bu	PhCHO	PhCH(OH)	74
t-Bu	Et_2NCOCl	Et_2NCO	20
t-Bu	$B(OMe)_3$	OH	70
t-Bu	I_2	I	35
t-Bu	Me_3SiCl	Me_3Si	70
t-Bu	Bu_3SnCl	Bu_3Sn	90
Ph	MeCHO	MeCH(OH)	81
Ph	PhCHO	PhCH(OH)	87
Ph	PhCOMe	PhC(OH)Me	90
1-naphthyl	PhCHO	PhCH(OH)	93
2-methoxynaphth-1-yl	PhCHO	PhCH(OH)	81
O-pyrrolidinyl	Ph_2CO	$Ph_2C(OH)$	70
O-piperidyl	Ph_2CO	$Ph_2C(OH)$	90
O-morpholinyl	Ph_2CO	$Ph_2C(OH)$	69

Directed lithiation of pyridine-2-carboxylic acid (**22**) has been achieved by the use of *n*-BuLi (one mole equivalent) at –75 or –50 °C followed by the addition of LTMP (three mole equivalents) at 0 °C in THF (Scheme 7; Table 5).[36,37]

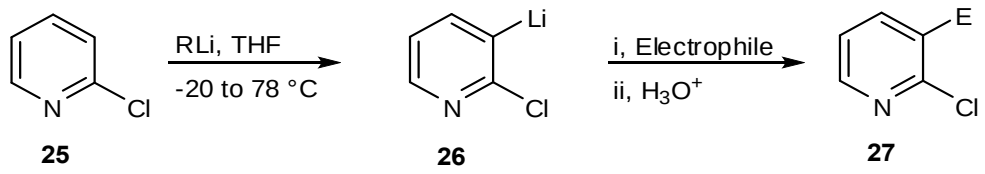


Scheme 7. Directed lithiation and substitution of pyridine-2-carboxylic acid (**22**)[36,37]

Table 5. Lithiation and substitution of **22** according to Scheme 7[36,37]

Electrophile	E	Yield (%)
D_2O	D	81
CO_2	CO_2H	85
C_2Cl_6	Cl	72
I_2	I	65

Lithiation of 2-halopyridines has received much attention.[38–44] For example, lithiation of 2-chloropyridine (**25**) with three mole equivalents of LTMP at –78 °C in THF followed by reaction with DCl/D_2O gave 2,3-disubstituted derivative **27** (E = D; Scheme 8) in 70% yield, indicating that lithium reagent **26** was formed *in-situ*.[38] Lithiation was found to be general with the use of 2.0 mole equivalents of *n*-BuLi (Table 6).[39] Moreover, directed lithiation of **25** has been achieved with one mole equivalent of LDA at –78 °C in THF.[40] By contrast, lithiation of **25** with *n*-BuLi–LiDMAE (lithium 2-dimethylaminoethoxide; 3.0 mole equivalents) at –78 °C in hexane followed by reaction with representative electrophiles gave the corresponding 2,6-disubstituted derivatives in 65–98% yields.[38] It seems that such a lithium reagent lithiation to the 6-position as a result of a combination of high basicity, a low propensity for coordination the DMG, and the steric bulk of the reagent.



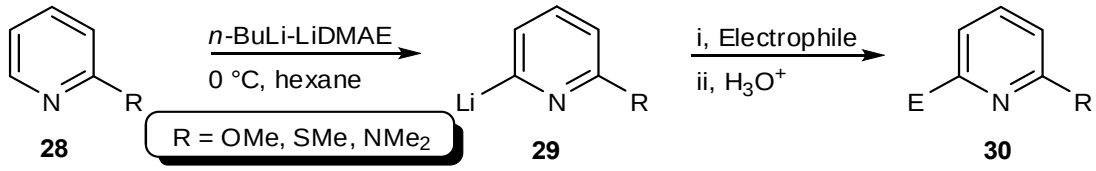
25 **26** **27**

Scheme 8. Directed lithiation and substitution of 2-chloropyridine (**25**)[38–40]

Table 6. Lithiation and substitution of 2-chloropyridine (**25**) according to Scheme 8[38–40]

RLi (T °C)	Electrophile	E	Yield (%)
LTMP (–78)	DCl/D_2O	D	70
n-BuLi (–70)	DCl/D_2O	D	75
n-BuLi (–40)	Me_2NCHO	CHO	50
n-BuLi (–70)	Me_3SiCl	Me_3Si	75
n-BuLi (–70)	MeI	Me	80
n-BuLi (–70)	CH_2=CH-CH_2I	CH_2=CH-CH_2	45
n-BuLi (–70)	MeCHO	MeCH(OH)	75
n-BuLi (–70)	$(CH_2)_5CO$	$(CH_2)_5C(OH)$	70
n-BuLi (–70)	PhCHO	PhCH(OH)	70
n-BuLi (–70)	Ph_2CO	$Ph_2C(OH)$	55
n-BuLi (–70)	EtCOEt	EtC(OH)Et	70
n-BuLi (–40)	Br_2	Br	30
n-BuLi (–70)	I_2	I	60
LDA (–78)	Me_3SiCl	Me_3Si	74

Lithiation of 2-methoxypyridne (**28**; R = OMe) with LTMP (3.2 mole equivalents) at –78 °C in THF followed by reaction with DCl/D_2O gave the corresponding 3-deuteriated derivative in 92% yield.[38] However, the use of *n*-BuLi–LiDMAE (3 mole equivalents) in hexane at –78 °C followed by reaction DCl/D_2O again diverted the reaction to the 6-deuteriated derivative **30** (Scheme 9: R = OMe, E = D) in yield.[38,45–47] The latter reaction was found to be general with other electrophiles.[38,45–47] The effect of the amount of *n*-BuLi–LiDMAE on the lithiation of 2-methoxypyridne (**28**; R = OMe) is interesting. With 4 equivalents of *n*-BuLi–LiDMAE at 0 °C in hexane the 6-substituted derivatives **30** (Scheme 9) were obtained in 30–71% yields along with 2-butyl-2,5-dihydro-6-methoxypyridine (14–64%), formed by addition of *n*-BuLi to the imine bond of the pyridine nucleus.[45]



Scheme 9. Lithiation and substitution of **28**[45]

Table 7. Lithiation and substitution of **28** using *n*-BuLi–LiDMAE (2 mole equivalents) according to Scheme 9 in the presence of lithium bromide as an additive[45]

R	Electrophile	E	Yield (%)
OMe	MeI	Me	59
OMe	Me_2SO_4	Me	62
OMe	EtI	Et	54
OMe	Et_2SO_4	Et	60
OMe	$Me(CH_2)_5I$	$Me(CH_2)_5$	40
OMe	Me_3SiCl	Me_3Si	75 (60)[a]
OMe	$(MeS)_2$	MeS	72 (63)[a]
OMe	DCl/D_2O	D	41 (34)[a]
OMe	MeCOMe	MeC(OH)Me	54 (43)[a]
OMe	EtCOMe	EtC(OH)Me	80
OMe	$(CH_2)_4CO$	$(CH_2)_4C(OH)$	63
OMe	PhCOPh	PhC(OH)Ph	43
OMe	Bu^tCHO	$Bu^tCH(OH)$	88
OMe	$Me(CH_2)_5CHO$	$Me(CH_2)_5CH(OH)$	53
SMe	Me_3SiCl	Me_3Si	80
SMe	MeI	Me	62
SMe	EtCOMe	EtC(OH)Me	75
NMe_2	Me_3SiCl	Me_3Si	52
NMe_2	MeI	Me	45
NMe_2	EtCOMe	EtC(OH)Me	44

[a] The figure in parentheses is the yield obtained when no lithium bromide was used.

When two mole equivalents of *n*-BuLi–LiDMAE were used in the presence of lithium bromide as an additive, the 2,6-disubstituted derivatives **30** were obtained in better yields (41–88%, Table 7) along with 2-butyl-2,5-dihydro-6-methoxypyridine (5–53%).[45] Under similar conditions, lithiation of 2-(methylthio)- and 2-(dimethylamino)- pyridines followed by reactions with electrophiles provided **30** (Scheme 9; R = SMe and R = NMe_2) in 44–80% yields (Table 7).[45]

3. DIRECTED LITHIATION AND SUBSTITUTION OF 3-SUBSTITUTED PYRIDINES

In contrast to 2-substituted pyridines, 3-substituted pyridines have two possible sites for DMG-encouraged lithiation, namely the 2- and 4-positions. Lithiation at the 2-position could benefit from the stabilisation effect of the pyridine nitrogen atom as well as the DMG effect, while lithiation at the 4-position would benefit only from the DMG effect (Figure 2). Therefore, a mixture of products might be expected as a result of such lithiation and the 2-position might be expected to be favored.

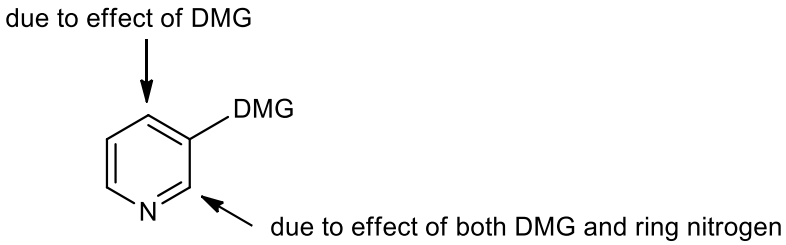


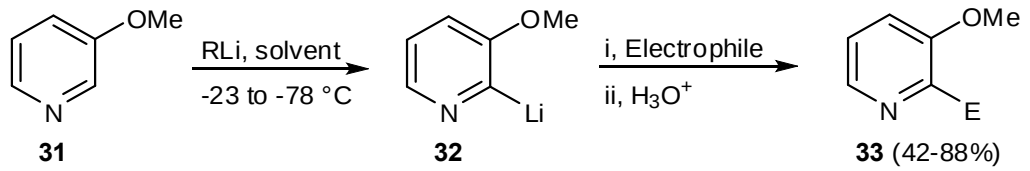
Figure 2. Possible positions for lithiation of 3-substituted pyridines

In the case of lithiation of 3-methoxypyridine (**31**) it is indeed the case that substitution mainly takes place at the 2-position to give the corresponding 2,3-disubstituted pyridines **33** (Scheme 10; Table 8).[48,49] The yields of 2-substituted products are dependent on the reaction conditions and the type of lithium reagent used, but the formation of lithium intermediate **32** is clearly favored.

Table 8. Lithiation and substitution of 3-methoxypyridine (**31**) according to Scheme 10[48,49]

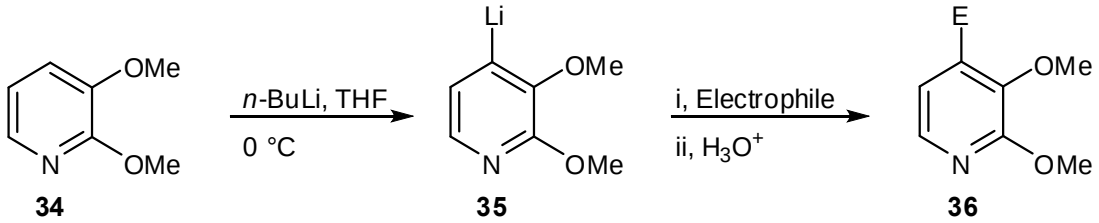
RLi	Solvent	T (°C)	Electrophile	E	Yield (%)
n-BuLi-LiDMAE	hexane	–78	$(MeS)_2$	MeS	88
n-BuLi-TMEDA	THF	–40	MeCHO	MeCH(OH)	49
Mesityllithium	THF	–23	$(MeS)_2$	MeS	82
Mesityllithium	THF	–23	PhCHO	PhCH(OH)	73
Mesityllithium	THF	–23	Me_2NCHO	CHO	85
LDA	THF	–42	Me_3SiCl	Me_3Si	42[a]

[a] 4-Substituted product was also obtained in 33% yield due to lithiation and substitution at the 4-position.



Scheme 10. Directed lithiation and substitution of 3-methoxypyridine (**31**)[48,49]

However, the presence of an additional 2-methoxy group in 2,3-dimethoxypyridine (**34**) causes lithiation with *n*-BuLi (2.2 mole equivalents) at 0 °C in THF to be diverted to the 4-position to give lithium intermediate **35**, which on reactions with electrophiles gave 2,3,4-trisubstituted pyridines **36** (Scheme 11) in 60–99% yields (Table 9).[50]

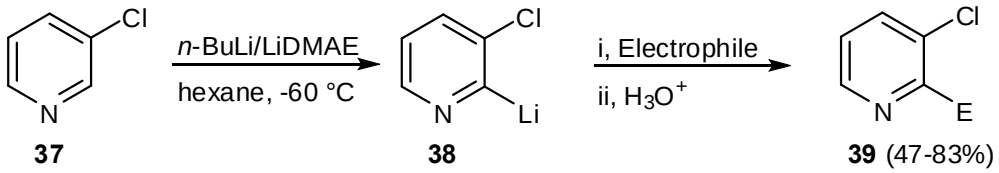


Scheme 11. Directed lithiation and substitution of 2,3-dimethoxypyridine (**34**)[50]

Table 9. Lithiation and substitution of **34** according to Scheme 11[50]

Electrophile	E	Yield (%)
DCl	D	99
PhCHO	PhCH(OH)	71
BrCN	Br	60
$B(OMe)_3$	OH	64

The site of lithiation for 3-chloropyridine (**37**) is much more variable and is highly influenced by the type of lithium reagent, temperature, and/or solvent.[40,41,51,57] For example, lithiation of **37** with *n*-BuLi/TMEDA (one mole equivalent) in diethyl ether at –60 °C for 1 h followed by reaction with trimethylsilyl chloride gave a mixture of products due to lithiation and substitution at the 2- and 4-positions in 60 and 9% yields, respectively.[55,56] However, use of *n*-BuLi/18-crown-8 (one mole equivalent) in diethyl ether at –60 °C for 1 h followed by reaction with trimethylsilyl chloride gave the corresponding 2,3- and 3,4-disubstituted products in 20 and 75% yields, respectively,[55,56] while lithiation of **37** with *n*-BuLi/LiDMAE (three mole equivalents) in hexane at –60 °C for 1 h followed by reactions with several electrophiles gave exclusively the corresponding 2,3-disubstituted pyridines **39** (Scheme 12) in 47–83% yields (Table 10).[54]



37 **38** **39** (47-83%)

Scheme 12. Lithiation and substitution of 3-chloropyridine (**37**) with BuLi/LiDMAE[54]

Table 10. Lithiation and substitution of 3-chloropyridine (**37**) according to Scheme 12[54]

Electrophile	E	Yield (%)
DCl/D_2O	D	66
$(MeS)_2$	MeS	83
Bu^tCHO	$Bu^tCH(OH)$	60
$PhCONMe_2$	PhCO	69
I_2	I	66
CBr_4	Br	47
C_2Cl_6	Cl	60

Predominant lithiation at the 2-position with *n*-BuLi/LiDMAE presumably reflects the greater stability of the 2-lithio reagent **38**, which may be further enhanced *via* complexation with an extra molecule of the lithiating reagent (Figure 3).[54]

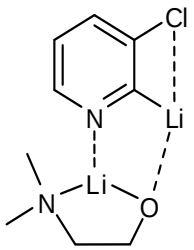
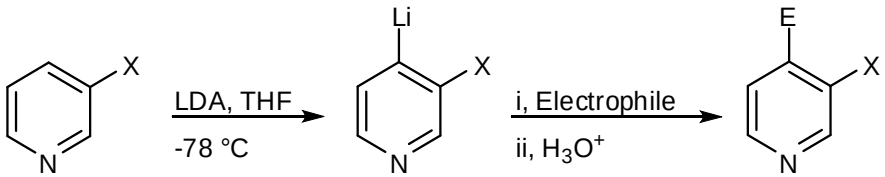


Figure 3. Possible stabilization of **38** by complexation with LiDMAE

On the other hand, lithiation of 3-halopyridines **40** with LDA in THF at –78 °C took place predominantly the 4-position (Scheme 13, Table 11).[30,40,54]



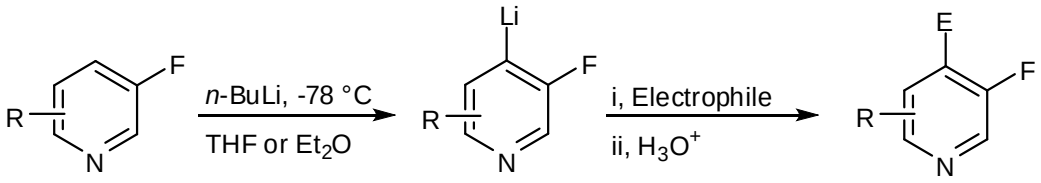
40 **41** **42**

Scheme 13. Lithiation and substitution of 3-halopyridines **40** with LDA[30,40,54]

Table 11. Lithiation and substitution of **40** according to Scheme 13[30,40,54]

X	Electrophile	E	Yield (%)
Cl	Me_3SiCl	Me_3Si	80
Cl	PhCHO	PhCH(OH)	57
Cl	Ph_2CO	$Ph_2C(OH)$	65
Cl	Me_2CO	$Me_2C(OH)$	28
Cl	Me_3SiCl	Me_3Si	96
Cl	$(PhS)_2$	PhS	75
Cl	$PhSO_2Cl$	$PhSO_2$	80
Cl	Br_2	Br	16
Cl	I_2	I	65
Br	$(PhS)_2$	PhS	61
Br	MeCHO	MeCH(OH)	79
Br	PhCOMe	PhC(OH)Me	36
F	Me_3SiCl	Me_3Si	87
F	I_2	I	50

For the 3-fluoropyridine case, the presence of an additional 5-fluoro substituent or a (2-(*tert*-butylcarbonylamino)phenyl) group at the 2-position and use of *n*-BuLi in THF or Et_2O at –78 °C also results in lithiation of 3-fluoropyridines **43** at the 4-position (Scheme 14, Table 12).[51,52]



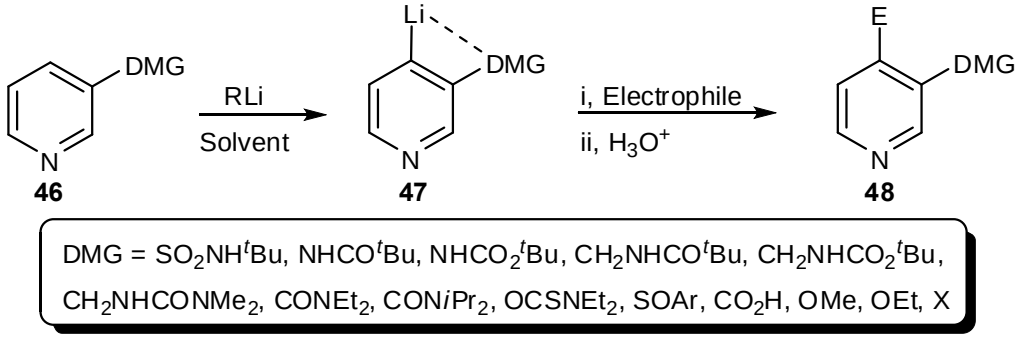
43 **44** **45**

Scheme 14. Directed lithiation and substitution of 3-fluoropyridines **43**[51,52]

Table 12. Lithiation and substitution of **43** according to Scheme 14[51,52]

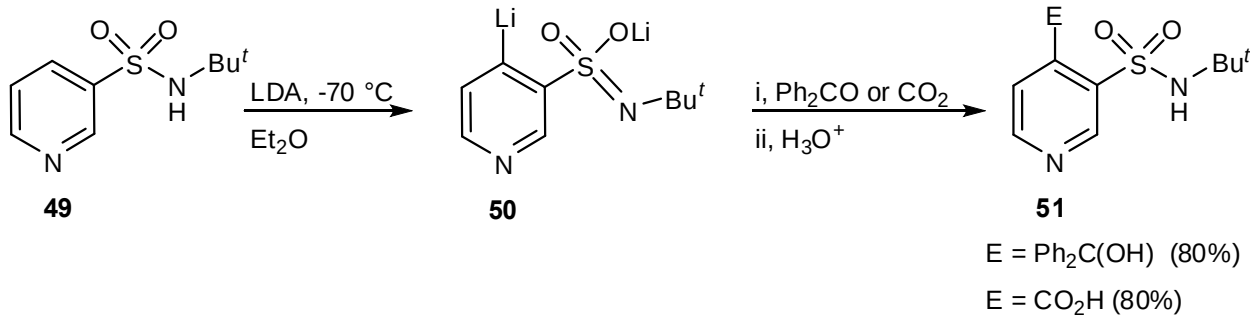
R	Electrophile	E	Yield (%)
5-F	Me_3SiCl	Me_3Si	65
2-[2-(Bu^tCONH)C_6H_4]	D_2O	D	95
2-[2-(Bu^tCONH)C_6H_4]	I_2	I	98
2-[2-(Bu^tCONH)C_6H_4]	C_2Cl_6	Cl	70
2-[2-(Bu^tCONH)C_6H_4]	MeI	Me	81
2-[2-(Bu^tCONH)C_6H_4]	EtI	Et	65
2-[2-(Bu^tCONH)C_6H_4]	MeCHO	MeCH(OH)	83
2-[2-(Bu^tCONH)C_6H_4]	PhCHO	PhCH(OH)	65
2-[2-(Bu^tCONH)C_6H_4]	Ph_2CO	$Ph_2C(OH)$	35
2-[2-(Bu^tCONH)C_6H_4]	Me_3SiCl	Me_3Si	62
2-[2-(Bu^tCONH)C_6H_4]	CO_2	CO_2H	41
2-[2-(Bu^tCONH)C_6H_4]	HCO_2Et	CHO	46

Similarly, and despite the presumed additional stability of the 2-lithio species, directed lithiation of many 3-substituted pyridines **46** takes place predominately at C-4 to afford the corresponding lithium intermediates **47** (Scheme 15), reactions of which with electrophiles give the corresponding 3,4-disubstituted pyridines **48**.[25,30,31,35–38,58–68] It seems likely, therefore, that in these cases the kinetic lithiation products are being generated and trapped before they rearrange to the more stable 2-lithio



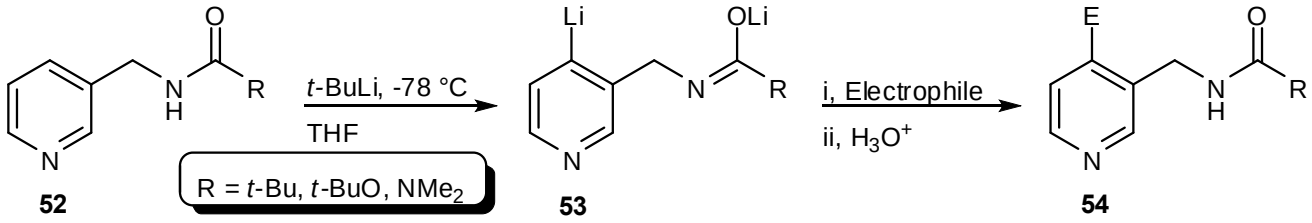
Scheme 15. Directed lithiation and substitution of 3-substituted pyridines **46**

For example, lithiation of *N*-*tert*-butylpyridine-3-sulfonamide (**49**) was achieved with LDA (3.0 mole equivalents) at –70 °C in Et_2O to give lithium reagent **50**.[35] Reactions of **50** with benzophenone and dioxide as representative electrophiles gave **51**, in both cases in 80% yield (Scheme 16).[35]



Scheme 16. Directed lithiation and substitution of **49**[35]

Directed lithiation of *N*-(pyridin-3-ylmethyl)pivalamide (**52**; R = *t*-Bu), *tert*-butyl *N*-(pyridin-3-ylmethyl)carbamate (**52**; R = *t*-BuO) and *N*′-(pyridin-3-ylmethyl)-*N*,*N*-dimethylurea (**52**; R NMe_2) with 3.3 mole equivalents of *t*-BuLi at –78 °C in THF gave the corresponding 4-lithio **53** (Scheme 17).[62] Reactions of **53** with several electrophiles afforded **54** in high yields (Table 13). By contrast, lithiation of **52** with LDA at –20 to 0 °C in THF followed by reactions with representative electrophiles gave side-chain substituted products in 52–75% yields.[62]

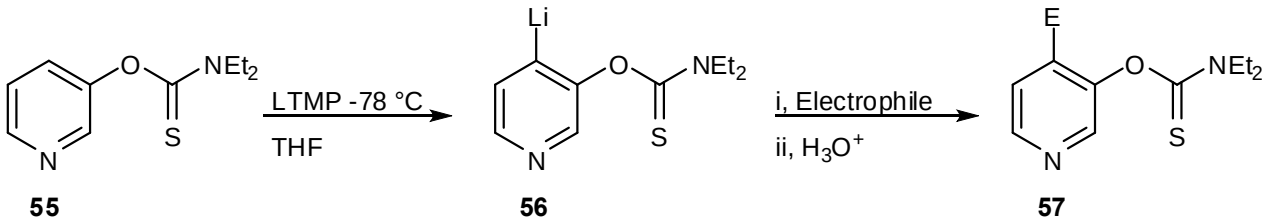


Scheme 17. Directed lithiation and substitution of **52**[62]

Table 13. Lithiation and substitution of **52** according to Scheme 17[62]

R	Electrophile	E	Yield (%)
t-Bu	Ph_2CO	$Ph_2C(OH)$	88
t-Bu	Me_2CO	$Me_2C(OH)$	91
t-Bu	4-$MeOC_6H_4CHO$	4-$MeOC_6H_4CH(OH)$	89
t-Bu	4-$Me_2NC_6H_4CHO$	4-$Me_2NC_6H_4CH(OH)$	85
t-Bu	EtI	Et	90
t-BuO	Ph_2CO	$Ph_2C(OH)$	88
t-BuO	PhCOMe	PhC(OH)Me	81
t-BuO	$(CH_2)_5CO$	$(CH_2)_5C(OH)$	84
t-BuO	PhCHO	PhCH(OH)	80
NMe_2	Ph_2CO	$Ph_2C(OH)$	66

Directed lithiation of *O*-pyridin-3-yl diethylcarbamothioate (**55**; Scheme 18) with LTMP (1.1 mole equivalents) in THF at –78 °C followed by reactions with electrophiles gave **57** (Table 14) *via* lithium intermediate **56**.[68]



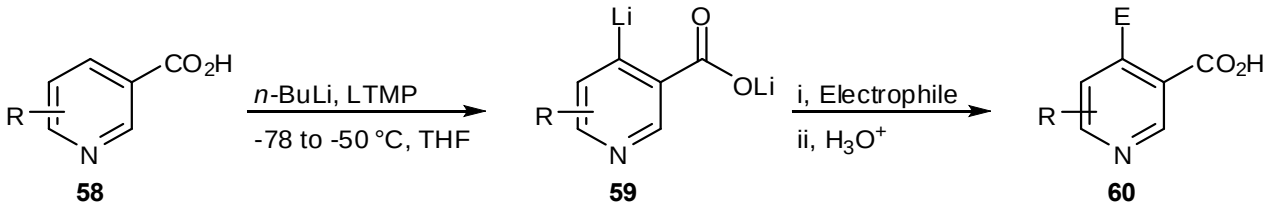
Scheme 18. Directed lithiation and substitution of **55**[68]

Table 14. Lithiation and substitution of **55** according to Scheme 18[68]

Electrophile	E	Yield (%)
Me_3SiCl	Me_3Si	87
$(PhS)_2$	PhS	82
PhCHO	PhCH(OH)	85
2-furfural	CH(OH)(2-furyl)	91

Directed lithiation of nicotinic acids **58** (Scheme 19) with LTMP (two mole equivalents) or a mixture of *n*-BuLi (one mole equivalent) and LTMP (three mole equivalents) at –75 to –50 °C in THF followed by

reactions with electrophiles gave **60** (Table 15).[36,37] This product is still the major one isolated even when there is a Cl or Br substituent elsewhere in the molecule. Lithiation of **58** (R = 5-Br) followed by reaction with benzaldehyde under similar conditions and then treatment with acetic acid gave the corresponding lactone *via* cyclization of the initially produced substituted derivative.[36,37]



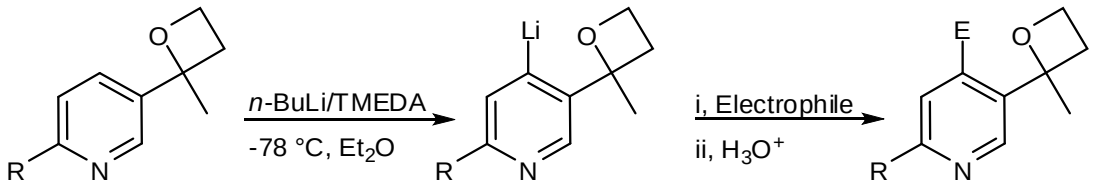
58 **59** **60**

Scheme 19. Directed lithiation and substitution of nicotinic acids **58**[36,37]

Table 15. Lithiation and substitution of nicotinic acids **58** according to Scheme 19[36,37]

R	Electrophile	E	Yield (%)
H	C_2Cl_6	Cl	79
H	I_2	I	71
H	D_2O	D	45
H	CO_2	CO_2H	73
2-Cl	D_2O	D	57
2-Cl	CO_2	CO_2H	69
6-Cl	D_2O	D	61
6-Cl	CO_2	CO_2H	73
5-Br	D_2O	D	58
5-Br	CO_2	CO_2H	60
5-Br	I_2	I	80

Similarly, directed lithiation of 3-(2-methyloxetan-2-yl)pyridines **61** with *n*-BuLi (1.4 mole equivalents) and TMEDA (3.0 mole equivalents) in Et_2O at –78 °C gave the corresponding 4-lithio intermediates **62** even with a chloro or methoxy substituent in the 6-position (Scheme 20).[69] Reactions of **62** with various electrophiles gave substituted pyridines **63** in 50–95% yields (Table 16).[69]



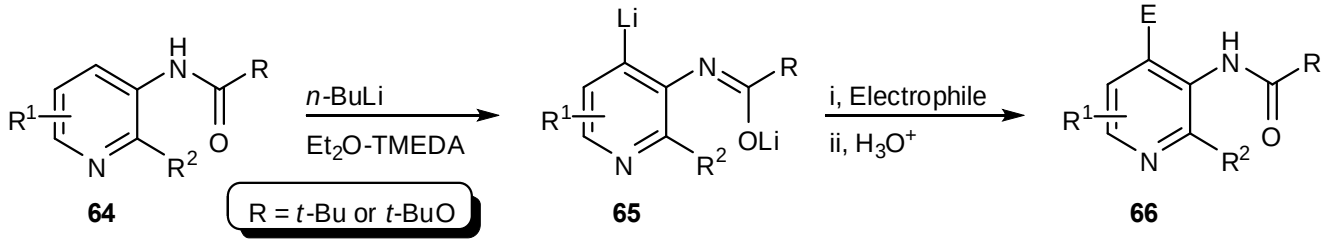
61 **62** **63**

Scheme 20. Directed lithiation and substitution of 3-(2-methyloxetan-2-yl)pyridines **61**[69]

Table 16. Lithiation and substitution of **61** according to Scheme 20[69]

R	Electrophile	E	Yield (%)
H	Me_3SiCl	Me_3Si	78
H	$(PhS)_2$	PhS	91
H	Me_2NCHO	CHO	78
H	PhNCO	PhNHCO	80
H	CNOCOEt	EtOCO	77
H	MeCHO	MeCH(OH)	70
H	4-ClC_6H_4CHO	4-$ClC_6H_4CH(OH)$	90
H	$PhCH_2NHSO_2Ph$	$PhC(H)NHSO_2Ph$	50
H	$PhCH_2NHPh$	PhC(H)NHPh	77
H	C_2Cl_6	Cl	85
H	$C_2H_4Br_2$	Br	82
H	I_2	I	79
OMe	I_2	I	77
Cl	I_2	I	61
H	CD_3OD	D	95
OMe	CD_3OD	D	95
Cl	CD_3OD	D	95

In some other cases the situation is more confused, because only products of 4-substitution have been reported, but in many examples there is already a substituent at the 2-position, so regioselectivity is probably not an issue. Sometimes when there is no 2-substituent, the reported yields of 4-substituted products may be relatively low, so it is not clear whether there is actual selectivity for lithiation at the 4-position or whether 2-substituted product was formed, but removed during isolation. For example, lithiation of *N*-(pyridin-3-yl)pivalamides (**64**; R = *t*-Bu) and *tert*-butyl pyridin-3-ylcarbamates (**64**; R = *t*-BuO) with two equivalents of *n*-BuLi at –78 to –10 °C in a mixture of Et_2O and TMEDA, or with or *n*-BuLi in THF at –78 °C (Scheme 21) gave the yields of 4-substituted products **66** reported in Table 17.[25,58–61]

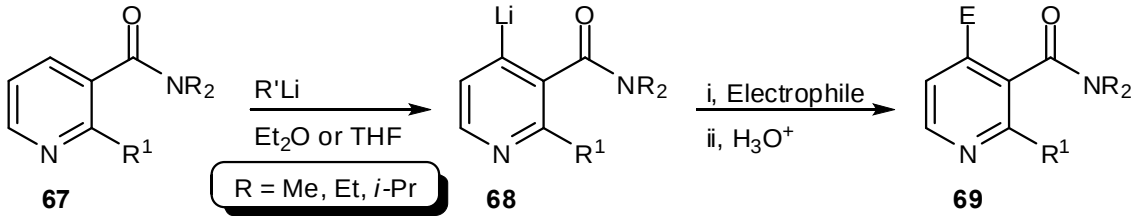


Scheme 21. Directed lithiation and substitution of **64**[25,58–61]

Similarly, lithiation of *N,N*-dialkylnicotinamides **67** (Scheme 22) with 1.5–3.0 mole equivalents of lithiating reagents in THF or Et_2O at low temperature gave only modest yields of 4-substituted products unless there was a further substituent at the 2-position (Table 18).[31,63–66]

Table 17. Lithiation and substitution of **64** according to Scheme 21[25,58–61]

R	R^1	R^2	Electrophile	E	Yield (%)
t-Bu	H	H	$(MeS)_2$	MeS	42
t-Bu	5-Me	H	I_2	I	47
t-Bu	5-Me	OMe	I_2	I	68
t-Bu	5-Me	OPr^i	I_2	I	60
t-Bu	5,6-di-Me	OPr^i	I_2	I	58
t-Bu	6-Me	OMe	I_2	I	87
t-BuO	H	OMe	MeI	Me	84
t-BuO	H	OMe	$PhCH_2Br$	$PhCH_2$	67
t-BuO	H	OMe	Bu_3SnCl	Bu_3Sn	86
t-BuO	H	OMe	$PhCH_2OCH_2Cl$	$PhCH_2OCH_2Cl$	73
t-BuO	H	OMe	Me_2NCHO	CHO	91
t-BuO	H	OMe	I_2	I	59
t-BuO	6-OMe	OMe	MeI	Me	77
t-BuO	6-OMe	OMe	$PhCH_2Br$	$PhCH_2$	63
t-BuO	6-OMe	OMe	Bu_3SnCl	Bu_3Sn	82
t-BuO	6-OMe	OMe	$PhCH_2OCH_2Cl$	$PhCH_2OCH_2Cl$	80
t-BuO	6-OMe	OMe	Me_2NCHO	CHO	89
t-BuO	6-OMe	OMe	I_2	I	47

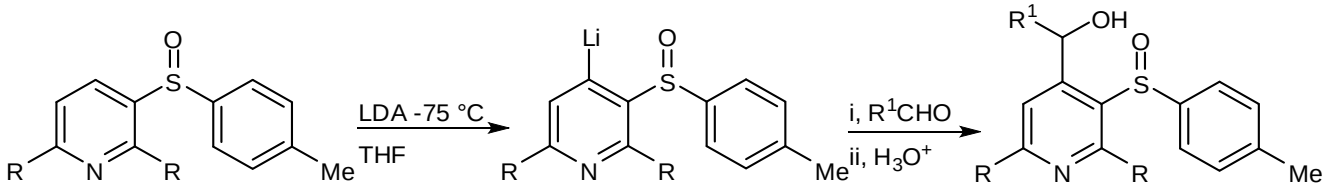


Scheme 22. Directed lithiation and substitution of **67**[31,63–66]

Table 18. Lithiation and substitution of **67** according to Scheme 22[31,63–66]

R	R^1	R′Li	Electrophile	E	Yield (%)
Me	H	Et_2NLi	D_2O	D	14
Et	H	Et_2NLi	D_2O	D	11
Et	2-Br	LDA	Et_2NCOCl	Et_2NCO	80
i-Pr	H	LDA	MeOD	D	46
i-Pr	H	LDA	Ph_2CO	$Ph_2C(OH)$	68
i-Pr	H	LDA	Me_2NCHO	CHO	39
i-Pr	2-OMe	LDA–TMEDA	D_2O	D	90
i-Pr	2-OMe	LTMP–TMEDA	MeOD	D	94
i-Pr	2-OMe	LTMP–TMEDA	Me_3SiCl	Me_3Si	79
i-Pr	2-OMe	LTMP–TMEDA	HCO_2Et	CHO	64
i-Pr	2-OMe	LTMP–TMEDA	Me_2NCHO	CHO	85
i-Pr	2-OMe	LTMP–TMEDA	CO_2	CO_2H	73
i-Pr	2-OMe	LTMP–TMEDA	$MeCO_2Et$	MeCO	49
i-Pr	2-OMe	LTMP–TMEDA	MeCONMe(OMe)	MeCO	45
i-Pr	2-OMe	LTMP–TMEDA	MeCHO	MeCH(OH)	79
i-Pr	2-OMe	*n*-BuLi–TMEDA	Me_2CO	$Me_2C(OH)$	68

This is also the situation for lithiation of enantiopure 3-(4-tolylsulfinyl)pyridines **70** (Scheme 23) with (3.2 mole equivalents) in THF at –75 °C to give the corresponding lithium reagents **71**.[67] Reactions of **71** with aldehydes gave **72** (Table 19) as mixtures of diastereoisomers,[67] but yields were not good in cases where there was no 2-substituent in the substrate. The diastereoselectivity was high (>99%) with hindered aldehydes (benzaldehyde and 2,2-dimethylpropanal), but low (0–38%) with unhindered ones (acetaldehyde and propionaldehyde). The new stereogenic center in the major diastereoisomer had the opposite designation of configuration to that of the sulfoxide unit.



Scheme 23. Directed lithiation and substitution of 3-(4-tolylsulfinyl)pyridines **70**[67]

Table 19. Lithiation and substitution of **70** according to Scheme 23[67]

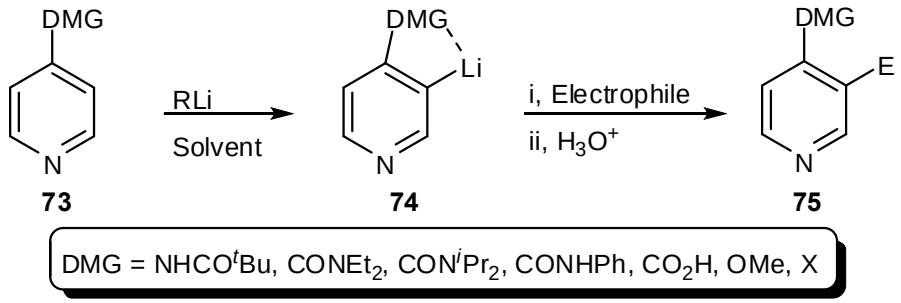
70	R	R^1	**72**, configuration at new stereogenic center (de%)	Yield (%)
S	H	Me	*R* (14)	27
S	H	Et	*R*(26)	27
S	H	*t*-Bu	*R*(>99)	25
S	H	Ph	*R* (>99)	13
R	H	Me	– (0)	27
R	H	Et	*S* (20)	18
R	H	*t*-Bu	*S*(>99)	37
R	H	Ph	*S* (>99)	18
S	OMe	Me	*R* (38)	75
S	OMe	Et	*R* (28)	53
S	OMe	*t*-Bu	*R*(>99)	58
S	OMe	Ph	*R*(>99)	60
R	OMe	Me	*S* (34)	89
R	OMe	Et	*R* (20)	73
R	OMe	*t*-Bu	*R* (>99)	63
R	OMe	Ph	*R* (>99)	77

Reactions of methoxypyridinecarboxaldehydes with lithium dialkylamides gave the corresponding α-aminoalkoxide addition products, which could be lithiated *in-situ* with an alkyllithium.[70] Reactions of lithiated species with iodomethane gave methylated derivatives in 65–82% yields. The site of lithiation found to be next to either the methoxy or carboxaldehyde group. Also, it was found to be dependent on

type of lithium dialkylamides used.[70] For example, lithiation of 6-methoxy-3-pyridinecarboxaldehyde lithium *N,N′,N′*-trimethylethylenediamide and *n*-BuLi followed by reaction with iodomethane gave a mixture of 3- and 5-methylated derivatives in 65% yield in a 97 to 3 ratio, respectively.[70] On the other when the reaction was carried out using lithium *N*-methylpiperazide, *t*-BuLi and TMEDA a mixture of 3- and 5-methylated derivatives was produced in 70% yield in a 7 to 93 ratio, respectively.[70]

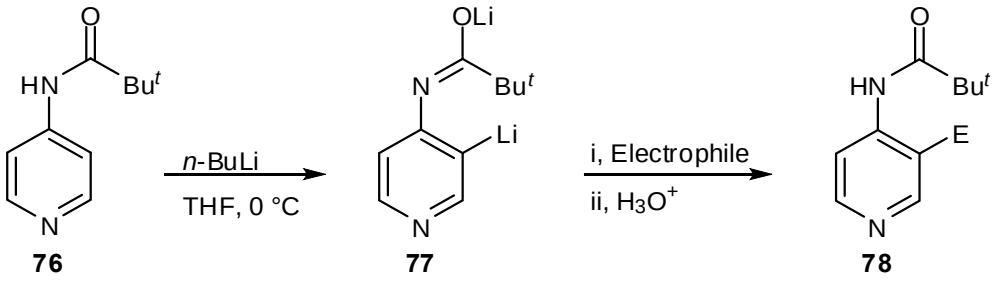
4. DIRECTED LITHIATION OF 4-SUBSTITUTED PYRIDINES

Lithiation of 4-substituted pyridines **73** takes place at C-3 to produce the 3-lithio intermediates **74**. Reactions of **74** with electrophiles give the corresponding 3,4-disubstituted pyridines **75** (Scheme 24).[25,28,30,31,36,37,49,53,71,72]



Scheme 24. Directed lithiation and substitution of 4-subtituted pyridines **73**

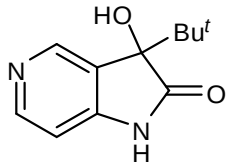
Directed lithiation of 4-(pivaloylamino)pyridine (**76**) with *n*-BuLi (two mole equivalents) at 0 or –78 °C THF followed by reactions with electrophiles gave 3,4-disubstituted pyridines **78** in 54–92% yields (Scheme 25; Table 20).[25,72] Carbonylation of **77** at 0 °C gave 3-*tert*-butyl-6-azadioxindole (**79**; Figure 4) 65% yield *via* cyclization and rearrangement of the initial carbon monoxide adduct.[20]



Scheme 25. Directed lithiation and substitution of 4-(pivaloylamino)pyridine (**76**)[25,72]

Table 20. Lithiation and substitution of **76** according to Scheme 25[25,72]

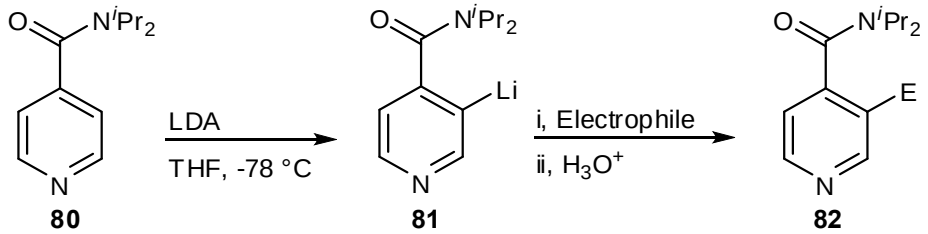
Electrophile	E	Yield (%)
D_2O	D	87
Me_3SiCl	Me_3Si	86
Me_2NCHO	CHO	54
$(MeS)_2$	SMe	67
MeI	Me	72
PhCHO	PhCH(OH)	63
$ClCO_2Et$	CO_2Et	65
$(^iPr_2NCS_2)_2$	$SCSN^iPr_2$	92



79

Figure 4. Structure of 3-*tert*-butyl-6-azadioxindole (**79**)[20]

Directed lithiation of *N,N*-diisopropylisonicotinamide (**80**) was successful with LDA in Et_2O at –78 °C to give lithium reagent **81**, which was reacted with electrophiles to give the corresponding substituted derivatives **82** in modest yields (Scheme 26; Table 21).[30,31]



80 **81** **82**

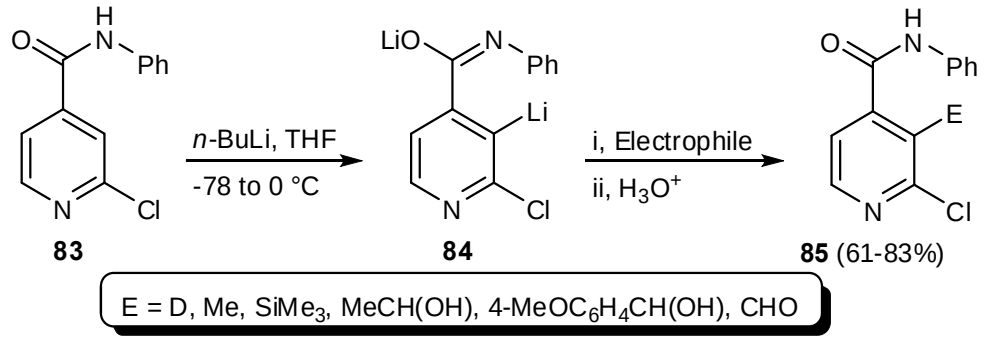
Scheme 26. Directed lithiation and substitution of **80**[30,31]

Table 21. Lithiation and substitution of **80** according to Scheme 26[30,31]

Electrophile	E	Yield (%)
MeOD	D	43
Ph_2CO	$Ph_2C(OH)$	55
Me_2NCHO	CHO	37
$PhCONMe_2$	COPh	36

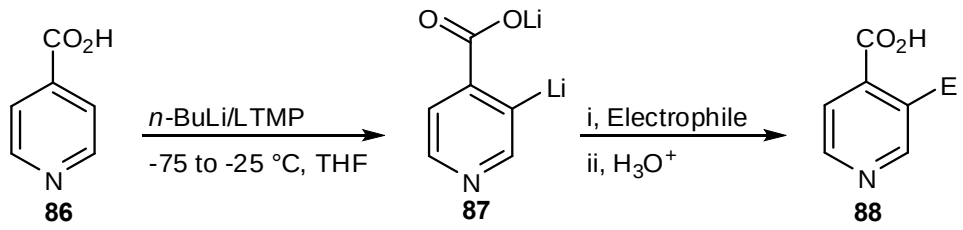
Directed lithiation of 2-chloro-*N*-phenylisonicotinamide (**83**) occurs at position 3 with *n*-BuLi (2.1 mole equivalents) in THF at –78 to 0 °C (Scheme 27).[28] A dimethylated product was obtained in 83% yield lithium reagent **84** was reacted with excess iodomethane (3.0 mole equivalents) due to methylation at

nitrogen and C-3.[28] The simple adducts obtained from use of aldehydes as electrophiles were not isolated, but were cyclized under acidic conditions to give the corresponding lactones.[28]



Scheme 27. Directed lithiation and substitution of **83**[28]

Directed lithiation of isonicotinic acid (**86**) was achieved with a mixture of *n*-BuLi (one mole equivalent) and LTMP (three mole equivalents) in THF at –75 to –25 °C (Scheme 28; Table 22).[36,37]

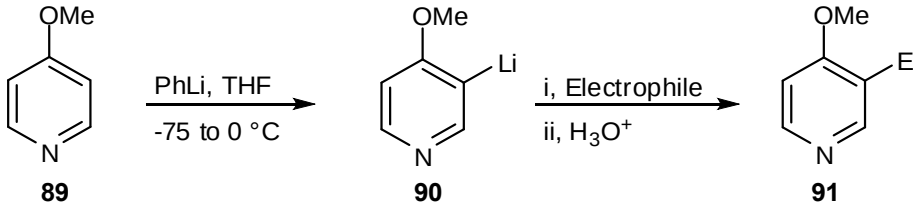


Scheme 28. Directed lithiation and substitution of isonicotinic acid (**86**)[36,37]

Table 22. Lithiation and substitution of **86** according to Scheme 28[36,37]

Electrophile	E	Yield (%)
C_2Cl_6	Cl	49
I_2	I	45
D_2O	D	78
CO_2	CO_2H	65

Directed lithiation of 4-methoxypyridine (**89**) has been achieved with phenyllithium (PhLi; 2.2 mole equivalents) in THF at 0 °C and subsequent reaction with electrophiles gave **91** (Scheme 29) in 67–90% yields (Table 23).[71] Lithiation of 3,4-dimethoxypyridine with *n*-BuLi (2.2 mole equivalents) at –78 to in THF took place at the 2-position.[71]

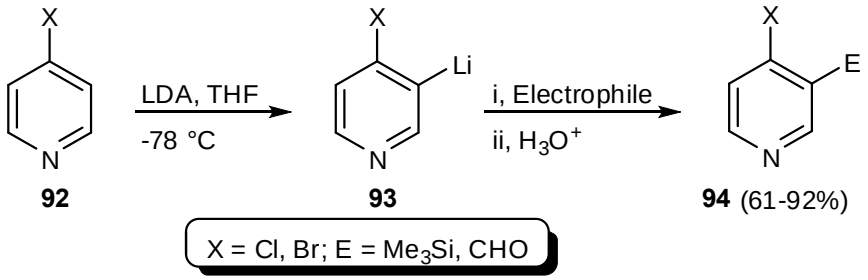


Scheme 29. Directed lithiation and substitution of 4-methoxypyridine (**89**)[71]

Table 23. Lithiation and substitution of **89** according to Scheme 29[71]

Electrophile	E	Yield (%)
PhCHO	PhCH(OH)	90
2-$MeOC_6H_4CHO$	2-$MeOC_6H_4CH(OH)$	89
$B(OMe)_3$	OH	65
I_2	I	76
BrCN	Br	67

Directed lithiation of 4-halopyridines **92** was successful with LDA at –78 °C in THF (Scheme 30).[40,49]



Scheme 30. Directed lithiation and substitution of 4-halopyridines **92**[40,49]

5. CONCLUSION

Directed lithiation of various DMG-substituted pyridines by lithium reagents at low temperatures followed by reactions with electrophiles often produces the corresponding pyridines substituted adjacent to the DMG. Directed lithiation of pyridines containing a DMG at the C-2 or C-4 position takes place at the 3-position, while under similar reaction conditions directed lithiation often takes place at the C-4 position for 3-substituted pyridines. The process is efficient for the production of various substituted pyridine derivatives in a single step. Such derivatives might be difficult to prepare by other means.

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