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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.

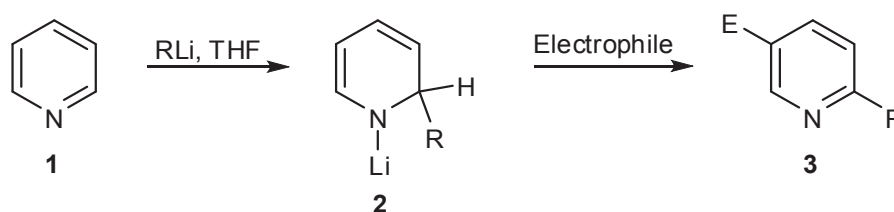
### CONTENTS

1. Introduction
2. Directed lithiation and substitution of 2-substituted pyridines
3. Directed lithiation and substitution of 3-substituted pyridines
4. Directed lithiation and substitution of 4-substituted pyridines
5. Conclusion
6. Acknowledgements
7. References

### 1. INTRODUCTION

Pyridine derivatives are interesting compounds<sup>1</sup> that have a broad range of biological activities.<sup>2,3</sup> 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.<sup>4-7</sup> 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).<sup>4,5</sup> 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<sup>5</sup> 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 **3** (R = Ph).<sup>5</sup>



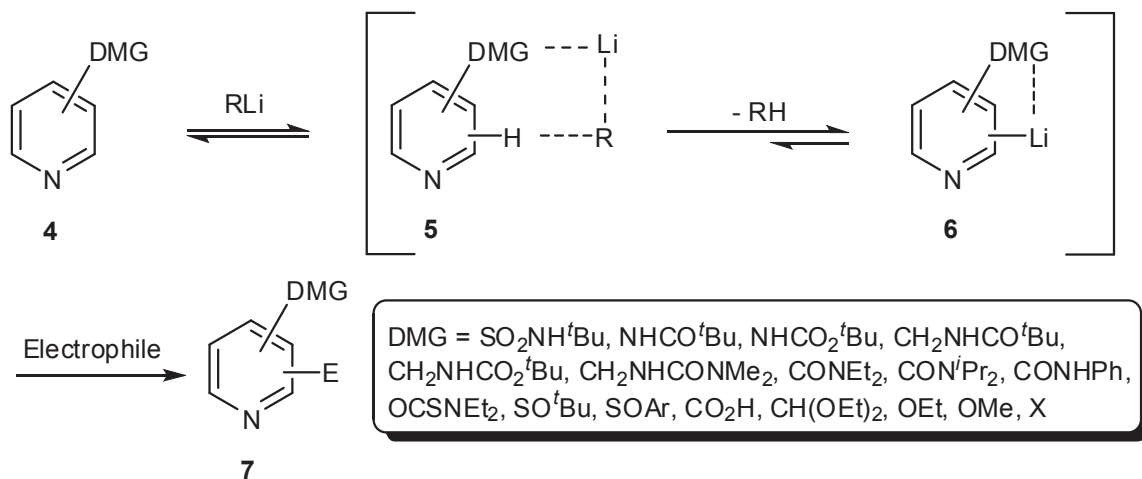
**Scheme 1.** Addition of organolithium reagents to pyridine (**1**)<sup>4-7</sup>

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

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.<sup>8-21</sup> The reactions of the substituted pyridines with lithium reagents usually take place at low temperatures in anhydrous diethyl ether (Et<sub>2</sub>O) 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**.<sup>16</sup> The complexation between the lithium reagent and the DMG prior to lithiation brings the lithium reagent into closer proximity to the proton in the adjacent position, which is then selectively removed.<sup>22,23</sup> 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

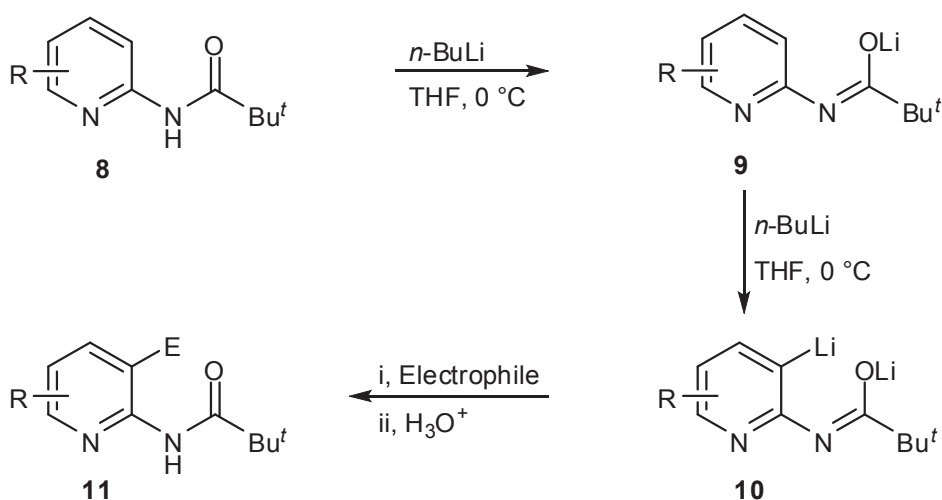
DMGs that encourage *ortho*-lithiation include  $\text{SO}_2\text{NR}_2$ ,  $\text{NHCOR}$ ,  $\text{CONR}_2$ ,  $\text{CSNHR}$ ,  $\text{CONHR}$ ,  $\text{OCONR}_2$ ,  $\text{CO}_2\text{R}$ ,  $\text{CH}_2\text{NHR}$ ,  $\text{OCH}_2\text{OMe}$ . Moderate DMGs include  $\text{OR}$ ,  $\text{NR}_2$ ,  $\text{SR}$ ,  $\text{CF}_3$  and  $\text{F}$ , while weak DMGs include  $\text{CH}_2\text{OH}$  and  $\text{CH}(\text{OR})_2$ .<sup>24</sup>



**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 ( $\alpha$ ) position takes place at the 3-position to provide the corresponding lithium intermediates, which on further reactions with electrophiles give the corresponding substituted derivatives.<sup>25–47</sup> 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  $-50\text{ }^\circ\text{C}$  to give monolithium intermediates **9** and then dilithium reagents **10**, which on reactions with electrophiles gave the corresponding substituted pyridines **11** (Scheme 3) in 40–94% yields (Table 1).<sup>25,26</sup>



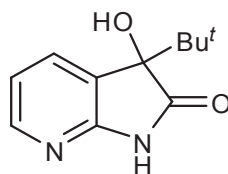
**Scheme 3.** Directed lithiation and substitution of 2-(pivaloylamino)pyridines **8**<sup>25,26</sup>

**Table 1.** Lithiation and substitution of **8** according to Scheme 3<sup>25,26</sup>

| R    | Electrophile   | E                                 | Yield (%) <sup>a</sup> |
|------|--|-----------------------------------|------------------------|
| H    | D <sub>2</sub> O   | D                                 | 87                     |
| H    | MeI  | Me                                | 72                     |
| H    | Me <sub>3</sub> SiCl   | Me <sub>3</sub> Si                | 86                     |
| H    | Me <sub>2</sub> NCHO   | CHO                               | 54                     |
| H    | (MeS) <sub>2</sub>   | MeS                               | 67                     |
| H    | EtCO <sub>2</sub> Cl   | CO <sub>2</sub> Et                | 65                     |
| H    | PhCHO  | PhCH(OH)                          | 63                     |
| H    | ( <sup>i</sup> Pr <sub>2</sub> NCS <sub>2</sub> ) <sub>2</sub> | SCSN <sup>i</sup> Pr <sub>2</sub> | 73                     |
| 4-Me | (MeS) <sub>2</sub>   | MeS                               | 40 (74) <sup>b</sup>   |
| 5-Me | (MeS) <sub>2</sub>   | MeS                               | 94                     |
| 6-Me | (MeS) <sub>2</sub>   | MeS                               | 59 (74) <sup>b</sup>   |
| 5-Cl | (MeS) <sub>2</sub>   | MeS                               | 86 <sup>c</sup>        |
| 6-Cl | (MeS) <sub>2</sub>   | MeS                               | 78 <sup>d</sup>        |

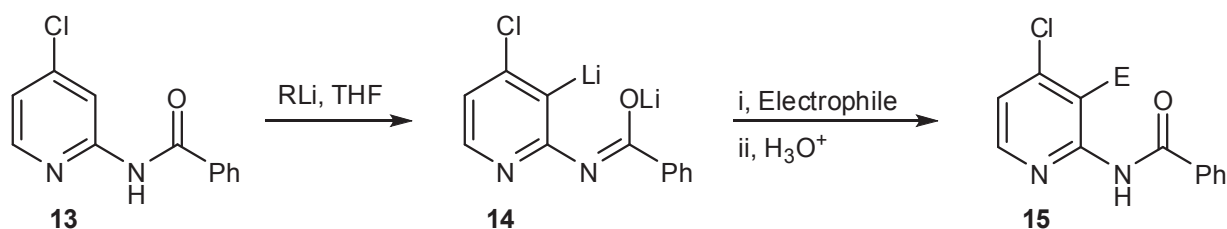
<sup>a</sup> Standard conditions involve *n*-BuLi, THF, 0 °C; <sup>b</sup> Figures in parentheses are for reactions involving *t*-butyllithium (*t*-BuLi), -78 °C, Et<sub>2</sub>O; <sup>c</sup> *t*-BuLi, -78 °C, THF; <sup>d</sup> *n*-BuLi, -20 °C, THF.

Carbonylation of **10** (R = H) with carbon monoxide at 0 °C gave 3-*tert*-butyl-7-azadioxindole (**12**; Figure 1) in 62% yield following cyclization and rearrangement of the initial carbon monoxide adduct.<sup>20</sup>

**12****Figure 1.** Structure of 3-*tert*-butyl-7-azadioxindole (**12**)<sup>20</sup>

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

Lithiation of 2-(benzoylamino)-4-chloropyridine (**13**) with two mole equivalents of LDA in THF at -78 °C 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).<sup>27</sup> Lithiation of **13** was also successful with *n*-BuLi (2.1 mole equivalents) at -20 to -78 °C.<sup>28</sup>

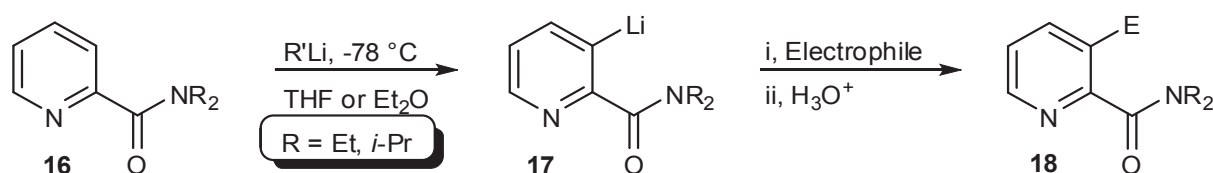


**Scheme 4.** Directed lithiation and substitution of 2-(benzoylamino)-4-chloropyridine (**13**)<sup>27,28</sup>

**Table 2.** Lithiation and substitution of **13** according to Scheme 4<sup>27,28</sup>

| RLi            | Electrophile         | E                  | Yield (%) |
|----------------|----------------------|--------------------|-----------|
| LDA            | MeI                  | Me                 | 67        |
| LDA            | Bu <sub>3</sub> SnCl | Bu <sub>3</sub> Sn | 84        |
| LDA            | Me <sub>3</sub> SnCl | Me <sub>3</sub> Sn | 87        |
| LDA            | I <sub>2</sub>       | I                  | 88        |
| LDA            | CO <sub>2</sub>      | CO <sub>2</sub> H  | 42        |
| <i>n</i> -BuLi | Me <sub>3</sub> SnCl | Me <sub>3</sub> Sn | 48        |
| <i>n</i> -BuLi | MeI                  | Me                 | 65        |
| <i>n</i> -BuLi | Me <sub>2</sub> NCHO | 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<sub>2</sub>O at -78 °C, followed by reactions with electrophiles, gave the corresponding 2,3-disubstituted derivatives **18** (Table 3) *via* lithium intermediates **17**.<sup>29-31</sup>



**Scheme 5.** Directed lithiation and substitution of *N,N*-dialkylpicolinamides **16**<sup>29-31</sup>

**Table 3.** Lithiation and substitution of **16** according to Scheme 5<sup>29-31</sup>

| R            | R'Li             | Electrophile         | E                     | Yield (%) |
|--------------|------------------|----------------------|-----------------------|-----------|
| Et           | <i>sec</i> -BuLi | MeI                  | Me                    | 53        |
| Et           | <i>sec</i> -BuLi | PhCHO                | PhCH(OH)              | 50        |
| <i>i</i> -Pr | LDA              | MeOD                 | D                     | 55        |
| <i>i</i> -Pr | LDA              | Ph <sub>2</sub> CO   | Ph <sub>2</sub> C(OH) | 81        |
| <i>i</i> -Pr | LDA              | Me <sub>2</sub> NCHO | CHO                   | 35        |
| <i>i</i> -Pr | LDA              | PhCONMe <sub>2</sub> | COPh                  | 52        |

Directed lithiation and substitution of 2-(substituted sulfinyl)pyridines **19** was successful with LDA (one mole equivalent) in THF at  $-78\text{ }^{\circ}\text{C}$  to give the corresponding substituted derivatives **21** (Scheme 6) in 20–93% yields (Table 4).<sup>32–35</sup>

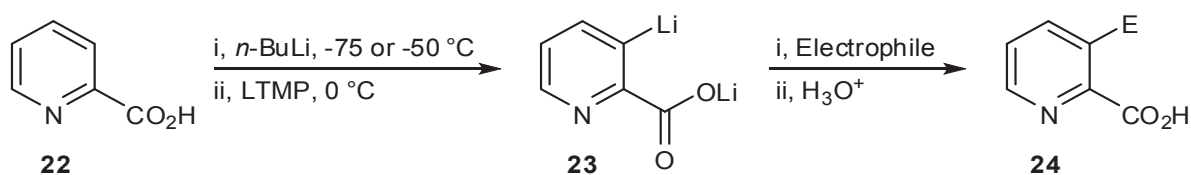


**Scheme 6.** Directed lithiation and substitution of **19**<sup>32–35</sup>

**Table 4.** Lithiation and substitution of **19** according to Scheme 6<sup>32–35</sup>

| R                      | Electrophile          | E                     | Yield (%) |
|------------------------|-----------------------|-----------------------|-----------|
| <i>t</i> -Bu           | MeOD                  | D                     | 75        |
| <i>t</i> -Bu           | MeI                   | Me                    | 82        |
| <i>t</i> -Bu           | PhCHO                 | PhCH(OH)              | 74        |
| <i>t</i> -Bu           | Et <sub>2</sub> NCOCl | Et <sub>2</sub> NCO   | 20        |
| <i>t</i> -Bu           | B(OMe) <sub>3</sub>   | OH                    | 70        |
| <i>t</i> -Bu           | I <sub>2</sub>        | I                     | 35        |
| <i>t</i> -Bu           | Me <sub>3</sub> SiCl  | Me <sub>3</sub> Si    | 70        |
| <i>t</i> -Bu           | Bu <sub>3</sub> SnCl  | Bu <sub>3</sub> Sn    | 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        |
| <i>O</i> -pyrrolidinyl | Ph <sub>2</sub> CO    | Ph <sub>2</sub> C(OH) | 70        |
| <i>O</i> -piperidyl    | Ph <sub>2</sub> CO    | Ph <sub>2</sub> C(OH) | 90        |
| <i>O</i> -morpholinyl  | Ph <sub>2</sub> CO    | Ph <sub>2</sub> C(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  $-50\text{ }^{\circ}\text{C}$  followed by the addition of LTMP (three mole equivalents) at  $0\text{ }^{\circ}\text{C}$  in THF (Scheme 7; Table 5).<sup>36,37</sup>

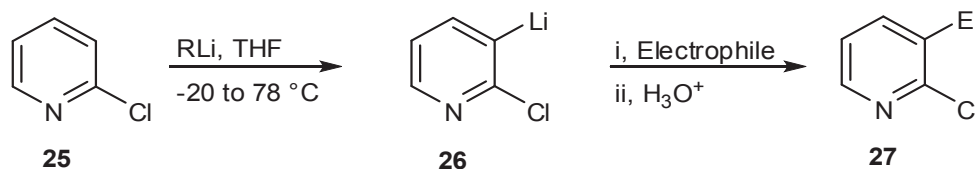


**Scheme 7.** Directed lithiation and substitution of pyridine-2-carboxylic acid (**22**)<sup>36,37</sup>

**Table 5.** Lithiation and substitution of **22** according to Scheme 7<sup>36,37</sup>

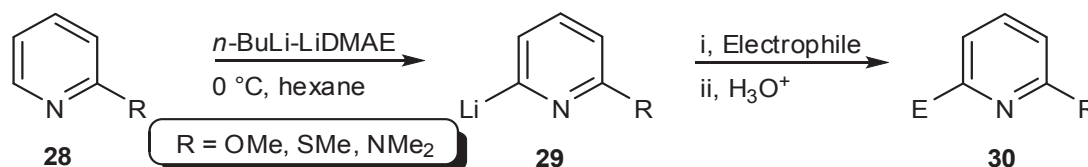
| Electrophile                   | E                 | Yield (%) |
|--------------------------------|-------------------|-----------|
| D <sub>2</sub> O               | D                 | 81        |
| CO <sub>2</sub>                | CO <sub>2</sub> H | 85        |
| C <sub>2</sub> Cl <sub>6</sub> | Cl                | 72        |
| I <sub>2</sub>                 | I                 | 65        |

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

**Scheme 8.** Directed lithiation and substitution of 2-chloropyridine (**25**)<sup>38–40</sup>**Table 6.** Lithiation and substitution of 2-chloropyridine (**25**) according to Scheme 8<sup>38–40</sup>

| RLi (T °C)           | Electrophile                          | E                                     | Yield (%) |
|----------------------|---------------------------------------|---------------------------------------|-----------|
| LTMP (–78)           | DCl/D <sub>2</sub> O                  | D                                     | 70        |
| <i>n</i> -BuLi (–70) | DCl/D <sub>2</sub> O                  | D                                     | 75        |
| <i>n</i> -BuLi (–40) | Me <sub>2</sub> NCHO                  | CHO                                   | 50        |
| <i>n</i> -BuLi (–70) | Me <sub>3</sub> SiCl                  | Me <sub>3</sub> Si                    | 75        |
| <i>n</i> -BuLi (–70) | MeI                                   | Me                                    | 80        |
| <i>n</i> -BuLi (–70) | CH <sub>2</sub> =CH-CH <sub>2</sub> I | CH <sub>2</sub> =CH-CH <sub>2</sub>   | 45        |
| <i>n</i> -BuLi (–70) | MeCHO                                 | MeCH(OH)                              | 75        |
| <i>n</i> -BuLi (–70) | (CH <sub>2</sub> ) <sub>5</sub> CO    | (CH <sub>2</sub> ) <sub>5</sub> C(OH) | 70        |
| <i>n</i> -BuLi (–70) | PhCHO                                 | PhCH(OH)                              | 70        |
| <i>n</i> -BuLi (–70) | Ph <sub>2</sub> CO                    | Ph <sub>2</sub> C(OH)                 | 55        |
| <i>n</i> -BuLi (–70) | EtCOEt                                | EtC(OH)Et                             | 70        |
| <i>n</i> -BuLi (–40) | Br <sub>2</sub>                       | Br                                    | 30        |
| <i>n</i> -BuLi (–70) | I <sub>2</sub>                        | I                                     | 60        |
| LDA (–78)            | Me <sub>3</sub> SiCl                  | Me <sub>3</sub> Si                    | 74        |

Lithiation of 2-methoxypyridine (**28**; R = OMe) with LTMP (3.2 mole equivalents) at  $-78$  °C in THF followed by reaction with DCl/D<sub>2</sub>O gave the corresponding 3-deuteriated derivative in 92% yield.<sup>38</sup> However, the use of *n*-BuLi–LiDMAE (3 mole equivalents) in hexane at  $-78$  °C followed by reaction with DCl/D<sub>2</sub>O again diverted the reaction to the 6-deuteriated derivative **30** (Scheme 9: R = OMe, E = D) in 68% yield.<sup>38,45–47</sup> The latter reaction was found to be general with other electrophiles.<sup>38,45–47</sup> The effect of the amount of *n*-BuLi–LiDMAE on the lithiation of 2-methoxypyridine (**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.<sup>45</sup>



**Scheme 9.** Lithiation and substitution of **28**<sup>45</sup>

**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<sup>45</sup>

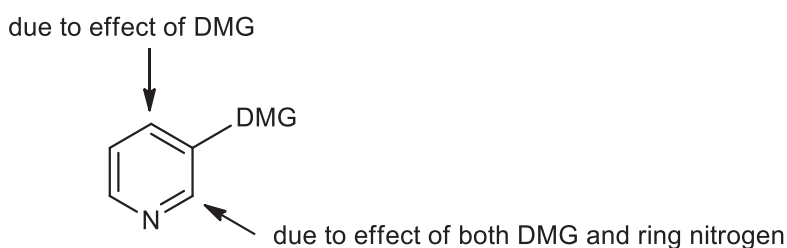
| R                | Electrophile                          | E  | Yield (%)            |
|------------------|---------------------------------------|--|----------------------|
| OMe              | MeI                                   | Me                                       | 59                   |
| OMe              | Me <sub>2</sub> SO <sub>4</sub>       | Me                                       | 62                   |
| OMe              | EtI                                   | Et                                       | 54                   |
| OMe              | Et <sub>2</sub> SO <sub>4</sub>       | Et                                       | 60                   |
| OMe              | Me(CH <sub>2</sub> ) <sub>5</sub> I   | Me(CH <sub>2</sub> ) <sub>5</sub>        | 40                   |
| OMe              | Me <sub>3</sub> SiCl                  | Me <sub>3</sub> Si                       | 75 (60) <sup>a</sup> |
| OMe              | (MeS) <sub>2</sub>                    | MeS                                      | 72 (63) <sup>a</sup> |
| OMe              | DCl/D <sub>2</sub> O                  | D  | 41 (34) <sup>a</sup> |
| OMe              | MeCOMe                                | MeC(OH)Me                                | 54 (43) <sup>a</sup> |
| OMe              | EtCOMe                                | EtC(OH)Me                                | 80                   |
| OMe              | (CH <sub>2</sub> ) <sub>4</sub> CO    | (CH <sub>2</sub> ) <sub>4</sub> C(OH)    | 63                   |
| OMe              | PhCOPh                                | PhC(OH)Ph                                | 43                   |
| OMe              | Bu <sup>o</sup> CHO                   | Bu <sup>o</sup> CH(OH)                   | 88                   |
| OMe              | Me(CH <sub>2</sub> ) <sub>5</sub> CHO | Me(CH <sub>2</sub> ) <sub>5</sub> CH(OH) | 53                   |
| SMe              | Me <sub>3</sub> SiCl                  | Me <sub>3</sub> Si                       | 80                   |
| SMe              | MeI                                   | Me                                       | 62                   |
| SMe              | EtCOMe                                | EtC(OH)Me                                | 75                   |
| NMe <sub>2</sub> | Me <sub>3</sub> SiCl                  | Me <sub>3</sub> Si                       | 52                   |
| NMe <sub>2</sub> | MeI                                   | Me                                       | 45                   |
| NMe <sub>2</sub> | EtCOMe                                | EtC(OH)Me                                | 44                   |

<sup>a</sup> 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%).<sup>45</sup> 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<sub>2</sub>) in 44–80% yields (Table 7).<sup>45</sup>

### 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.



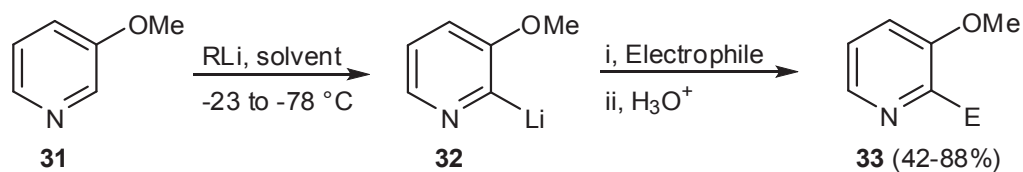
**Figure 2.** Possible positions for lithiation of 3-substituted pyridines

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).<sup>48,49</sup> 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<sup>48,49</sup>

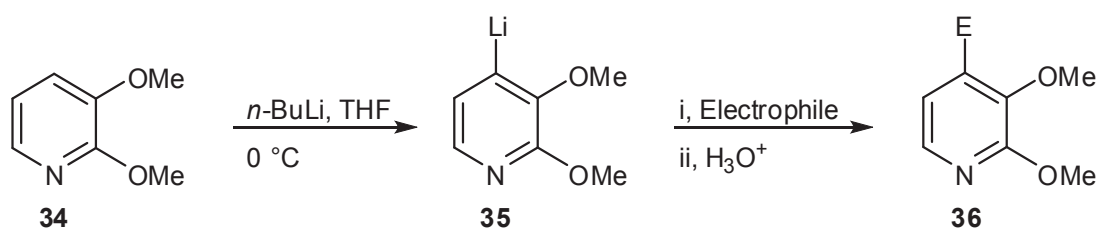
| RLi                   | Solvent | T (°C) | Electrophile         | E                  | Yield (%)       |
|-----------------------|---------|--------|----------------------|--------------------|-----------------|
| <i>n</i> -BuLi–LiDMAE | hexane  | –78    | (MeS) <sub>2</sub>   | MeS                | 88              |
| <i>n</i> -BuLi–TMEDA  | THF     | –40    | MeCHO                | MeCH(OH)           | 49              |
| Mesityllithium        | THF     | –23    | (MeS) <sub>2</sub>   | MeS                | 82              |
| Mesityllithium        | THF     | –23    | PhCHO                | PhCH(OH)           | 73              |
| Mesityllithium        | THF     | –23    | Me <sub>2</sub> NCHO | CHO                | 85              |
| LDA                   | THF     | –42    | Me <sub>3</sub> SiCl | Me <sub>3</sub> Si | 42 <sup>a</sup> |

<sup>a</sup> 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**)<sup>48,49</sup>

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).<sup>50</sup>

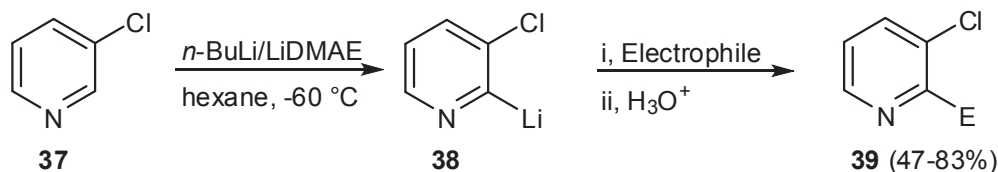


**Scheme 11.** Directed lithiation and substitution of 2,3-dimethoxypyridine (**34**)<sup>50</sup>

**Table 9.** Lithiation and substitution of **34** according to Scheme 11<sup>50</sup>

| Electrophile        | E        | Yield (%) |
|---------------------|----------|-----------|
| DCI                 | D        | 99        |
| PhCHO               | PhCH(OH) | 71        |
| BrCN                | Br       | 60        |
| B(OMe) <sub>3</sub> | 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.<sup>40,41,51–57</sup> 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.<sup>55,56</sup> 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,<sup>55,56</sup> 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).<sup>54</sup>

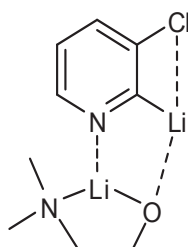


**Scheme 12.** Lithiation and substitution of 3-chloropyridine (**37**) with BuLi/LiDMAE<sup>54</sup>

**Table 10.** Lithiation and substitution of 3-chloropyridine (**37**) according to Scheme 12<sup>54</sup>

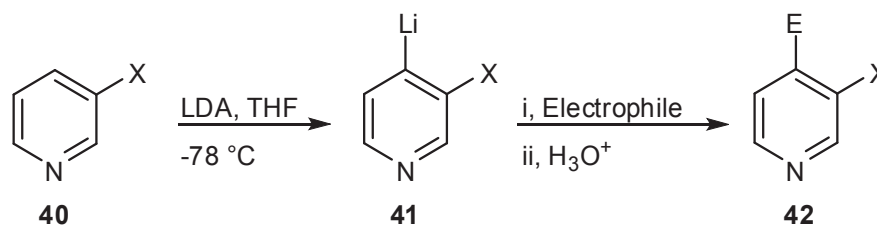
| Electrophile                   | E         | Yield (%) |
|--------------------------------|-----------|-----------|
| DCI/D <sub>2</sub> O           | D         | 66        |
| (MeS) <sub>2</sub>             | MeS       | 83        |
| Bu'CHO                         | Bu'CH(OH) | 60        |
| PhCONMe <sub>2</sub>           | PhCO      | 69        |
| I <sub>2</sub>                 | I         | 66        |
| CBr <sub>4</sub>               | Br        | 47        |
| C <sub>2</sub> Cl <sub>6</sub> | 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).<sup>54</sup>



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

On the other hand, lithiation of 3-halopyridines **40** with LDA in THF at  $-78\text{ }^\circ\text{C}$  took place predominantly at the 4-position (Scheme 13, Table 11).<sup>30,40,54</sup>

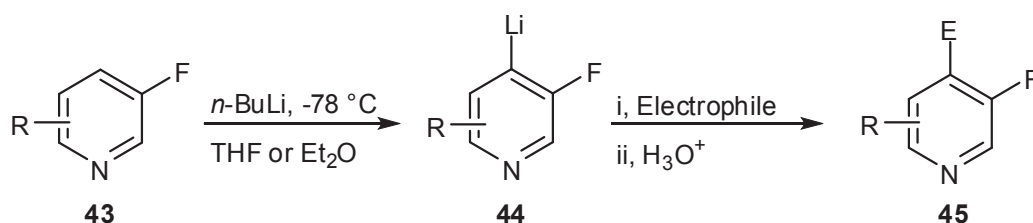


**Scheme 13.** Lithiation and substitution of 3-halopyridines **40** with LDA<sup>30,40,54</sup>

**Table 11.** Lithiation and substitution of **40** according to Scheme 13<sup>30,40,54</sup>

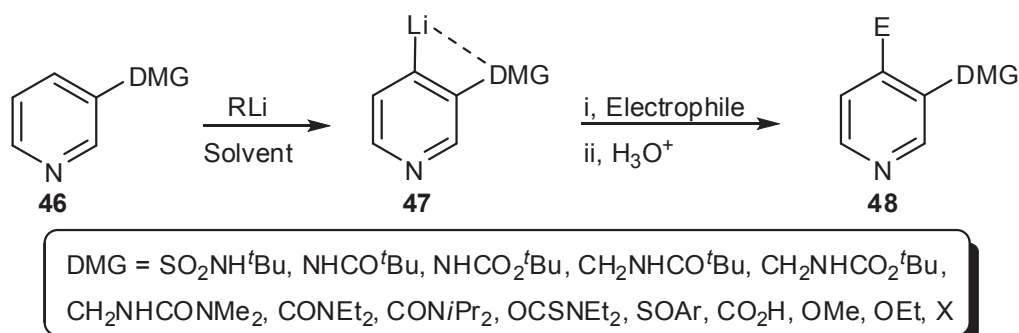
| X  | Electrophile         | E                     | Yield (%) |
|----|----------------------|-----------------------|-----------|
| Cl | Me <sub>3</sub> SiCl | Me <sub>3</sub> Si    | 80        |
| Cl | PhCHO                | PhCH(OH)              | 57        |
| Cl | Ph <sub>2</sub> CO   | Ph <sub>2</sub> C(OH) | 65        |
| Cl | Me <sub>2</sub> CO   | Me <sub>2</sub> C(OH) | 28        |
| Cl | Me <sub>3</sub> SiCl | Me <sub>3</sub> Si    | 96        |
| Cl | (PhS) <sub>2</sub>   | PhS                   | 75        |
| Cl | PhSO <sub>2</sub> Cl | PhSO <sub>2</sub>     | 80        |
| Cl | Br <sub>2</sub>      | Br                    | 16        |
| Cl | I <sub>2</sub>       | I                     | 65        |
| Br | (PhS) <sub>2</sub>   | PhS                   | 61        |
| Br | MeCHO                | MeCH(OH)              | 79        |
| Br | PhCOMe               | PhC(OH)Me             | 36        |
| F  | Me <sub>3</sub> SiCl | Me <sub>3</sub> Si    | 87        |
| F  | I <sub>2</sub>       | 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<sub>2</sub>O at -78 °C also results in lithiation of 3-fluoropyridines **43** at the 4-position (Scheme 14, Table 12).<sup>51,52</sup>

**Scheme 14.** Directed lithiation and substitution of 3-fluoropyridines **43**<sup>51,52</sup>**Table 12.** Lithiation and substitution of **43** according to Scheme 14<sup>51,52</sup>

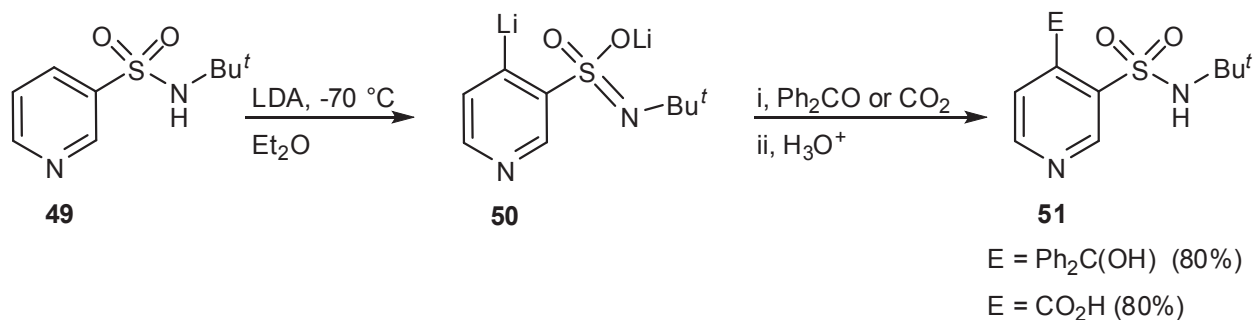
| R  | Electrophile                   | E                     | Yield (%) |
|--|--------------------------------|-----------------------|-----------|
| 5-F  | Me <sub>3</sub> SiCl           | Me <sub>3</sub> Si    | 65        |
| 2-[2-(Bu <sup>t</sup> CONH)C <sub>6</sub> H <sub>4</sub> ] | D <sub>2</sub> O               | D                     | 95        |
| 2-[2-(Bu <sup>t</sup> CONH)C <sub>6</sub> H <sub>4</sub> ] | I <sub>2</sub>                 | I                     | 98        |
| 2-[2-(Bu <sup>t</sup> CONH)C <sub>6</sub> H <sub>4</sub> ] | C <sub>2</sub> Cl <sub>6</sub> | Cl                    | 70        |
| 2-[2-(Bu <sup>t</sup> CONH)C <sub>6</sub> H <sub>4</sub> ] | MeI                            | Me                    | 81        |
| 2-[2-(Bu <sup>t</sup> CONH)C <sub>6</sub> H <sub>4</sub> ] | EtI                            | Et                    | 65        |
| 2-[2-(Bu <sup>t</sup> CONH)C <sub>6</sub> H <sub>4</sub> ] | MeCHO                          | MeCH(OH)              | 83        |
| 2-[2-(Bu <sup>t</sup> CONH)C <sub>6</sub> H <sub>4</sub> ] | PhCHO                          | PhCH(OH)              | 65        |
| 2-[2-(Bu <sup>t</sup> CONH)C <sub>6</sub> H <sub>4</sub> ] | Ph <sub>2</sub> CO             | Ph <sub>2</sub> C(OH) | 35        |
| 2-[2-(Bu <sup>t</sup> CONH)C <sub>6</sub> H <sub>4</sub> ] | Me <sub>3</sub> SiCl           | Me <sub>3</sub> Si    | 62        |
| 2-[2-(Bu <sup>t</sup> CONH)C <sub>6</sub> H <sub>4</sub> ] | CO <sub>2</sub>                | CO <sub>2</sub> H     | 41        |
| 2-[2-(Bu <sup>t</sup> CONH)C <sub>6</sub> H <sub>4</sub> ] | HCO <sub>2</sub> Et            | 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**.<sup>25,30,31,35–38,58–68</sup> 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 species.



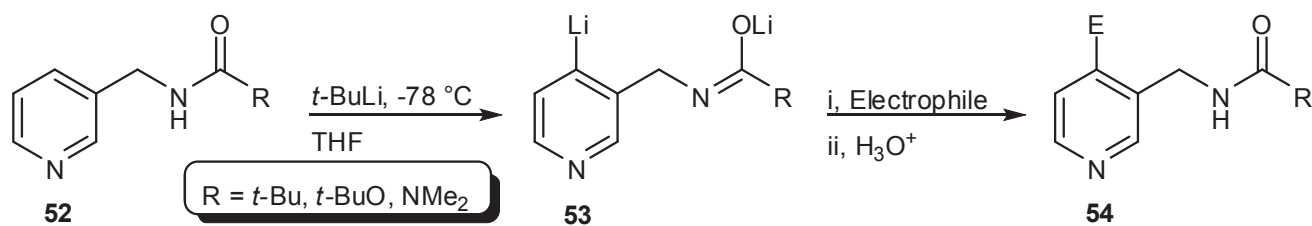
**Scheme 15.** Directed lithiation and substitution of 3-substituted pyridines **46**

For example, lithiation of *N*-*tert*-butylpyridine-3-sulfonamide (**49**) was achieved with LDA (3.0 mole equivalents) at  $-70\text{ }^\circ\text{C}$  in Et<sub>2</sub>O to give lithium reagent **50**.<sup>35</sup> Reactions of **50** with benzophenone and carbon dioxide as representative electrophiles gave **51**, in both cases in 80% yield (Scheme 16).<sup>35</sup>



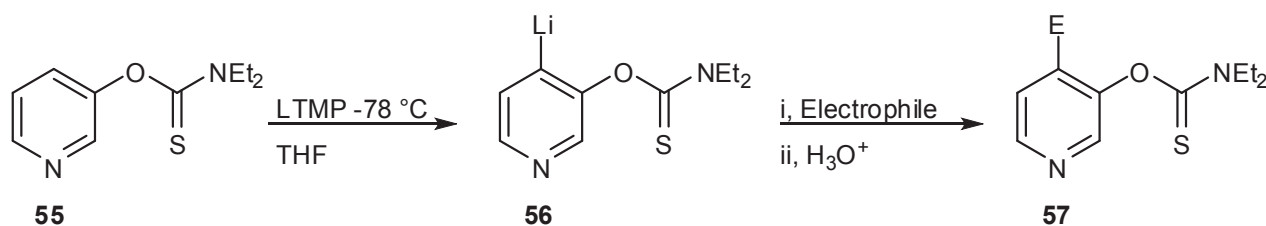
**Scheme 16.** Directed lithiation and substitution of **49**<sup>35</sup>

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<sub>2</sub>) with 3.3 mole equivalents of *t*-BuLi at  $-78\text{ }^\circ\text{C}$  in THF gave the corresponding 4-lithio intermediates **53** (Scheme 17).<sup>62</sup> Reactions of **53** with several electrophiles afforded **54** in high yields (Table 13). By contrast, lithiation of **52** with LDA at  $-20$  to  $0\text{ }^\circ\text{C}$  in THF followed by reactions with representative electrophiles gave side-chain substituted products in 52–75% yields.<sup>62</sup>

Scheme 17. Directed lithiation and substitution of **52**<sup>62</sup>Table 13. Lithiation and substitution of **52** according to Scheme 17<sup>62</sup>

| R                | Electrophile   | E   | Yield (%) |
|------------------|--|---|-----------|
| <i>t</i> -Bu     | Ph <sub>2</sub> CO                                   | Ph <sub>2</sub> C(OH)                                   | 88        |
| <i>t</i> -Bu     | Me <sub>2</sub> CO                                   | Me <sub>2</sub> C(OH)                                   | 91        |
| <i>t</i> -Bu     | 4-MeOC <sub>6</sub> H <sub>4</sub> CHO               | 4-MeOC <sub>6</sub> H <sub>4</sub> CH(OH)               | 89        |
| <i>t</i> -Bu     | 4-Me <sub>2</sub> NC <sub>6</sub> H <sub>4</sub> CHO | 4-Me <sub>2</sub> NC <sub>6</sub> H <sub>4</sub> CH(OH) | 85        |
| <i>t</i> -Bu     | EtI  | Et  | 90        |
| <i>t</i> -BuO    | Ph <sub>2</sub> CO                                   | Ph <sub>2</sub> C(OH)                                   | 88        |
| <i>t</i> -BuO    | PhCOMe   | PhC(OH)Me   | 81        |
| <i>t</i> -BuO    | (CH <sub>2</sub> ) <sub>5</sub> CO                   | (CH <sub>2</sub> ) <sub>5</sub> C(OH)                   | 84        |
| <i>t</i> -BuO    | PhCHO  | PhCH(OH)  | 80        |
| NMe <sub>2</sub> | Ph <sub>2</sub> CO                                   | Ph <sub>2</sub> C(OH)                                   | 66        |

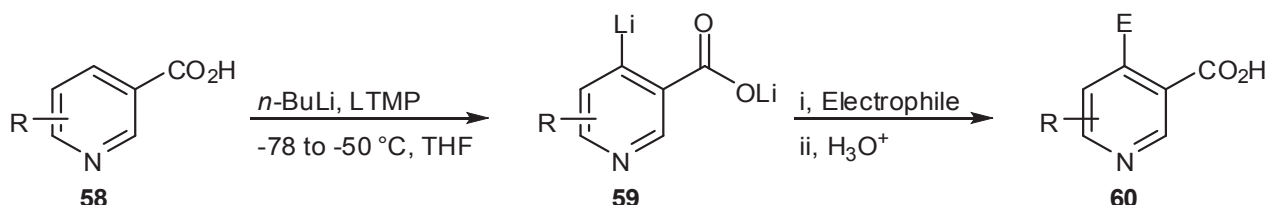
Directed lithiation of *O*-pyridin-3-yl diethylcarbamothioate (**55**; Scheme 18) with LTMP (1.1 mole equivalents) in THF at  $-78\text{ }^{\circ}\text{C}$  followed by reactions with electrophiles gave **57** (Table 14) *via* lithium intermediate **56**.<sup>68</sup>

Scheme 18. Directed lithiation and substitution of **55**<sup>68</sup>Table 14. Lithiation and substitution of **55** according to Scheme 18<sup>68</sup>

| Electrophile         | E                  | Yield (%) |
|----------------------|--------------------|-----------|
| Me <sub>3</sub> SiCl | Me <sub>3</sub> Si | 87        |
| (PhS) <sub>2</sub>   | 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  $-50\text{ }^{\circ}\text{C}$  in THF followed by

reactions with electrophiles gave **60** (Table 15).<sup>36,37</sup> 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.<sup>36,37</sup>

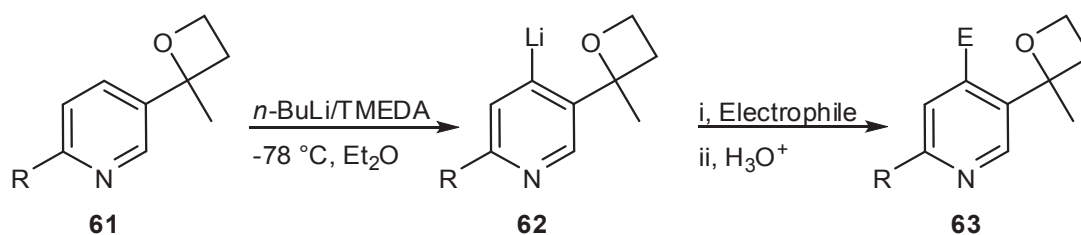


**Scheme 19.** Directed lithiation and substitution of nicotinic acids **58**<sup>36,37</sup>

**Table 15.** Lithiation and substitution of nicotinic acids **58** according to Scheme 19<sup>36,37</sup>

| R    | Electrophile                   | E                 | Yield (%) |
|------|--------------------------------|-------------------|-----------|
| H    | C <sub>2</sub> Cl <sub>6</sub> | Cl                | 79        |
| H    | I <sub>2</sub>                 | I                 | 71        |
| H    | D <sub>2</sub> O               | D                 | 45        |
| H    | CO <sub>2</sub>                | CO <sub>2</sub> H | 73        |
| 2-Cl | D <sub>2</sub> O               | D                 | 57        |
| 2-Cl | CO <sub>2</sub>                | CO <sub>2</sub> H | 69        |
| 6-Cl | D <sub>2</sub> O               | D                 | 61        |
| 6-Cl | CO <sub>2</sub>                | CO <sub>2</sub> H | 73        |
| 5-Br | D <sub>2</sub> O               | D                 | 58        |
| 5-Br | CO <sub>2</sub>                | CO <sub>2</sub> H | 60        |
| 5-Br | I <sub>2</sub>                 | 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<sub>2</sub>O at -78 °C gave the corresponding 4-lithio intermediates **62** even with a chloro or methoxy substituent in the 6-position (Scheme 20).<sup>69</sup> Reactions of **62** with various electrophiles gave substituted pyridines **63** in 50–95% yields (Table 16).<sup>69</sup>

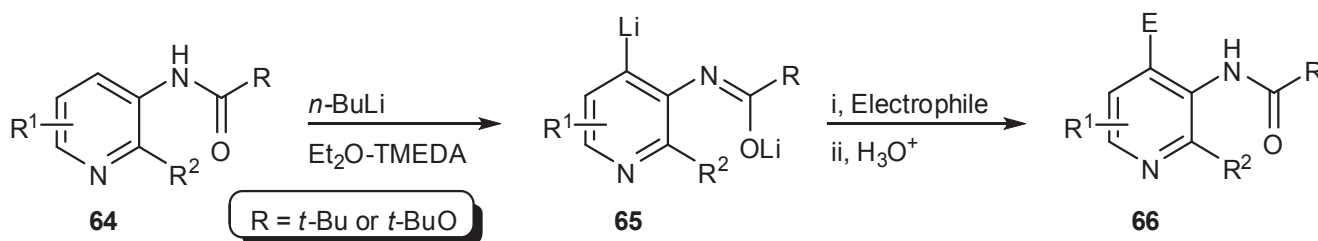


**Scheme 20.** Directed lithiation and substitution of 3-(2-methyloxetan-2-yl)pyridines **61**<sup>69</sup>

**Table 16.** Lithiation and substitution of **61** according to Scheme 20<sup>69</sup>

| R   | Electrophile                                  | E  | Yield (%) |
|-----|---|--|-----------|
| H   | Me <sub>3</sub> SiCl                          | Me <sub>3</sub> Si                       | 78        |
| H   | (PhS) <sub>2</sub>                            | PhS                                      | 91        |
| H   | Me <sub>2</sub> NCHO                          | CHO                                      | 78        |
| H   | PhNCO   | PhNHCO                                   | 80        |
| H   | CNOCOEt                                       | EtOCO                                    | 77        |
| H   | MeCHO   | MeCH(OH)                                 | 70        |
| H   | 4-ClC <sub>6</sub> H <sub>4</sub> CHO         | 4-ClC <sub>6</sub> H <sub>4</sub> CH(OH) | 90        |
| H   | PhCH <sub>2</sub> NHSO <sub>2</sub> Ph        | PhC(H)NHSO <sub>2</sub> Ph               | 50        |
| H   | PhCH <sub>2</sub> NHPh                        | PhC(H)NHPh                               | 77        |
| H   | C <sub>2</sub> Cl <sub>6</sub>                | Cl                                       | 85        |
| H   | C <sub>2</sub> H <sub>4</sub> Br <sub>2</sub> | Br                                       | 82        |
| H   | I <sub>2</sub>                                | I  | 79        |
| OMe | I <sub>2</sub>                                | I  | 77        |
| Cl  | I <sub>2</sub>                                | I  | 61        |
| H   | CD <sub>3</sub> OD                            | D  | 95        |
| OMe | CD <sub>3</sub> OD                            | D  | 95        |
| Cl  | CD <sub>3</sub> OD                            | D  | 95        |

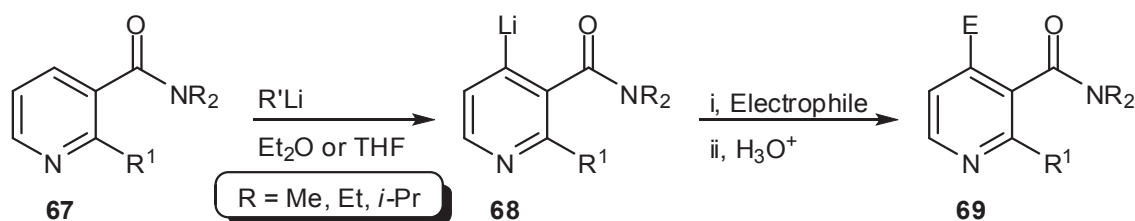
In some other cases the situation is more confused, because only products of 4-substitution have been reported, but in many examples there is already a substituent at the 2-position, so regioselectivity is probably not an issue. Sometimes when there is no 2-substituent, the reported yields of 4-substituted 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<sub>2</sub>O and TMEDA, or with *t*-BuLi or *n*-BuLi in THF at  $-78$  °C (Scheme 21) gave the yields of 4-substituted products **66** reported in Table 17.<sup>25,58–61</sup>

**Scheme 21.** Directed lithiation and substitution of **64**<sup>25,58–61</sup>

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

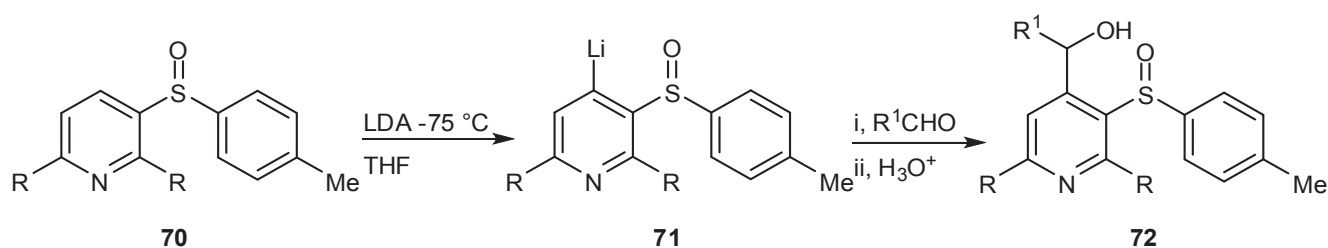
**Table 17.** Lithiation and substitution of **64** according to Scheme 21<sup>25,58–61</sup>

| R             | R <sup>1</sup> | R <sup>2</sup>          | Electrophile                          | E                                     | Yield (%) |
|---------------|----------------|-------------------------|---------------------------------------|---------------------------------------|-----------|
| <i>t</i> -Bu  | H              | H                       | (MeS) <sub>2</sub>                    | MeS                                   | 42        |
| <i>t</i> -Bu  | 5-Me           | H                       | I <sub>2</sub>                        | I                                     | 47        |
| <i>t</i> -Bu  | 5-Me           | OMe                     | I <sub>2</sub>                        | I                                     | 68        |
| <i>t</i> -Bu  | 5-Me           | OPr <sup><i>i</i></sup> | I <sub>2</sub>                        | I                                     | 60        |
| <i>t</i> -Bu  | 5,6-di-Me      | OPr <sup><i>i</i></sup> | I <sub>2</sub>                        | I                                     | 58        |
| <i>t</i> -Bu  | 6-Me           | OMe                     | I <sub>2</sub>                        | I                                     | 87        |
| <i>t</i> -BuO | H              | OMe                     | MeI                                   | Me                                    | 84        |
| <i>t</i> -BuO | H              | OMe                     | PhCH <sub>2</sub> Br                  | PhCH <sub>2</sub>                     | 67        |
| <i>t</i> -BuO | H              | OMe                     | Bu <sub>3</sub> SnCl                  | Bu <sub>3</sub> Sn                    | 86        |
| <i>t</i> -BuO | H              | OMe                     | PhCH <sub>2</sub> OCH <sub>2</sub> Cl | PhCH <sub>2</sub> OCH <sub>2</sub> Cl | 73        |
| <i>t</i> -BuO | H              | OMe                     | Me <sub>2</sub> NCHO                  | CHO                                   | 91        |
| <i>t</i> -BuO | H              | OMe                     | I <sub>2</sub>                        | I                                     | 59        |
| <i>t</i> -BuO | 6-OMe          | OMe                     | MeI                                   | Me                                    | 77        |
| <i>t</i> -BuO | 6-OMe          | OMe                     | PhCH <sub>2</sub> Br                  | PhCH <sub>2</sub>                     | 63        |
| <i>t</i> -BuO | 6-OMe          | OMe                     | Bu <sub>3</sub> SnCl                  | Bu <sub>3</sub> Sn                    | 82        |
| <i>t</i> -BuO | 6-OMe          | OMe                     | PhCH <sub>2</sub> OCH <sub>2</sub> Cl | PhCH <sub>2</sub> OCH <sub>2</sub> Cl | 80        |
| <i>t</i> -BuO | 6-OMe          | OMe                     | Me <sub>2</sub> NCHO                  | CHO                                   | 89        |
| <i>t</i> -BuO | 6-OMe          | OMe                     | I <sub>2</sub>                        | I                                     | 47        |

**Scheme 22.** Directed lithiation and substitution of **67**<sup>31,63–66</sup>**Table 18.** Lithiation and substitution of **67** according to Scheme 22<sup>31,63–66</sup>

| R            | R <sup>1</sup> | R'Li                 | Electrophile          | E                     | Yield (%) |
|--------------|----------------|----------------------|-----------------------|-----------------------|-----------|
| Me           | H              | Et <sub>2</sub> NLi  | D <sub>2</sub> O      | D                     | 14        |
| Et           | H              | Et <sub>2</sub> NLi  | D <sub>2</sub> O      | D                     | 11        |
| Et           | 2-Br           | LDA                  | Et <sub>2</sub> NCOC1 | Et <sub>2</sub> NCO   | 80        |
| <i>i</i> -Pr | H              | LDA                  | MeOD                  | D                     | 46        |
| <i>i</i> -Pr | H              | LDA                  | Ph <sub>2</sub> CO    | Ph <sub>2</sub> C(OH) | 68        |
| <i>i</i> -Pr | H              | LDA                  | Me <sub>2</sub> NCHO  | CHO                   | 39        |
| <i>i</i> -Pr | 2-OMe          | LDA–TMEDA            | D <sub>2</sub> O      | D                     | 90        |
| <i>i</i> -Pr | 2-OMe          | LTMP–TMEDA           | MeOD                  | D                     | 94        |
| <i>i</i> -Pr | 2-OMe          | LTMP–TMEDA           | Me <sub>3</sub> SiCl  | Me <sub>3</sub> Si    | 79        |
| <i>i</i> -Pr | 2-OMe          | LTMP–TMEDA           | HCO <sub>2</sub> Et   | CHO                   | 64        |
| <i>i</i> -Pr | 2-OMe          | LTMP–TMEDA           | Me <sub>2</sub> NCHO  | CHO                   | 85        |
| <i>i</i> -Pr | 2-OMe          | LTMP–TMEDA           | CO <sub>2</sub>       | CO <sub>2</sub> H     | 73        |
| <i>i</i> -Pr | 2-OMe          | LTMP–TMEDA           | MeCO <sub>2</sub> Et  | MeCO                  | 49        |
| <i>i</i> -Pr | 2-OMe          | LTMP–TMEDA           | MeCONMe(OMe)          | MeCO                  | 45        |
| <i>i</i> -Pr | 2-OMe          | LTMP–TMEDA           | MeCHO                 | MeCH(OH)              | 79        |
| <i>i</i> -Pr | 2-OMe          | <i>n</i> -BuLi–TMEDA | Me <sub>2</sub> CO    | Me <sub>2</sub> C(OH) | 68        |

This is also the situation for lithiation of enantiopure 3-(4-tolylsulfinyl)pyridines **70** (Scheme 23) with LDA (3.2 mole equivalents) in THF at  $-75\text{ }^{\circ}\text{C}$  to give the corresponding lithium reagents **71**.<sup>67</sup> Reactions of **71** with aldehydes gave **72** (Table 19) as mixtures of diastereoisomers,<sup>67</sup> but yields were not good in cases where there was no 2-substituent in the substrate. The diastereoselectivity was high (>99%) with somewhat 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**<sup>67</sup>

**Table 19.** Lithiation and substitution of **70** according to Scheme 23<sup>67</sup>

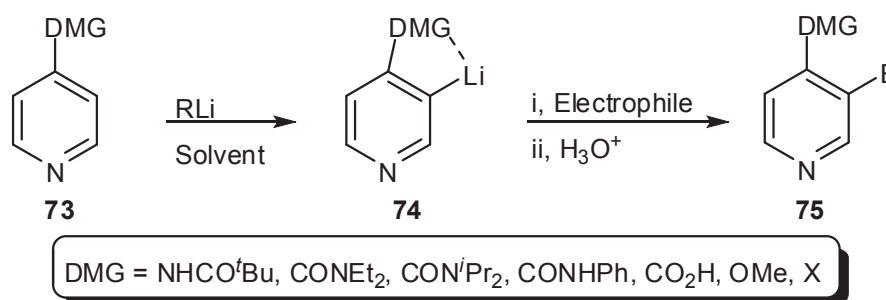
| <b>70</b> | R   | R <sup>1</sup> | <b>72</b> , configuration at new stereogenic center (de%) | Yield (%) |
|-----------|-----|----------------|---|-----------|
| <i>S</i>  | H   | Me             | <i>R</i> (14)   | 27        |
| <i>S</i>  | H   | Et             | <i>R</i> (26)   | 27        |
| <i>S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

Reactions of methoxypyridinecarboxaldehydes with lithium dialkylamides gave the corresponding  $\alpha$ -aminoalkoxide addition products, which could be lithiated *in-situ* with an alkyl lithium.<sup>70</sup> Reactions of the lithiated species with iodomethane gave methylated derivatives in 65–82% yields. The site of lithiation was found to be next to either the methoxy or carboxaldehyde group. Also, it was found to be dependent

on the type of lithium dialkylamides used.<sup>70</sup> For example, lithiation of 6-methoxy-3-pyridinecarboxaldehyde with 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.<sup>70</sup> On the other hand, 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.<sup>70</sup>

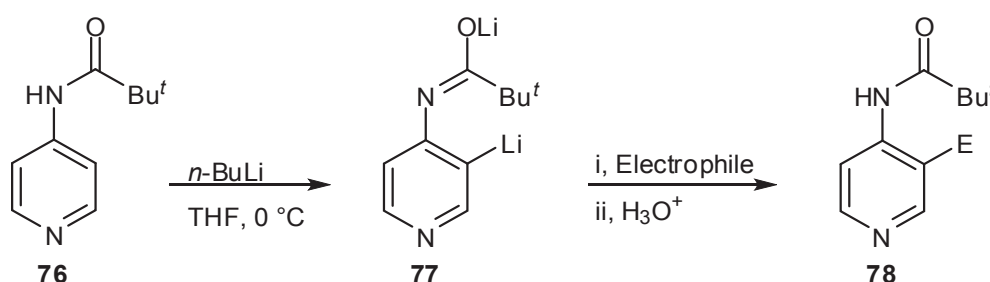
#### 4. DIRECTED LITHIATION OF 4-SUBSTITUTED PYRIDINES

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).<sup>25,28,30,31,36,37,49,53,71,72</sup>



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

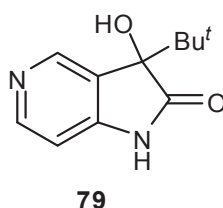
Directed lithiation of 4-(pivaloylamino)pyridine (**76**) with *n*-BuLi (two mole equivalents) at 0 or  $-78$  °C in THF followed by reactions with electrophiles gave 3,4-disubstituted pyridines **78** in 54–92% yields (Scheme 25; Table 20).<sup>25,72</sup> Carbonylation of **77** at 0 °C gave 3-*tert*-butyl-6-azadioxindole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



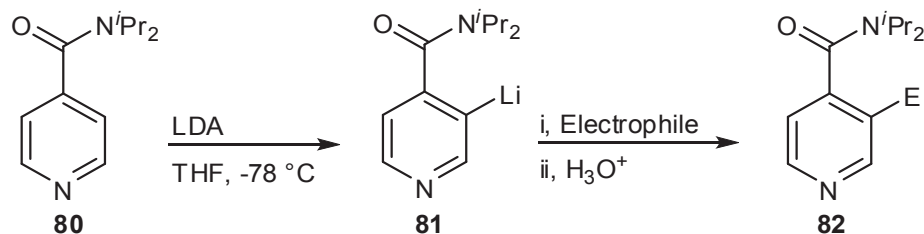
**Scheme 25.** Directed lithiation and substitution of 4-(pivaloylamino)pyridine (**76**)<sup>25,72</sup>

**Table 20.** Lithiation and substitution of **76** according to Scheme 25<sup>25,72</sup>

| Electrophile   | E                                 | Yield (%) |
|--|-----------------------------------|-----------|
| D <sub>2</sub> O   | D                                 | 87        |
| Me <sub>3</sub> SiCl   | Me <sub>3</sub> Si                | 86        |
| Me <sub>2</sub> NCHO   | CHO                               | 54        |
| (MeS) <sub>2</sub>   | SMe                               | 67        |
| MeI  | Me                                | 72        |
| PhCHO  | PhCH(OH)                          | 63        |
| ClCO <sub>2</sub> Et   | CO <sub>2</sub> Et                | 65        |
| ( <sup>t</sup> Pr <sub>2</sub> NCS <sub>2</sub> ) <sub>2</sub> | SCSN <sup>t</sup> Pr <sub>2</sub> | 92        |

**Figure 4.** Structure of 3-*tert*-butyl-6-azadioxindole (**79**)<sup>20</sup>

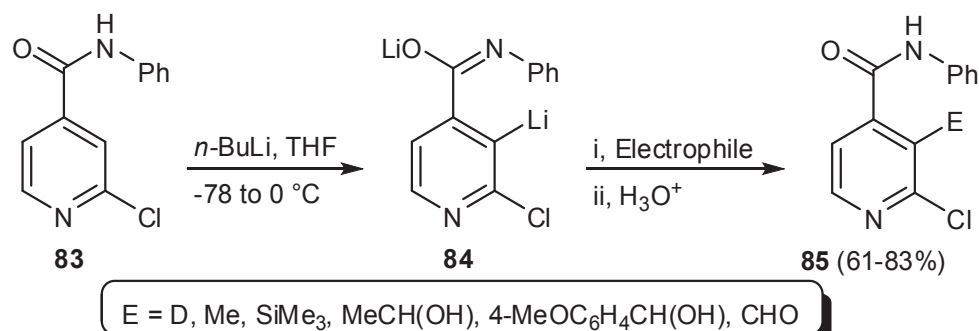
Directed lithiation of *N,N*-diisopropylisonicotinamide (**80**) was successful with LDA in Et<sub>2</sub>O at –78 °C to give lithium reagent **81**, which was reacted with electrophiles to give the corresponding substituted derivatives **82** in modest yields (Scheme 26; Table 21).<sup>30,31</sup>

**Scheme 26.** Directed lithiation and substitution of **80**<sup>30,31</sup>**Table 21.** Lithiation and substitution of **80** according to Scheme 26<sup>30,31</sup>

| Electrophile         | E                     | Yield (%) |
|----------------------|-----------------------|-----------|
| MeOD                 | D                     | 43        |
| Ph <sub>2</sub> CO   | Ph <sub>2</sub> C(OH) | 55        |
| Me <sub>2</sub> NCHO | CHO                   | 37        |
| PhCONMe <sub>2</sub> | COPh                  | 36        |

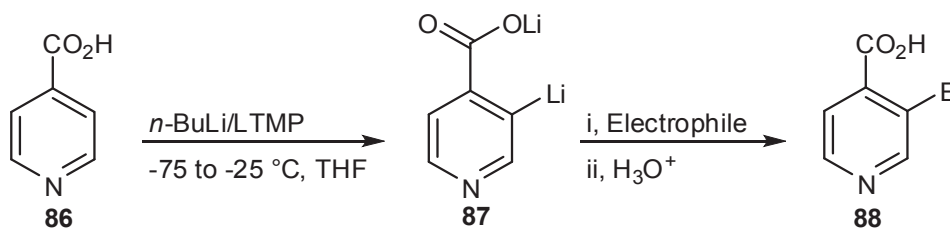
Directed lithiation of 2-chloro-*N*-phenylisonicotinamide (**83**) occurs at position 3 with *n*-BuLi (2.1 mole equivalents) in THF at –78 to 0 °C (Scheme 27).<sup>28</sup> A dimethylated product was obtained in 83% yield when

lithium reagent **84** was reacted with excess iodomethane (3.0 mole equivalents) due to methylation at both nitrogen and C-3.<sup>28</sup> The simple adducts obtained from use of aldehydes as electrophiles were not isolated, but were cyclized under acidic conditions to give the corresponding lactones.<sup>28</sup>



**Scheme 27.** Directed lithiation and substitution of **83**<sup>28</sup>

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).<sup>36,37</sup>

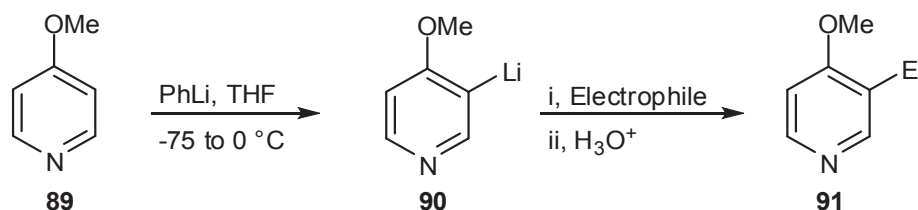


**Scheme 28.** Directed lithiation and substitution of isonicotinic acid (**86**)<sup>36,37</sup>

**Table 22.** Lithiation and substitution of **86** according to Scheme 28<sup>36,37</sup>

| Electrophile                   | E                 | Yield (%) |
|--------------------------------|-------------------|-----------|
| C <sub>2</sub> Cl <sub>6</sub> | Cl                | 49        |
| I <sub>2</sub>                 | I                 | 45        |
| D <sub>2</sub> O               | D                 | 78        |
| CO <sub>2</sub>                | CO <sub>2</sub> H | 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).<sup>71</sup> Lithiation of 3,4-dimethoxypyridine with *n*-BuLi (2.2 mole equivalents) at  $-78$  to 0 °C in THF took place at the 2-position.<sup>71</sup>

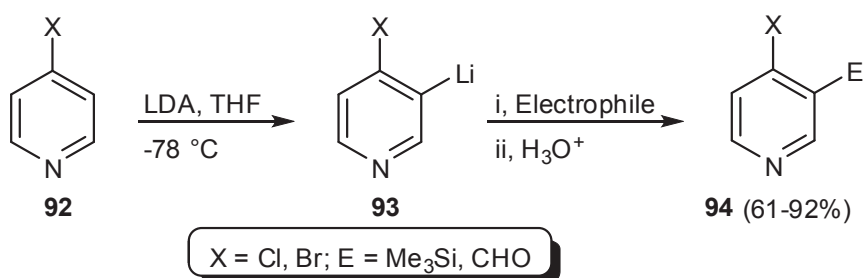


**Scheme 29.** Directed lithiation and substitution of 4-methoxypyridine (**89**)<sup>71</sup>

**Table 23.** Lithiation and substitution of **89** according to Scheme 29<sup>71</sup>

| Electrophile                           | E   | Yield (%) |
|--|---|-----------|
| PhCHO                                  | PhCH(OH)                                  | 90        |
| 2-MeOC <sub>6</sub> H <sub>4</sub> CHO | 2-MeOC <sub>6</sub> H <sub>4</sub> CH(OH) | 89        |
| B(OMe) <sub>3</sub>                    | OH  | 65        |
| I <sub>2</sub>                         | I   | 76        |
| BrCN                                   | Br  | 67        |

Directed lithiation of 4-halopyridines **92** was successful with LDA at  $-78\text{ }^{\circ}\text{C}$  in THF (Scheme 30).<sup>40,49</sup>



**Scheme 30.** Directed lithiation and substitution of 4-halopyridines **92**<sup>40,49</sup>

## 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.

## 6. ACKNOWLEDGEMENTS

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