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Advances in the directed metallation of azines and diazines (pyridines, pyrimidines, pyrazines, pyridazines, quinolines, benzodiazines and carbolines). Part 1: Metallation of pyridines, quinolines and carbolines

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1. Introduction

The purpose of this review is to update the previous summary[1] of directed *ortho*-metallation (DoM) reactions in the pyridine, quinoline, isoquinoline and carboline series. The review will be divided according to the various directed metallation groups (DMGs) (halo and trifluoromethyl, OH, OR, $OCONR_2$ and $OSONR_2$, SO_2NR_2 and SOR, NHCOR and NHCOOR, COOH, 2-oxazolino, CONHR, $CONR_2$, COR, and masked CHO and COR), and metallation chemistry of *N*-oxides, activated heterocycles, and parent heterocycles will then be presented.

This report will only cover deprotonation of an azine ring. Those investigations which have been published on lateral metallation, halogen–metal exchange or on metallation followed by elimination of a metal salt to give heteroarynes will not be presented. The results of studies on the DoM reaction in the pyrimidine, pyrazine, pyridazine and benzodiazine series will be published as a separate report and applications of the method will also be described in another review.

In this introduction[2] it should first be pointed out that the chemistry of azines is of great importance for research in the pharmaceutical industry and for bioorganic chemistry. The development of DoM reactions involving azines is therefore of crucial importance as it provides a route to exploit organometallic chemistry in this field.

The regiospecific exchange of an aryl hydrogen by metals such as lithium and magnesium generally requires the

presence of substituents with heteroatoms. This transformation (known as the DoM reaction) has great synthetic potential. While the metallation of π-excessive heterocycles has long been recognized and explored, however, applications of the *ortho*-functionalization strategy to π-deficient heteroaromatics (pyridine, diazines, quinoline, isoquinoline and carbolines) have received less attention, one complication being that the 'soft' alkyllithiums commonly used to metallate π-excessive heterocycles can undergo a facile nucleophilic addition to the azomethine (C=N) bond of the azine, even at low temperature. Following a careful study of the factors responsible for metallation and nucleophilic addition it is, nevertheless, possible to achieve clean metallation with alkyllithiums for many DMGs (NHCOR, OR, Cl, F, $OCONR_2$, CONHR). For substrates that are more reactive towards nucleophilic addition or halogen–metal exchange (DMGs like I, Br, Cl, F, $CONR_2$, SOR, etc.), the harder and less basic lithium di-*i*-propylamide (LDA, pK_a 35.7) or lithium 2,2,6,6-tetramethylpiperidide (LTMP, pK_a 37.3) can usually be relied upon to effect deprotonation.

The regioselective DoM effects can often be rationalized in terms of the kinetic or thermodynamic control of a reaction. The main factors are:

1. the inductive electron-withdrawing effect of the DMG;
2. the strength of coordination between the heteroatom-containing DMG and the metal; and
3. electronic repulsion between the carbanion and the lone pair of the azine nitrogen.

The reaction is usually under thermodynamic control when metal amides are used as the bases and the regioselectivity then observed is the result of effects such as stabilization by chelation of the metal with the DMG (a), stabilization by the electron-withdrawing effect of the DMG (b) and destabilization by electronic repulsion between the carbanion and the lone pair of the azine nitrogen (c). As a result, the formation of pyridine 3- and 4-carbanions is a more favourable process than that of the 2-carbanion analogue on thermodynamic grounds. These effects can be 'oversimplified' (Fig. 1).

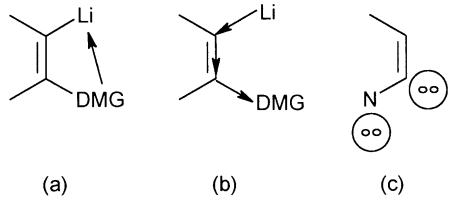


Figure 1. Effects under thermodynamic control.

When alkyllithiums are used as the bases at low temperature, the reaction mainly proceeds under kinetic control. The acid–base (inductive) mechanism (d) and chelation in the transition state (e) direct the course of the reaction and coordination of a heteroatom-containing DMG to the Lewis acidic metal allows disaggregation of the metallating agent. This reinforces the electron-withdrawing effect of the DMG and increases the proximity effect of the complexed base. The solvent effect becomes more important when no strong DMG is present on the ring and, in the absence of a chelating solvent such as THF, the azine nitrogen can promote deprotonation at C2 through complexation of the base (Fig. 2).

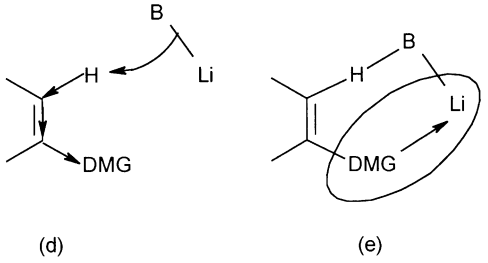


Figure 2. Effects under kinetic control.

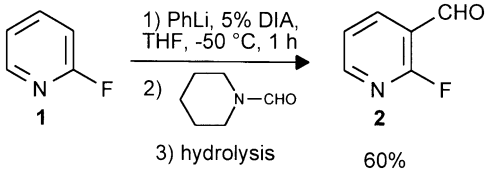
2. Halogen- and trifluoromethyl-based DMGs

2.1. Fluoro derivatives

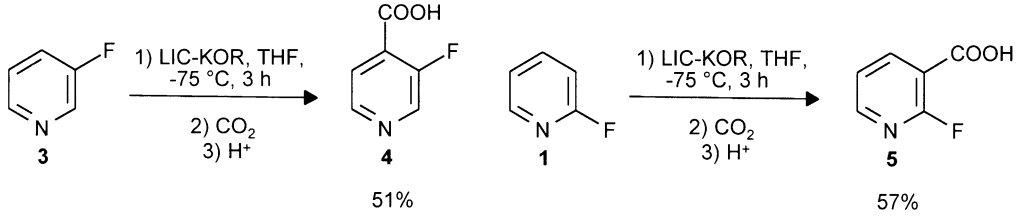
2.1.1. Fluoropyridines. It was known in 1990 that LDA could be used to metallate both 2- and 3-fluoropyridines. Proton abstraction from the latter compound using a BuLi–TMEDA complex or LDA in THF occurred at C4 (thermodynamic control) whereas treatment with BuLi–TMEDA or BuLi–DABCO complexes in diethyl ether led to C2 metallation (kinetic control).[1]

In 1991, a catalytic metallation process was developed by Mallet in which a mixture of phenyllithium (PhLi) and 5 mol% di-*i*-propylamine (DIA) was used to deprotonate 2-fluoropyridine (**1**) giving **2** (Scheme 1).[3]

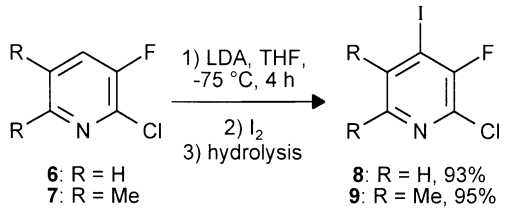
Schlosser showed in 1994 that LIC–KOR (a mixture of



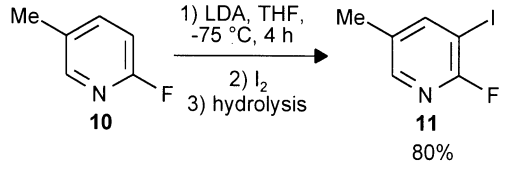
Scheme 1.



Scheme 2.



Scheme 3.



Scheme 4.

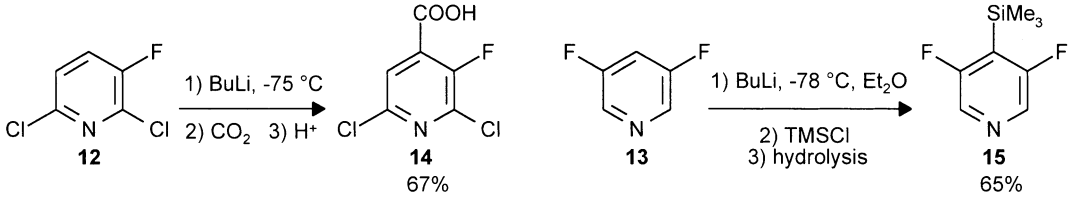
BuLi and *t*-BuOK), which does not add nucleophilically to the pyridine ring, favoured proton abstraction from the most acidic 4-position of 3-fluoropyridine (**3**). In the same way, 2-fluoropyridine (**1**) was metallated at C3. Fluoropyridinecarboxylic acids **4** and **5** were obtained (Scheme 2).[4]

Metallation using LDA was then extended to substituted fluoropyridines such as 2-chloro-3-fluoropyridine (**6**)[5] and 2-chloro-3-fluoro-5,6-dimethylpyridine (**7**),[6] to afford **8** and **9**, respectively. No lithiation of the methyl groups was observed in **7** (Scheme 3). Under the same conditions, 2-fluoro-5-methylpyridine (**10**) was regioselectively deprotonated at C3 and compound **11** was obtained (Scheme 4).[7]

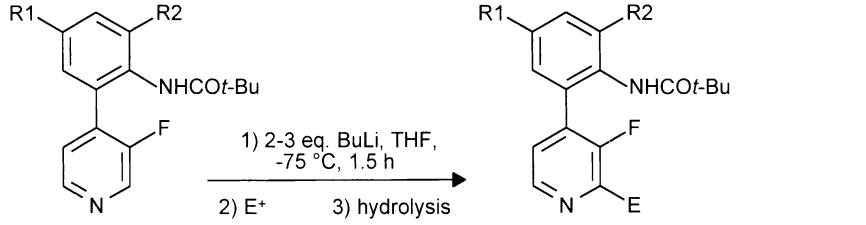
BuLi was used to metallate 3-fluoropyridine **12** at −75°C, the proton abstraction occurring at C4 (product **14**).[8] 3,5-Difluoropyridine (**13**) was likewise deprotonated at C4 (product **15**) (Scheme 5).[9]

In the course of synthesizing various natural products, the metallation of 3-fluoropyridines substituted at C2 or C4 was studied. Notably, when the 4-phenyl-3-fluoropyridines **16**–**18** were lithiated with BuLi at low temperature,[5,10,11] fluoro-directed metallation at C2 of the pyridine (to give **19**–**21**) was favoured over metallation of the phenyl ring containing the *ortho*-directing pivaloylamino group (Scheme 6).

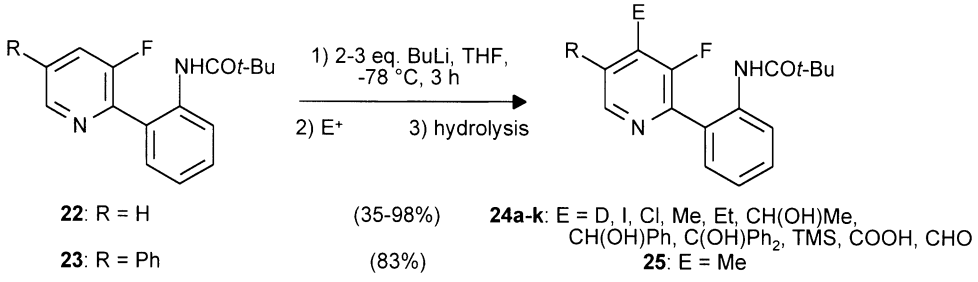
Metallation of the 2-phenyl-3-fluoropyridines **22** and **23** was performed under the same conditions to allow the synthesis of **24** and **25**. The reactions were quantitative and regioselective, with the fluorine atom directing



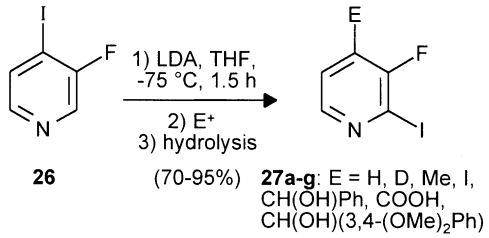
Scheme 5.



Scheme 6.



Scheme 7.



Scheme 8.

metallation to the most acidic C4 position of the pyridine ring (Scheme 7).[12,13]

3-Fluoro-4-iodopyridine (**26**) has likewise been metallated with LDA. Lithiation under kinetic control was directed by the fluorine to C2. Interestingly, a rapid isomerization of the intermediate 3-fluoro-2-lithiopyridine to the more stable 3-fluoro-4-lithiopyridine takes place through a series of equilibria involving halogen–metal exchange. Overall, this results in the migration of the iodo group from C4 to C2, as demonstrated in **27** (Scheme 8).[7]

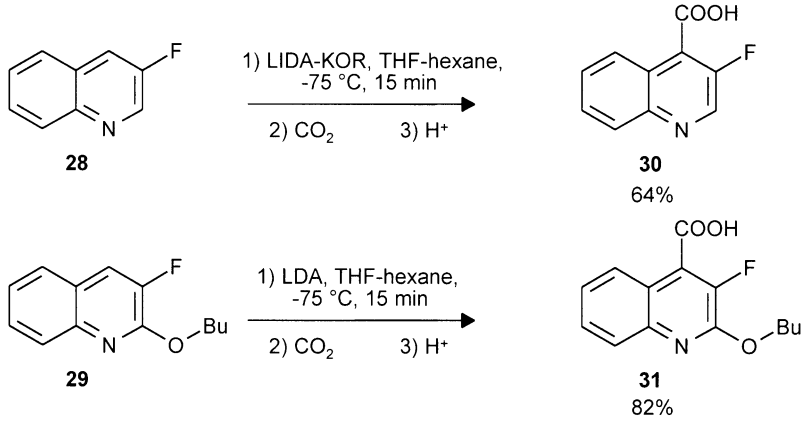
2.1.2. Fluoroquinolines. Due to its lower LUMO level, quinoline is more prone to nucleophilic addition than pyridine. 2-, 3-, 5-, 6- and 7-Fluoroquinolines have nevertheless been deprotonated adjacent to fluorine with LDA.[1] Under the same conditions, no DoM reaction was observed with 8-fluoroquinoline. Metallation of 3-fluoroquinoline (**28**) required the use of LDA activated by *t*-BuOK (LIDA–KOR). Metallation using LDA has also been extended to substituted fluoroquinolines such as 2-butoxy-3-fluoroquinoline (**29**). Fluoroquinolinecarboxylic acids **30** and **31** were obtained (Scheme 9).[4]

For 8-fluoro-6-methoxymethoxyquinoline (**32**), MeLi was successfully used to prepare **33**, whereas 1,2-addition compounds were simultaneously formed when **32** was treated with BuLi and *t*-BuLi (Scheme 10).[14]

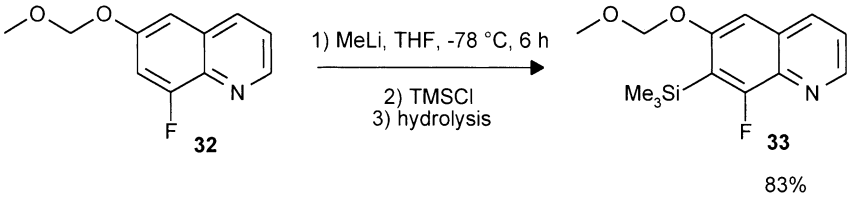
The halogen migration noted for 3-fluoro-4-iodopyridine (**26**) was additionally observed with 3-fluoro-4-iodoquinoline (**34**), leading to **35** (Scheme 11).[15,16]

2.2. Trifluoromethyl derivatives

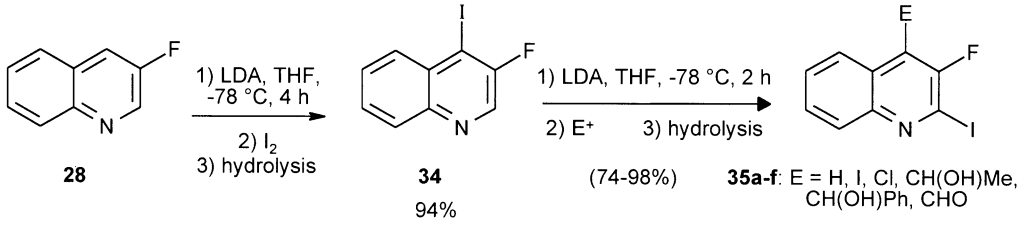
2.2.1. (Trifluoromethyl)pyridines. The reactions of 3-(trifluoromethyl)pyridine (**36**), 3,4-bis(trifluoromethyl)pyridine (**37**), 3,5-bis(trifluoromethyl)pyridine (**38**) and 2,5-bis(trifluoromethyl)pyridine (**39**) with BuLi in diethyl



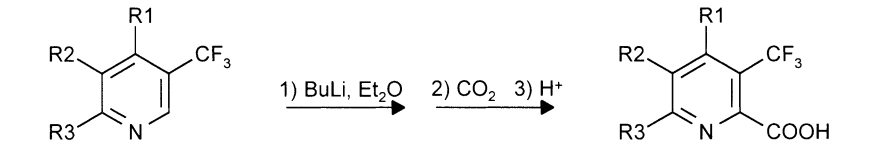
Scheme 9.



Scheme 10.



Scheme 11.



36: R1 = R2 = R3 = H	-60 °C, 50 min	(74%)	**40**: R1 = R2 = R3 = H
37: R1 = CF_3, R2 = R3 = H	-40 °C, 40 min	(57%)	**41**: R1 = CF_3, R2 = R3 = H
38: R1 = R3 = H, R2 = CF_3	-10 °C, 10 min	(85%)	**42**: R1 = R3 = H, R2 = CF_3
39: R1 = R2 = H, R3 = CF_3	-40 °C, 40 min	(55%)	**43**: R1 = R2 = H, R3 = CF_3

Scheme 12.

ether resulted in highly regioselective lithiation at C2 (compounds **40**–**43**) (Scheme 12).[17]

The regioselectivity of the lithiation could be rationalized by coordination of the base to the ring nitrogen, thereby promoting proton abstraction at C2 by a proximity effect. It was noted that 2-(trifluoromethyl)pyridine, 2,4-bis(trifluoromethyl)pyridine, 2,6-bis(trifluoromethyl)pyridine and 2,4,6-tris(trifluoromethyl)pyridine underwent addition of the alkyllithium reagent or polymerization under the same reaction conditions.

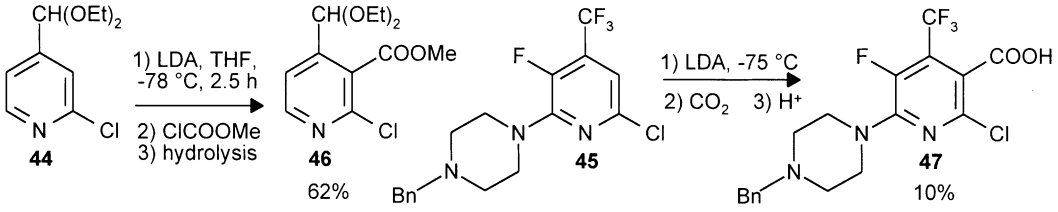
2.3. Chloro derivatives

2.3.1. Chloropyridines. In 1990, it was known that LDA could be used to metallate 2-, 3- and 4-chloropyridines.[1] This method has since been extended to other substituted chloropyridines, such as **44**[18] and **45**[8] (Scheme 13).

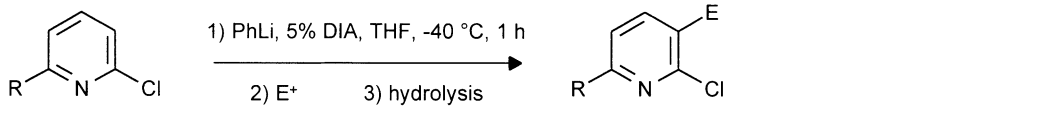
Deprotonation of the 2-chloro-6-substituted pyridines **48**–**50** has been effected using a combination of PhLi and DIA to allow the synthesis of **51**–**53** (Scheme 14),[3] with 2-chloro-6-methoxypyridine (**50**) showing a good regioselectivity for the position adjacent to chlorine.

Lithiation of 2,4-dichloropyridine (**54**) with LDA or BuLi was highly regioselective for lithiation at C3, affording **55**. Importantly, nucleophilic addition of BuLi to **54** was not observed, in contrast to the monosubstituted pyridine analogues (Scheme 15).[19] Metallation of 3,5-dichloropyridine (**56**) occurred at C4 on treatment with LDA and gave the formyl derivative **57** (Scheme 16).[20,21] 2,5-Dichloropyridine (**58**) was similarly deprotonated at C4 on exposure to LDA, leading to **59** (Scheme 17).[22]

When 2,6-dichloropyridine (**60**) was lithiated with LDA, 3-substituted pyridines **61** were primarily obtained with compound **61a** being formed as the only product of the reaction when **60** was lithiated over 150 min. With BuLi as the lithiating agent, 4-substituted pyridines **62** were



Scheme 13.

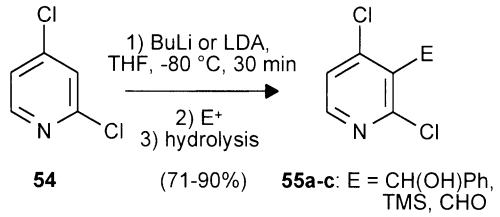


48: R = H (30-80%) **51a-k**: E = D, CHO, TMS, Me, CH_2-CH=CH_2, $C(OH)Et_2$, CH(OH)Ph, $C(OH)Ph_2$, CH(OH)(2-Cl-3-py), Br, I

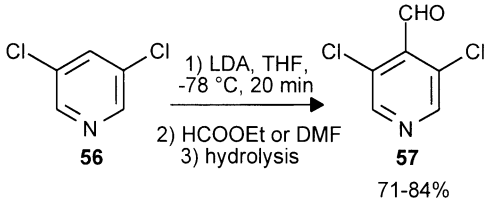
49: R = Cl (55%) **52**: E = CHO

50: R = OMe (55%, but at 0 °C instead of -40 °C) **53**: E = CHO

Scheme 14.

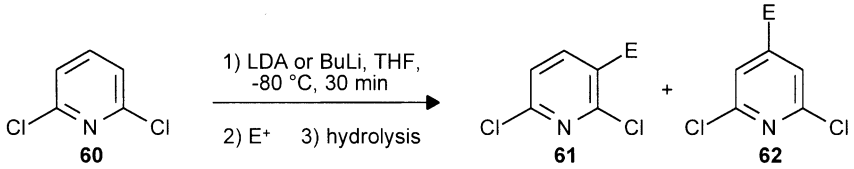


Scheme 15.



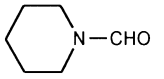
Scheme 16.

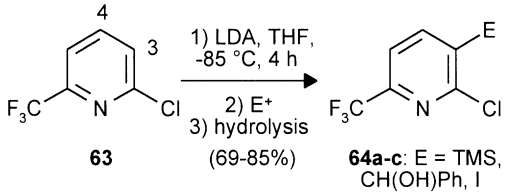
Scheme 17.



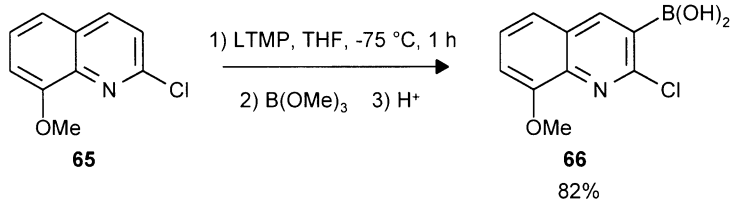
Scheme 18.

Table 1. Lithiation of 2,6-dichloropyridine

E^+	Yields (%) with LDA		Yields (%) with BuLi	
PhCHO	**61a**: 61	**62a**: 35	**61a**: 21	**62a**: 60
TMSCl	**61b**: 76	**62b**: 8	**61b**: 10	**62b**: 64
CH_3I	**61c**: 78	**62c**: 8	**61c**: 20	**62c**: 71
	**61d**: 60	**62d**: 6	**61d**: 50	**62d**: 12



Scheme 19.



Scheme 20.

predominantly obtained (except when *N*-formylpiperidine was used as an electrophile), the highest selectivity (85:15) being achieved for **62a** (76% yield) when lithiation was effected with *s*-BuLi. An acid–base (inductive) mechanism was suggested by Radinov to explain this observation (Scheme 18, Table 1).[19]

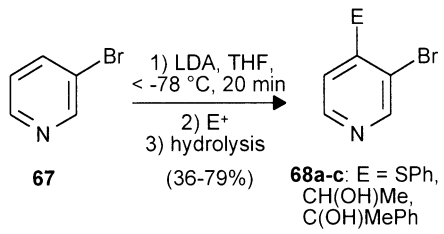
Analogous results were obtained with 2-chloro-6-(trifluoromethyl)pyridine (**63**). Under reversible conditions (LDA at −85°C), the thermodynamic 3-lithio derivative was favoured, affording **64** (Scheme 19), while alkyl and phenyllithiums, as well as LDA at lower temperatures, simultaneously abstracted protons from the 3- and 4-positions.[23] When the mixture of 3- and 4-lithio derivatives resulting from deprotonation with LDA at −110°C was quenched with iodine, only 2-chloro-4-iodo-6-(trifluoromethyl)pyridine was formed.

2.3.2. Chloroquinolines. Metallation of 2-chloroquinoline at C3 with LDA is known to be facile.[1] Its 8-methoxy derivative **65** has since been deprotonated at C3 using the more hindered and basic LTMP in the synthesis of the quinolineboronic acid **66** (Scheme 20).[24]

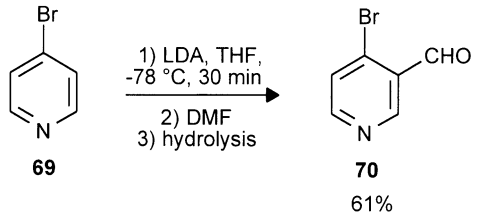
2.4. Bromo derivatives

2.4.1. Bromopyridines. It has been known for some time that 2-bromopyridine can be deprotonated with LDA at C3.[1] More recently it has been found that in situ trapping with chlorotrimethylsilane gave a mixture of 3- and 4-substituted compounds, showing that deprotonation occurs at both C3 and C4.[25]

It was also known that metallation of 3-bromopyridine (**67**) with LDA promoted halogen migration, to afford 4-bromo-3-substituted pyridines as the major product after addition of an electrophile.[1] Subsequently, it has been shown that, at temperatures below −78°C, no bromine migration takes place and 3-bromo-4-substituted pyridines **68a–c** can be obtained in reasonable yields (Scheme 21).[26] Conducting the reactions at −100°C, or with chlorotrimethylsilane as



Scheme 21.



Scheme 22.

an in situ trap, gave rise to mixtures of 2- and 4-substituted 3-bromopyridines.[25]

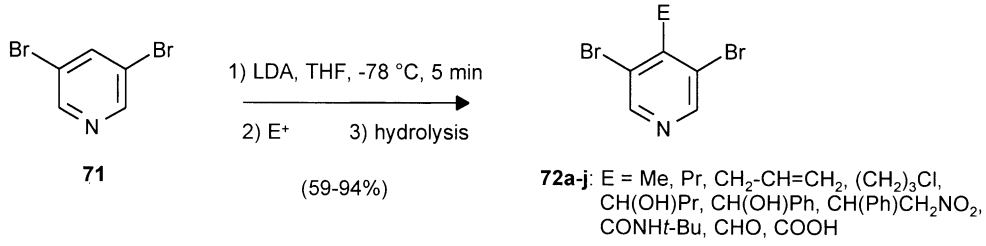
4-Bromopyridine (**69**) has been deprotonated with LDA, this method being used to introduce an aldehyde at C3 (product **70**) (Scheme 22),[27] and the procedure was successfully extended to 3,5-dibromopyridine (**71**), thereby allowing a range of groups to be introduced at C4 (compounds **72**) (Scheme 23).[28]

During the synthesis of atpenin B, the 5-bromopyridine **73** was deprotonated with LDA and the 6-lithio derivative which formed rearranged to the more stable 5-lithio compound flanked by bromine and *N*,*N*-di-*i*-propylcarbamate stabilizing groups before the ethanolysis, leading to **74** (Scheme 24).[29] The same results were observed using 5-bromo-3,4-dimethoxy-2,2′-bipyridine (**75**) to give **76** (Scheme 25).[30]

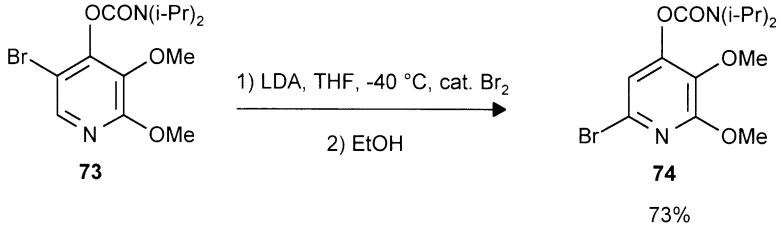
2.4.2. Bromoquinolines. The deprotonation of 2-bromoquinoline (**77**) to afford **78** has been described by Comins and co-workers (Scheme 26).[31]

2.5. Iodo derivatives

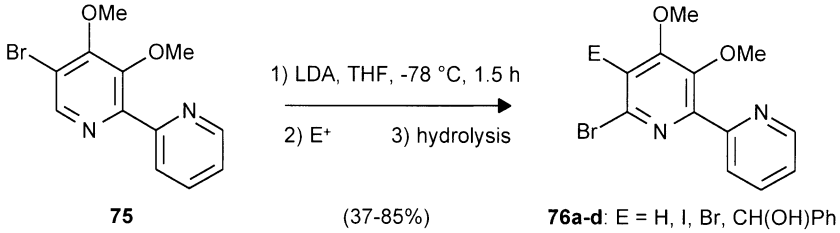
2.5.1. Iodopyridines. An attempted metallation of 3-iodopyridine with LDA at −95°C was unsuccessful, the dark polymeric material formed suggesting a rapid decomposition of the 3-iodo-4-lithiopyridine to 3,4-pyridyne.[26]



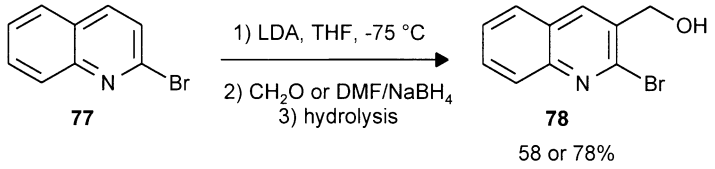
Scheme 23.



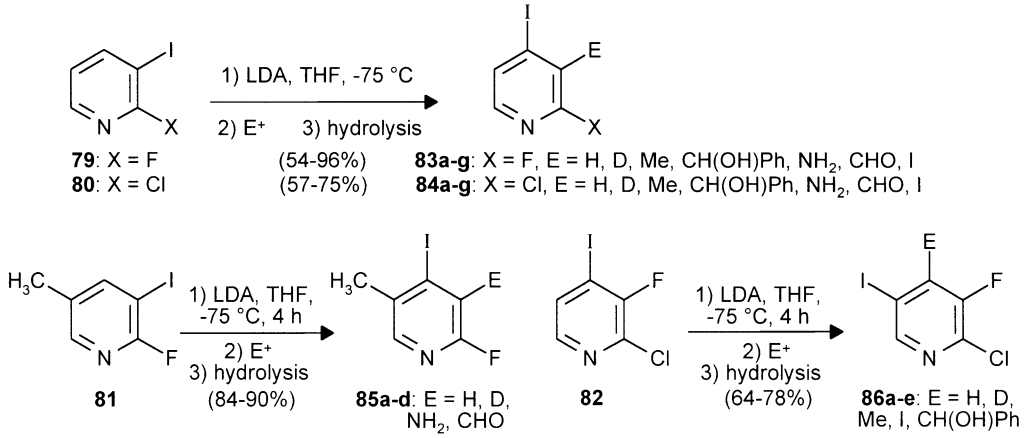
Scheme 24.



Scheme 25.



Scheme 26.



Scheme 27.

Metallation of iodopyridines may be feasible when the pyridine nucleus bears a second substituent. For the halogenated iodopyridines, **79**–**82**, iodine migration leading to a more stable lithio derivative was observed under the conditions used and allowed the synthesis of **83**–**86** (Scheme 27).[7]

The behaviour of 3-iodo-*N,N*-di-*i*-propylpyridine-2-carboxamides (**87** and **88**) towards metallation was very similar. 3-Substituted 4-iodo derivatives **89** and **90** were obtained. With **87**, the initially formed 4-lithio derivative could be intercepted by in situ quenching with chlorotrimethylsilane to give **91** (Scheme 28).[32,33]

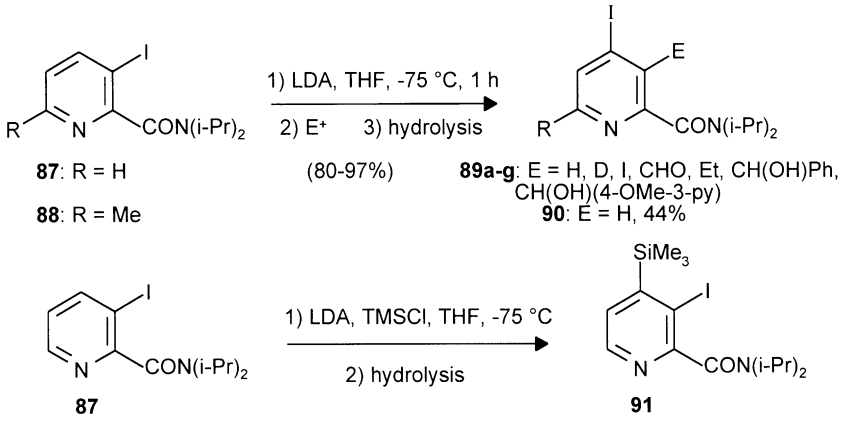
Metallation of the 4-iodopyridine **92** at C5 was achieved using LDA. Under these conditions, equilibration also took place to afford the more stable C4 lithio derivative, leading to **93** (Scheme 29).[13]

In all the aforementioned examples, elimination of lithium halide was avoided by using a low reaction temperature. Although alkyllithium derivatives are seldom useful for effecting the metallation of halo-substituted azines, they are often the reagent of choice when metallating pyridines containing electron-donating substituents.

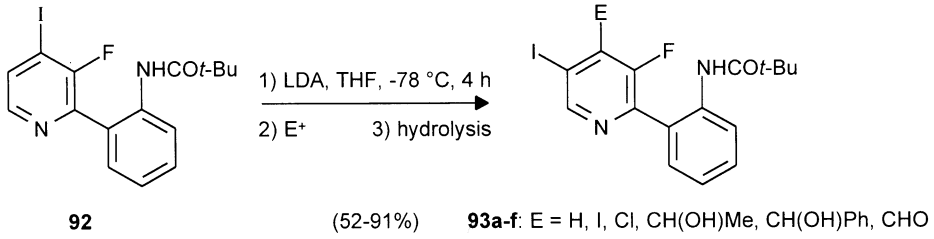
3. Oxygen-based DMGs

3.1. Hydroxy derivatives

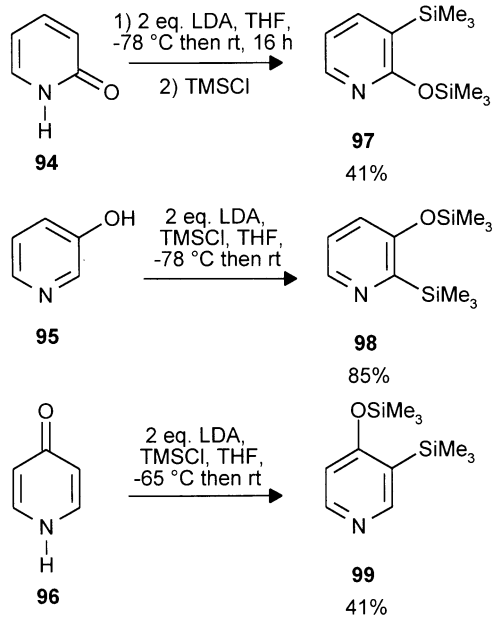
3.1.1. Pyridones. In 1988, Joule showed that lithiation of



Scheme 28.



Scheme 29.



Scheme 30.

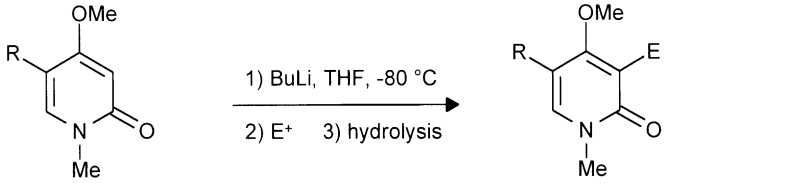
N-masked 4-pyridones occurred at C2.[34] Ab initio calculations were later performed on *N*-methylpyridones lithiated on the aromatic ring.[35]

Effenberger reported in 1991 the dideprotonation of 2-pyridone **94** using LDA. Metallation and in situ quenching with TMSCl was achieved with the isomers **95** and **96**, leading to **98** and **99**, respectively (Scheme 30).[25]

Whereas *N*-methyl-2-pyridone was predominantly lithiated at the methyl group when exposed to BuLi,[34] reaction between BuLi and the 4-methoxy-*N*-methyl-2-pyridones **100**–**103** resulted in deprotonation at C3, affording **104**–**107** (Scheme 31).[36]

3.1.2. Quinolones. Joule showed in 1992 that the reverse addition of *N*-methyl-4-quinolone (**108**) or quinolinethione (**109**) to LDA was efficient for lithiation at C2 (Scheme 32).[37]

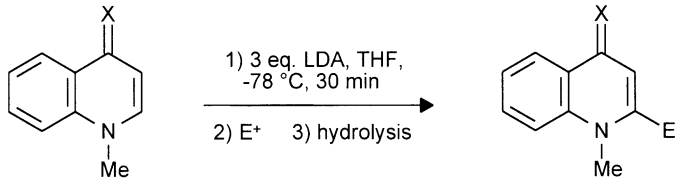
2-Quinolone (**112**) was cleanly deprotonated using the BuLi–TMEDA chelate (Scheme 33),[38–40] in contrast to *N*-methyl-2-quinolone which gave a complex mixture of products when treated similarly. Avendaño observed that metallation at C3 also occurred when an additional methoxy



100: R = H
101: R = Ph
102: R = Me
103: R = 4-(OMe)Ph

104a-d: E = D, Me, COOH, CH(OH)Ph
105: E = D, 75%
106: E = D, 92%
107: E = *(E)*-CH(OH)CH=CH-Me, 41%

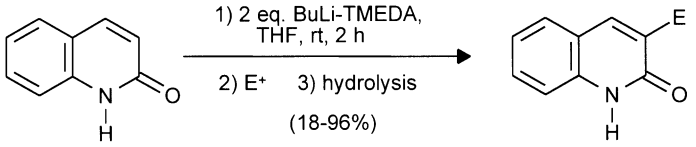
Scheme 31.



108: X = O (14-71%)
109: X = S (40-82%)

110a-k: E = D, Et, CH(OH)Ph, CH(OH)(4-(NO_2)Ph), CH(OH)(4-(OMe)Ph), CH(OH)(3-py), COPh, CO(3-py), CH_2OH, C(OH)PhMe, $C(OH)Ph_2$
111a-c: E = CH(OH)Ph, CH(OH)(3-py), CH(OH)(4-(OMe)Ph)

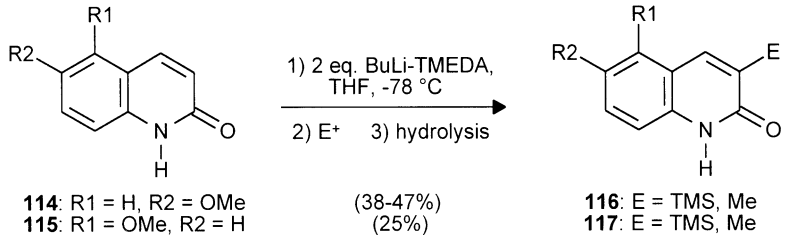
Scheme 32.



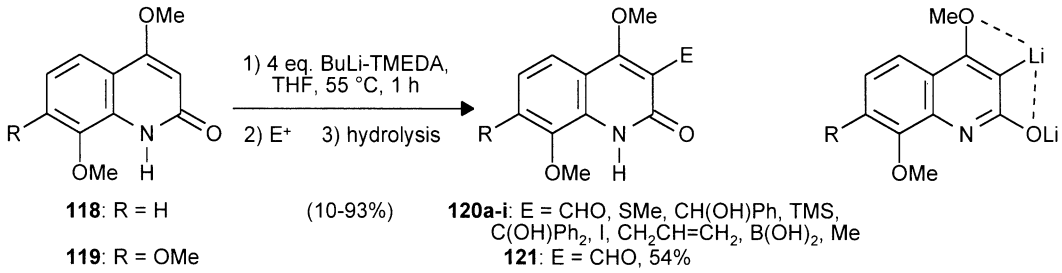
112

113a-l: E = Me, CH(OH)Ph, CH(OH)(4-(OMe)Ph), CH(OH)(4-FPh), CH(OH)(2-FPh), CH(OH)(4-ClPh), CH(OH)(2-ClPh), $C(OH)Ph_2$, TMS, SMe, CHO, COOH

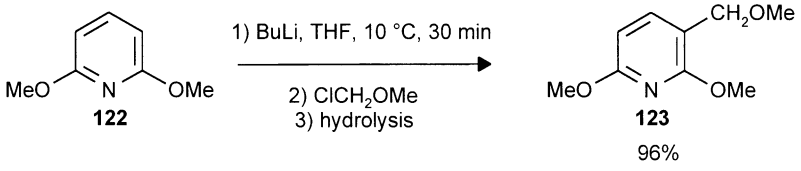
Scheme 33.



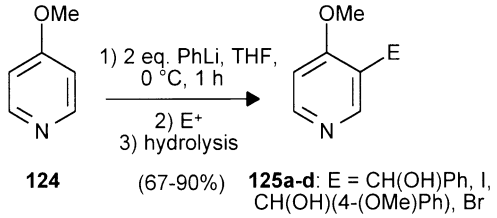
Scheme 34.



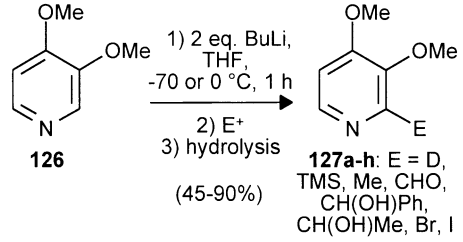
Scheme 35.



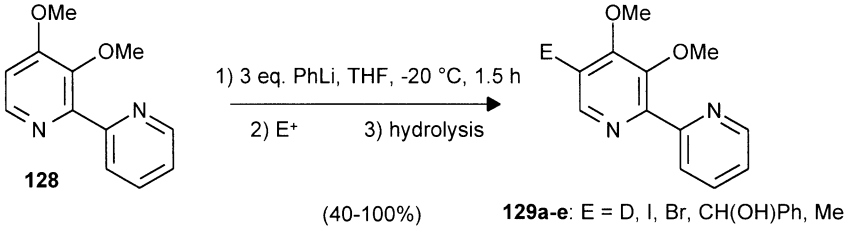
Scheme 36.



Scheme 37.



Scheme 38.



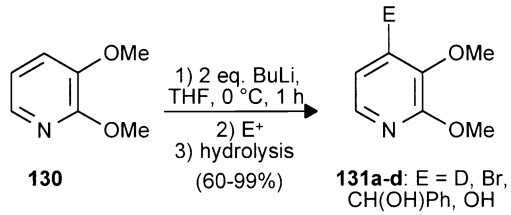
Scheme 39.

group was present at C5 or C6 (compounds **114** and **115**), leading to **116**–**117** (Scheme 34).[41]

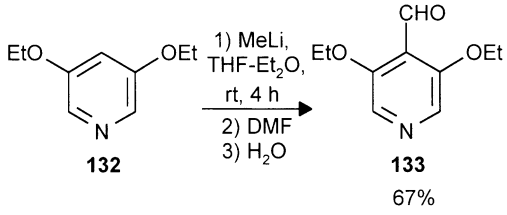
Whereas addition compounds were formed from 8-methoxy-2-quinolone,[41] lithiation at C3 was successful in the case of the 4,8-dimethoxy-2-quinolones **118** and **119**, affording **120**–**121**. Since the *N*-methylated derivative of **118** could not be deprotonated under the same reaction conditions, the phenoxide anion was assumed to stabilize the lithio derivative at C3 (Scheme 35).[42]

3.2. Alkoxy derivatives

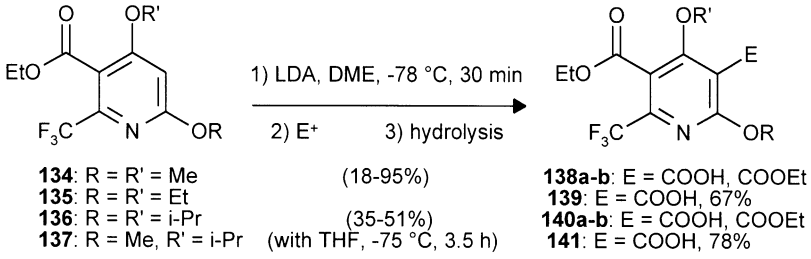
3.2.1. Methoxypyridines. In 1990, various techniques were used to deprotonate 2-methoxypyridine.[1] *t*-BuLi was found to be convenient for this purpose.[43] The catalytic process (PhLi and 5% DIA) was also effective in the metallation of 2-methoxypyridine and 2,6-dimethoxypyridine.[3] Unlike 2-methoxypyridine, no addition compounds were observed when a second substituent was present at C6,[44,45] e.g. when



Scheme 40.



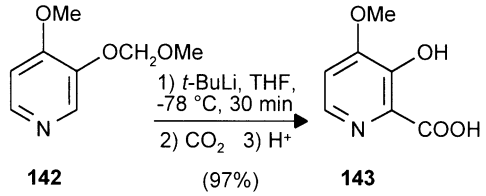
Scheme 41.



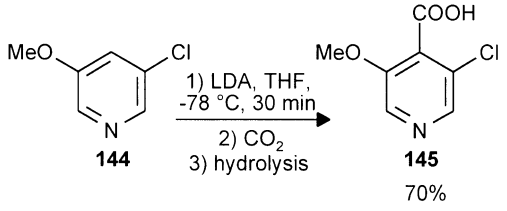
Scheme 42.

2,6-dimethoxypyridine (**122**) was treated with BuLi (Scheme 36).[44]

Metallation of 4-methoxypyridine (**124**) using LDA was optimized by Comins.[46] Deprotonation of **124** has additionally been achieved with mesityllithium and PhLi for the synthesis of **125** (Scheme 37),[47] and 3,4-dimethoxypyridine (**126**) has been deprotonated at C2 with mesityllithium.[48] BuLi was also employed successfully to give the lithio derivative at C2, leading to **127** (Scheme 38).[47]



Scheme 43.



Scheme 44.

During the course of the synthesis of caerulomycin C, metallation of 3,4-dimethoxy-2,2′-bipyridine (**128**) was studied. Whereas LDA only afforded deprotonation at C5 under in situ trapping conditions, PhLi was successfully used to deprotonate **128** at C5 (Scheme 39).[30]

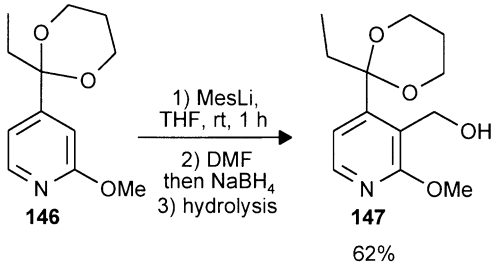
Lithiation was observed at C4 when 2,3-dimethoxypyridine (**130**) was treated with 2 equiv. of BuLi, and led to **131**. It appears that 1 equiv. of the base is entirely chelated by the two methoxy groups and/or the nitrogen atom of the pyridine (Scheme 40).[29]

3.2.2. Other alkoxypyridines. It has been known for many years that deprotonation of 3-ethoxypyridine could occur either at C4 using MeLi or at C2 with BuLi–TMEDA chelate.[1] More recently, 3,5-diethoxypyridine (**132**) has been shown to undergo regioselective deprotonation at C4 with MeLi, affording **133** (Scheme 41).[21]

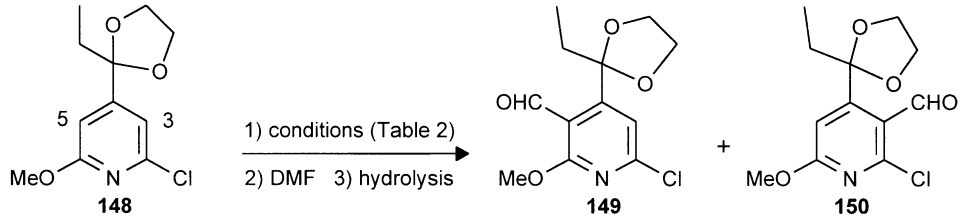
Deprotonation of the more activated dialkoxypyridines **134**–**137** has been achieved with LDA, leading to **138**–**141** (Scheme 42).[49,50]

3.2.3. Methoxymethoxypyridines. A few studies using the methoxymethoxy group as DMG have been reported.[1] During the synthesis of the natural product UK-2A, for example, metallation of 3-methoxymethoxypyridine (**142**) for the synthesis of **143** was examined using several lithiating reagents under various conditions and *t*-BuLi was found to give the best regioselectivity (>98%) (Scheme 43).[51,52]

3.2.4. Halomethoxypyridines. 3-Chloro-5-methoxypyridine (**144**) was deprotonated between the two DMGs with LDA (product **145**) (Scheme 44),[53] and the catalytic process (PhLi and 5% DIA) has been used to metallate 2-chloro-6-methoxypyridine. Under these conditions, 2-chloro-3-lithio-6-methoxypyridine was formed,[3] whereas the 2-chloro-5-lithio-6-methoxy isomer was obtained using *t*-BuLi.[54]



Scheme 45.



Scheme 46.

Table 2. Metallation conditions for **148**

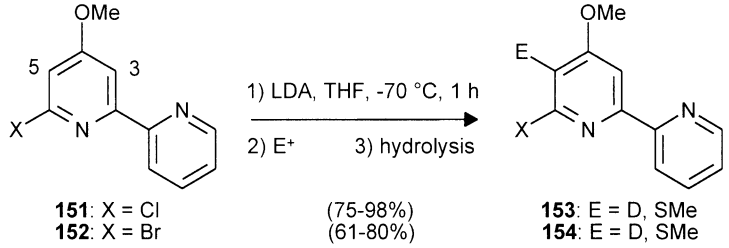
Conditions	Yield	**149**:**150**
BuLi, heptane, 0°C, 30 min	71%	95:5
s-BuLi, THF, −40°C		10:90

The use of mesityllithium as a base for the deprotonation of the 4-substituted 2-methoxypyridine **146** during the synthesis of some homocamptothecins intermediate **147** is of interest (Scheme 45).[55] An optional site selectivity arose for the chloro derivative **148**. In an apolar solvent such as heptane, reinforced coordination between the base and the methoxy substituent favoured reaction at C5, leading to **149**, whereas the use of a polar solvent such as THF favoured abstraction of the proton at C3, leading to **150** (Scheme 46, Table 2).[56]

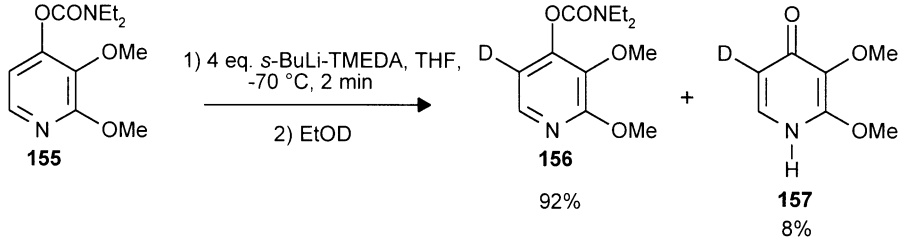
The metallation of 6-halo-4-methoxy-2,2′-bipyridines (**151** and **152**) was studied during the synthesis of some natural products and it was observed that LDA effected metallation at C5, affording **153** and **154** (Scheme 47).[57]

3.3. *O*-Carbamates

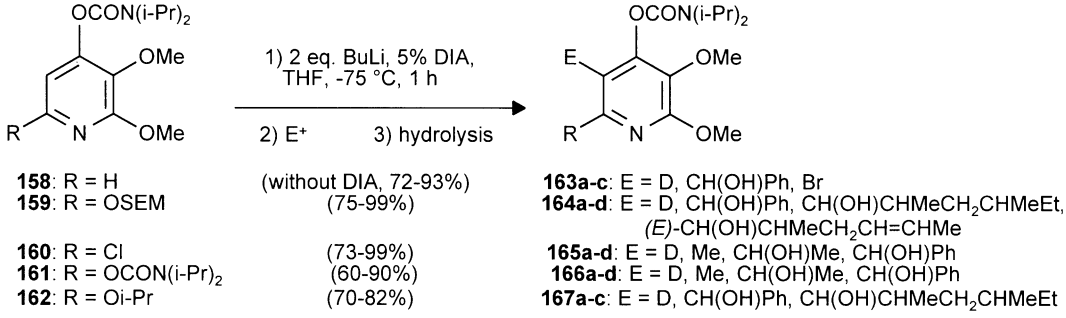
3.3.1. *O*-(Pyridyl)carbamates. Metallation of all isomeric *N*,*N*-diethylpyridinecarbamates occurred with *s*-BuLi–TMEDA.[1] For the 2,3-dimethoxy analogue **155**, the reaction time to obtain **156** was drastically reduced in order to avoid side reactions such as addition of the alkyllithium to the carbonyl group of the carbamate, giving **157** (Scheme 48).[29] The reaction proceeded well with a more bulky DMG group such as *N*,*N*-di-*i*-propylcarbamate present in **158**–**162**, deprotonation with BuLi being catalyzed by DIA in this case, leading to **163**–**167** (Scheme 49).[29,58]



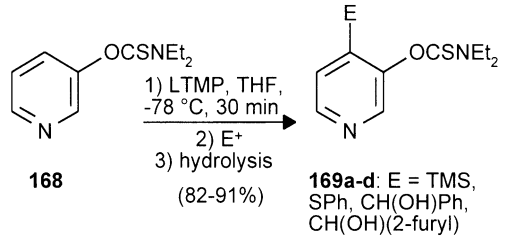
Scheme 47.



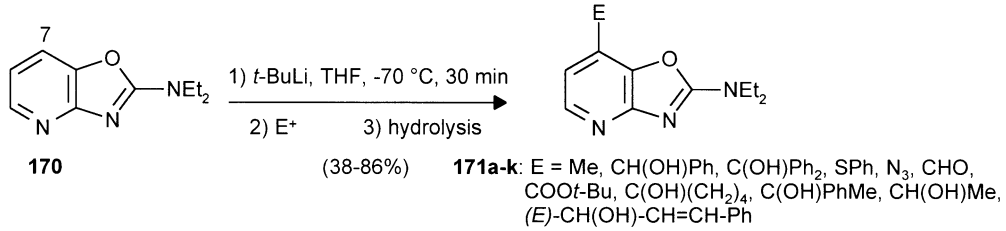
Scheme 48.



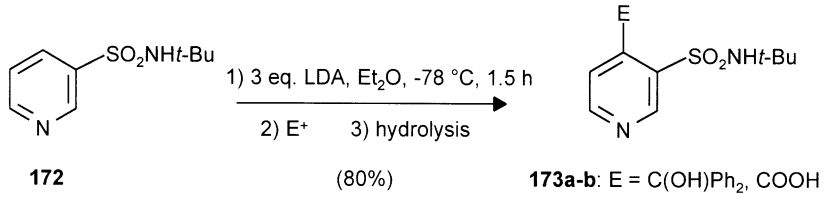
Scheme 49.



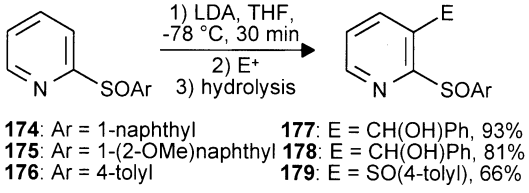
Scheme 50.



Scheme 51.



Scheme 52.



Scheme 53.

3.4. *O*-Thiocarbamates

3.4.1. *O*-(Pyridyl)thiocarbamates. Metallation of all of the *N*,*N*-diethylpyridinethiocarbamate isomers has been investigated. Only the 3-isomer **168** was cleanly deprotonated at C4 when LTMP was used as the base and functionalized at C4 (product **169**) (Scheme 50), concurrent deprotonation at C3 and C6 being observed when the directing group was attached at C2.[59]

3.5. Oxacycle-based DMGs

3.5.1. Furopyridines. The metallation of various 2-methylfuropyridines was examined by Shiotani. Although deprotonation of the methyl group was often favoured, deprotonation of the pyridine ring was also observed for some derivatives.[60]

3.5.2. Oxazolopyridines. Lever has reported the regioselective metallation of 2-diethylaminooxazolo[4,5-*b*]pyridine (**170**) at C7, leading to **171** (Scheme 51).[61]

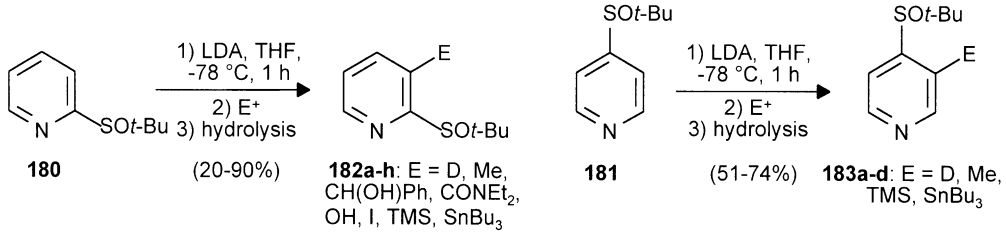
4. Sulfur-based DMGs

4.1. Sulfonamides

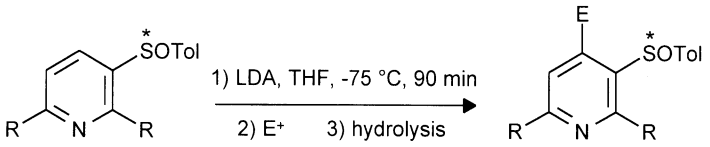
4.1.1. Pyridinesulfonamides. The metallation of tertiary pyridinesulfonamides with LDA in diethyl ether was known in 1990.[1] Under the same reaction conditions, *N*-*t*-butylpyridine-3-sulfonamide (**172**) was deprotonated at C4 and furnished **173**. The metallation of a secondary pyridinesulfonamide was described for the first time in 1992 (Scheme 52).[62]

4.2. Sulfoxides

4.2.1. Pyridinesulfoxides. The metallation of phenyl pyridinesulfoxides, discovered by Furukawa,[1] has been extended to aryl pyridine-2-sulfoxides **174**–**176** in work aimed at studying the diastereoisomeric ratio after reaction with electrophiles (compounds **177**–**179**) (Scheme 53).[63,64]

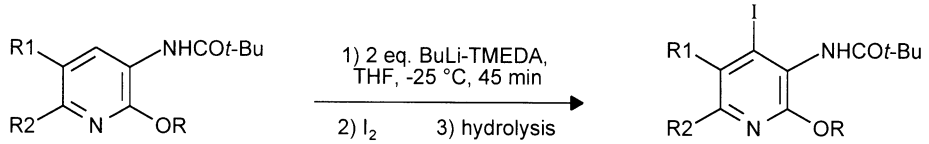


Scheme 54.



184: (S), R = H (13-27%) (de, 14->99%) **188a-d**: E = CH(OH)Me, CH(OH)Et, CH(OH)*t*-Bu, CH(OH)Ph
185: (R), R = H (18-37%) (de, 0->99%) **189a-d**: E = CH(OH)Me, CH(OH)Et, CH(OH)*t*-Bu, CH(OH)Ph
186: (S), R = OMe (53-75%) (de, 28->99%) **190a-d**: E = CH(OH)Me, CH(OH)Et, CH(OH)*t*-Bu, CH(OH)Ph
187: (R), R = OMe (63-89%) (de, 0->99%) **191a-d**: E = CH(OH)Me, CH(OH)Et, CH(OH)*t*-Bu, CH(OH)Ph

Scheme 55.



192: R = i-Pr, R1 = H, R2 = 1,3-dioxan-1-yl
193: R = R2 = Me, R1 = H
194: R = R1 = Me, R2 = H
195: R = i-Pr, R1 = Me, R2 = H
196: R = i-Pr, R1 = R2 = Me

197, 80%
198, 87%
199, 68%
200, 60%
201, 58%

Scheme 56.

S-*t*-Butylpyridine-2- and -4-sulfoxides (**180** and **181**) have likewise been deprotonated by Snieckus under conditions similar to those used by Furukawa and **182** and **183** were prepared (Scheme 54).[65]

The chiral 3-(4-tolylsulfinyl)pyridines **184**–**187** have been deprotonated using LDA and, in subsequent reactions with electrophiles, they often display a remarkably high diastereoselectivity, benzaldehyde and 2,2-dimethylpropanal giving a single diastereoisomer (**188**–**191**) in modest yield (Scheme 55).[66]

5. Nitrogen-based DMGs

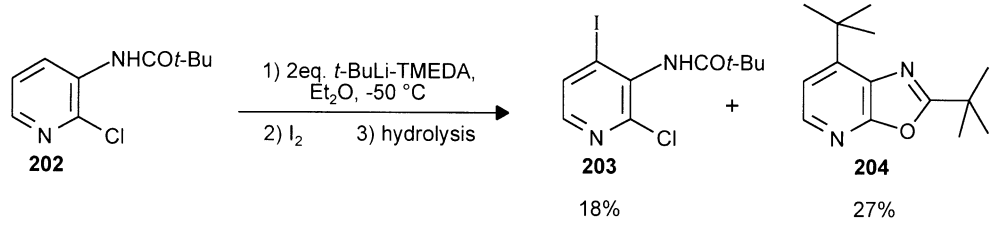
5.1. *N*-Protected amino derivatives

5.1.1. *N*-(Pyridyl)amides and *N*-(pyridyl)carbamates.

Methods to effect the metallation of various 2,2-dimethyl-*N*-(pyridyl)propanamides and *N*-pyridyl-*O*-(*t*-butyl)carbamates have been known for many years.[1] More recently, deprotonation of the 2,2-dimethyl-*N*-(2-alkoxy-3-pyridyl)-propanamides **192**–**196** was accomplished to prepare intermediates **197**–**201** during a synthesis of streptonigrin and lavendamycin analogues. Metallation was found to be regioselective and to occur at C4. The reaction was even effective for compounds **193** and **196** that have a methyl group at C6 (Scheme 56).[67,68]

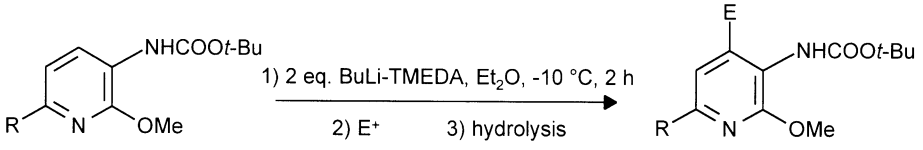
The reaction of BuLi with 2,2-dimethyl-*N*-(2-chloro-3-pyridyl)propanamide (**202**) leads to the corresponding 2-butylated pyridine derivative. With *t*-BuLi, the expected 4-iodo compound **203** is generated, albeit in poor yield (Scheme 57).[69]

Davies has studied the metallation of 2,2-dimethyl-*N*-(2-



202
203 18%
204 27%

Scheme 57.



205: R = H (59-91%) **207a-f**: E = Me, CH_2Ph, $SnBu_3$, I, CH_2OBn, CHO
206: R = OMe (47-89%) **208a-f**: E = Me, CH_2Ph, $SnBu_3$, I, CH_2OBn, CHO

Scheme 58.

pyridyl)propanamide, this work leading to the isolation and characterization of a structural model for such lithiated intermediates.[70] As the *t*-butoxycarbonylamino unit is a poorer activating group for DoM,[1] it has been the subject of fewer investigations. Kelly has shown that deprotonation of the *N*-(2-methoxy-3-pyridyl)-*O*-(*t*-butyl)carbamates **205** and **206** is facile to prepare **207** and **208** during a synthesis of nevirapine and noted that reaction occurred at C4 even when a methoxy group was present at C6 (Scheme 58).[71]

Metallation of substituted *N*-(2-methoxy-3-pyridyl)-*O*-(*t*-butyl)carbamate **209** has also featured in some synthetic studies directed towards streptonigrin and lavendamycin analogues via **210** (Scheme 59).[68]

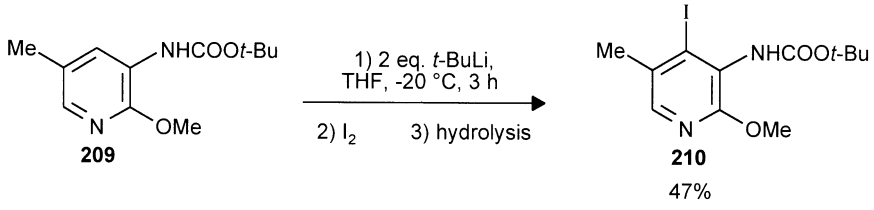
Halo-magnesiation at C4 has been observed in the metallation of the commercially available compound **211** with (2,2,6,6-tetramethylpiperidino)magnesium chloride (TMPMgCl), leading to **212** (Scheme 60).[72]

5.1.2. *N*-(Carbolyl)amides and *N*-(carbolyl)carbamates. Whereas the action of BuLi or *s*-BuLi on 2,2-dimethyl-*N*-(9-methyl-3-(α-carbolyl))propanamide (**213**) gave only addition compounds and starting material when used from −70 to −20°C, *t*-BuLi proved to be a convenient alternative for effecting metallation at C4 (product **214**) (Scheme 61).[73,74]

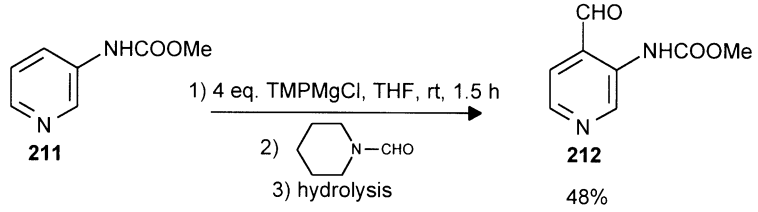
Attempts to metallate 2,2-dimethyl-*N*-(9-methyl-2-(γ-carbolyl))propanamide (**215**), *N*-(9-methyl-2-(γ-carbolyl))-*O*-(*t*-butyl)carbamate (**216**) and *N*-(9-methyl-3-(α-carbolyl))-*O*-(*t*-butyl)carbamate (**217**) with various alkyllithiums failed, an observation explained by steric hindrance arising from the bulky methyl and amido groups in **215** and **216** (and the proximity of H5 in **217**). The mixtures of starting material and addition products obtained were in good agreement with the computed LUMO energy values for the carbolines, which are always lower than those of their pyridine analogues (Scheme 62).[73,75]

5.2. Azacycle-based DMGs

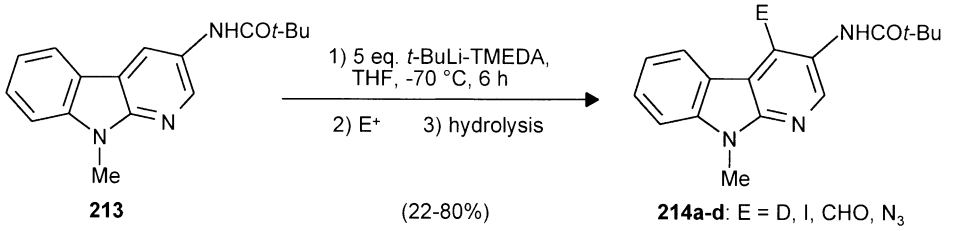
5.2.1. Bipyridines. In 1996, Zoltewicz showed that the 2-pyridyl group in 2,2′-bipyridine (**218**) and 2,4′-bipyridine (**219**) was capable of direct lithiation, allowing the synthesis of **220** and **221** (Scheme 63).[76]



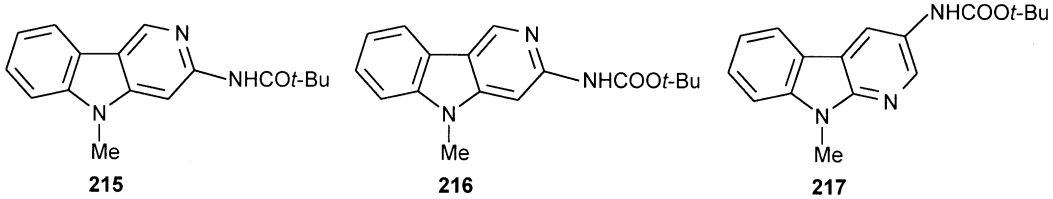
Scheme 59.



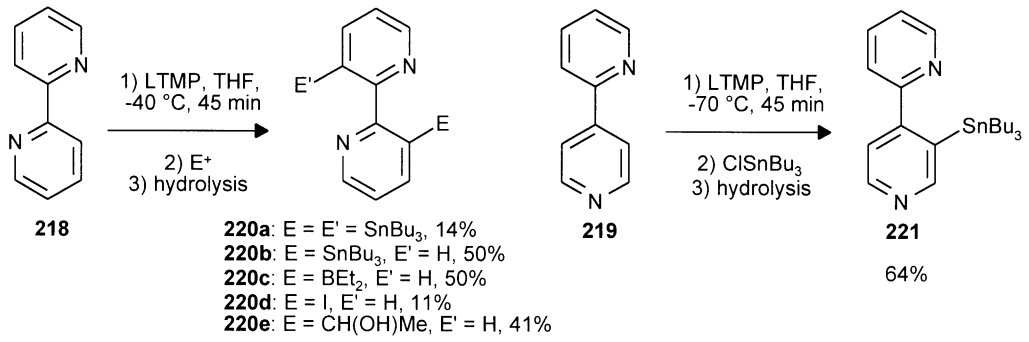
Scheme 60.



Scheme 61.



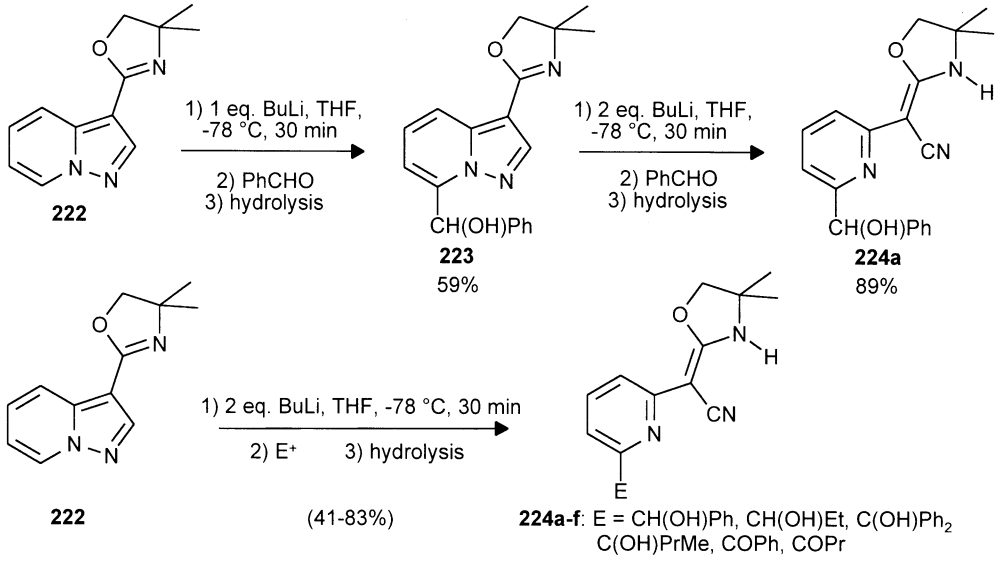
Scheme 62.



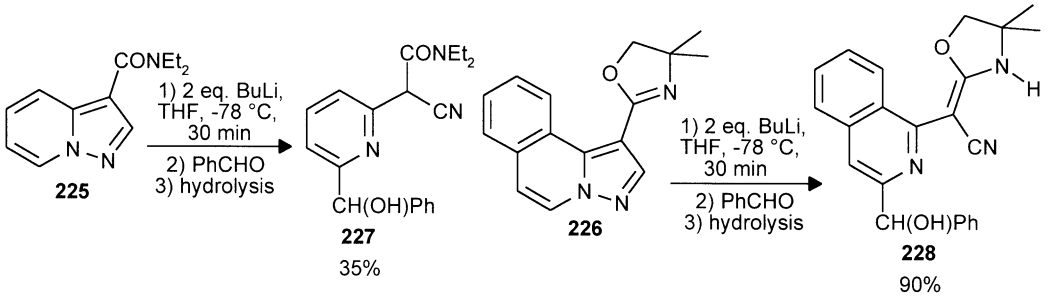
Scheme 63.

5.2.2. Pyrazolopyridines. Pyrazolo[1,5-*a*]pyridines may be deprotonated at C7 using BuLi. For example, treatment of 3-(4,4-dimethyl-2-oxazol-2-yl)pyrazolo[1,5-*a*]pyridine (**222**) with BuLi (1 equiv.) followed by benzaldehyde produced the 7-substituted compounds **223**. Subsequent treatment of **223** with 1 equiv. of BuLi or of **222** with 2 equiv. of BuLi unexpectedly yielded the 6-substituted pyridine-2-acetonitriles **224a–f** through cleavage of the pyrazole ring (Scheme 64).[77] Metallation of **225** and **226** also induced fragmentation of the pyrazole ring to give **227** and **228** (Scheme 65).[77]

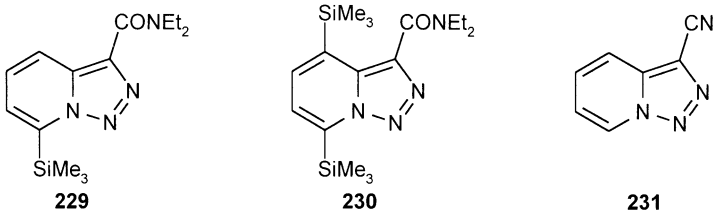
5.2.3. Triazolopyridines. It was known in 1990 that deprotonation of 1,2,3-triazolo[1,5-*a*]pyridine occurred at C7, even when a powerful DoM group, such as *N*,*N*-diethylcarbamoyl, was present at C3.[1] Jones has examined the deprotonation of the trimethylsilyl derivative **229**. No lithiation could be achieved using LDA, BuLi or *s*-BuLi–TMEDA, whilst LTMP gave the 4,7-bis(trimethylsilyl) derivative **230** in a very low yield (5%). Lithiation of 3-cyano-1,2,3-triazolo[1,5-*a*]pyridine (**231**) has also been investigated and this resulted in a mixture of products (Scheme 66).[78]



Scheme 64.



Scheme 65.

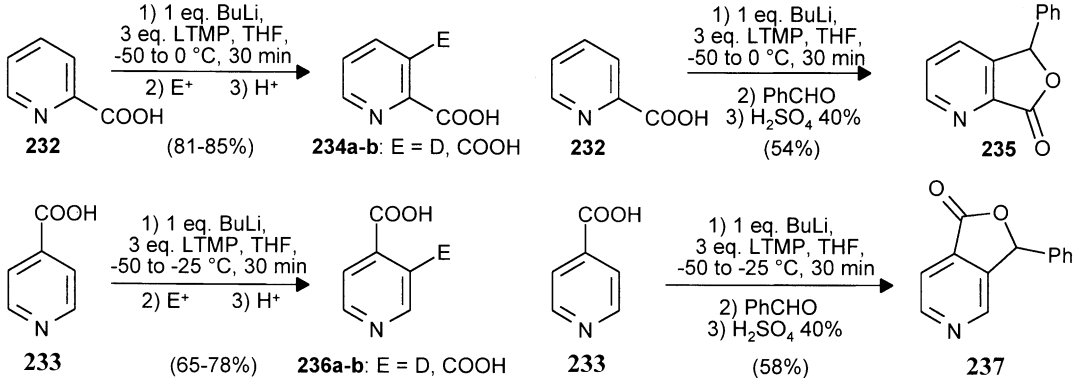


Scheme 66.

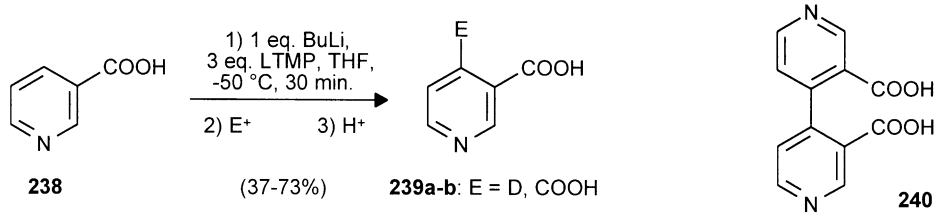
6. Carbon-based DMGs

6.1. Carboxylates

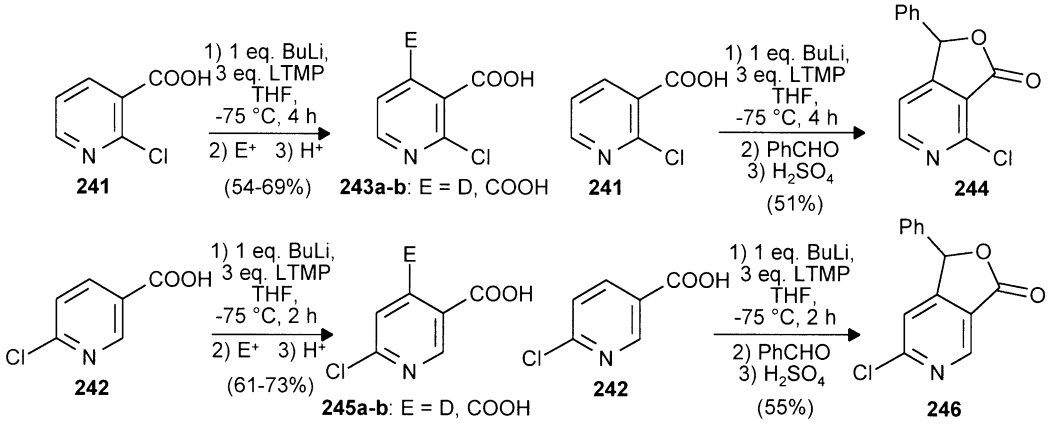
6.1.1. Pyridinecarboxylic acids. Pyridine-2- and -4-carboxylic acids (**232** and **233**) were transformed to their lithium salts with BuLi and these underwent deprotonation at the position adjacent to the carboxylate group when treated with LTMP at 0°C and −25°C, respectively; subsequent trapping gave **234**–**237** (Scheme 67).[79] Lower reaction temperatures were desirable with pyridine-3-carboxylic acid (**238**), in order to minimize formation of the dimer **240** (Scheme 68).[79] Deprotonation of the more reactive chloropyridine-3-carboxylic acids (**241** and **242**)



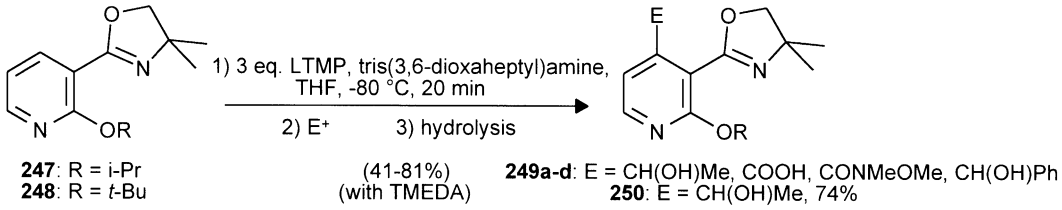
Scheme 67.



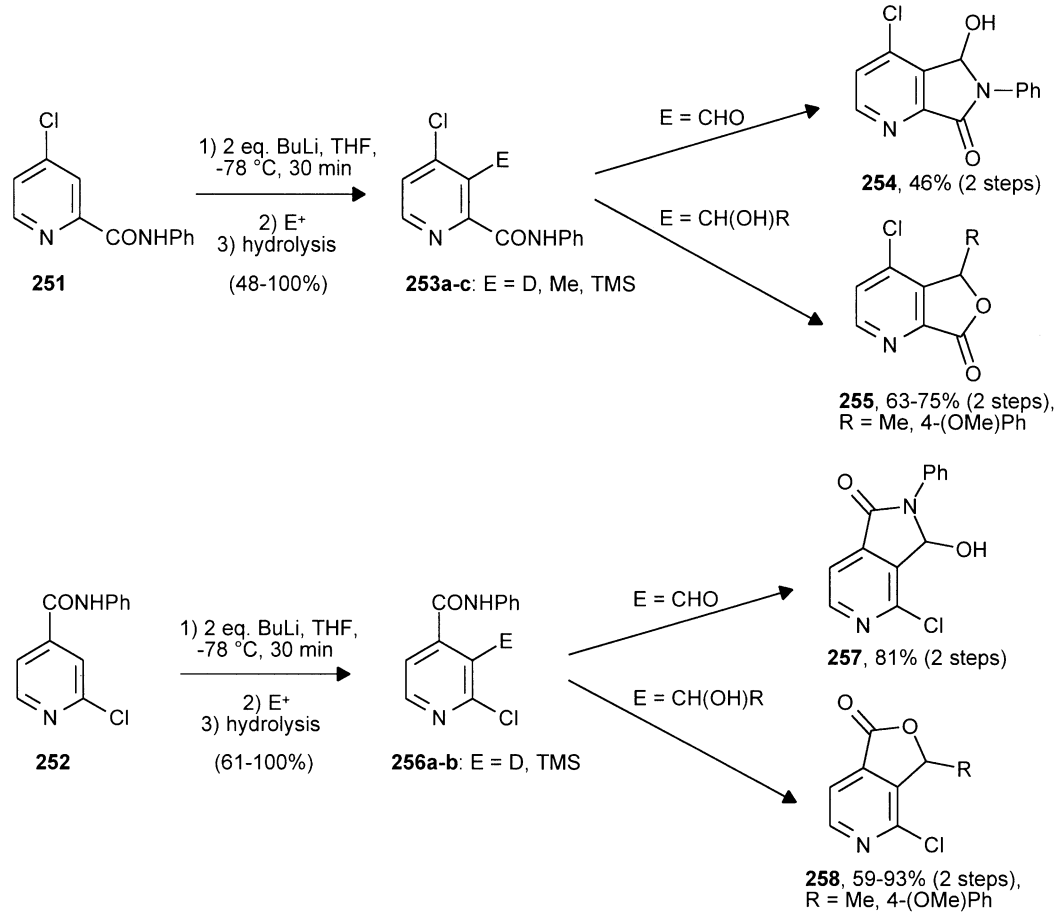
Scheme 68.



Scheme 69.



Scheme 70.



Scheme 71.

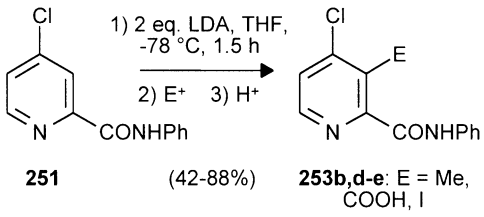
was performed at −75°C and, when benzaldehyde was used as the electrophile, the lactones **244** and **246** were obtained (Scheme 69).[79]

6.2. Oxazolines

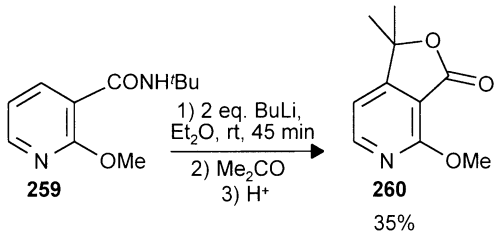
6.2.1. Pyridineoxazolines. Metallation of pyridineoxazolines[1] has been extended to various substituted compounds. The use of 2-chloro- or 2-methoxy-3-(4,4-dimethyl-2-oxazolyl)pyridines led to substitution of the substituent at C2 by dialkylamide. Metallation was achieved, however, with the 2-*i*-propoxy and 2-*t*-butoxy derivatives **247** and **248** and compounds **249** and **250** were obtained (Scheme 70).[80]

6.3. Secondary carboxamides

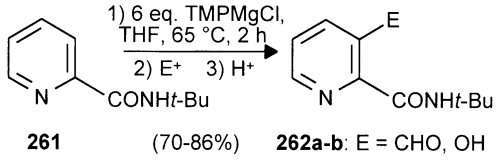
6.3.1. Secondary pyridinecarboxamides. Deprotonation of pyridines containing the powerful DoM group, *N*-(phenyl)carboxamide, was observed by Epsztajn.[1] Chloro derivatives of *N*-(phenyl)pyridinecarboxamides **251** and **252** were also metallated under the same conditions to prepare **254** and **257**. When the electrophile was an aldehyde or a formylating agent, further cyclization occurred, giving **255** and **258** (Scheme 71).[81]



Scheme 72.



Scheme 73.

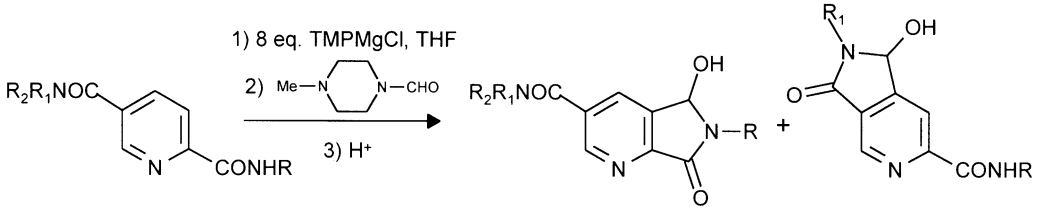


Scheme 74.

LDA proved convenient for the deprotonation of the secondary pyridinecarboxamide **251** (Scheme 72).[82] The 2-methoxypyridine-3-carboxamide **259** has also been lithiated during a synthesis of cerpegin via **260** (Scheme 73).[83]

More recently, a method of deprotonating pyridinecarboxamides using TMPMgCl has been developed by Mulzer. An excess of base was necessary to obtain **262** in good yields with the pyridine-2-carboxamide **261** (Scheme 74).[72] The same reagent was used to deprotonate the pyridinedicarboxamides **263**–**269**, metallation occurring predominantly or exclusively at C3, leading to **270**–**280** (Scheme 75).[84]

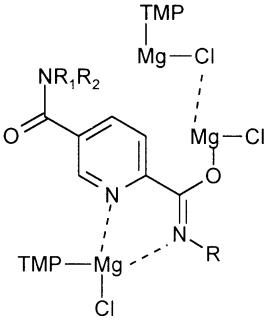
The formation of a complex between the amido group at C2, the pyridine nitrogen atom and the TMPMgCl provides a plausible rationalization of these observations (Scheme 76).



263: R = R_1 = *t*-Bu, R_2 = H 70 °C, 2 h
264: R = *t*-Bu, R_1 = Me, R_2 = H 70 °C, 2 h
265: R = *t*-Bu, R_1 = Ph, R_2 = H 55 °C, 1.5 h
266: R = *t*-Bu, R_1 = R_2 = i-Pr 65 °C, 2 h
267: R = Ph, R_1 = *t*-Bu, R_2 = H 70 °C, 2 h
268: R = Pr, R_1 = *t*-Bu, R_2 = H 70 °C, 2 h
269: R = Me, R_1 = *t*-Bu, R_2 = H 70 °C, 2 h

270, 70%, **271**, 18%
272, 22%, **273**, 65%
274, 50%
275, 90%
276, 68%, **277**, 19%
278, 77%, **279**, 17%
280, 34%, **281**, 34%

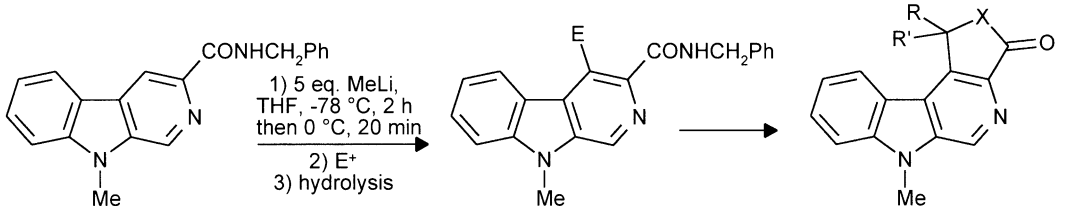
Scheme 75.



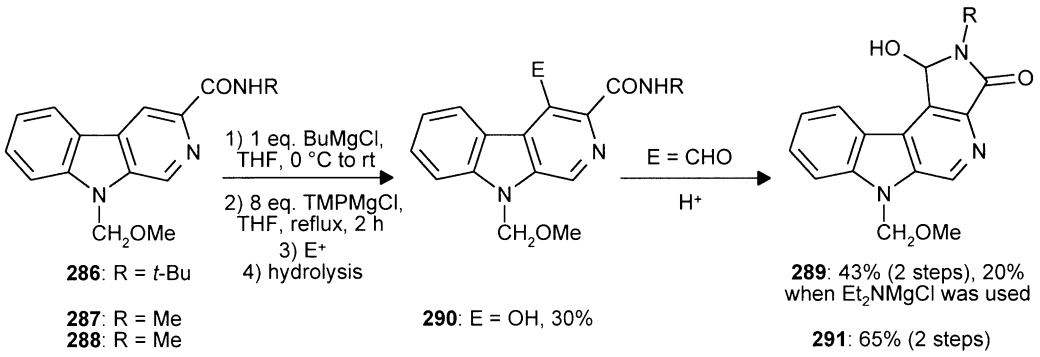
Scheme 76.

6.3.2. Secondary β-carbolinecarboxamides. Lithiation in the β-carboline series has been studied by Dodd, who found that most alkyllithiums and LDA (with or without TMEDA) gave side reactions such as addition, but MeLi successfully led to deprotonation of the β-carbolinecarboxamide **282** at C4, affording **283**–**285**. The effectiveness of this reagent in promoting lithiation at the sterically encumbered C4 position may be attributed to its small size (Scheme 77).[85]

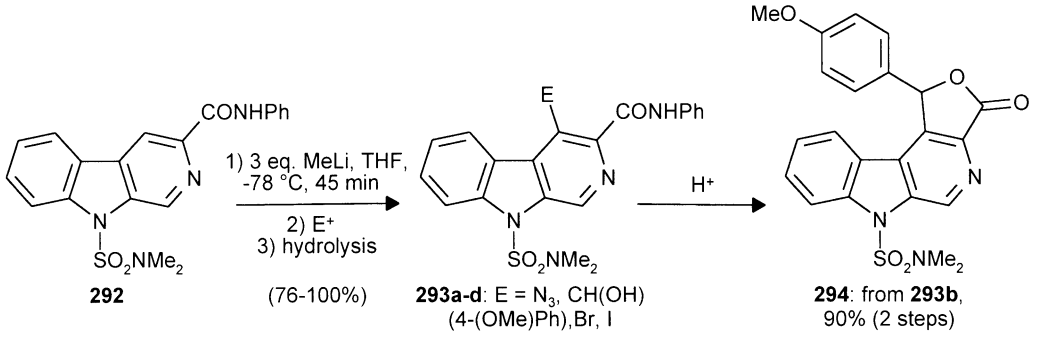
Halo-magnesiation of the β-carbolinecarboxamides **286** and **287** has been achieved using TMPMgCl and it was noted that the DoM effect of the carboxamide group was much



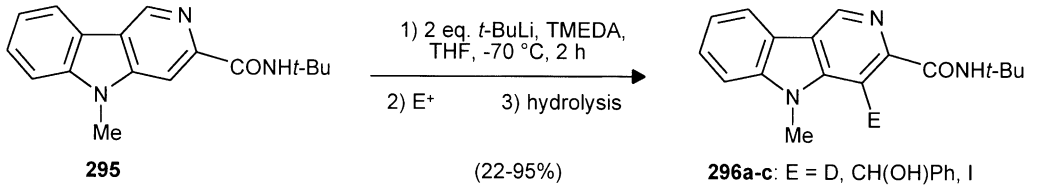
Scheme 77.



Scheme 78.



Scheme 79.



Scheme 80.

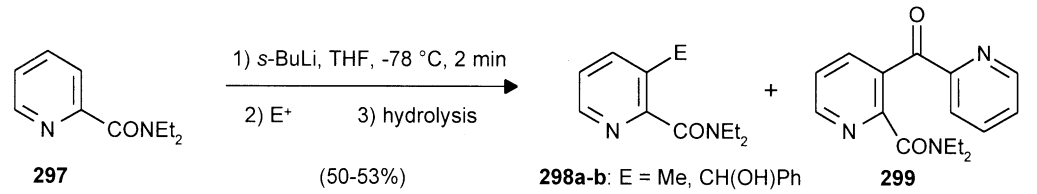
greater than that of the *N*-methoxymethyl moiety. Subsequent trapping afforded **289**–**291** (Scheme 78).[86]

It was discovered more recently that the *N*,*N*-dimethylsulfonamide moiety was an excellent protecting group for the indolic NH. Protected substrates such as **292** could then be metallated with MeLi to afford **293** and **294**, a reaction that failed when applied to the corresponding free β-carbolinecarboxamide (Scheme 79).[87,88]

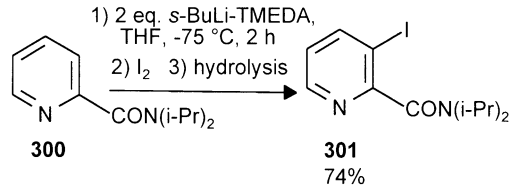
6.3.3. Secondary γ-carbolinecarboxamides. Metallation of the γ-carbolinecarboxamide **295** was studied by Dupas, who showed that *t*-BuLi was efficient at promoting deprotonation at C2 and suppressing the formation of addition compounds (Scheme 80).[75]

6.4. Tertiary carboxamides

6.4.1. Tertiary pyridinecarboxamides. The self-condensation of *N*,*N*-diethylpyridinecarboxamides when treated with LDA or LTMP has been highlighted in an earlier review.[1] With the amide **297**, the formation of adducts such as **299**, during the synthesis of **298**, could not be avoided using *s*-BuLi. The lithiated amide was sufficiently stable, however, to allow the introduction of electrophiles at C3 (Scheme 81).[89] The chelate, *s*-BuLi–TMEDA, was shown



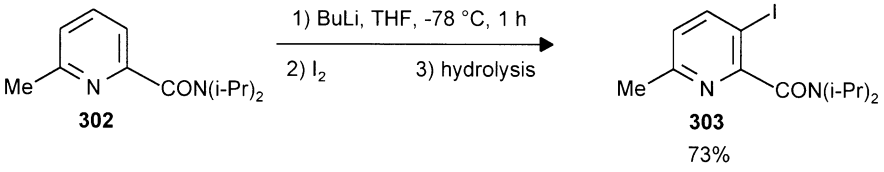
Scheme 81.



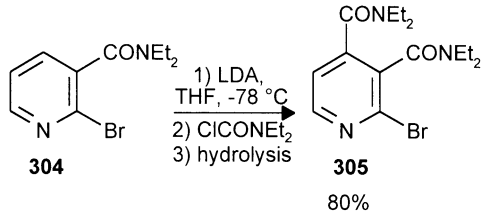
Scheme 82.

to be superior to LDA in the metallation of *N*,*N*-di-*i*-propylpyridinecarboxamide **300**, leading to **301** (Scheme 82).[32] The 6-methyl analogue **302** could likewise be deprotonated at C3 through the action of BuLi, giving **303** (Scheme 83).[33]

Metallation of various 2-substituted pyridine-3-carboxamides has been examined. Deprotonation of the 2-bromopyridine-3-carboxamide **304**, for example, was reported by Snieckus (Scheme 84).[90] Attempts to



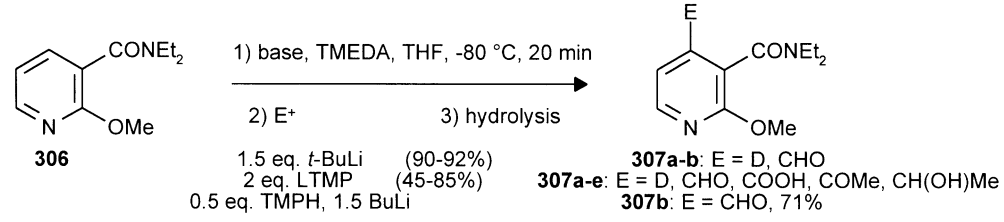
Scheme 83.



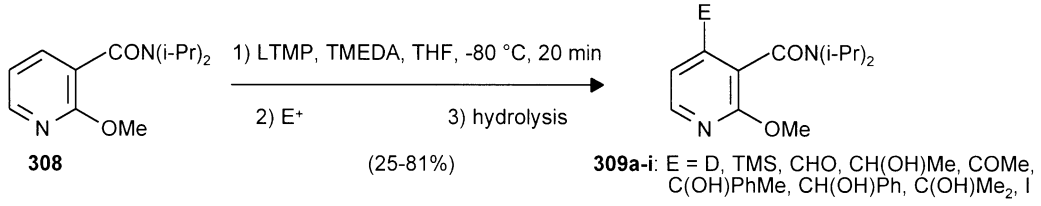
Scheme 84.

deprotonate *N*,*N*-dialkyl-2-chloropyridine-3-carboxamides have proved to be unsuccessful.[80]

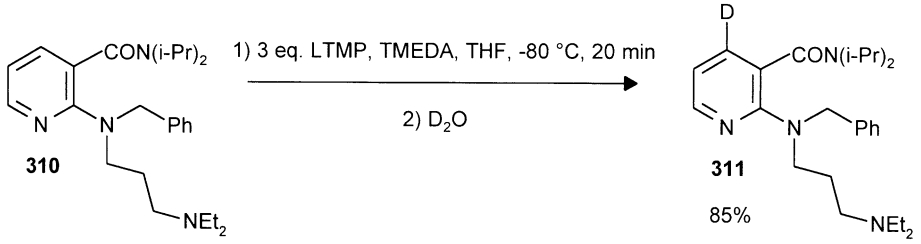
Metallation of *N*,*N*-diethyl-2-methoxypyridine-3-carboxamide (**306**) was studied by Dormoy using various conditions, with *t*-BuLi giving the best results (compounds **307**) (Scheme 85).[80] Metallation of the *N*,*N*-di-*i*-propyl derivative **308** was achieved with LTMP (products **309**), the use of LDA being ineffective (Scheme 86).[80,91,92]



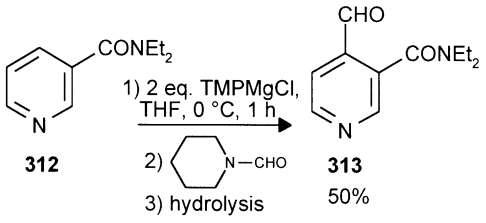
Scheme 85.



Scheme 86.



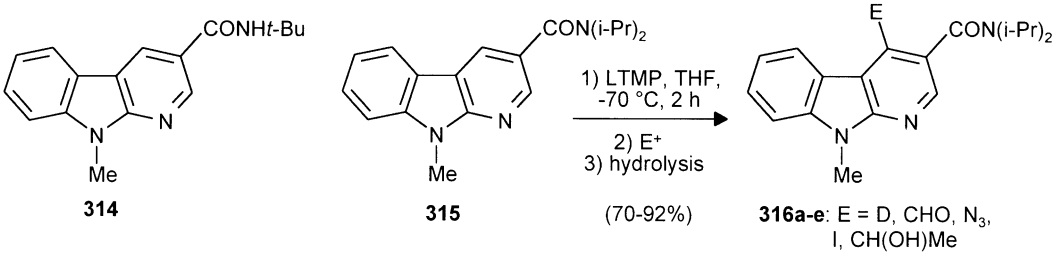
Scheme 87.



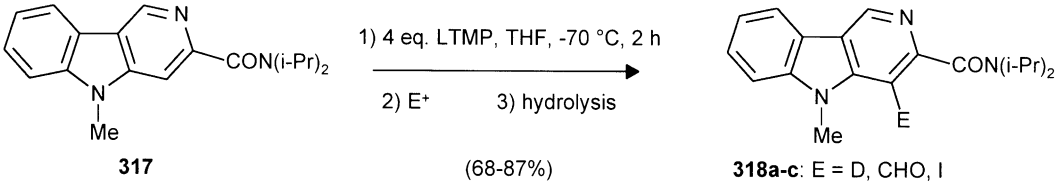
Scheme 88.

carboxamide (**312**) and prepare **313** (Scheme 88). *N*,*N*-Diethylpyridine-2-carboxamide could similarly be functionalized at C3, albeit in poor yield due to the lability of the tertiary amide moiety under the metallation conditions.[72]

6.4.2. Tertiary α-carbolinecarboxamides. While metallation experiments on the secondary α-carbolinecarboxamide **314** always afforded mixtures comprising addition products



Scheme 89.



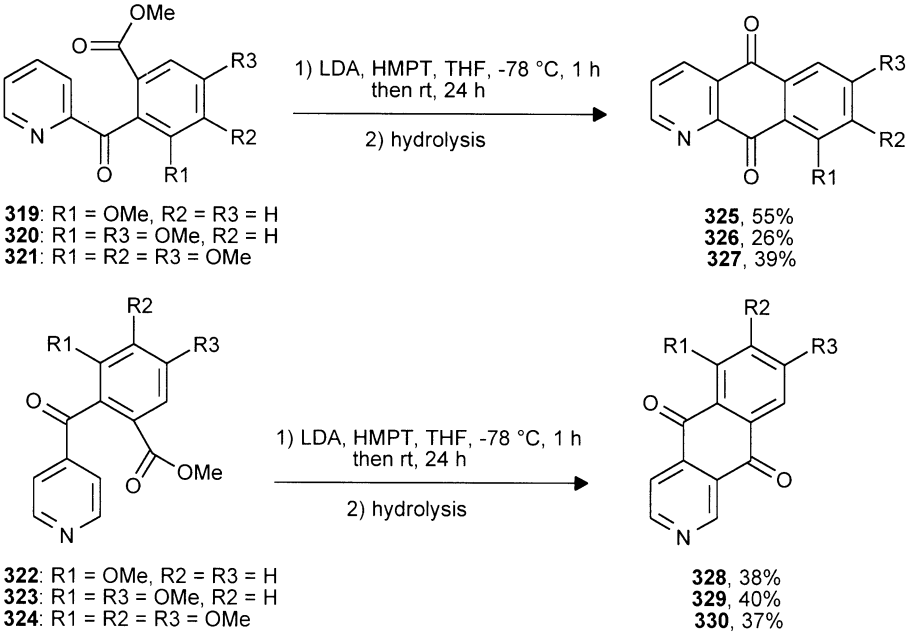
Scheme 90.

When a series of *N*,*N*-di-*i*-propyl-2-(dialkylamino)pyridine-3-carboxamides were submitted to LTMP as above, metallation was only observed for compound **310**, leading to **311** (Scheme 87).[80]

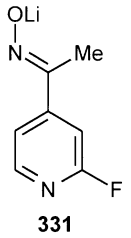
The halo-magnesiation method developed by Mulzer has been used to deprotonate *N*,*N*-diethylpyridine-3-

and unreacted starting material, the tertiary α-carbolinecarboxamide **315** could be cleanly lithiated at C4 with LTMP (Scheme 89).[73]

6.4.3. Tertiary γ-carbolinecarboxamides. The metallation of tertiary γ-carbolinecarboxamides **317** may also be effected with LTMP (Scheme 90).[75]



Scheme 91.



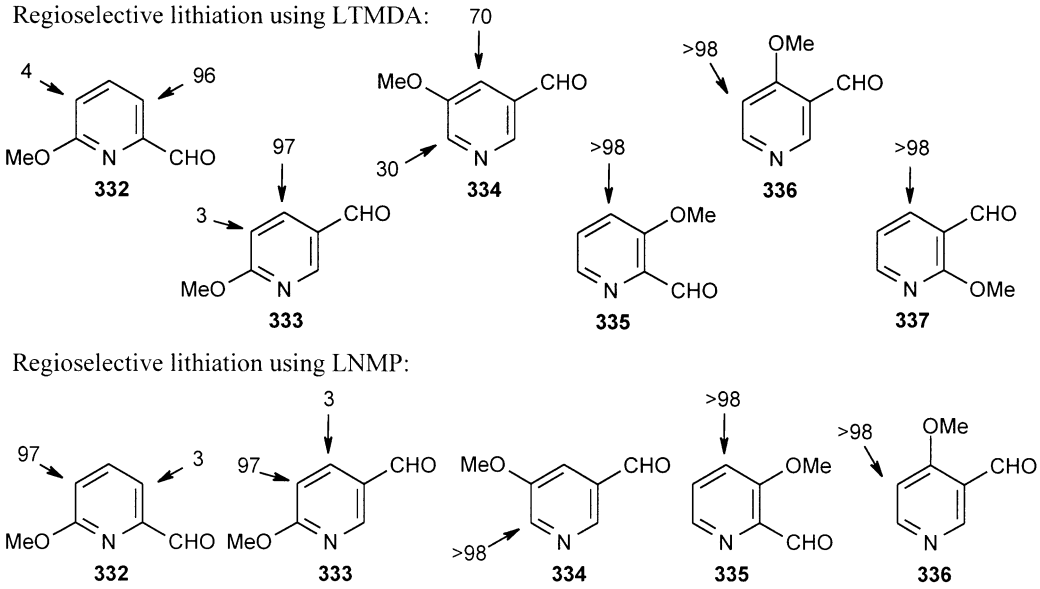
Scheme 92.

6.6. Oximes

6.6.1. Pyridineoximes. Deprotonation of the fluorooxime **331** (Scheme 92) with LDA under a range of conditions led to metallation at C3 and the pendant methyl group.[69]

6.7. Masked aldehydes

6.7.1. Pyridine α-aminoalkoxides. Comins has reviewed the processes that involve simultaneous activation and protection of aromatic aldehydes by the in situ generation of α-aminoalkoxides using lithium *N*,*N*,*N*′-trimethylethylenediamide (LTMDA) and lithium *N*-methylpiperazide (LNMP). The lithiation regioselectivity of the methoxypyridinecarboxaldehydes **332**–**337** was found to be largely dependent on the α-aminoalkoxide used (Scheme 93).[94]

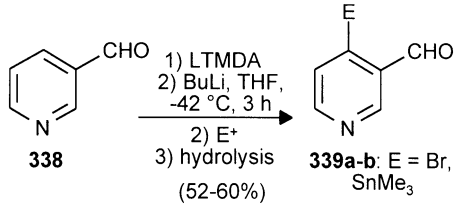


Scheme 93.

6.5. Ketones

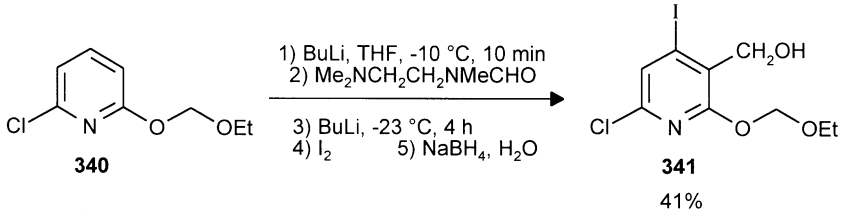
6.5.1. Pyridineketones. It was observed that the ketoesters **319**–**324** were readily deprotonated at C3 using LDA. The resulting lithiated pyridine, however, instantly cyclized by intramolecular attack of the ester group to furnish the azaanthraquinones **325**–**330** (Scheme 91).[93]

In a study of the synthesis of schumanniophytine and isoschumanniophytine, Kelly reported the regiospecific lithiation of pyridine-3-carboxaldehyde (**338**) at C4 under the conditions described by Comins, leading to **339** (Scheme 94).[95,96]

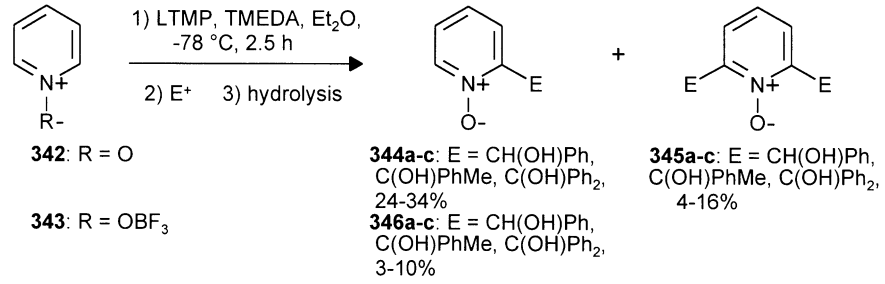


Scheme 94.

During the course of a synthesis of camptothecin alkaloids, the pyridine derivative **340** was subjected to directed lithiation and trapping with *N*-formyl-*N*,*N*′,*N*′-trimethylethylenediamine to give an α-aminoalkoxide in situ.



Scheme 95.



342: R = O

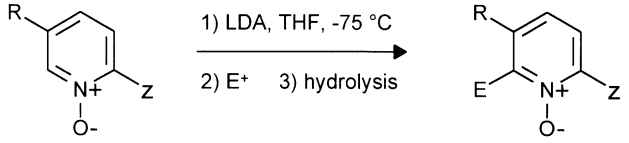
343: R = OBF_3

344a-c: E = CH(OH)Ph, C(OH)PhMe, $C(OH)Ph_2$, 24-34%

346a-c: E = CH(OH)Ph, C(OH)PhMe, $C(OH)Ph_2$, 3-10%

345a-c: E = CH(OH)Ph, C(OH)PhMe, $C(OH)Ph_2$, 4-16%

Scheme 96.



347: Z = $CON(i\text{-}Pr)_2$, R = H (50-100%)
348: Z = NHCO*t*-Bu, R = H (48-80%)
349: Z = NHCO*t*-Bu, R = Me (57-100%)

350a-f: E = D, CH(OH)Ph, $C(OH)Ph_2$, $C(OH)(CH_2)_5$, COOH, I
351a-f: E = D, CH(OH)Ph, $C(OH)(CH_2)_5$, CHO, COOH, I
352a-e: E = D, Me, CHO, COOH, CN

Scheme 97.

Addition of BuLi effected its directed lithiation at C4 and quenching with iodine followed by reduction afforded **341** (Scheme 95).[45,54,97]

7. Heterocycle *N*-oxides

7.1. Pyridine *N*-oxides

The lithiation of pyridine *N*-oxides, first developed by Abramovitch, has been extended to many other substituted pyridines.[1] Goto and Hamana examined the deprotonation of pyridine *N*-oxide (**342**) and its BF_3 complex (**343**) using LTMP and found that the latter underwent deprotonation less easily than **342** (products **344**–**346**) (Scheme 96).[98]

The lithiation of 2-substituted pyridine *N*-oxides **347**–**349** has also been investigated. Although directing carboxamide and pivaloylamino groups were present at C2, the reaction was selective for metallation at C6, leading to **350**–**352** (Scheme 97).[99]

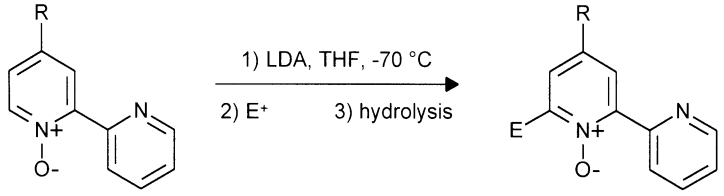
During the course of a synthesis of the caerulomycins and collismycins, the metallation of 2,2′-bipyridine *N*-oxides **353** and **354** was investigated. With LDA, deprotonation occurred at C6 (Scheme 98),[57] and LTMP proved to be more convenient, giving **356c** in 94% yield when 1 equiv. of the base was used.

The lithiation of 3,4-dimethoxypyridine *N*-oxide (**357**) has also been investigated. Deprotonation with BuLi gives rise to both C2 and C6 metallated products, which subsequently affords **358** and **359**. Surprisingly, the nature of the electrophile has a pronounced effect on the regiochemical course of the reaction, most electrophiles adding at C2. With iodine, however, a complex mixture of products was obtained comprising the 2,6-diiodo compound **362**, the 2-iodo derivative **360** and a small quantity of the 6-iodo derivative **361**. It therefore seems likely that the C2 and C6 metallated intermediates rapidly equilibrate under the reaction conditions (Scheme 99).[99]

A 2,6-diiodo compound **364** was additionally obtained when 4-(pyrrolid-1-yl)pyridine *N*-oxide (**363**) was exposed to an excess of LDA and quenched with an excess of iodine (Scheme 100).[33]

7.2. Quinoline *N*-oxides

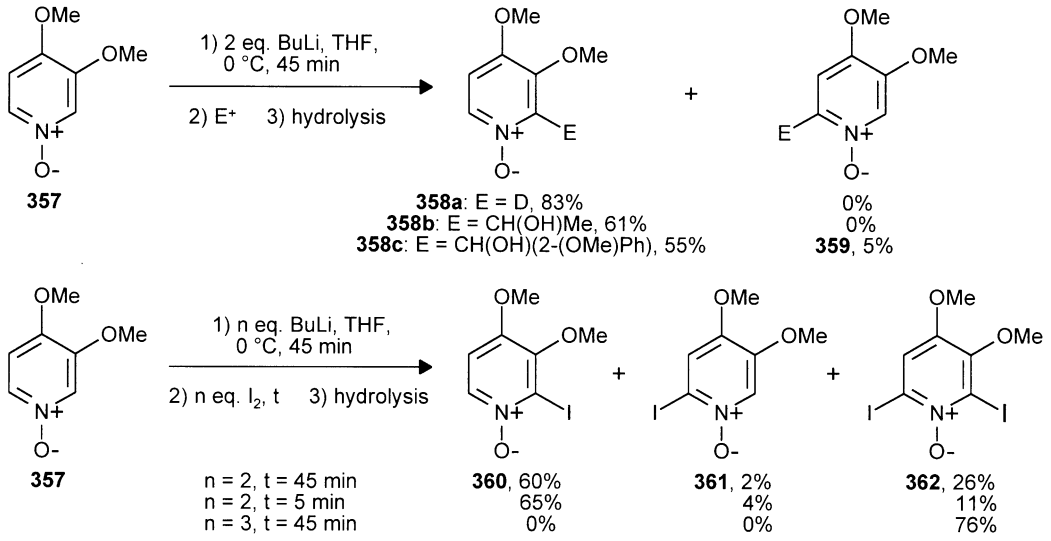
Deprotonation is less useful in the quinoline *N*-oxide than the pyridine *N*-oxide series since addition giving dimers such as **367** cannot be avoided. Conversion of quinoline



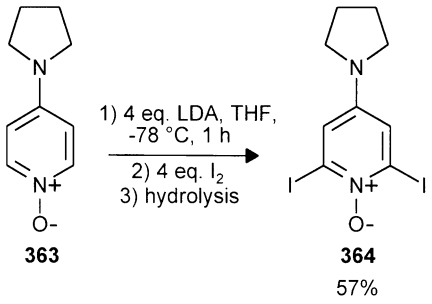
353: R = H (55-70%)
354: R = OMe (15-80%)

355a-b: E = Br, I
356a-c: E = D, Br, I

Scheme 98.



Scheme 99.

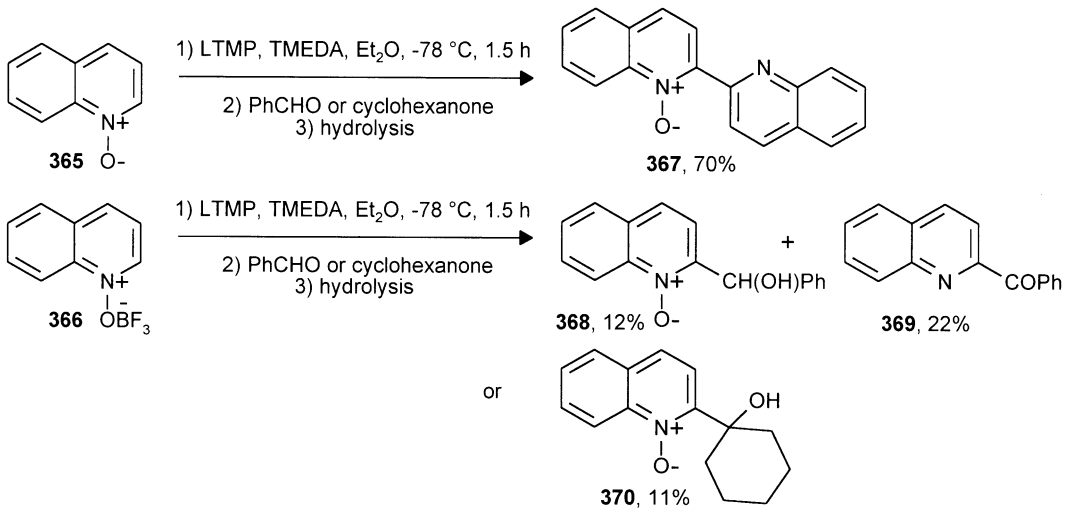


Scheme 100.

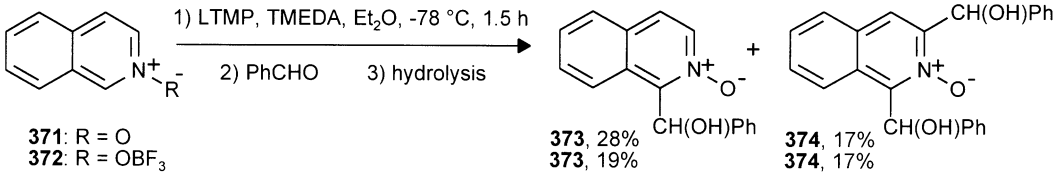
N-oxide (**365**) to its BF_3 complex **366** may help to facilitate the desired reaction (products **368–370**) (Scheme 101).[100]

7.3. Isoquinoline *N*-oxides

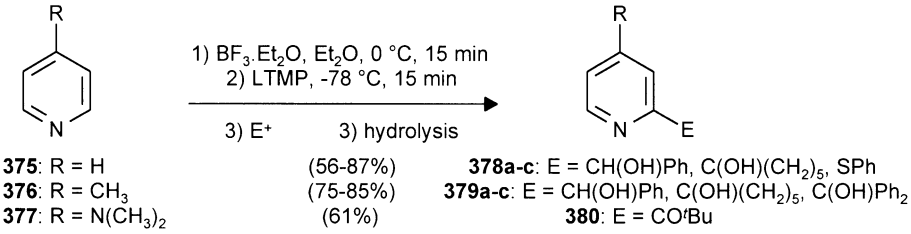
In the isoquinoline *N*-oxide series, similar results were observed starting from the *N*-oxide **371** or its BF_3 complex **372**. Compounds **373** and **374** were obtained and no addition reaction was observed (Scheme 102).[98]



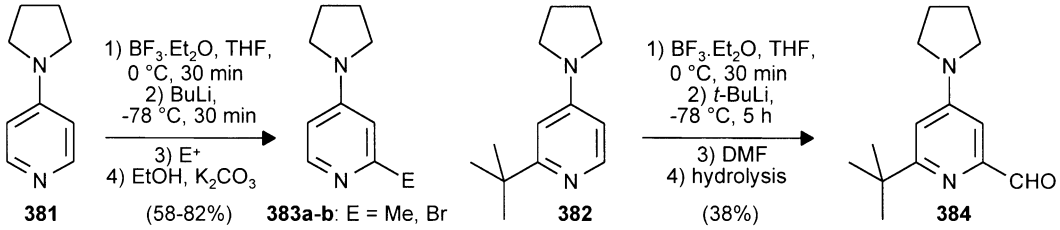
Scheme 101.



Scheme 102.



Scheme 103.



Scheme 104.

8. *N*-Activated heterocycles

8.1. *N*-Activated pyridines

Whereas deprotonation of pyridine with the highly hindered base LTMP afforded only 2,2′-bipyridine at −78°C, treatment of the BF_3 complexes of **375**–**377** afforded the 2-lithio derivative, as evidenced by electrophilic trapping giving **378**–**380**. 4-Methylpyridine (**376**) was deprotonated at the methyl group, whilst the corresponding BF_3 complex was lithiated at C2 under the same reaction conditions (Scheme 103).[101–103]

Alkyllithiums were also successfully used to metallate the BF_3 complexes of 4-(pyrrolid-1-yl)pyridines **381** and **382** (products **383** and **384**) (Scheme 104).[33] Metallation of the BF_3 complex of **381** at C2 followed by trapping with chlorotrimethylsilane to give **385** enabled a second metallation at C6 to be achieved, allowing the synthesis of the 2,6-disubstituted pyridine **386** (Scheme 105).[33]

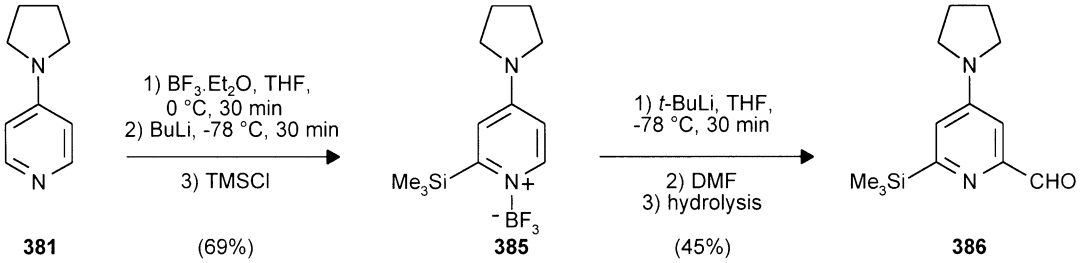
8.2. *N*-Activated quinolines and isoquinolines

Attempts to effect the metallation of BF_3 complexes of quinoline and isoquinoline were unsuccessful.[98]

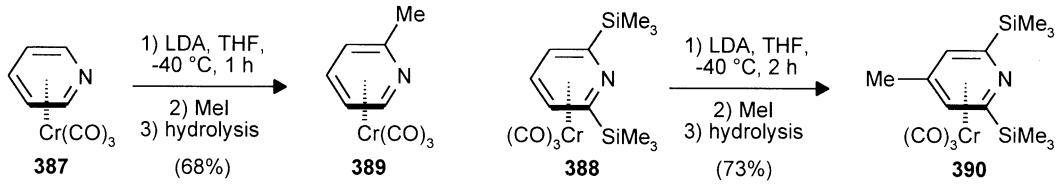
9. Other activated heterocycles

9.1. Tricarbonylchromium(0) activated pyridines

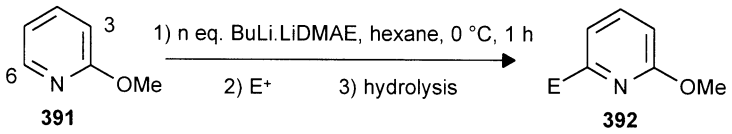
Metallation of tricarbonyl(η6-pyridine)chromium(0) complexes **387** and **388** has been studied by Davies. Complexation of pyridine to tricarbonylchromium(0) increased the acidity of the pyridinic protons sufficiently to allow deprotonation with LDA. The only product formed



Scheme 105.



Scheme 106.



Scheme 107.

Table 3. Quenching with various electrophiles

E^+	*n*	Yields of recovered **391**	Yields of **392**	Yields of addition compounds
$ClSiMe_3$	2	27, 5[a]	60, 75[a]	13, 15[a]
MeSSMe	2	20, 10[a]	63, 72[a]	15, 15[a]
DCl/D_2O	2	5, 6[a]	34, 41[a]	61, 53[a]
Me_2CO	2	8, 9[a]	43, 54[a]	49, 28[a]
$(CH_2)_5CO$	2	7[a]	63[a]	27[a]
MeCOEt	2	4[a]	80[a]	9[a]
$(C_3H_5)_2CO$	2	2[a]	83[a]	9[a]
$(CH_2)_7CO$	2	9[a]	45[a]	45[a]
$(CH{=}CH\text{-}(CH_2)_3)CO$	2	5[a]	49[a]	44[a]
Ph_2CO	2	10[a]	43[a]	44[a]
t-BuCHO	2	5[a]	88[a]	5[a]
HexCHO	2	10[a]	53[a]	32[a]
Et_2NCOCl	4	–[b]	65	–[b]
MeI	4	0	70	25
Me_2SO_4	4	7	70	14
EtI	4	0	64	29
Et_2SO_4	4	5	71	16
HexI	4	–[b]	60	34
HexBr	4	–[b]	30	64
c-$C_6H_{11}(CH_2)_3I$	4	2	52	44

[a] LiBr (0.25 equiv was added).
[b] Not determined.

was that elaborated at C2 (**389**). Deprotonation occurred at C4 with the 2,6-disubstituted pyridine **388**, leading to **390** (Scheme 106).[104]

10. Heterocycles without DMG

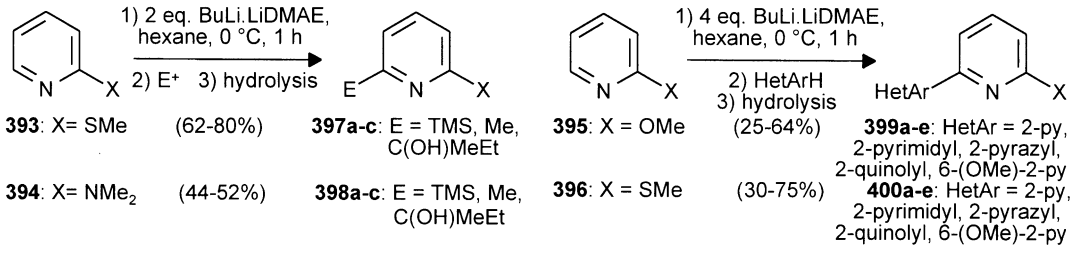
10.1. Aggregated activated azines

Recently, Caubère has achieved the metallation of pyridines with unimetallic superbases. This study focussed on the metallation of 2-methoxypyridine (**391**) with BuLi in the presence of various activating agents such as lithium alkoxides (ROLi). Nucleophilic addition of BuLi was observed in the absence of an activating agent and when the reactions were performed in the presence of *t*-BuOLi or 3-dimethylaminopropoxide. Metallation at C6 nevertheless dominated with the complex base, BuLi–lithium 2-dimethylaminoethanolate (LiDMAE). Various homogeneous BuLi–ROLi complex bases were also investigated and it was observed that the lithium salts of aminoethanols were the most effective activating agents, with LiDMAE being the most efficient.

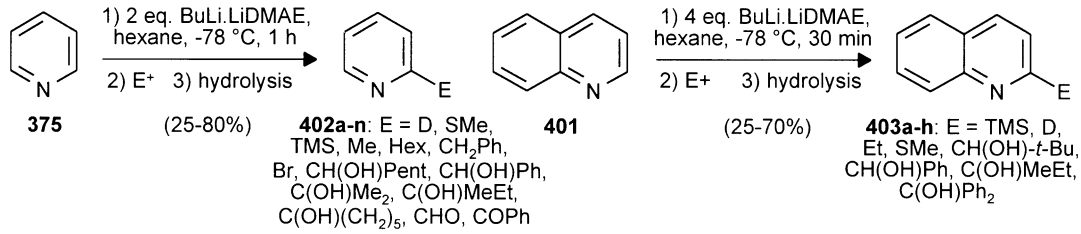
Addition of lithium bromide and THF to the electrophile usually promoted the condensation step with the electrophile, but the yields of addition compounds of BuLi varied with the nature of the electrophile (Scheme 107, Table 3).[105–107]

As butane evolution was observed during the condensation reaction with electrophiles rather than the metallation step, a common precursor to both **392** and the addition compounds of BuLi has been suggested. A radical intermediate formed between the substrate and the aggregates of the complex base was postulated.

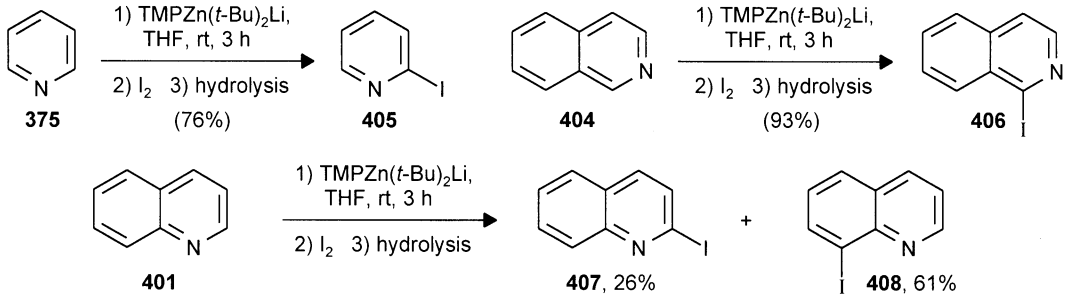
The reaction was not limited to 2-alkoxypyridines, replacement of the oxygen atom by sulfur or nitrogen leading to similar results, as exemplified by the coupling of the C6



Scheme 108.



Scheme 109.



Scheme 110.

lithiated 2-heterosubstituted pyridines **393** and **394** with various heterocycles, affording **397–400** (Scheme 108).[106,108] Pyridine **375** and quinoline **401** have similarly been deprotonated by the complex base BuLi–LiDMAE and **402** and **403** were obtained (Scheme 109).[109]

The use of mixed superbases for deprotonation of 2-methoxypyridine was also studied by Caubère. The incorporation of sodium-containing bases such as $NaNH_2$ into BuLi–LiDMAE induced a change in the regioselectivity of the metallation, which occurred at C3 rather than C6.[110]

When LIC–KOR (BuLi–*t*-BuOK) was used to deprotonate pyridine, the reaction occurred unselectively, mainly at the C2 and C4 positions.[1] Under these conditions, 2-*i*-propylpyridine was deprotonated unselectively with metallation at Cα, C4 and C6 being observed.[111]

Kondo has recently achieved the chemoselective deprotonation of pyridine and quinoline through the formation of an arylzincate. Using lithium di-*t*-butyl(2,2,6,6-tetramethylpiperidino)zincate (TMP-zincate) as a base and conducting the reactions at room temperature, pyridine **375** was metallated at C2 (product **405**). Under the same reaction conditions, quinoline **401** was deprotonated at C2 and C8 (products **407** and **408**) whereas isoquinoline **404** was deprotonated selectively at C1 (product **406**) (Scheme 110).[112]

11. Conclusions

The main problem encountered in the metallation of azines is nucleophilic addition of the base to the substrate. The electron-withdrawing effect of the ring nitrogen affords some advantages, however, as the ring hydrogens are more acidic and the stabilities of the corresponding lithio derivatives are greater. With the appropriate experimental conditions, alkyllithiums may therefore be used to deprotonate azines containing various DMGs. Metal amide bases, although less basic (pK_a 35.7 for LDA or 37.3 for LTMP compared to ca. 45 for alkyllithiums), can help to bias the reactions in favour of deprotonation and an even larger set of DMGs are then compatible.

For azines with little or no activation by DMGs, the use of an additive such as TMEDA, which is known to enhance the basicity of alkyllithiums, can often promote metallation. Similarly, unimetallic and mixed metal complex bases that are less nucleophilic and more basic than alkyllithium reagents are increasingly finding application in the metallation of azines. Importantly, such bases can often facilitate the metallation of azines containing no DMG. These reactions will doubtless prove to be synthetically useful and assist a fundamental understanding of azine metallation.

Attention has largely focussed to date on the generation and application of lithiated azines. Increasingly other organometallic derivatives are finding favour. Advances in this field will further widen the scope and application of azine metallation chemistry.

Acknowledgements

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Biographical sketch

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Guy Quéguiner received his Ph.D. in 1969 from the University of Rouen. He accepted the position of director of the Laboratory of Fine Heterocyclic Organic Chemistry in 1969 (CNRS research unit since 1989) and Professor at the University of Rouen in 1970. He became director of the Institute of Research in Fine Organic Chemistry in 1984 (creation of a 6400 m^2 building, in 1997, 177 researchers) and also director of the UPRESA 6014 in 1996. He currently holds the position of Professor 'exceptional class' degree at the University of Rouen. He has been a supervisor of 95 Ph.D. students and contributed to 265 publications and book and review articles. His main research topics are heterocycles (synthesis, reactivities, biologically active molecules), organometallics of azines and diazines (first efficient syntheses, applications), models of NADH, molecular recognition and artificial enzymes, and applied research (sugars, azasteroids, biomolecules, 'green chemistry', etc.).