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Advances in the directed metallation of azines and diazines (pyridines, pyrimidines, pyrazines, pyridazines, quinolines, benzodiazines and carbolines). Part 2: Metallation of pyrimidines, pyrazines, pyridazines and benzodiazines

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Contents

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1. Introduction

The purpose of this review is to update previous summaries[1–3] of directed *ortho*-metallation (DoM) reactions of diazines (pyridazines, pyrazines and pyrimidines) and benzodiazines. The review is divided according to the various directed metallation groups (DMGs) and is only concerned with reactions leading to the deprotonation of a diazine ring. Lateral metallation, halogen–metal exchange and processes involving metallation and elimination of a metal salt to give heteroarynes are not presented.

Metallation of diazines represents a more difficult challenge than the metallation of pyridines due to the lower energy level of their LUMOs. Nucleophilic addition therefore becomes a very facile competitive reaction. The use of alkyllithiums to metallate diazines often fails because they are good nucleophiles. Fortunately, the strong electron-withdrawing effect of the two nitrogen atoms makes the ring hydrogens more acidic. This allows less efficient metallating agents, such as alkylamides, to be used for DoM of diazines. Lithium di-i-propylamide (LDA) and especially lithium 2,2,6,6-tetramethylpiperidide (LTMP) usually give good results.

2. Halogen- and trifluoromethyl-based DMGs

2.1. Fluoro derivatives

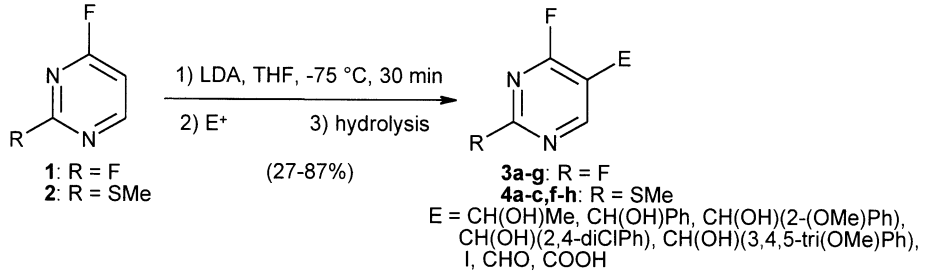
2.1.1. Fluoropyrimidines. The only lithiated fluorodiazines described in 1990 were those derived by deprotonation of 1,3-dialkyl-5-fluorouracils and 5-fluorouridine with LDA.[2] Fluoropyrimidines **1** and **2** were metallated in 1994 with LDA, affording the trisubstituted compounds **3** and **4** (Scheme 1).[4]

2.1.2. Fluoropyrazines. Fluoropyrazine (**5**) was lithiated in 1998 with LDA and LTMP and disubstituted products **6** were obtained, the LTMP giving superior yields (Scheme 2).[5] Metallation of **5** was also accomplished with in situ trapping of chlorotributylstannane at −100°C to give 2-fluoro-3,6-bis(tributylstannyl)pyrazine (**7**) (Scheme 3). When 2-fluoro-3-(diphenylhydroxymethyl)pyrazine (**6c**) was reacted with LTMP, a regioselective metallation took place and substituted products at C6 (**8**) were obtained (Scheme 4).

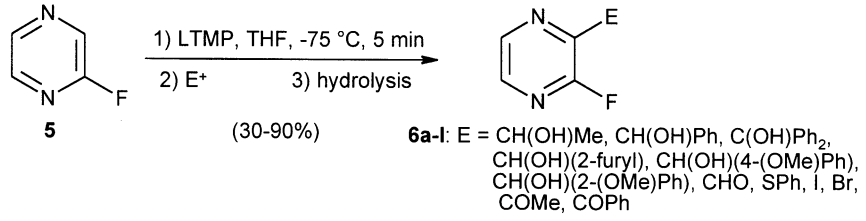
To our knowledge, there have been no reports on the lithiation of fluoropyridazines or fluorobenzodiazines.

2.2. Trifluoromethyl derivatives

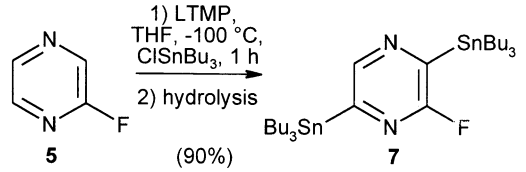
Metallation of 2-methylsulfanyl-4-trifluoromethylpyrimidine (**9**) with LTMP represents the only example of metallation of a trifluoromethyldiazine.[6] The metallation was regioselective at C6, leading to compounds **10a–e** together with traces of dimer **11** (Scheme 5). When the same reaction was performed by the in situ trapping method, the yields of **10c–e** were not enhanced. With chlorotrimethylsilane, benzophenone and dimethyl disulfide as electrophiles, good yields (77–98%) were obtained using this method.



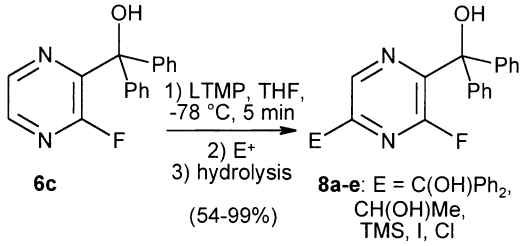
Scheme 1.



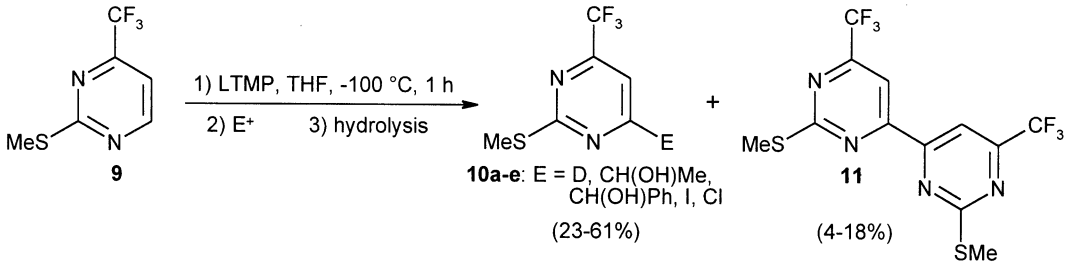
Scheme 2.



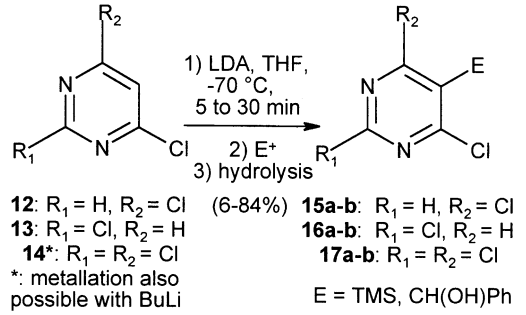
Scheme 3.



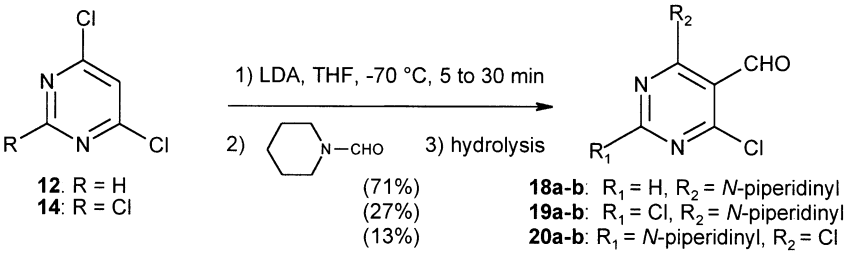
Scheme 4.



Scheme 5.



Scheme 6.



Scheme 7.

2.3. Chloro derivatives

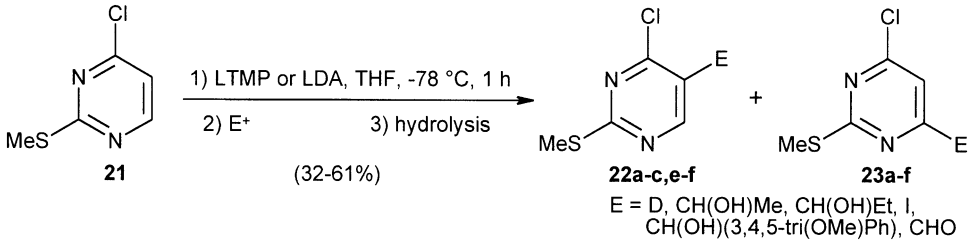
2.3.1. Chloropyrimidines. Metallation of chloropyrimidines with LDA, LTMP and BuLi was known in 1990.[2] Radinov later described a regioselective metallation of polychloropyrimidines **12**–**14** with LDA and BuLi (Scheme 6),[7] the products **15**–**17** being obtained. When *N*-formylpiperidine was used as the electrophile, substitution of one chlorine atom by the piperidinyl moiety occurred, and the compounds **18**–**20** (Scheme 7) were formed.

The metallation of 2,4-dichloropyrimidine (**13**) has been reinvestigated. With LTMP as the metallating agent, equal amounts of 5- and 6-substituted pyrimidines were obtained, whereas with LDA the metallation was more regioselective and only 6–10% of the 6-substituted compounds were found.[8]

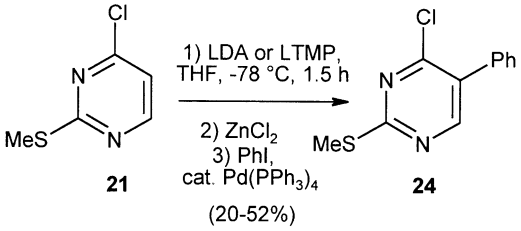
In the same paper, 2-methylsulfanyl-4-chloropyrimidine (**21**) was lithiated leading to regioisomers **22** and **23** on quenching with electrophiles (Scheme 8). Importantly, when LDA was used, a 19:1 ratio of **22** and **23** was obtained, whereas with LTMP a 1:2 mixture of regioisomers resulted. With iodine as the electrophile, both metallating agents led to **23d**.

The lithio derivative obtained from **21** was also reacted with $ZnCl_2$ and the resulting organozinc compound was cross-coupled with iodobenzene, giving **24** (Scheme 9).[9]

2.3.2. Chloropyrazines. The metallation of chloropyrazine (**25**) has been known for over a decade[2] and has subsequently been used to synthesize pyrazine ketone flavouring agents.[10] The metallation of 2,6-dichloropyridazine (**26**) with LTMP provides disubstituted products **28c**, **g**, **h** when benzaldehyde, iodine and chlorotrimethylstannane, respectively, were used as the electrophiles (Scheme 10).[11]



Scheme 8.



Scheme 9.

This result suggests that formation of **27c**, **g**, **h** promotes further metallation at C5, since many other electrophiles provide only the monosubstituted product **27**.

Interestingly, the antiarhythmic drug, arglecin, has been prepared by metallation of chloropyrazine (**25**) and quenching with isobutanal.[12] Pyrazine C-ribosides have been synthesized in a similar manner via DoM reaction of **25** and **26**, and the compounds **29** and **30** (Scheme 11) were formed.[13]

2.3.3. Chloropyridazines. The metallation of 2,6-dichloropyridazine was reviewed in 1990,[2] and there have been no further publications of note in the last decade.

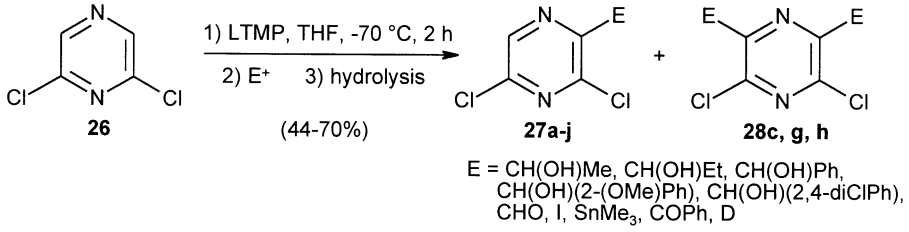
2.3.4. Chloroquinoxalines. In 1991, Ward described unsuccessful attempts to prepare quinoxaline ketones via metallation of 2-chloroquinoxaline (**31**).[10] The metallation of **31** was subsequently shown to provide the dimer **33** as the major product (59%) when DCl was used as the electrophile. With acetaldehyde and benzaldehyde as electrophiles, the products **32a** and **b** were obtained in 66 and 52% yield, respectively, while with acetaldehyde, dimer **34** was produced in 46% yield (Scheme 12).[14]

2.3.5. Chlorocinnolines. Metallation of 3- and 4-chlorocinnolines (**35** and **36**) with LTMP has been used to introduce substituents at C4 and C3, respectively, in good yields (products **37** and **38**) (Scheme 13).[15] For 4-chlorocinnoline (**36**), a trace amount (10%) of dimer was obtained when acetaldehyde was used as the electrophile.

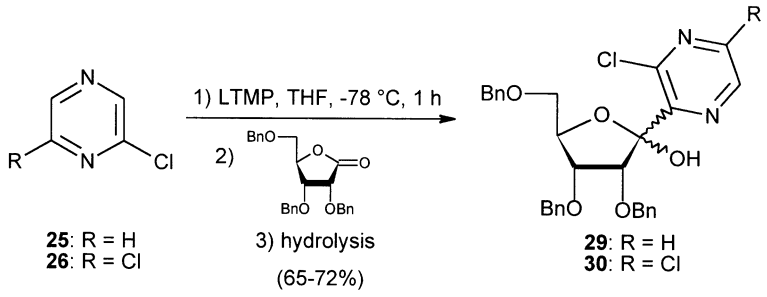
Metallations of bromodiazines have yet to be reported.

2.4. Iodo derivatives

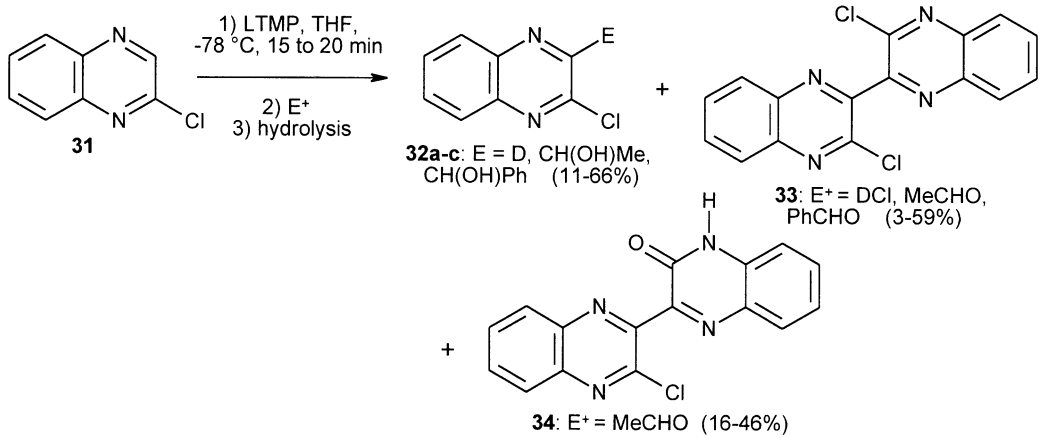
2.4.1. Iodopyrimidines. The metallation of iodouridine has been known for some time.[2] More recently, this has been extended to 2-methylsulfanyl-4-iodopyrimidine (**39**) where the best results were obtained when the reactions were conducted at a very low temperature (−100°C), with short metallation times (10 min) and using a very hindered base



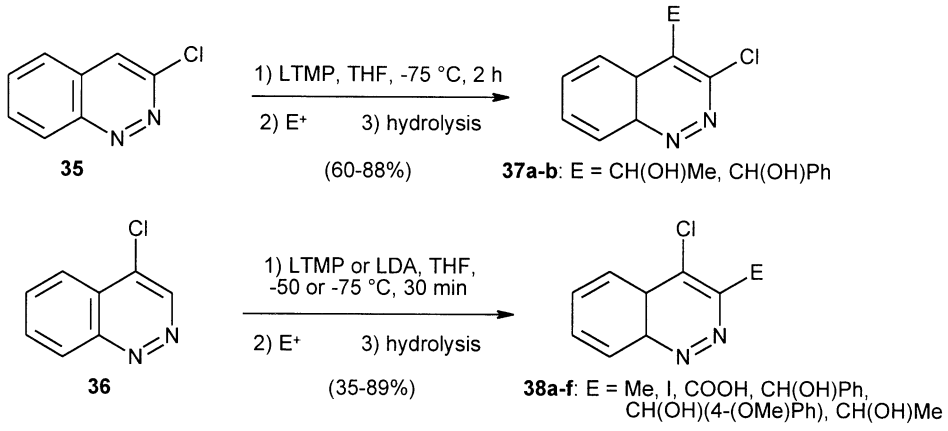
Scheme 10.



Scheme 11.

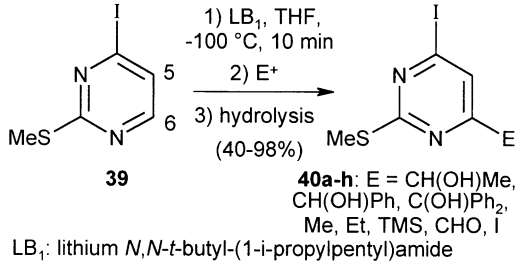


Scheme 12.

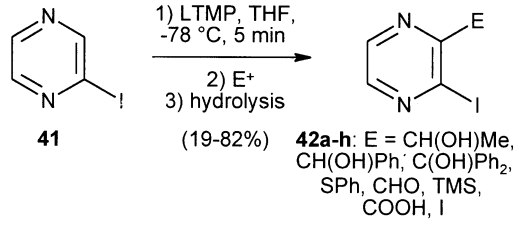


Scheme 13.

(Scheme 14).[16] Functionalization of **39**, affording products **40**, occurred at C6, *ortho* to the nitrogen rather than the iodine, presumably reflecting a greater stability for the 6-lithio derivative.



Scheme 14.



Scheme 15.

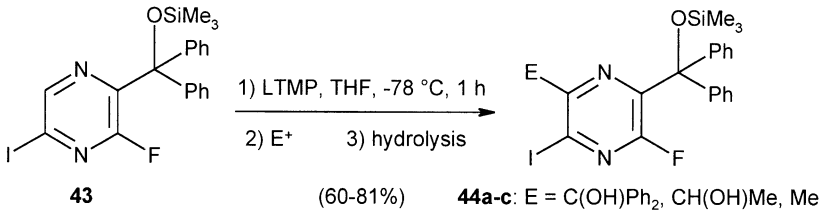
2.4.2. Iodopyrazines. Metallation of iodopyrazine (**41**) also benefitted from a short reaction time (5 min) and occurred at C3, leading to products **42** (Scheme 15).[16] The polysubstituted iodopyrazine **43** has likewise been metallated *ortho* to the iodine (products **44**) (Scheme 16).[5]

3. Oxygen-based DMGs

3.1. Methoxy derivatives

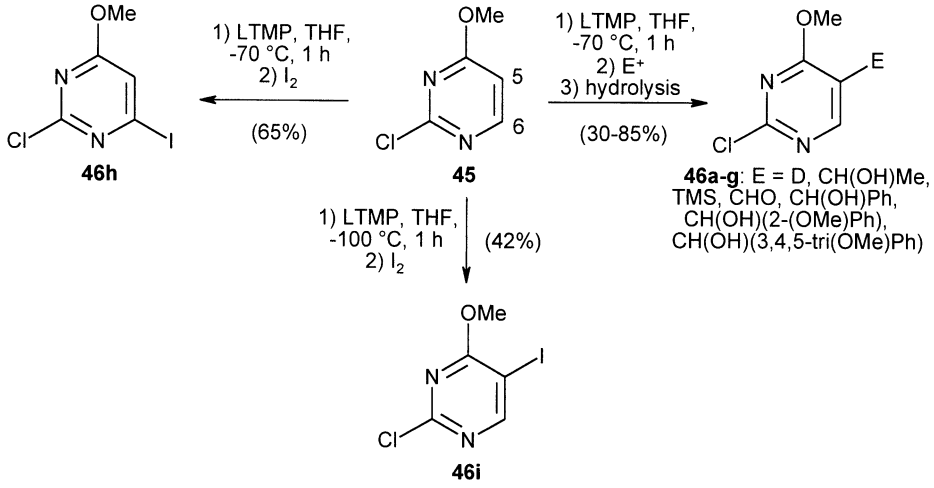
3.1.1. Methoxypyrimidines. Methoxy and polymethoxypyrimidines were amongst the first diazines to be metallated in good yield.[2] This chemistry has recently been used to prepare an analogue of the antibacterial agent, trimethoprim, starting from **45** (Scheme 17).[17] With iodine as the electrophile, the 6-iodo derivative **46h** was obtained in a 85% yield. It was also possible to effect iodination at C5 by modification of the experimental procedure, and product **46i** was obtained. The other electrophiles reacted at C5 and afforded products **46a**–**g**.[18]

In order to prepare 4-amino-5-methoxypyrimidine (**49**), 5-methoxypyrimidine (**47**) was metallated with LTMP and reacted with tosyl azide to afford **48**. Subsequent treatment of **48** with triphenylphosphine gave the aminopyrimidine **49**



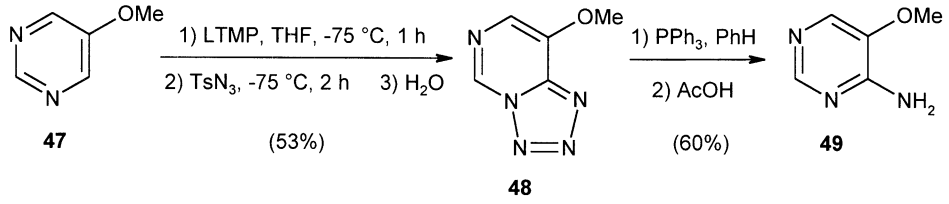
43

Scheme 16.



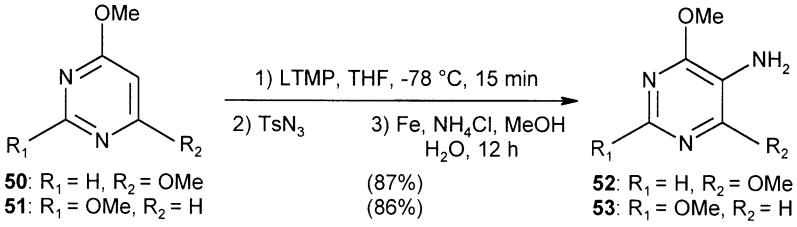
46h 45 46i

Scheme 17.



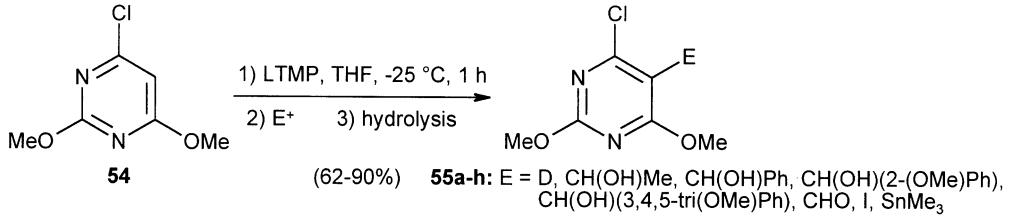
47 48 49

Scheme 18.



50: R_1 = H, R_2 = OMe
51: R_1 = OMe, R_2 = H
52: R_1 = H, R_2 = OMe
53: R_1 = OMe, R_2 = H

Scheme 19.



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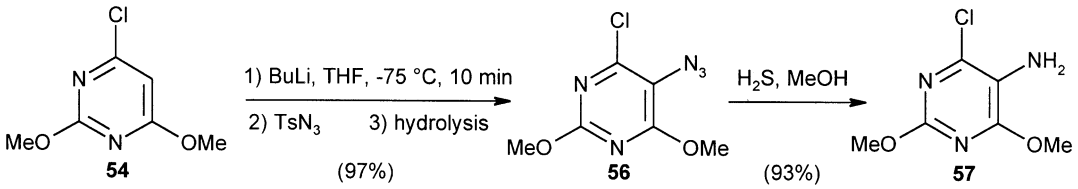
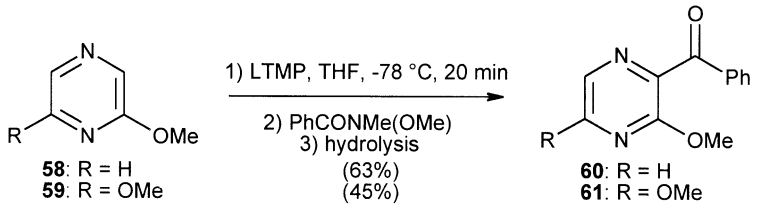
Scheme 20.



Scheme 21.



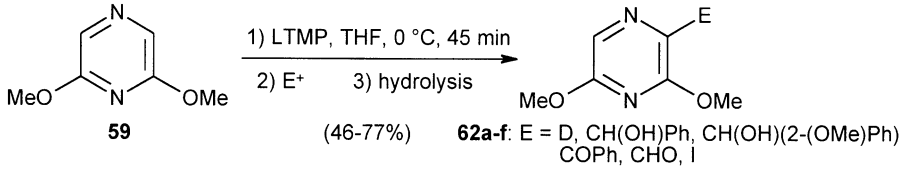
Scheme 22.

(Scheme 18).[19] The same tactic was used by Cho to introduce amines at C5 (**52** and **53**) in the dimethoxypyrimidines **50** and **51** (Scheme 19).[20]

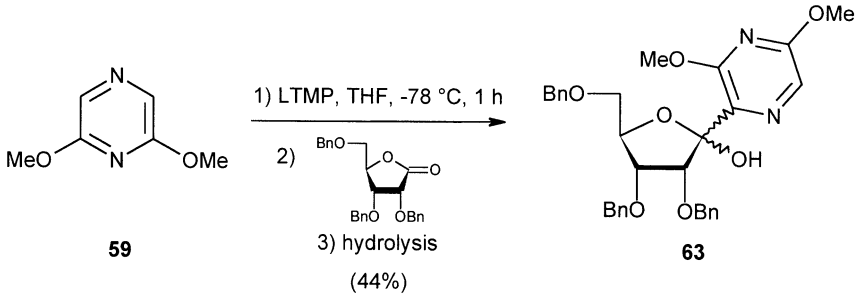
Lithiation of 4-chloro-2,6-dimethoxypyrimidine (**54**) has been used to prepare compounds **55**, the product **55e** allowing the preparation of an analogue of bacimethrin (Scheme 20).[21] Metallation of **54** with BuLi has also provided the C5 amino derivative **57** in good yield via **56** (Scheme 21).[19] Cushman used the same method to metallate **54** and reacted with diiodoalkanes to prepare inhibitors of lumazine synthase.[22]

3.1.2. Methoxypyrazines. Metallation of methoxy and dimethoxypyrazines[2] has recently been used by Ward to prepare pyrazine ketones **60** and **61** (Scheme 22).[10]

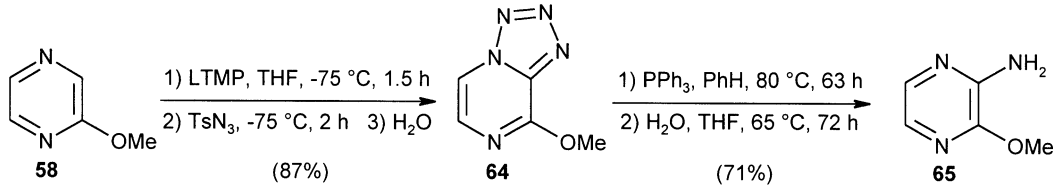
Various electrophiles have been introduced at C5 using this methodology and gave products **62** (Scheme 23).[11] Interestingly, when iodine was used as the electrophile, a mixture of



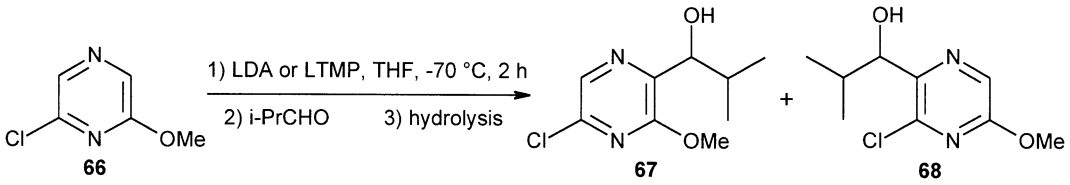
Scheme 23.



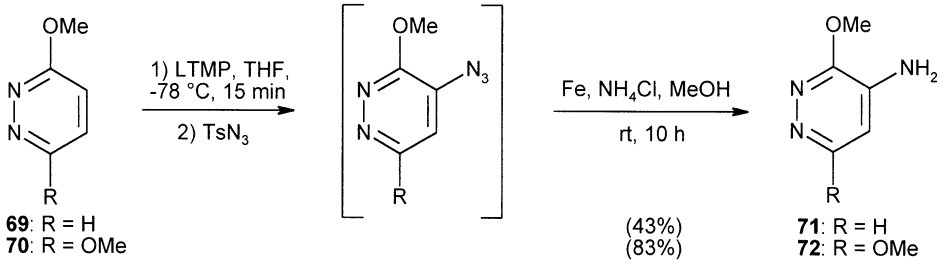
Scheme 24.



Scheme 25.



Scheme 26.



Scheme 27.

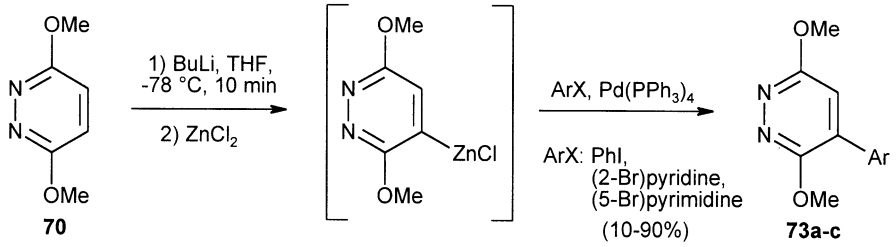
5-iodo- and 2,5-diiodopyrazines was obtained in 46 and 54% yield, respectively. Metallation of 2,6-dimethoxypyrazine (**59**) has also been used by Townsend to prepare pyrazine C-riboside **63** (Scheme 24).[13]

In order to prepare a key intermediate of kelfizine or sulfalene, 2-amino-3-methoxypyrazine (**65**) was synthesized via metallation of methoxypyrazine (**58**) giving **64** (Scheme 25).[19] More recently, methoxypyrazine (**58**) was metallated and reacted with $ZnCl_2$. The resulting organozinc derivative was then coupled with iodobenzene, leading to 2-methoxy-3-phenylpyrazine (88% yield).[9]

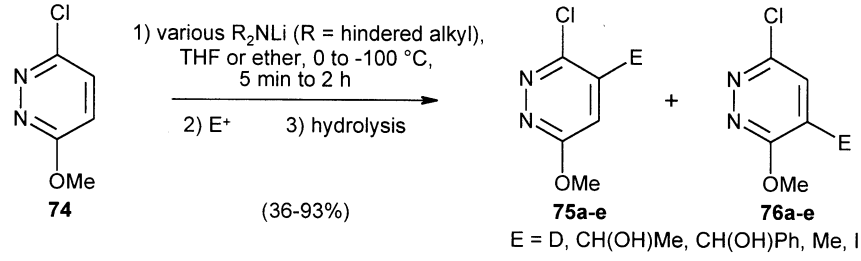
The regioselectivity of the metallation of 2-chloro-6-methoxypyrazine (**66**) with LTMP and LDA has been studied (Scheme 26).[12] The ratio **67**/**68** was close to 85/15, but the yield was greater with LDA (90%) than LTMP (57%). 2-Iodo-6-methoxypyrazine was also metallated with LDA (71%) and the reaction was found to be regioselective, with the electrophile introduced *ortho* to the methoxy group. A similar result was noted in the preparation of pyrazine C-ribosides from **66**.[13]

3.1.3. Methoxypyridazines. The metallation of 3-methoxy- and 3,6-dimethoxypyridazines[2] (**69** and **70**) has been used to introduce amino and aryl substituents at C4. For the former compound, quenching of the intermediate lithio derivative with tosyl azide first provides a pyridazine azide which is reduced with iron (Scheme 27)[20] or by catalytic hydrogenation[19] to the amine (products **71** and **72**). Introduction of the aryl group likewise required preparation of an intermediate organozinc reagent, palladium-catalyzed coupling with a haloarene then giving **73a–c** (Scheme 28).[9]

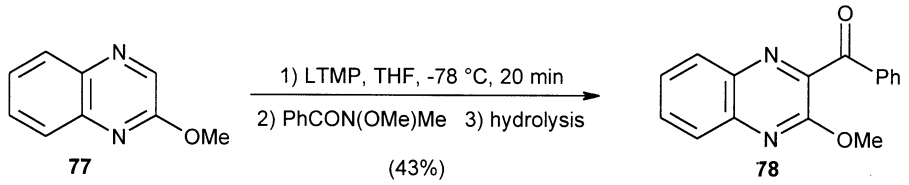
In the course of the synthesis of minaprine, 3-chloro-6-methoxypyridazine (**74**) was lithiated with LTMP. The



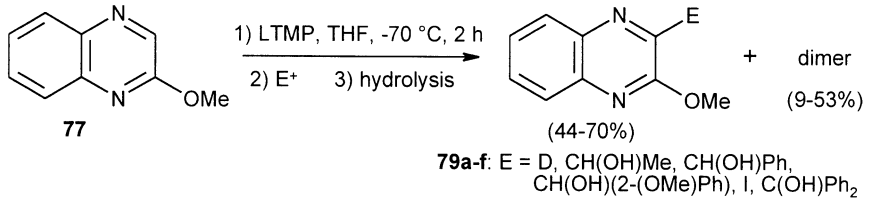
Scheme 28.



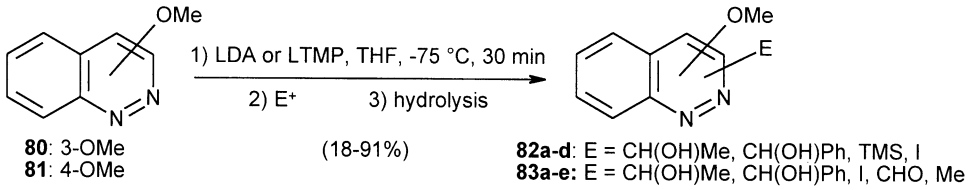
Scheme 29.



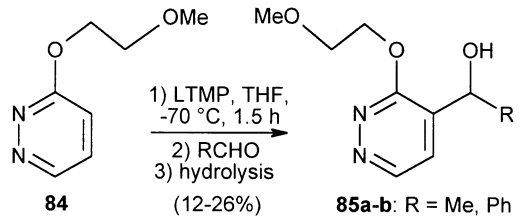
Scheme 30.



Scheme 31.



Scheme 32.



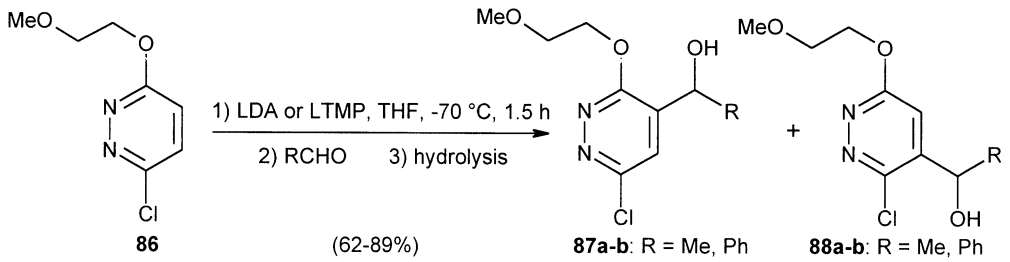
Scheme 33.

two regioisomers **75** and **76** were produced, with substitution *ortho* to the methoxy group being strongly favoured (>80/20).[23] Using the in situ trapping method, **74** was regioselectively metallated *ortho* to the methoxy group with LDA and with LTMP when chlorotrimethylsilane was employed as the electrophile (in 70 or 88% yield, respectively).[24]

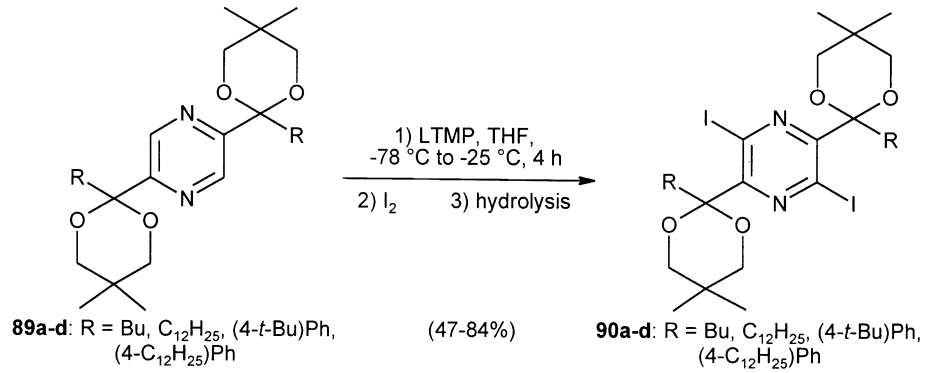
A systematic study of the metallation of **74** has been performed using a variety of lithium alkylamides, temperatures and solvents (THF and ether).[25] Regioselectivity was >95/5 *ortho* to the methoxy group with various electrophiles when hindered lithium alkylamides were used at very low temperatures (Scheme 29). Lithium *N*,*N*-*t*-butyl-(1-*i*-propylpentyl)amide, a very hindered base, has been used to introduce an amino group at C4 of **74**.[19]

3.1.4. Methoxybenzodiazines. In 1991, Ward metallated 2-methoxyquinoxaline (**77**) to obtain quinoxaline ketone **78** (Scheme 30).[10] A more complete investigation of the metallation of **77** has shown that substantial dimerization occurs, thereby limiting the efficiency of electrophilic trapping reactions. The products **79** were, however, isolated (Scheme 31).[14]

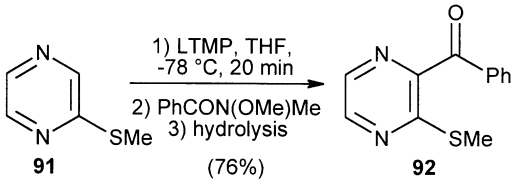
The metallation of 3- and 4-methoxycinnolines (**80** and **81**) with lithium amides has been achieved (Scheme 32),[15] the monosubstituted products **82** and **83** mostly being obtained. Using iodine as the electrophile, however, afforded some



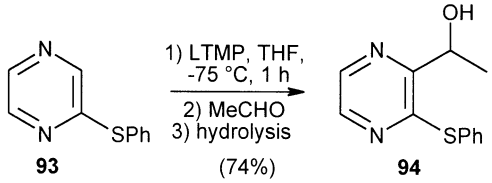
Scheme 34.



Scheme 35.



Scheme 36.



Scheme 37.

diiodo compounds, the second iodide being introduced at C8.

3.2. Methoxyethoxy derivatives

3.2.1. Methoxyethoxypyridazines. 3-Methoxyethoxypyridazine (**84**) has been metallated in low yield with LTMP and the alcohols **85a–b** were prepared (Scheme 33).[26]

Higher yields were obtained with 3-chloro-6-methoxyethoxypyridazine (**86**) (Scheme 34),[26] where quenching the organolithium intermediate formed with LTMP gave regioisomer **87** as the major product, while, with LDA, regioisomer **88** predominated.

3.3. Oxacycles

Acetals have also been used to direct lithiation of pyrazines. Tour, for example, metallated diketals **89** and reacted the lithio derivatives with iodine (Scheme 35),[27] the resulting diiodides **90** then being used to prepare pyrazine ladder polymers.

4. Sulfur-based DMGs

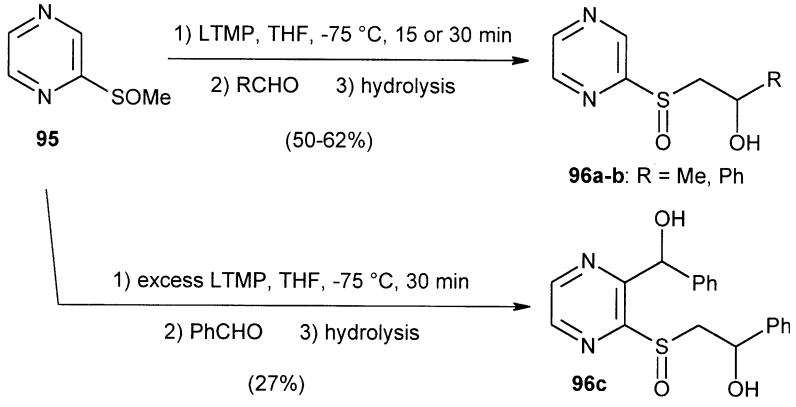
4.1. Pyrimidines

The metallation of 5-(*p*-tolylsulfinyl)pyrimidine has been attempted, but without success.[28] To our knowledge, no other sulfur DMG has been used in the pyrimidine series.

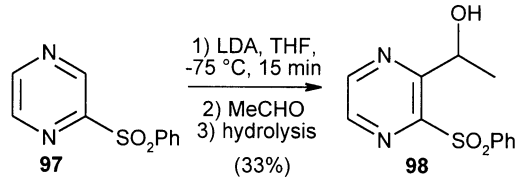
4.2. Pyrazines

Ward has metallated methylsulfanylpyrazine (**91**) and obtained ketone **92** (Scheme 36).[10] More recently, the metallation of various sulfur derivatives of pyrazine (sulfanyl, sulfinyl and sulfonyl) has been studied,[29] the metallation of phenylsulfanylpyrazine (**93**) with LTMP occurring at C3, leading to **94** (Scheme 37).

With methylsulfinylpyrazine (**95**), metallation occurred on



Scheme 38.



Scheme 39.

the methyl group (**96a** and **b**) but, with an excess of LTMP, an *ortho*-metallation could be achieved, leading to **96c** (Scheme 38). The metallation of methylsulfonylpyrazine also led to deprotonation of the methyl group, but *ortho*-metallation could be performed in low yield with phenylsulfonylpyrazine (**97**), the product **98** being obtained (Scheme 39). For the metallation of *t*-butylsulfinyl and *t*-butylsulfonylpyrazines (**99** and **100**), modest yields of C3 substitution products **101** and **102** (Scheme 40) have been achieved in recent studies.[30]

4.3. Pyridazines

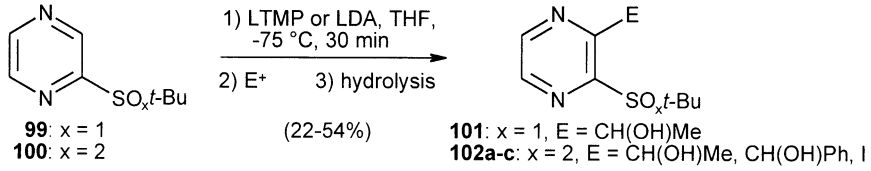
In the pyridazine series, studies comparing sulfur- and methoxy-based DMGs have been conducted.[29] Metallation of the phenylsulfanyl derivative **103** (x=0) was regioselective, occurring *ortho* to the methoxy group and giving the isomer **106a**. For the phenylsulfinyl derivative **104** (x=1), the regioselectivity was again complete for metallation *ortho* to this group, leading to isomers **107a–d**. A mixture of the two isomers **108** and **109** was obtained from **105** (x=2), with the phenylsulfonyl group being a better DMG than the methoxy group (Scheme 41). The metallation of a 3-methylsulfanyl-6-methoxypyridazine led to metallation of the methyl moiety. The same study was performed with *t*-butylsulfinyl and *t*-butylsulfonyl derivatives **110** and **111** and gave comparable results (products **112–115**) (Scheme 42).[30]

The competitive metallation between a sulfonamide and a chloro group has also been examined with product **116** and only metallation *ortho* to the sulfonamide group was observed (product **117**) (Scheme 43).

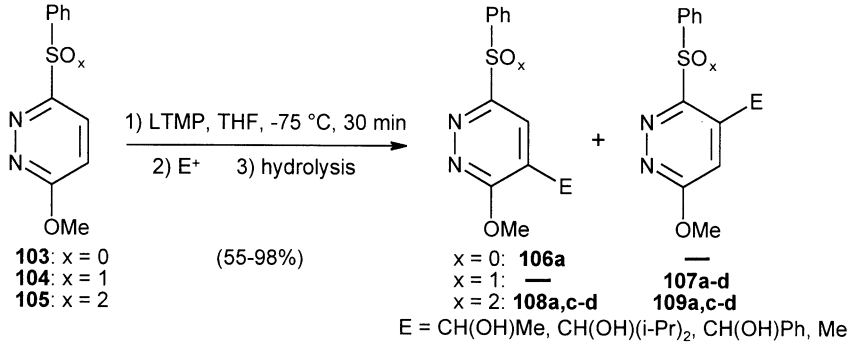
The use of chiral sulfoxides as directing groups for *ortho*-metallation of pyridazines has been studied. Lithiation of the chiral pyridazine sulfoxide **118**, followed by trapping with various aldehydes, proceeded in a highly diastereoselective manner (de >93%), giving compounds **119** (Scheme 44).[28]

4.4. Benzodiazines

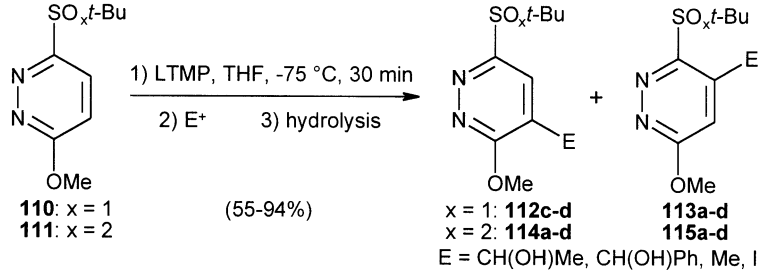
The only benzodiazine sulfur derivative to have been



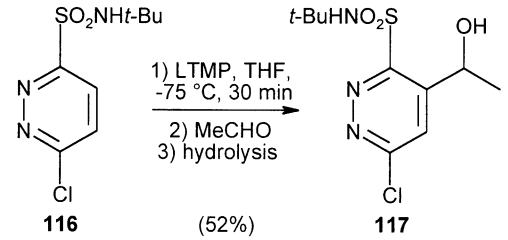
Scheme 40.



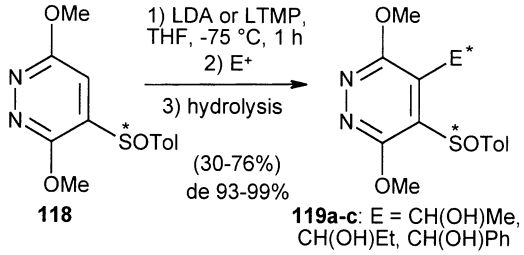
Scheme 41.



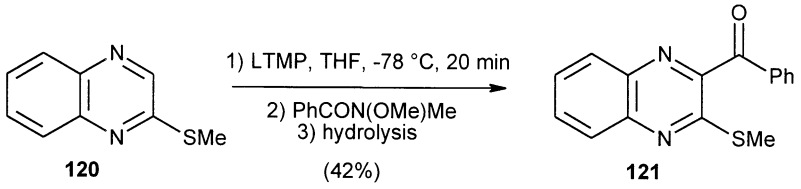
Scheme 42.



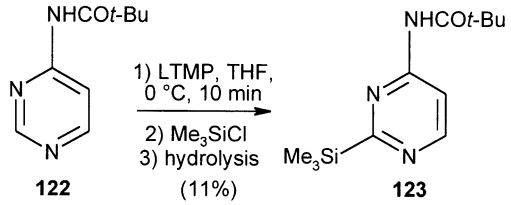
Scheme 43.



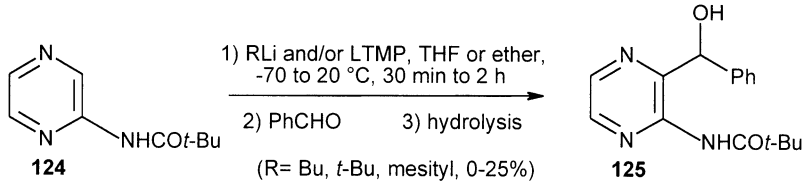
Scheme 44.



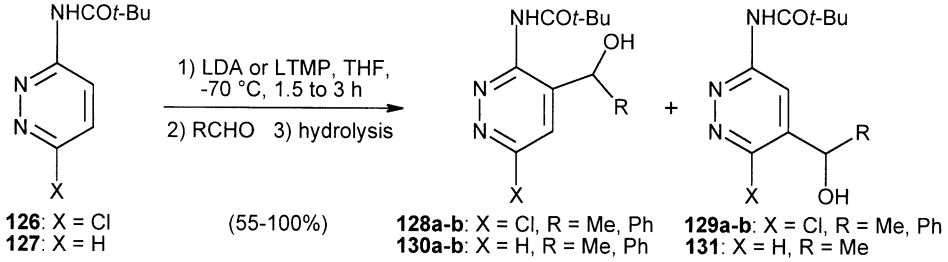
Scheme 45.



Scheme 46.



Scheme 47.



Scheme 48.

lithiated is 2-methylsulfanylquinoxaline (**120**); the ketone **121** was obtained (Scheme 45).[10]

5. Nitrogen-based DMGs

5.1. Pyrimidines

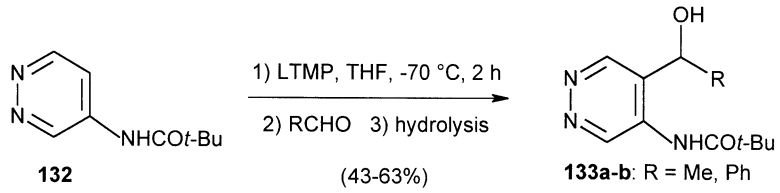
The DoM reaction of 2,2-dimethyl-*N*-(4-pyrimidyl)-propanamide (**122**) was attempted in 1990 without success and only a low yield of the 2-silylated product **123** was obtained (Scheme 46).[31] No other papers dealing with this subject in the pyrimidine series have been reported.

5.2. Pyrazines

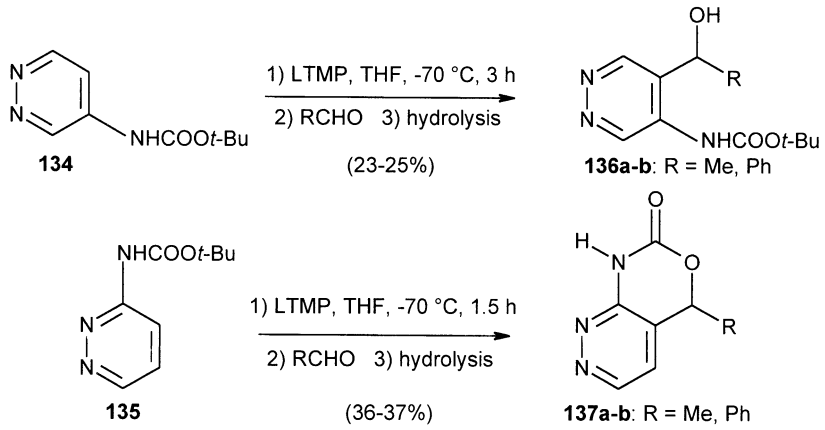
Low yields have also been reported for the metallation of 2,2-dimethyl-*N*-(pyrazyl)propanamide (**124**). Various metallating agents and reaction temperatures were investigated but, on quenching with benzaldehyde, the yield of **125** was always ≤25% (Scheme 47).[32]

5.3. Pyridazines

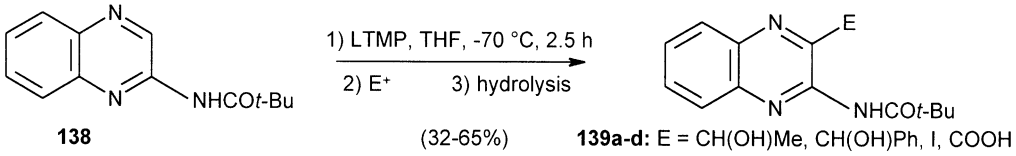
The lithiation of 2,2-dimethyl-*N*-(3-pyridazyl)propanamides (**126** and **127**) was successful and the products **128**–**131** were obtained in good yields (Scheme 48).[26] From **126** (X=Cl), isomers **129** derived from a metallation *ortho* to the chlorine atom predominated, whilst from **127** (X=H), only a low percentage (4%) of isomer **131** was obtained.



Scheme 49.



Scheme 50.



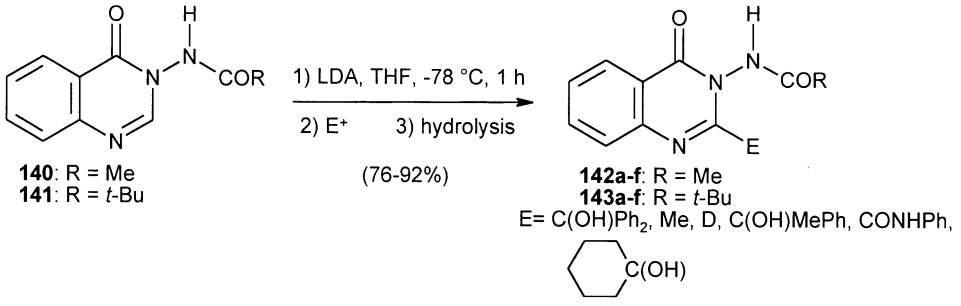
Scheme 51.

Metallation was also studied when the *t*-butylcarbonylamino group was present at C4 (compound **132**) and occurred exclusively at C5, giving **133** (Scheme 49).[33] In the same paper, metallation of *t*-butoxycarbonylaminopyridazine (**134**) was described as taking place with complete regioselectivity at C5 (products **136a** and **b**). With the carbamate moiety at C3 (**135**), functionalization at C4 was followed by a cyclization giving **137a** and **b** (Scheme 50).[26]

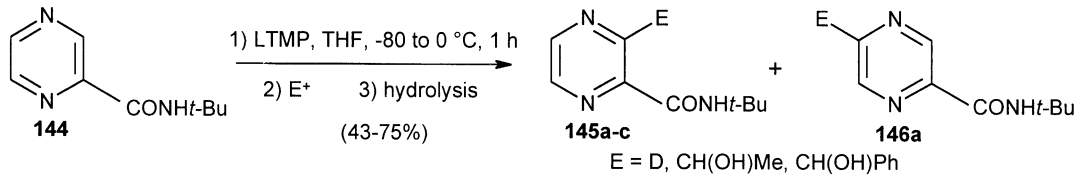
5.4. Benzodiazines

2,2-Dimethyl-*N*-(2-quinoxalyl)propanamide (**138**) was lithiated in 1993, leading to *ortho*-substituted derivatives **139** in modest yields (Scheme 51).[14]

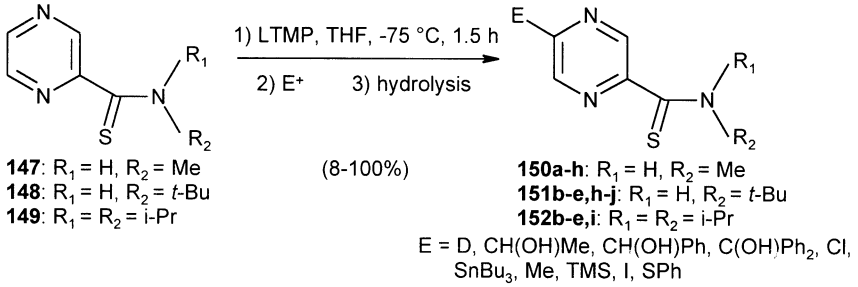
More recently, Smith lithiated *N*-acylaminoquinazolinones **140** and **141** and obtained a substitution between the two nitrogen atoms (products **142** and **143**) (Scheme 52).[34]



Scheme 52.



Scheme 53.



Scheme 54.

When *t*-BuLi or MeLi were used as the metallating agents, 1,2-addition products were obtained in good yields.

6. Carbon-based DMGs

6.1. Pyrimidinecarboxamides and thiocarboxamides

To the best of our knowledge, there have been no publications on this topic between 1990 and 2000.

6.2. Pyrazinecarboxamides and thiocarboxamides

When *N*-(*t*-butyl)pyrazinecarboxamide (**144**) was metallated, the two isomers **145** and **146** were obtained; their ratio was dependent on the experimental conditions (Scheme 53).[32] A study of the reaction at various temperatures indicated that the 2,3-disubstituted isomer was the thermodynamic product and the 2,5-disubstituted isomer was the kinetic product. When the in situ trapping method was used with chlorotrimethylsilane as the electrophile, a 3,5-disilylated compound was obtained, together with the expected 5-silylated derivatives.

The metallation of pyrazinethiocarboxamides **147**–**149** has been described very recently and this unexpectedly proceeded with complete regioselectivity at C5, leading to **150**–**152** (Scheme 54).[35] The structure was established by NMR spectroscopy using ^{1}H–^{15}N correlations.

6.3. Pyridazinecarboxamides

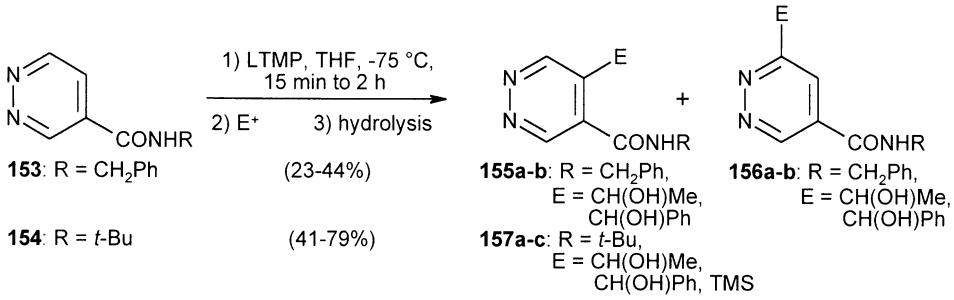
Lithiation of pyridazine-4-carboxamides also gave rise to some unexpected results. With the *N*-benzyl derivative **153**, *meta*-functionalized compounds **156a** and **b** were obtained, along with the *ortho*-substituted **155a** and **b**. Lithiation of the *N*-*t*-butyl derivative **154** was regioselective at C5, affording **157** (Scheme 55).[33] When chlorotrimethylsilane was used as the electrophile, the C5 silylated product was formed, together with 15% of the 3,5-disilylated product.

7. Heterocycle *N*-oxides

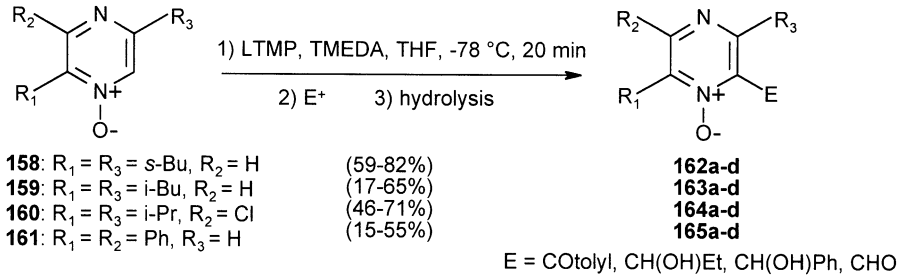
The metallation of pyrazine *N*-oxides was known in 1990. More recently, polyalkylpyrazine *N*-oxides **158**–**161** have been metallated with LTMP with some success, the products **162**–**165** being obtained (Scheme 56).[36]

8. Heterocycles without DMG

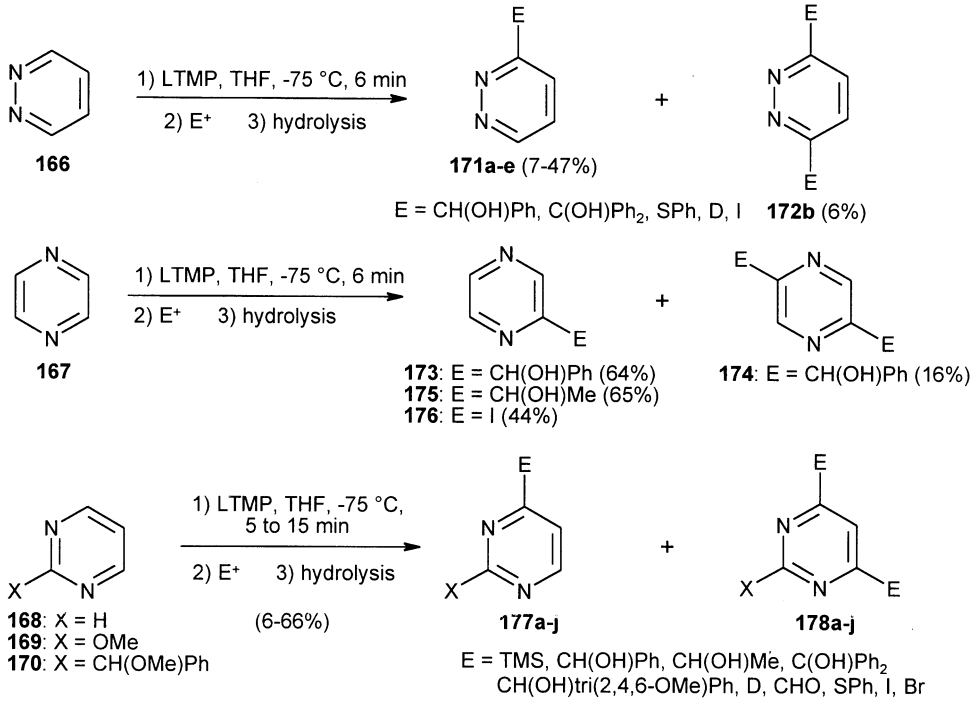
The electron-withdrawing effect of the diazine nitrogens makes the hydrogens of these heterocycles reasonably



Scheme 55.



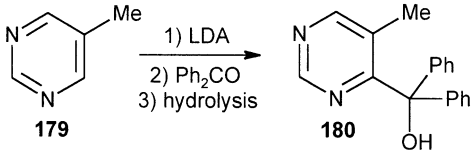
Scheme 56.



Scheme 57.

acidic. Indeed, the presence of a DMG is not mandatory, and all three diazines **166**–**168** have been successfully metallated. A very short metallation time was required and both mono- (**171**, **173**, **175**–**177**) and disubstituted (**172**, **174**, **178**) products were obtained on quenching of the organometallic intermediate. The same reaction conditions also allowed the metallation of compounds **169** and **170** (Scheme 57).[37]

The presence of an alkyl group on the diazine ring led almost invariably to lateral metallation of this group. 5-Methylpyrimidine (**179**) was an exception to this rule, its *ortho*-metallation being reported in an unspecified yield (product **180**) (Scheme 58).[38]



Scheme 58.

9. Conclusions

The numerous examples of diazine metallation highlighted in this review demonstrate the synthetic utility of this methodology. It has become a very powerful tool to functionalize diazines and benzodiazines, and often proceeds in a highly diastereoselective manner.

In general, the metalation times are short, <1 h, and lithium alkylamides are employed as bases to avoid the production of addition products. Long reaction times and elevated temperatures (>-75°C) usually lead to lower yields and the formation of tarry products. Recently, the syntheses of other organometallic derivatives of diazines (Mg, Zn) have expanded this field and provided further scope for development of the chemistry.

Acknowledgements

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Biographical sketch

Alain Turck received his PhD in 1985 in the Laboratory of Fine Heterocyclic Organic Chemistry in Rouen. His PhD research focused on the functionalization of pyridazines. He became Professor at the University of Rouen in 1995 and is codirector with Nelly Plé of the diazine group in the LFHOC. The main research area deals with the metallation of diazines and syntheses of biologically active heterocyclic molecules. His main hobby is the building of advanced audio systems.

Nelly Plé received her PhD in 1987 on 'Synthesis and properties of pyridotriazines' working in the Laboratory of Fine Heterocyclic Organic Chemistry under the direction of Guy Quéguiner. She was appointed Professor at the University of Rouen in 1997. She is currently, with Alain Turck, codirector of a research group working on metallation and functionalization of diazines with a strong focus on synthesis of biologically active molecules. Her research interests also included synthesis of organic molecules with nonlinear optical properties and studies of molecule structures by NMR.

Florence Mongin received her PhD from Rouen University, France, in 1994 under the supervision of Guy Quéguiner. Her PhD research focused on the regioselectivity of bromination, halogen–metal exchange and cross-coupling reactions of quinoline derivatives to synthesize pyridocarbazoles. She spent 2 years in the laboratories of Manfred Schlosser, at the University of Lausanne, where she studied the metallation of halo arenes. In 1997, she obtained a position at Rouen University. Her research interest is in the area of organic synthesis including methodologies development using organometallic chemistry.

Guy Quéguiner received his PhD 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 PhD 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 researches (sugars, azasteroids, biomolecules, 'green chemistry'…).