



HAL
open science

Functionalization of diazines and benzo derivatives through deprotonated intermediates.

Floris Chevallier, Florence Mongin

► **To cite this version:**

Floris Chevallier, Florence Mongin. Functionalization of diazines and benzo derivatives through deprotonated intermediates.. *Chemical Society Reviews*, 2008, 37 (3), pp.595-609. 10.1039/b709416g . hal-00842708

HAL Id: hal-00842708

<https://hal.science/hal-00842708>

Submitted on 6 Jun 2014

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

Functionalization of diazines and benzo derivatives through deprotonated intermediates

Floris Chevallier and Florence Mongin

Received (in XXX, XXX) 1st January 2007, Accepted 1st January 2007

5 First published on the web 1st January 2007

DOI: 10.1039/b000000x

Diazines and benzo derivatives can undergo deprotonative metalation provided that the base is properly chosen. Indeed, these substrates are prone to nucleophilic additions or substitutions in relation to lower energy levels of their LUMOs. Metalation reactions of a large range of substrates
10 can be performed using hindered lithium dialkylamides such as lithium diisopropylamide or above all lithium 2,2,6,6-tetramethylpiperide. New bases including magnesates and zincates have recently emerged and proved convenient to allow reactions of more sensitive substrates. Subsequent reactions with electrophiles open an entry to a great variety of building blocks, notably for the synthesis of biologically active compounds (83 references).

15

1 Introduction

Diazines belong to the most important heterocycles containing nitrogen. Many natural products are derived from pyrimidine. Thymine, cytosine and uracil are for example important as
20 building blocks for the nucleic acids, orotic acid is the key compound in the biosynthesis of almost all naturally occurring pyrimidine derivatives, and aneurin (thiamine, vitamin B1) is present in yeast, in rice polishing and in various cereals. A few pyrimidine antibiotics possess potent antitumor properties
25 (*e.g.* bleomycin). Several natural products contain the quinazoline structure; examples are the quinazoline alkaloids isolated from rutaceae (*e.g.*, arborine). In addition, the pyrimidine core is present in many pharmaceuticals such as trimethoprim, sulfadiazine, pyrimethamine, hexetidine, 5-
30 fluorouracil and zidovudin, as well as in herbicides (*e.g.*, bensulfuronmethyl), and the quinazoline ring occurs in pharmaceuticals such as methaqualone, quinethazone, proquazone and prazosin.¹

Few natural compounds contain the pyridazine ring.
35 Derivatives such as pyrazon and pyridaben show biological activity and are applied as herbicides and anthelmintics. In contrast, pyrazines occur frequently as flavor constituents in foodstuffs that undergo heating (coffee, meat...). Alkylpyrazines also act as ant pheromons. Since a high degree
40 of structural complexity characterizes such compounds, there is a need for highly selective, flexible and efficient synthetic methods.¹

Pyridazines can be prepared using one of the following approaches: (1) cyclocondensation reactions between 1,4-
45 dicarbonyl compounds and hydrazine, (2) cyclocondensation reactions between 1,2-diketones, reactive α -methylene esters and hydrazine² and (3) cycloaddition/cycloreversion sequences.³ Bare pyridazine is produced from maleic anhydride: reaction of the latter with hydrazine yields maleic
50 hydrazide which, upon treatment with $\text{POCl}_3/\text{PCl}_5$, affords

3,6-dichloropyridazine, a precursor of pyridazine (reductive dehalogenation using catalytic hydrogenation). Cinnolines can be generated by intramolecular cyclization of *ortho*-alkenyl or
ortho-alkynyl aryldiazonium salts, and phthalazines by
55 cyclocondensation of *ortho*-diacylbenzenes with hydrazine.¹

Pyrimidines are mainly synthesized by cyclocondensation reactions of 1,3-dicarbonyl compounds (or other 1,3-bis-electrophiles) with amidines, ureas, thioureas, guanidines and urethanes.⁴ Phosphazenes containing an amidine moiety can
60 be converted to pyrimidines by reaction with α,β -unsaturated aldehydes (aza-Wittig reaction) followed by oxidative electrocyclic ring closure.⁵ Condensation of 1,1,3,3-tetraethoxypropane with formamide furnishes bare
pyrimidine.⁶ Several methods exist to access to quinazolines.¹

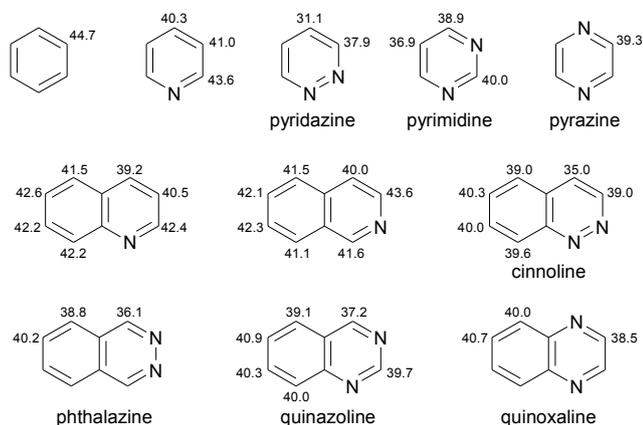
Pyrazines are generally produced by self-condensation of
65 α -amino carbonyl compounds and the combination of α -diketones with vicinal diamines followed by dehydrogenation,⁷ but these methods disappoint in the preparation of unsymmetrically substituted pyrazines.
70 Alternative syntheses include cyclizing aza-Wittig reactions of two molecules of α -phosphazanyl ketones or oxidation of dioxopiperazines. Few regioselective syntheses exist.⁸ Similar approaches are described to reach quinoxalines.¹

The reactions of diazines are determined by the presence of
75 the ring N atoms. The latter are attacked by electrophiles, but deactivate the ring C atoms. Hence, few $\text{S}_{\text{E}}\text{Ar}$ processes take place, and if so, in moderate yields. Diazines are more reactive than pyridine towards nucleophiles (addition and substitution reactions). Concerning benzodiazines, $\text{S}_{\text{E}}\text{Ar}$
80 reactions take place, when possible, on the benzene ring, whereas nucleophilic substitutions occur in the diazine ring, particularly if substituted by halogens.¹

Site selectivity could be easily achieved of course if the electrophile could react with a specific diazinylnmetal rather
85 than with the unmodified heterocycle. Non-deprotonative accesses to diazinylnmetals such as halogen/metal exchange have been developed,⁹ but the problem is only deferred since

the preparation of bromo- and polybromodiazines that could be used as substrates is generally not trivial. The metalation (hydrogen/metal permutation) avoids the use of heavy halogen-substituted diazines.

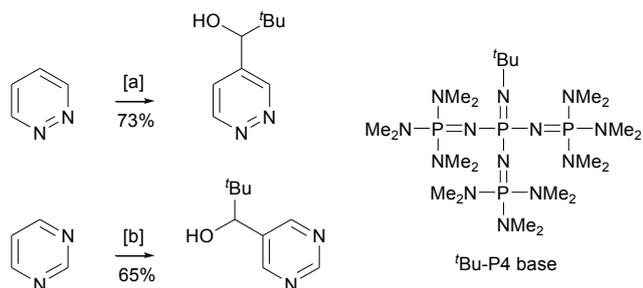
5 The acidities of hydrogens in diazines are related to the less highly-conjugated p orbitals (decrease in aromaticity) in the ring when compared to azines (and of course benzene). The pK_a values for C-H bonds of numerous aromatic heterocyclic compounds including diazines have been recently calculated.¹⁰ The strongest acidity on diazines was estimated to be the 4-position of pyridazine (31.1), and the weakest one the 2-position of pyrimidine (40.0) (Scheme 1).



Scheme 1 Estimated pK_a values for C-H bonds.

15 Unlike five-membered heterocycles, for which protons adjacent to heteroatom have the strongest acidity, six-membered heterocycles have the weakest acidic protons adjacent to nitrogens, a result of the more important repulsion between the lone electron pair of nitrogen and the negative charge of the carbanion for the latter, due to the smaller angle between the two electron clouds.¹⁰

As a consequence, using the nonmetallic ^tBu-P4 organic base ($pK_a = 42.7$ in MeCN), which is highly chemoselective and proceeds without coordination to ring nitrogen, pyridazine and pyrimidine are regioselectively deprotonated at the most acidic 4- and 5-positions, respectively, as evidenced by trapping by a carbonylated compound (Scheme 2).¹¹



Scheme 2 Deprotonative functionalization of pyridazine and pyrimidine using ^tBu-P4 base. Reaction conditions: [a] ^tBuCHO, ^tBu-P4, ZnI₂, toluene, -75 °C to rt; [b] ^tBuCHO, ^tBu-P4, ZnI₂, toluene, -75 °C to rt.

When metallic bases are employed to deprotonate π -

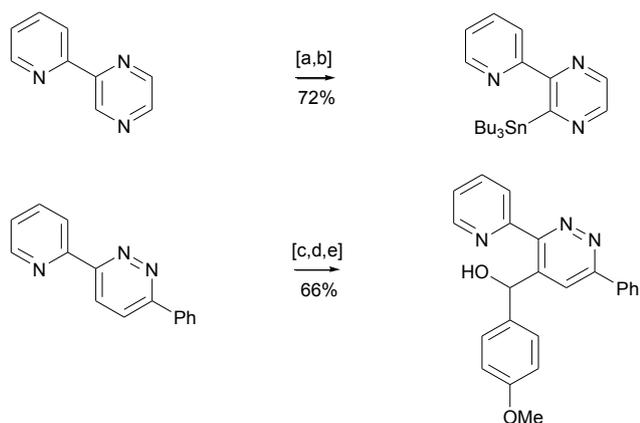
deficient aza-heterocycles, the regioselectivity of the reaction is generally different because of additional effects.¹²

35 Coordination of the/a ring nitrogen to the metal (particularly in the absence of a chelating solvent such as THF) causes the disaggregation of the base (which becomes more reactive), increases the electron-withdrawing effect of the nitrogen, and (thus) favors the deprotonation at an adjacent position. Since diazines (pyridazine: $pK_a = 2.3$, pyrimidine: $pK_a = 1.3$, pyrazine: $pK_a = 0.4$) are less basic than pyridine ($pK_a = 5.2$), this effect is supposed to be less important. In addition, it should be noted that the compound lithiated at the nitrogen adjacent position is on the one hand stabilized by the electron-
45 withdrawing effect of the nitrogen(s), but on the other hand destabilized by electronic repulsion between the carbanion and the lone pair of the adjacent nitrogen.

The electron-withdrawing effect of the diazine nitrogens decreases the energy level of the LUMO of these substrates and makes them more sensitive to nucleophilic addition.^{12a,13}

As a consequence, "soft" alkyllithiums, which are strong bases ($pK_a \sim 40-50$), have to be avoided since they easily add nucleophilically to the diazine ring, even at low temperatures. It is advisable to rely upon the "harder", though less basic
55 lithium diisopropylamide (LDA, $pK_a = 35.7$) and lithium 2,2,6,6-tetramethylpiperidide (LTMP, $pK_a = 37.3$) to effect deprotonation. Nevertheless, this still happens to be difficult with bare heterocycles, for which formation of dimeric products -either by addition of lithiated substrate to another
60 molecule¹⁴ or by dimerization of "radical anions"- can hardly be avoided.¹⁵ When compared to pyridine, nitrogens of diazines are less chelating but the ring hydrogens are more acidic. For these reasons, reactions should be less regioselective.

65 Using lithium amides as the bases, the reaction is usually under thermodynamic control, and the regioselectivity observed is the result of different effects such as stabilization by the electron-withdrawing effect of the ring nitrogens and destabilization by electronic repulsion between the carbanion and the lone pair of the adjacent ring nitrogen. These effects are modulated by the aggregation state of the lithium species, which largely depends on the solvent, for example. A rationalization of the regioselectivity becomes more complicated when substituted diazines are concerned. As the
75 ring nitrogen, the substituent can stabilize by inductive electron-withdrawing effect. It can also chelate the Lewis acidic metal of the base, an effect that is important for the few reactions carried out under kinetic control using alkyllithiums since it allows the disaggregation of the base, reinforces the
80 electron-withdrawing effect of the substituent and increases the proximity effect of the complexed base. Under thermodynamic control, unlike the ring nitrogen the substituent can stabilize the metalated substrate by chelation, which reinforces the electron-withdrawing effect. Steric hindrance caused by the substituent has an impact on the outcome of the reaction too. Some of these effects could explain the regioselectivity observed in the examples depicted in Scheme 3.¹⁶

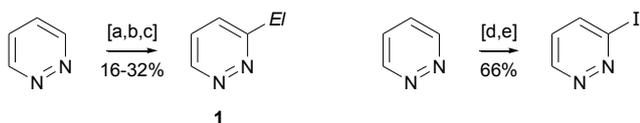


Scheme 3 Deprotonative functionalization of (2-pyridyl)pyrazine and 3-phenyl-6-(2-pyridyl)pyridazine. *Reaction conditions:* [a] LTMP, THF, $-100\text{ }^{\circ}\text{C}$, 15 min; [b] *Electrophile:* Bu_3SnCl ; [c] LTMP, THF, $-78\text{ }^{\circ}\text{C}$, 15 min; [d] *Electrophile:* 4-MeOC₆H₄CHO; [e] hydrolysis.

2 Metalation of pyridazines, cinnolines and phthalazines

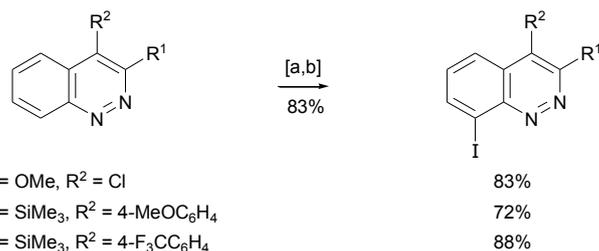
2.1 Metalation of bare pyridazine and long range activated cinnolines

Few attempts to deprotonate bare pyridazine have been described in the literature. Monometalation next to nitrogen was found possible with 4 molar equiv. of LTMP and very short reaction times at $-75\text{ }^{\circ}\text{C}$, a result evidenced by interception with deuterium chloride, benzaldehyde, acetaldehyde or elemental iodine to give the functionalized pyridazines **1** though in 16 to 32% yields. When *tert*-butyldimethylsilyl chloride was used instead, the 4-substituted pyridazine was produced in a very low 10% yield.¹⁷ Using an *in situ* prepared mixture of $\text{ZnCl}_2\cdot\text{TMEDA}$ (0.5 equiv.) and LTMP (1.5 equiv.) in THF containing 5 extra equiv. of TMEDA, the zincation could be performed at reflux to give after quenching with elemental iodine a 83:9:8 mixture of 3-iodo, 4-iodo and 3,5-diiodopyridazine, respectively, from which the main compound was isolated in 66% yield¹⁸ (Scheme 4).



Scheme 4 Deprotonative functionalization of pyridazine. *Reaction conditions:* [a] LTMP, THF, $-75\text{ }^{\circ}\text{C}$, 6 min; [b] *Electrophile {EI}*: DCI {D}, PhCHO {CH(OH)Ph}, MeCHO {CH(OH)Me}, I₂ {I}; [c] hydrolysis; [d] $\text{ZnCl}_2\cdot\text{TMEDA}$, LTMP, TMEDA, THF, reflux, 2 h; [e] *Electrophile:* I₂.

Provided that their pyridazine ring are completely substituted, cinnolines can be deprotonated on the benzene ring, next to the ring nitrogen (Scheme 5).¹⁹ Interception with iodine allowed subsequent arylation through Suzuki or Stille cross-couplings.



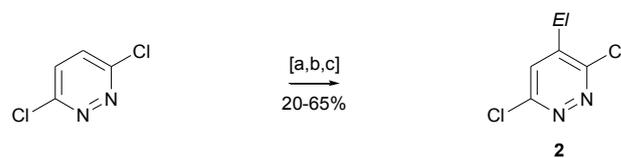
Scheme 5 Deprotonative functionalization of 4-chloro-3-methoxy-, 4-(4-methoxyphenyl)-3-trimethylsilyl- and 4-(4-trifluoromethylphenyl)-3-trimethylsilylcinnoline. *Reaction conditions:* [a] LTMP, THF, $-75\text{ }^{\circ}\text{C}$, 30 min to 1 h; [b] *Electrophile:* I₂.

In general, the substituents help in steering the metal to the targeted location.

2.2 Metalation of halo- pyridazines, cinnolines and phthalazines

Metalation of 3-bromo-6-phenylpyridazine was achieved using a twofold excess of LDA in THF at $-100\text{ }^{\circ}\text{C}$. The complete regioselectivity next to the bromo group was inferred by trapping the lithio compound with 4-anisaldehyde (84% yield).²⁰

Starting from 3,6-dichloropyridazine, the LTMP-mediated deprotonation proceeded in THF at $-70\text{ }^{\circ}\text{C}$, and led to the 4-substituted derivatives **2** in variable yields after subsequent trapping (Scheme 6).²¹



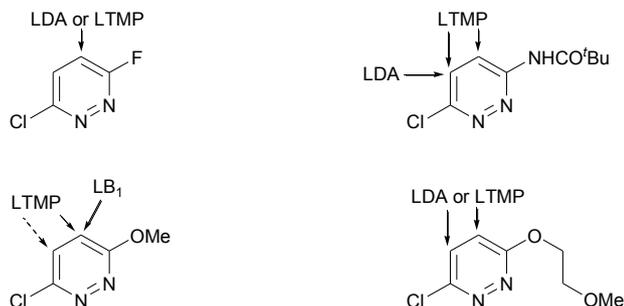
Scheme 6 Deprotonative functionalization of 3,6-dichloropyridazine. *Reaction conditions:* [a] LTMP, THF, $-70\text{ }^{\circ}\text{C}$, 1.5 h; [b] *Electrophile {EI}*: MeCHO {CH(OH)Me}, PhCHO {CH(OH)Ph}, 4-MeOC₆H₄CHO {CH(OH)(4-MeOC₆H₄)}, 2-MeOC₆H₄CHO {CH(OH)(2-MeOC₆H₄)}, PhCONMe₂ {COPh}, Me₃SiCl {SiMe₃}, HCONMe₂ {CHO}, Ph₂CO {C(OH)Ph₂}, I₂ {I}; [c] hydrolysis.

Replacing one of the chloro groups by another substituent offered challenging model compounds to test the regioselectivity of the reaction. With 3-chloro-6-fluoropyridazine, metalation using either LDA or LTMP in THF at low temperature took place next to the smaller halogen.²² With a pivaloylamino group instead, reaction using LTMP in THF at $-70\text{ }^{\circ}\text{C}$ occurred randomly whereas employing LDA (4 equiv.) exclusively afforded deprotonation at the position adjacent to the halogen, providing after trapping with acetaldehyde or benzaldehyde the expected alcohols in 68-82% yields.²³

The situation became more complex with 3-chloro-6-methoxypyridazine. The 4- (next to the chloro group) and 5- (next to the methoxy group) substituted derivatives were produced in a 20:80 ratio after reaction with LTMP in THF at $-70\text{ }^{\circ}\text{C}$ followed by trapping with iodomethane.²⁴ Recourse to very hindered bases such as lithium *N-tert*-butyl-*N*-(1-isopropylpentyl)amide (LB₁) allowed to reach a 1:99 ratio using the same electrophile.²⁵ It was noted that using the *in*

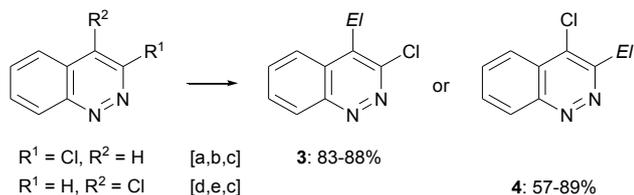
situ trapping method metalation also occurred regioselectively next to the methoxy group.²⁶

When one of the chloro groups was replaced with a methoxyethoxy, using LDA or LTMP in THF at $-70\text{ }^{\circ}\text{C}$ gave a mixture of both possible lithio compounds²³ (Scheme 7).



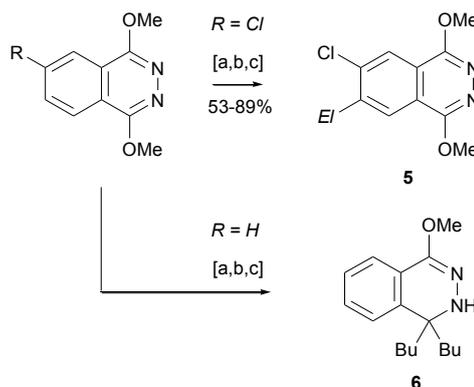
Scheme 7 Regioselectivity of the metalation of 3-chloro-6-fluoropyridazine, *N*-pivaloyl protected 3-amino-6-chloropyridazine, 3-chloro-6-methoxy-pyridazine and 3-chloro-6-(methoxyethoxy)pyridazine using hindered lithium amides.

Functionalization of 3- and 4-chlorocinnoline at the vacant 4- and 3-position, respectively, was achieved in satisfying yields through deprotonation using LTMP in THF at low temperatures, to furnish the compounds **3** and **4**, respectively (Scheme 8).^{19a}



Scheme 8 Deprotonative functionalization of 3- and 4-chlorocinnoline. *Reaction conditions*: [a] LTMP, THF, $-75\text{ }^{\circ}\text{C}$, 2 h; [b] *Electrophile* {El}: MeCHO {CH(OH)Me}, PhCHO {CH(OH)Ph}; [c] hydrolysis; [d] LDA, THF, $-75\text{ }^{\circ}\text{C}$, 30 min; [e] *Electrophile* {El}: MeCHO {CH(OH)Me}, PhCHO {CH(OH)Ph}, 4-MeOC₆H₄CHO {CH(OH)(4-MeOC₆H₄)}, MeI {Me}, I₂ {I}, CO₂ {CO₂H}.

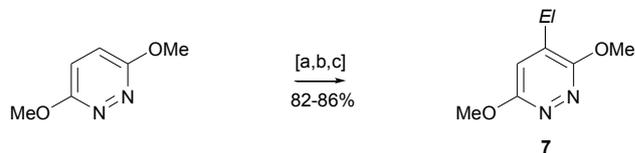
Butyllithium surprisingly gave better results than LTMP when used to functionalize 6-chloro-1,4-dimethoxyphthalazine. Metalation solely occurred at the 7-position, leading to the compounds **5**. In the absence of chloro group, the addition product **6** was formed instead (Scheme 9).²⁷



Scheme 9 Deprotonative functionalization of 6-chloro-1,4-dimethoxyphthalazine. *Reaction conditions*: [a] BuLi, THF, $-75\text{ }^{\circ}\text{C}$, 30 min; [b] *Electrophile* {El}: MeCHO {CH(OH)Me}, PhCHO {CH(OH)Ph}, MeI {Me}, I₂ {I}; [c] hydrolysis.

2.3 Metalation of alkoxy-pyridazines and cinnolines

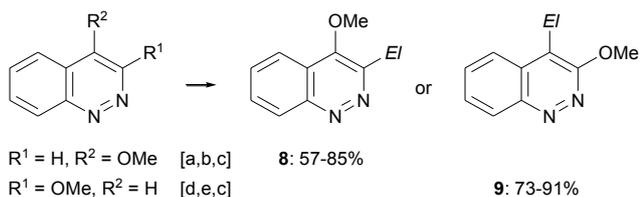
When subsequently treated with LTMP in THF at $-70\text{ }^{\circ}\text{C}$ and electrophiles, 3,6-dimethoxy-pyridazine was converted to the 4-substituted derivatives **7**. Good yields were obtained when benzaldehyde, iodomethane, chlorotrimethylsilane and tosyl azide were chosen to trap the lithio intermediate (Scheme 10).²⁸ In contrast, the low conversion observed quenching the reaction mixture with DCl tends to show that metalation still takes place after the introduction of the electrophiles, by equilibrium shift.^{13c} Alternatively, butyllithium can be used to bring about the deprotonation step.²⁹



Scheme 10 Deprotonative functionalization of 3,6-dimethoxy-pyridazine. *Reaction conditions*: [a] LTMP, THF, $-70\text{ }^{\circ}\text{C}$, 15 min; [b] *Electrophile* {El}: PhCHO {CH(OH)Ph}, MeI {Me}, Me₃SiCl {SiMe₃}, TsN₃ {N₃}; [c] hydrolysis.

Starting from 3-(methoxyethoxy)pyridazine, only low yields (12-15%) of 4-substituted derivatives were obtained after treatment with LTMP (2 equiv.) in THF at $-70\text{ }^{\circ}\text{C}$ and subsequent quenching with acetaldehyde or benzaldehyde.²³

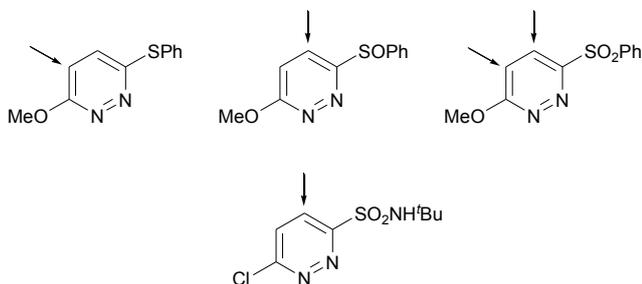
The metalation of 3- and 4-methoxycinnolines was achieved under similar conditions. Starting from 4-methoxycinnoline, the 3-substituted derivatives **8** were obtained in good yields when 2 equiv. of LDA were used. Complications were encountered with 3-methoxycinnoline since both the 4-substituted derivatives **9** and the 4,8-disubstituted derivatives were obtained after reaction with 2 equiv. of LTMP followed by trapping with chlorotrimethylsilane (74 and 14%, respectively) or elemental iodine (73 and 22%) (Scheme 11).^{19a}



Scheme 11 Deprotonative functionalization of 4- and 3-methoxycinnoline. *Reaction conditions*: [a] LDA, THF, -75°C , 30 min; [b] *Electrophile* {*El*}: PhCHO {CH(OH)Ph}, HCO₂Et {CHO}, I₂ {I}; [c] hydrolysis; [d] LTMP, THF, -75°C , 30 min; [e] *Electrophile* {*El*}: PhCHO {CH(OH)Ph}, Me₃SiCl {SiMe₃}, I₂ {I}.

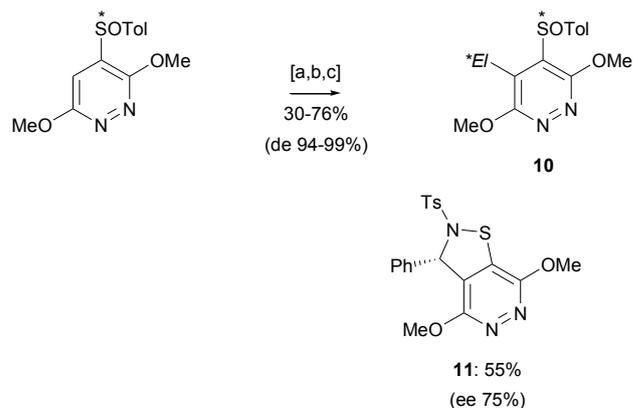
2.4 Metalation of sulfanyl-, sulfinyl- and sulfonyl- pyridazines and cinnolines

Studies have been performed in order to compare the ability to direct the metalation of the methoxy group with sulfanyl, sulfinyl and sulfonyl groups. It emerged from the results that the phenylsulfanyl and phenylsulfonyl groups are able to compete with the methoxy group to orient the reaction on the neighboring site using LTMP in THF at -75°C .³⁰ Comparable results were obtained with the *tert*-butylsulfinyl and *tert*-butylsulfonyl groups.³¹ A sulfonamide group was also compared to a chloro group with the help of a 3,6-disubstituted pyridazine, and proved to be the more able to direct the reaction (Scheme 12).



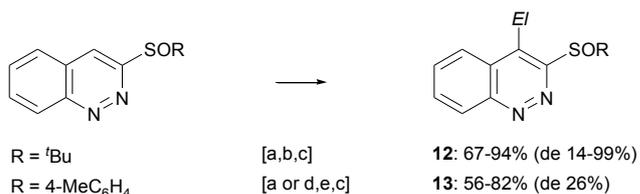
Scheme 12 Regioselectivity of the metalation of 6-sulfur derivatives of 3-methoxy- and 3-chloropyridazine using LTMP in THF at -75°C .

Chiral sulfoxides have been used to direct deprotonation reactions of diazines. In the case of 3,6-dimethoxy-4-(4-tolylsulfinyl)pyridazine, metalation using LTMP (3 equiv.) in THF at -75°C followed by trapping with various aldehydes to afford the compounds **10** proceeded with high diastereoselectivity.³² When the tosylimine of benzaldehyde was used as an electrophile, the cyclic sulfenamide **11** was isolated instead of the expected adduct, probably through 1,2-elimination or [2,3] sigmatropic process leading to isobutene and a sulfenic acid, whose amino group attacks the electrophilic sulfenic acid before elimination of water.³³ (Scheme 13).



Scheme 13 Deprotonative functionalization of 3,6-dimethoxy-4-(4-tolylsulfinyl)pyridazine. *Reaction conditions*: [a] LTMP, THF, -75°C , 1 h; [b] *Electrophile* {*El*}: MeCHO {CH(OH)Me}, EtCHO {CH(OH)Et}, PhCHO {CH(OH)Ph}; [c] hydrolysis.

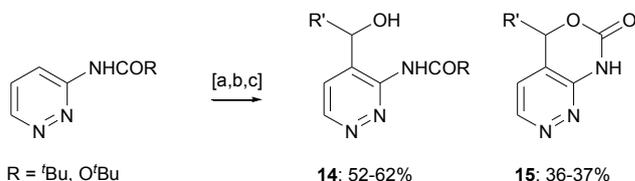
The sensitivity of the sulfoxide group to nucleophilic addition prevented clean deprotonation reactions from taking place when present at the 4-position of cinnoline. In contrast, 3-*tert*-butyl- and 3-(4-tolyl)sulfinylcinnoline were metalated with success (2 equiv. of base) to furnish the compounds **12-13**, and a diastereoisomeric excess was observed (Scheme 14).³⁴



Scheme 14 Deprotonative functionalization of 3-*tert*-butylsulfinyl- and 3-phenylsulfinylcinnoline. *Reaction conditions*: [a] LTMP, THF, -75°C , 1 h; [b] *Electrophile* {*El*}: MeCHO {CH(OH)Me}, PhCHO {CH(OH)Ph}, 4-MeOC₆H₄CHO {CH(OH)(4-MeOC₆H₄)}, *t*BuCHO {CH(OH)*t*Bu}, I₂ {I}, Bu₃SnCl {SnBu₃}; [c] hydrolysis; [d] LDA, THF, -75°C , 30 min; [e] *Electrophile* {*El*}: DCl {D}, 4-MeOC₆H₄CHO {CH(OH)(4-MeOC₆H₄)}.

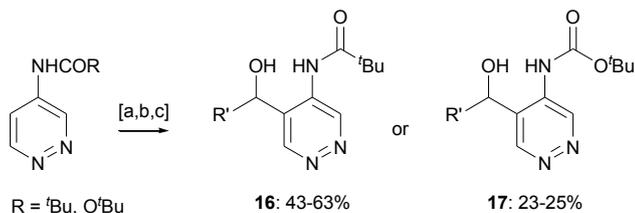
2.5 Metalation of *N*-monoprotected aminopyridazines

The metalation of *N*-pivaloyl protected 3-aminopyridazine occurred on treatment with 4 equiv. of LTMP in THF at -70°C , as evidenced by trapping with aldehydes to give the derivatives **14**. *N*-*tert*-butoxycarbonyl protected 3-aminopyridazine was similarly deprotonated; the compound **15** was isolated after reaction with aldehydes and subsequent cyclization during the work-up (Scheme 15).²³



Scheme 15 Deprotonative functionalization of *N*-pivaloyl and *N*-*tert*-butoxycarbonyl protected 3-aminopyridazine. *Reaction conditions*: [a] LTMP, THF, -70°C ; [b] *Electrophile* {*R'*}: MeCHO {Me}, PhCHO {Ph}; [c] hydrolysis.

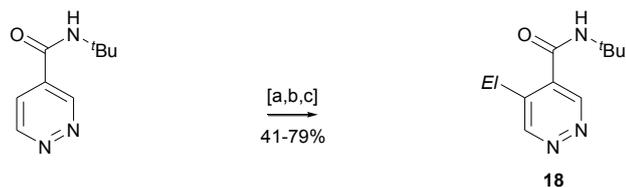
With *N*-pivaloyl and *N*-*tert*-butoxycarbonyl protected 4-aminopyridazine, reaction with LTMP in THF at $-70\text{ }^{\circ}\text{C}$ exclusively occurred at the 5-position. This was evidenced by further transformation of the lithio intermediates to afford the compounds **16** and **17**, respectively (Scheme 16).³⁵



Scheme 16 Deprotonative functionalization of *N*-pivaloyl and *N*-*tert*-butoxycarbonyl protected 4-aminopyridazine. *Reaction conditions*: [a] LTMP, THF, $-70\text{ }^{\circ}\text{C}$, 2.5 h; [b] *Electrophile* {*R*'}: MeCHO {Me}, PhCHO {Ph}; [c] hydrolysis.

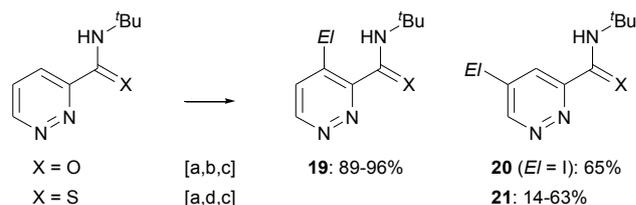
2.6 Metalation of pyridazinecarboxamides and pyridazinethiocarboxamides

Lithiation of *N*-(*tert*-butyl)pyridazine-4-carboxamide using LTMP in THF at low temperature occurred regioselectively at the 5-position, leading to the compounds **18** (Scheme 17). In contrast, mixtures of 5- and 6-substituted derivatives were obtained starting from *N*-benzylpyridazine-4-carboxamide.³⁵



Scheme 17 Deprotonative functionalization of *N*-(*tert*-butyl)pyridazine-4-carboxamide. *Reaction conditions*: [a] LTMP, THF, $-75\text{ }^{\circ}\text{C}$, 15 min to 2 h; [b] *Electrophile* {*El*}: MeCHO {CH(OH)Me}, PhCHO {CH(OH)Ph}, Me₃SiCl {SiMe₃}; [c] hydrolysis.

Reaction of *N*-(*tert*-butyl)pyridazine-3-carboxamide was reported later under similar conditions. Deprotonation generally led to the 4-substituted derivatives **19**, except with elemental iodine for which a halogen migration occurred (compound **20**), probably promoted by the excess of base (4 equiv. were used) during the trapping step. Turning to the corresponding thiocarboxamide modified the regioselectivity in favor of the 5-position. This opened an entry to the 5-substituted derivatives **21** though in moderate yields, probably in relation with the absence of stabilization of the lithio derivative by chelation (Scheme 18). It was noted that when a methylsulfanyl group was located at the 6-position of *N*-(*tert*-butyl)pyridazine-3-carboxamide, reaction took place in its vicinity using LDA.³⁶



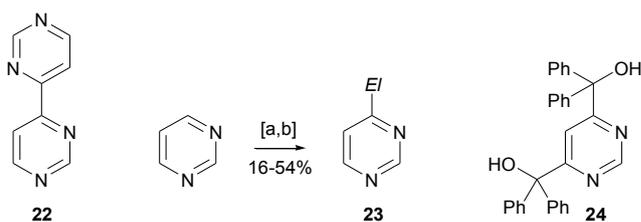
Scheme 18 Deprotonative functionalization of *N*-(*tert*-butyl)pyridazine-3-carboxamide. *Reaction conditions*: [a] LTMP, THF, $-75\text{ }^{\circ}\text{C}$, 1 h; [b] *Electrophile* {*El*}: MeCHO {CH(OH)Me}, PhCHO {CH(OH)Ph}, I₂ {I}; [c] hydrolysis; [d] *Electrophile* {*El*}: MeCHO {CH(OH)Me}, PhCHO {CH(OH)Ph}, Ph₂CO {C(OH)Ph₂}, Bu₃SnCl {SnBu₃}, MeI {Me}, I₂ {I}, C₂Cl₆ {Cl}.

3 Metalation of pyrimidines and quinazolines

3.1 Metalation of bare pyrimidine and long range activated pyrimidines and quinazolines

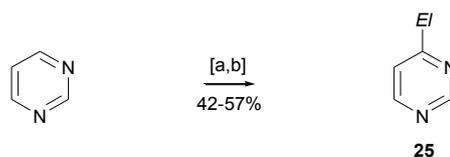
Alkyldiazines are in general prone to lateral metalation. 5-Methylpyrimidine is an exception since it was deprotonated at the 4-position on treatment with LDA, a result evidenced by trapping with benzophenone.¹⁴ This is the first pyrimidine metalation.

The reaction of bare pyrimidine with LTMP is not very tempting under a synthesis point of view. When attempted at various temperatures in THF or DEE, only small amounts of substrate and 4,4'-dimer **22** were identified, due to the instability of the lithio compound under the conditions applied. The compatibility of hindered lithium amides with some electrophiles allowed the *in situ* quenching of the 4-lithio compound to furnish the derivatives **23** though the 4,6-disubstituted product **24** was produced together using benzophenone (Scheme 19).¹⁷



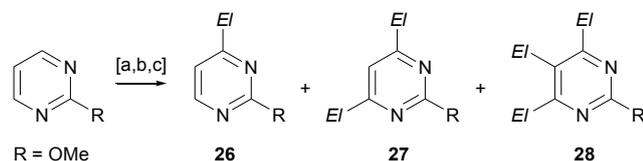
Scheme 19 Deprotonative functionalization of pyrimidine using the *in situ* trapping technique. *Reaction conditions*: [a] LTMP, THF, $-70\text{ }^{\circ}\text{C}$; [b] *Electrophile* {*El*}: Me₃SiCl {SiMe₃}, PhCHO {CH(OH)Ph}, Ph₂CO {C(OH)Ph₂}; [b] hydrolysis.

Combining LTMP (1.5 equiv.) with ZnCl₂·TMEDA (0.5 equiv.) in THF at $25\text{ }^{\circ}\text{C}$, the 4-metalated compound could be accumulated to give, after trapping, the products **25** (Scheme 20).¹⁸



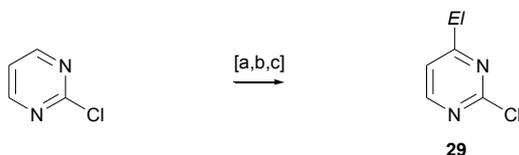
Scheme 20 Deprotonative functionalization of pyrimidine using a mixed Li/Zn amide. *Reaction conditions:* [a] ZnCl₂·TMEDA, LTMP, THF, 25 °C, 2 h; [b] Electrophile {El}: I₂ {I}, CIPPh₂ {PPh₂}.

With a methoxy group located at the 2-position, the 4-lithio derivative could be accumulated using 4 equiv. of LTMP (albeit a short reaction time has to be used) owing to an increase of the acidity of the hydrogens and a stabilization by electron-withdrawing effect. The 4-functionalized derivatives **26** were isolated in moderate yields after trapping with "hard" electrophiles such as deuterium chloride (56%), benzaldehyde (29%), acetaldehyde (26%) or 2,3,4-trimethoxybenzaldehyde (28%). Using electrophiles more compatible with lithium amides, the formation of 4,6-disubstituted pyrimidines **27** (41% using chlorotrimethylsilane and 25% using phenyl disulfide) and even 4,5,6-trisubstituted pyrimidines **28** (7% using elemental iodine) could not be avoided (Scheme 21). Similar results have been observed starting from 2-(4-methoxyphenyl)pyrimidine.¹⁷



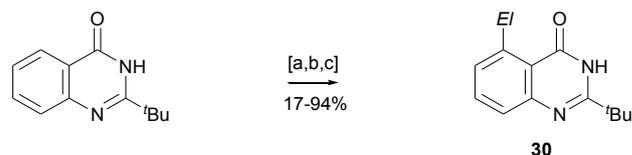
Scheme 21 Deprotonative functionalization of 2-methoxypyrimidine. *Reaction conditions:* [a] LTMP, THF, -75 °C, 5 min; [b] Electrophile {El}: DCI {D}, PhCHO {CH(OH)Ph}, MeCHO {CH(OH)Me}, 2,3,4-tri(MeO)C₆H₂CHO {CH(OH)(2,3,4-tri(MeO)C₆H₂)}, Me₃SiCl {SiMe₃}, (PhS)₂ {SPh}, I₂ {I}; [c] hydrolysis.

With a chloro group located at the 2-position, the accumulation of a 4-metallated derivative proved not satisfactory using LTMP.¹⁷ Nevertheless, using the mixed Mg/Li amide TMPMgCl·LiCl (1 equiv.), it became possible when used in THF at temperatures between -55 and -40 °C, as demonstrated by interception with electrophiles to furnish the 4-functionalized derivatives **29** (Scheme 22).³⁷



Scheme 22 Deprotonative functionalization of 2-chloropyrimidine. *Reaction conditions:* [a] TMPMgCl·LiCl, THF, -55 to -40 °C, 2 h; [b] Electrophile {El}: MeSSO₂Me {SMe}, 4-BrC₆H₄CHO {CH(OH)(4-BrC₆H₄)}; [c] hydrolysis.

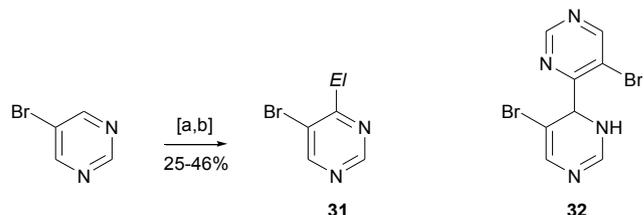
Owing to the substituent at the 2-position, which avoids a nucleophilic attack of the base at this position, 2-*tert*-butyl-4(3*H*)-quinazolinone was lithiated on the benzene moiety upon treatment with TMEDA-chelated *sec*-butyllithium (4 equiv.) at -20 °C, regioselectively leading to the 5-substituted derivatives **30** (Scheme 23).³⁸ 5-Aryl derivatives were then prepared by coupling from compounds **30** (El = B(OH)₂).



Scheme 23 Deprotonative functionalization of 2-*tert*-butyl-4(3*H*)-quinazolinone. *Reaction conditions:* [a] ^tBuLi, TMEDA, THF, -20 °C, 1 h; [b] Electrophile {El}: MeCHO {CH(OH)Me}, PhCHO {CH(OH)Ph}, (PhS)₂ {SPh}, Bu₃SnCl {SnBu₃}, I₂ {I}, B(OMe)₃ {B(OH)₂}; [c] hydrolysis.

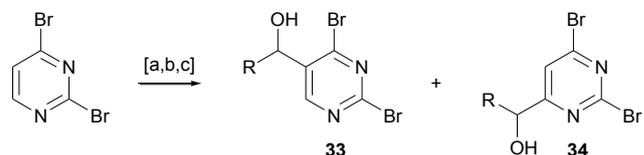
3.2 Metalation of halopyrimidines

In the bromodiazine series, the success of the metalation depends closely on the reaction conditions. When a mixture of 5-bromopyrimidine and a carbonyl compound was treated by LDA (1 equiv.) in DEE at -100 °C for 2 h, the 4-substituted 5-bromopyrimidines **31** were obtained after hydrolysis in moderate yields. In the absence of electrophile, the dihydropyrimidylpyrimidine **32** was isolated after hydrolysis in 32% yield (Scheme 24).³⁹ Accumulation of a 4-metallated 5-bromopyrimidine proved possible using the mixed Mg/Li amide TMPMgCl·LiCl in THF at temperatures between -55 and -40 °C.³⁷



Scheme 24 Deprotonative functionalization of 5-bromopyrimidine using the *in situ* trapping technique. *Reaction conditions:* [a] LDA, DEE, -100 °C, Electrophile {El}: 4-FC₆H₄C(O)(2-CIC₆H₄) {COH(4-FC₆H₄)(2-CIC₆H₄)}, 4-CIC₆H₄C(O)^tPr {COH(4-CIC₆H₄)(^tPr)}, PhCHO {CH(OH)Ph}; [b] hydrolysis.

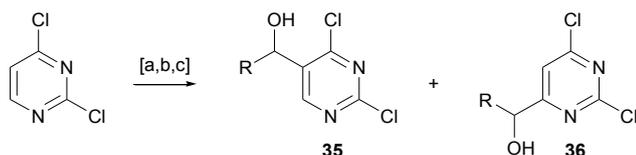
Starting from 2,4-dibromopyrimidine, lithio compounds could be accumulated at -100 °C using 3 equiv. of LDA or more hindered and basic LTMP. The 5-lithio derivative was mainly generated using the former and the 6-lithio using the latter. This was shown by interception with acetaldehyde or 4-methoxybenzaldehyde (20-26% of **33** and 2-5% of **34** using LDA, and 21-24% of **34** and 0-8% of **33** using LTMP) (Scheme 25).²⁰



Scheme 25 Deprotonative functionalization of 2,4-dibromopyrimidine. *Reaction conditions:* [a] LDA or LTMP, THF, -100 °C, 30 min; [b] Electrophile {R}: MeCHO {Me}, 4-MeOC₆H₄CHO {CH(OH)(4-MeOC₆H₄)}; [c] hydrolysis.

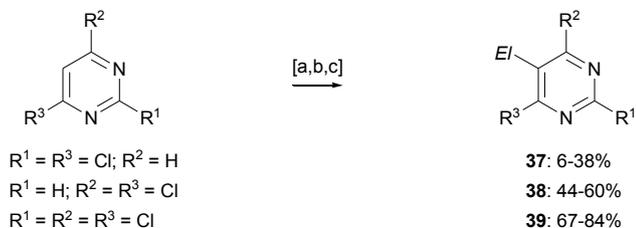
When the corresponding dichloropyrimidine was treated with LTMP, the regioselectivity of the reaction proved to be

dependent on the reaction conditions. 1:1 Mixtures of 5- and 6-substituted derivatives were obtained when the substrate was successively treated with LTMP in THF at $-70\text{ }^{\circ}\text{C}$ and an electrophile. The 5-lithio compound was generated in a THF-DEE mixture at $-100\text{ }^{\circ}\text{C}$ whereas the 6-lithio was formed in a THF-HMPA mixture at $-70\text{ }^{\circ}\text{C}$; trapping with acetaldehyde afforded the corresponding alcohols **35** and **36** in 11 and 18% yield, respectively (Scheme 26).²¹



Scheme 26 Deprotonative functionalization of 2,4-dichloropyrimidine. *Reaction conditions:* [a] LTMP; [b] Electrophile: MeCHO; [c] hydrolysis.

Using LDA in THF at $-80\text{ }^{\circ}\text{C}$ resulted in the regioselective formation of the 5-lithio derivative, as demonstrating by trapping with benzaldehyde or chlorotrimethylsilane to furnish the compounds **37** in low yields. The derivatives **38** and **39** were analogously accessed from the 5-lithio compounds of 4,6-dichloro- and 2,4,6-trichloropyrimidine, benefiting from doubly activated positions (Scheme 27). Butyllithium could also be used for the deprotonation of 4,6-dichloro- and 2,4,6-trichloropyrimidine, but the expected alcohols were given in lower yields after trapping with benzaldehydes.⁴⁰

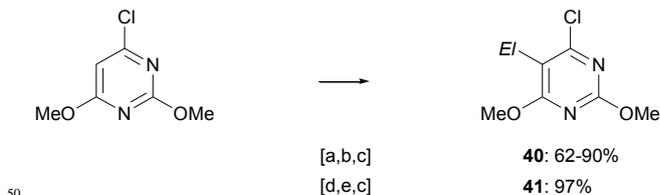


Scheme 27 Deprotonative functionalization of 2,4-dichloro-, 4,6-dichloro- and 2,4,6-trichloropyrimidine. *Reaction conditions:* [a] LDA, THF, $-80\text{ }^{\circ}\text{C}$, 30 min; [b] Electrophile {El}: PhCHO {CH(OH)Ph}, Me₃SiCl {SiMe₃}; [c] hydrolysis.

A similar problem of regioselectivity arose in the case of 2,4-dichloropyrimidine and 2-(methylsulfanyl)-4-chloropyrimidine. Whereas LDA in THF at $-70\text{ }^{\circ}\text{C}$ mainly metalated both substrates at the 5-position next to the chloro group (9:1 and 19:1 ratio, respectively, when aldehydes were used to trap the lithio intermediates), LTMP concomitantly attacked the hydrogen next to the ring nitrogen (1:1 and 1:2 ratio, respectively). Surprisingly, when elemental iodine was used to trap the mixture of lithio compounds generated with LDA or LTMP from 2-(methylsulfanyl)-4-chloropyrimidine, only the 6-iodo derivative was obtained; this result could be due to a quick TMP-promoted isomerization of the 5-iodo derivative during the trapping step.⁴¹ Conversion of the 6-iodo derivative to 6-aryl-4-chloro-2-(methylsulfanyl)pyrimidine-5-carbonitriles endowed with antileishmanial activities, was performed using cross-coupling with phenylboronic acid or 3-

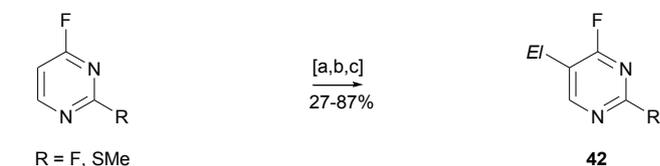
anisylzinc chloride, and subsequent lithiation at the 5 position as key steps.

4-Chloro-2,6-dimethoxypyrimidine was converted into the 5-lithio derivative using either LTMP to give the compounds **40**⁴² or butyllithium to afford the compound **41**.^{25b,43} Better yields were obtained using the former (Scheme 28).



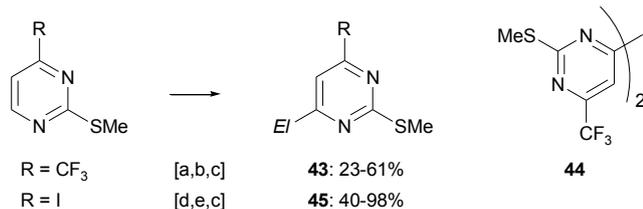
Scheme 28 Deprotonative functionalization of 4-chloro-2,6-dimethoxypyrimidine. *Reaction conditions:* [a] LTMP, THF, $-25\text{ }^{\circ}\text{C}$, 1 h; [b] Electrophile {El}: DCl/EtOD {D}, MeCHO {CH(OH)Me}, PhCHO {CH(OH)Ph}, 2-MeOC₆H₄CHO {CH(OH)(2-MeOC₆H₄)}, 3,4,5-tri(MeO)C₆H₂CHO {CH(OH)(3,4,5-tri(MeO)C₆H₂)}, HCO₂Et {CHO}, I₂ {I}, Me₃SnCl {SnMe₃}; [c] hydrolysis; [d] BuLi, THF, $-75\text{ }^{\circ}\text{C}$, 10 min; [e] Electrophile {El}: TsN₃ {N₃}.

2,4-Difluoro- and 4-fluoro-2-(methylsulfanyl)pyrimidine regioselectively underwent LDA-promoted metalation at the 5-position in THF at $-75\text{ }^{\circ}\text{C}$ to give the trisubstituted compounds **42** after electrophilic trapping (Scheme 29).⁴⁴ Halogenated and dihalogenated 2- or 4-(trifluoromethyl)pyrimidine were similarly amenable to deprotonation at the 5-position using LDA in THF at $-75\text{ }^{\circ}\text{C}$.¹⁵



Scheme 29 Deprotonative functionalization of 2,4-difluoro- and 4-fluoro-2-(methylsulfanyl)pyrimidine. *Reaction conditions:* [a] LDA, THF, $-75\text{ }^{\circ}\text{C}$, 30 min; [b] Electrophile {El}: MeCHO {CH(OH)Me}, PhCHO {CH(OH)Ph}, 2-MeOC₆H₄CHO {CH(OH)(2-MeOC₆H₄)}, 2,4-diClC₆H₃CHO {CH(OH)(2,4-diClC₆H₃)}, 3,4,5-tri(MeO)C₆H₂CHO {CH(OH)(3,4,5-tri(MeO)C₆H₂)}, I₂ {I}, HCO₂Et {CHO}, CO₂ {CO₂H}; [c] hydrolysis.

Conversely, LTMP in THF at $-100\text{ }^{\circ}\text{C}$ was found to deprotonate 2-(methylsulfanyl)-4-trifluoromethylpyrimidine regioselectively next to nitrogen, leading to the 6-substituted derivatives **43**. The 4,4'-dimer **44** ranked among the most abundant by-products.⁴⁵ 4-Iodo-2-(methylsulfanyl)pyrimidine behaved similarly. It was converted to the 6-lithio derivative when treated with a very hindered base in THF at $-100\text{ }^{\circ}\text{C}$ for 10 min, affording the compounds **45**⁴⁶ (Scheme 30).

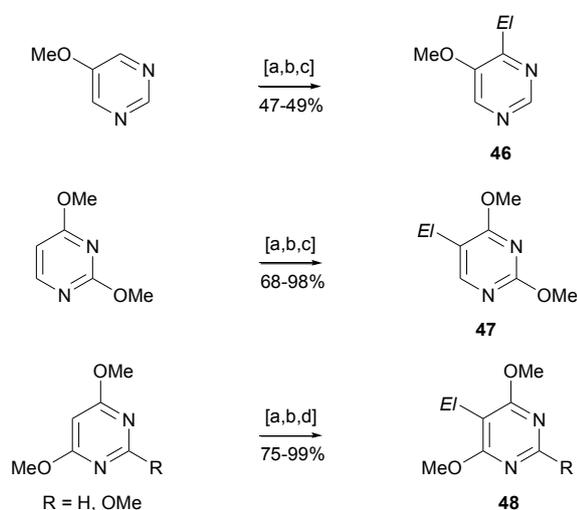


Scheme 30 Deprotonative functionalization of 2-(methylsulfanyl)-4-trifluoromethyl- and 2-(methylsulfanyl)-4-iodopyrimidine. *Reaction conditions*: [a] LTMP, THF, -100 °C, 1 h; [b] *Electrophile {El}*: MeCHO {CH(OH)Me}, PhCHO {CH(OH)Ph}, 2-MeOC₆H₄CHO {CH(OH)(2-MeOC₆H₄)}, 2,4-dichloro-5-hydroxybenzaldehyde {CH(OH)(2,4-dichloro-5-hydroxybenzyl)}, 3,4,5-tri(methoxy)benzaldehyde {CH(OH)(3,4,5-tri(methoxy)benzyl)}, I₂ {I}, HCO₂Et {CHO}, CO₂ {CO₂H}; [c] hydrolysis; [d] lithium *N*-tert-butyl-*N*-(1-isopropylpentyl)amide, THF, -100 °C, 10 min; [e] *Electrophile {El}*: MeCHO {CH(OH)Me}, PhCHO {CH(OH)Ph}, Ph₂CO {C(OH)Ph₂}, MeI {Me}, EtI {Et}, Me₃SiCl {SiMe₃}, HCO₂Et {CHO}, I₂ {I}.

3.3 Metalation of alkoxy-pyrimidines and quinazolines

Unlike 2,4-dihalo-pyrimidines, 2,4-dimethoxypyrimidine was regioselectively metalated at the methoxy-adjacent position when treated with LTMP in DEE at 0 °C. This was shown by trapping the lithio compounds with aldehydes, carbon dioxide, dimethylformamide, ethyl chloroformate or chlorotrimethylsilane in yields ranging from 4 to 65%.⁴⁷ These deprotonation conditions were also applied to functionalize a series of pyrimidines including *N*-pivaloyl protected 4-aminopyrimidine (chlorotrimethylsilane quench) in low yields.

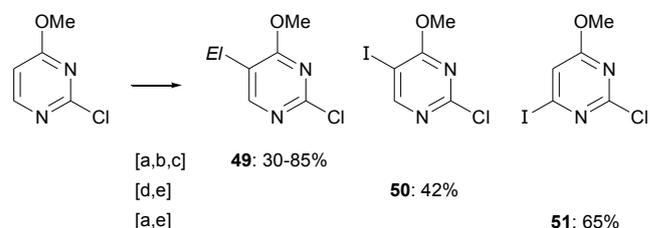
5-Methoxy-, 2,4-dimethoxy (or 2,4-dibenzyloxy), 4,6-dimethoxy and 2,4,6-trimethoxypyrimidine were all lithiated next to the methoxy (or benzyloxy) group using LTMP in THF at -78 °C for 15 min, leading to substituted derivatives **46–48** in medium to high yields, depending on the ability of the electrophile to coexist with the base long enough to allow equilibrium shift of the deprotonation reaction (Scheme 31).^{25b,28}



Scheme 31 Deprotonative functionalization of 5-methoxy-, 2,4-dimethoxy-, 4,6-dimethoxy- and 2,4,6-trimethoxypyrimidine. *Reaction conditions*: [a] LTMP, THF, -78 °C, 15 min; [b] *Electrophile {El}*: PhCHO {CH(OH)Ph}, MeI {Me}, Me₃SiCl {SiMe₃}; [c] hydrolysis; [d]

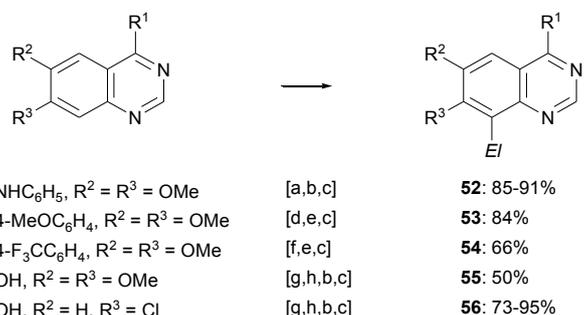
Electrophile {El}: PhCHO {CH(OH)Ph}, MeI {Me}, Me₃SiCl {SiMe₃}, PhCOCl {COPh}.

Similar results were obtained starting from 2-chloro-4-methoxypyrimidine, allowing the synthesis of the 5-substituted derivatives **49**. Trapping with elemental iodine only furnished the expected 5-iodo derivative **50** when the reaction was performed at -100 °C. At -75 °C, 2-chloro-6-iodo-4-methoxypyrimidine **51** was formed instead, as previously noted with 2-(methylsulfanyl)-4-chloropyrimidine **45** (Scheme 32).⁴⁸



Scheme 32 Deprotonative functionalization of 2-chloro-4-methoxypyrimidine. *Reaction conditions*: [a] LTMP, THF, -70 °C, 1 h; [b] *Electrophile {El}*: DCI/EtOD {D}, MeCHO {CH(OH)Me}, PhCHO {CH(OH)Ph}, 2-MeOC₆H₄CHO {CH(OH)(2-MeOC₆H₄)}, 3,4,5-tri(methoxy)benzaldehyde {CH(OH)(3,4,5-tri(methoxy)benzyl)}, Me₃SiCl {SiMe₃}, HCO₂Et {CHO}; [c] hydrolysis; [d] LTMP, THF, -100 °C, 1 h; [e] I₂.

Metalation of the benzene ring of 4-substituted quinazoline was more easily observed when substituents can orient the deprotonation. Thus, metalation of 4-anilino-,²⁷ 4-(4-methoxyphenyl)-,^{19b} and 4-(4-trifluoromethylphenyl)-6,7-dimethoxyquinazoline^{19b} using 4-5 equiv. of lithium amide in THF at -75 °C affected the 8-position. A similar result was noted when 6,7-dimethoxyquinazolinone was successively subjected to the reaction with 1 equiv. of butyllithium and 4 equiv. of LTMP. Functionalization of the lithio intermediates furnished the compounds **52–55**, respectively. 7-Chloroquinazolinone behaved similarly (compounds **56**) (Scheme 33).^{27,34} Compounds **53** and **54** allowed subsequent arylation through Suzuki or Stille cross-couplings.



Scheme 33 Deprotonative functionalization of 4-anilino-, 4-(4-methoxyphenyl)- and 4-(4-trifluoromethylphenyl)-6,7-dimethoxyquinazolinone, 6,7-dimethoxy- and 7-chloroquinazolinone. *Reaction conditions*: [a] LTMP, THF, -75 °C, 2 h; [b] *Electrophile {El}*: MeCHO {CH(OH)Me}, PhCHO {CH(OH)Ph}; [c] hydrolysis; [d] LTMP, THF, -75 °C, 1 h; [e] *Electrophile {El}*: I₂ {I}; [f] LDA, THF, -75 °C, 1 h; [g] BuLi, THF, -75 °C, 15 min; [h] LTMP, THF, -75 °C, 1.5 h.

The metalation of other substituted pyrimidines has been

only scarcely examined up to now.

3.4 Metalation of *N*-protected aminopyrimidines

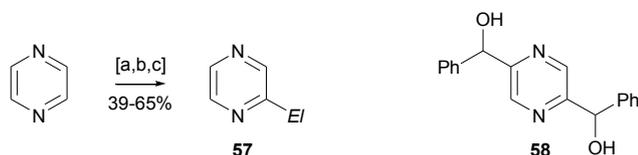
4-(*Tert*-butoxycarbonyl)amino-2-(trimethylsilyl)pyrimidine was made accessible in a low 11% yield after consecutive exposition of 4-(*tert*-butoxycarbonyl)aminopyrimidine to the action of LTMP and chlorotrimethylsilane.^{47b} This remains the sole example of a pyrimidine deprotonation at the 2-position known so far.

4 Metalation of pyrazines and quinoxalines

4.1 Metalation of bare and long range activated pyrazines

First mentions to a pyrazine deprotonation date from 1971, when it was observed as a competitive reaction in nucleophilic addition of alkylolithiums,⁴⁹ and above all 1974,⁵⁰ when ring metalation was observed together with lateral metalation by treating 2-ethyl-3-methylpyrazine with methylolithium.

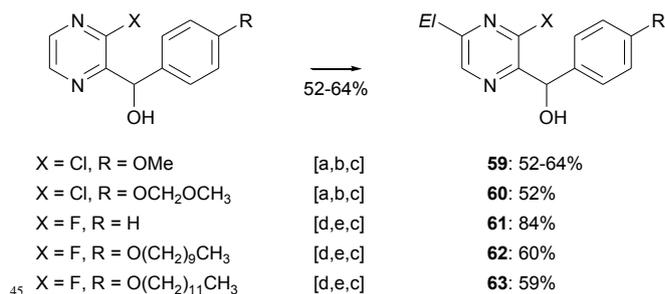
As described for pyridazine, regioselective metalation of pyrazine was found possible using 4 equiv. of LTMP and very short exposure times at $-75\text{ }^{\circ}\text{C}$, a result evidenced by interception with benzaldehyde, acetaldehyde or elemental iodine to give the functionalized pyrazines **57** in 39 to 65% yields. When benzaldehyde was used in excess (3 equiv.), the 2,5-disubstituted pyrazine **58** was inevitably produced, probably by competitive deprotonation of the already 2-functionalized pyrazine during the trapping step (Scheme 34).¹⁷



Scheme 34 Deprotonative functionalization of pyrazine. *Reaction conditions:* [a] LTMP, THF, $-75\text{ }^{\circ}\text{C}$, 6 min; [b] *Electrophile* {*El*}: PhCHO {CH(OH)Ph}, MeCHO {CH(OH)Me}, I₂ {I}; [c] hydrolysis.

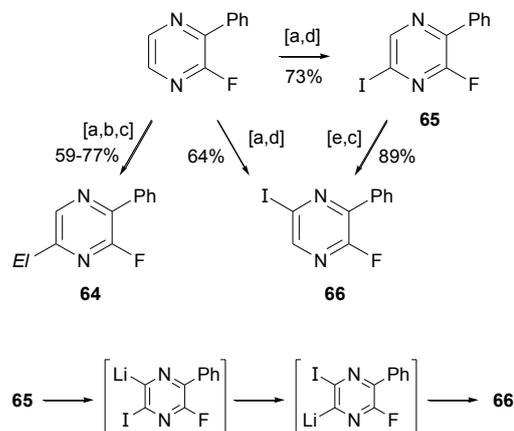
Using an *in situ* prepared mixture of ZnCl₂-TMEDA (0.5 equiv.) and LTMP (1.5 equiv.) in THF, the metalated compound could be accumulated at room temperature to give after trapping the monosubstituted derivatives (*e.g.* iodopyrazine in 59% yield). Starting from quinoxaline resulted in mixtures of 2-iodo, 2,5-diiodo and 2,2'-biquinoxaline under the same reaction conditions.¹⁸

3-Chloro- α -arylpyrazine-2-methanols got deprotonated at the 5-position upon treatment with LTMP (3 equiv.) in THF at $-75\text{ }^{\circ}\text{C}$, leading to the derivatives **59–63** (Scheme 35).⁵¹ High yields were obtained using a similar protocol with 2,3-dichloropyrazine.⁵² Compounds **59** and **60** (*El* = I) were next functionalized using a Negishi procedure as key step to furnish septorin, the main agent of a wheat disease impeding growth.



Scheme 35 Deprotonative functionalization of 3-chloro- and 3-fluoro- α -arylpyrazine-2-methanols. *Reaction conditions:* [a] LTMP, THF, $-75\text{ }^{\circ}\text{C}$, 15 min; [b] *Electrophile* {*El*}: MeCHO {CH(OH)Me}, PhCHO {CH(OH)Ph}, C₂Cl₆ {Cl}, I₂ {I}; [c] hydrolysis; [d] LTMP, THF, $-75\text{ }^{\circ}\text{C}$, 50 min; [e] *Electrophile* {*El*}: I₂ {I}.

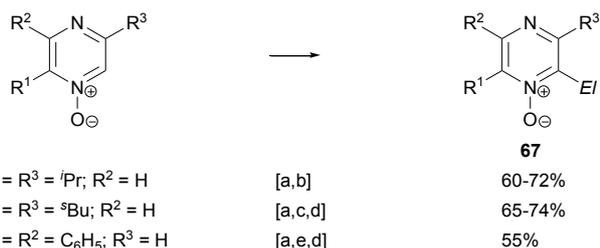
2-Fluoro-3-phenylpyrazine was similarly deprotonated (3 equiv. of LTMP), as demonstrated by trapping with most of the electrophiles to afford the 6-substituted derivatives **64**. When elemental iodine was used, the 6-iodo compound **65** was isolated only when 1 equiv. of LTMP was employed. Using LTMP in excess (3 equiv.) and 1 equiv. of iodine, the 5-iodo compound **66** was formed instead. The latter could result from a deprotonation of the 6-substituted derivatives **65** with the excess of LTMP during the quenching step with iodine, followed by iodine migration, as depicted in Scheme 36.^{51b,53}



Scheme 36 Deprotonative functionalization of 2-fluoro-3-phenylpyrazine. *Reaction conditions:* [a] LTMP, THF, $-75\text{ }^{\circ}\text{C}$, 5 min; [b] *Electrophile* {*El*}: MeCHO {CH(OH)Me}, PhCHO {CH(OH)Ph}, Me₃SiCl {SiMe₃}, Bu₃SnCl {SnBu₃}; [c] hydrolysis; [d] *Electrophile* {*El*}: I₂ {I}; [e] LTMP, THF, $-75\text{ }^{\circ}\text{C}$, 30 min.

4.2 Metalation of pyrazine-1-oxides

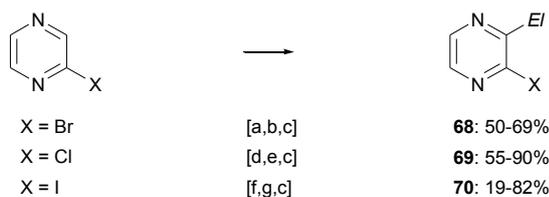
Base and solvent optimization for the deprotonation of 2,5-*sec*-butylpyrazine-1-oxide was carried out at low temperature. The best results were obtained using LTMP in THF in the presence of TMEDA. The method was extended to other substrates, affording the corresponding 2-substituted pyrazine-1-oxides **67** in good yields (Scheme 37).⁵⁴



Scheme 37 Deprotonative functionalization of pyrazine-1-oxide. *Reaction conditions:* [a] LTMP, THF, TMEDA, -75°C , 20 min; [b] *Electrophile* {*El*}: HCO_2Me {CHO}, $4\text{-MeC}_6\text{H}_4\text{COCl}$ {C(O)(4-MeC₆H₄)}, $4\text{-MeC}_6\text{H}_4\text{CO}_2\text{Me}$ {C(O)(4-MeC₆H₄)}; [c] *Electrophile* {*El*}: EtCHO {CH(OH)Et}, PhCHO {CH(OH)Ph}; [d] hydrolysis; [e] *Electrophile* {*El*}: PhCHO {CH(OH)Ph}.

4.3 Metalation of halo-pyrazines and quinoxalines

Bromopyrazine was deprotonated next to the bromo group using 3 equiv. of LDA in THF at -75°C . This was evidenced by quenching after 15 min with acetaldehyde, benzaldehyde, phenyl disulfide or elemental iodine to give the expected products **68** in 62, 69, 53 and 50% yield, respectively.²⁰ Chloro- and iodopyrazine were similarly regioselectively metalated, but LTMP proved to be a better base than LDA. Due to the better stability of 2-chloro-3-lithiopyrazine, the accumulation time could be extended to 30 min (no change was observed using longer exposure times) to give the 3-functionalized chloropyrazines **69** in satisfying yields.⁵⁵ In contrast, the accumulation time was shortened with iodopyrazine in order to obtain the 3-substituted 2-iodopyrazines **70** in satisfying yields⁴⁶ (Scheme 38). The metalation next to the iodo group was extended to a disubstituted iodopyrazine.^{48a}

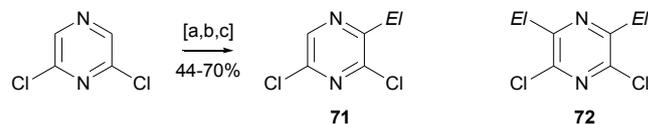


Scheme 38 Deprotonative functionalization of iodo-, bromo- and chloropyrazine. *Reaction conditions:* [a] LDA, THF, -75°C , 15 min; [b] *Electrophile* {*El*}: MeCHO {CH(OH)Me}, PhCHO {CH(OH)Ph}, $(\text{PhS})_2$ {SPh}, I_2 {I}; [c] hydrolysis; [d] LTMP, THF, -70°C , 30 min; [e] *Electrophile* {*El*}: DCI {D}, MeCHO {CH(OH)Me}, PhCHO {CH(OH)Ph}, 2-furylCHO {CH(OH)(2-furyl)}, $4\text{-MeOC}_6\text{H}_4\text{CHO}$ {CH(OH)(4-MeOC₆H₄)}, $2\text{-MeOC}_6\text{H}_4\text{CHO}$ {CH(OH)(2-MeOC₆H₄)}, Ph_2CO {C(OH)Ph₂}, HCO_2Et {CHO}; [f] LTMP, THF, -75°C , 5 min; [g] *Electrophile* {*El*}: MeCHO {CH(OH)Me}, PhCHO {CH(OH)Ph}, Ph_2CO {C(OH)Ph₂}, $(\text{PhS})_2$ {SPh}, HCO_2Et {CHO}, Me_3SiCl {SiMe₃}, CO_2 {CO₂H}, I_2 {I}.

Metalation of chloropyrazines next to the halogen still proved feasible when a substituent such as a ketal or an aryl group was present at the 6-position.⁵²

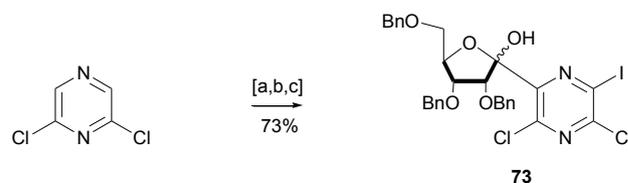
The metalation/functionalization sequence was applied to 2,6-dichloropyrazine to give the compounds **71** in moderate to good yields. Nevertheless, the outcome of the reaction largely depends on the amount of base used since the formation of 3,5-difunctionalized products **72** could not be avoided using an excess of metalating agent and electrophiles compatible

with *in situ* trapping such as benzaldehyde, elemental iodine or chlorotributylstannane (Scheme 39).^{55c,56}



Scheme 39 Deprotonative functionalization of 2,6-dichloropyrazine. *Reaction conditions:* [a] LTMP, THF, -70°C , 2 h; [b] *Electrophile* {*El*}: MeCHO {CH(OH)Me}, EtCHO {CH(OH)Et}, PhCHO {CH(OH)Ph}, $2\text{-MeOC}_6\text{H}_4\text{CHO}$ {CH(OH)(2-MeOC₆H₄)}, $2,4\text{-diClC}_6\text{H}_3\text{CHO}$ {CH(OH)(2,4-diClC₆H₃)}, HCO_2Et {CHO}, I_2 {I}, Me_3SnCl {SnMe₃}; [c] hydrolysis.

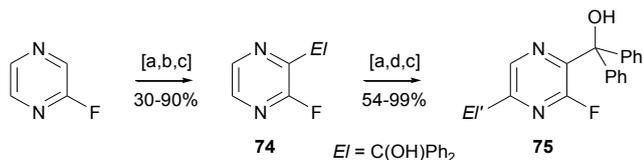
2,6-Dichloropyrazine could serve as attractive starting material as it offered the possibility to replace one hydrogen by a first electrophile and the other one by a second electrophile. The dideprotonation was optimized using 2.5 equiv. of LTMP in THF at -100°C , and the sequential introduction of two different electrophiles allowed the synthesis of 2,6-dichloro-3,5-disubstituted compounds including **73** (Scheme 40).⁵⁷



Scheme 40 Deprotonative functionalization of 2,6-dichloropyrazine. *Reaction conditions:* [a] LTMP, THF, -100°C , 1 h; [b] *First electrophile*: I_2 ; [c] *Second electrophile*: 2,3,5-tri-O-benzyl-D-ribofuranose-1,4-lactone.

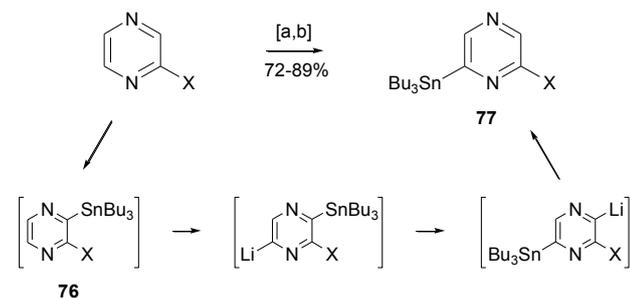
The situation becomes more complex when one has to metalate 2-chloroquinoxaline. First attempts to use LTMP were unsuccessful.^{56a} The reaction was next shown to provide the 3,3'-dimer in 59% yield when DCI was used to quench the lithio intermediate. 3-Substituted derivatives were obtained after reaction of LTMP at -75°C for 15-20 min and subsequent trapping with acetaldehyde or benzaldehyde in medium yields.⁵⁸

Fluoropyrazine proved prone to proton abstraction next to the halogen when treated with hindered lithium dialkylamides (1 equiv.) in THF at low temperatures, LTMP giving the best yields with a short contact time of 5 min (compounds **74**). 3-Fluoro- α,α -diphenylpyrazine-2-methanol was subjected to deprotonation too when allowed to react with LTMP at low temperature to give the compounds **75** (Scheme 41). When the reaction from fluoropyrazine was conducted in the presence of an excess of base and chlorotributylstannane at -100°C , 2-fluoro-3,6-bis(tributylstannyl)pyrazine, which probably results from deprotonation at C6 of intermediate 2-fluoro-3-(tributylstannyl)pyrazine under the *in situ* trapping conditions used, was isolated in 90% yield.^{53,59}



Scheme 41 Deprotonative functionalization of fluoropyrazine and 3-fluoro- α,α -diphenylpyrazine-2-methanol. *Reaction conditions:* [a] LTMP, THF, $-75\text{ }^\circ\text{C}$, 5 min; [b] *Electrophile* {EI}: MeCHO {CH(OH)Me}, PhCHO {CH(OH)Ph}, Ph₂CO {C(OH)Ph₂}, 2-furylCHO {CH(OH)(2-furyl)}, 4-MeOC₆H₄CHO {CH(OH)(4-MeOC₆H₄)}, 2-MeOC₆H₄CHO {CH(OH)(2-MeOC₆H₄)}, HCO₂Et {CHO}, (PhS)₂ {SPh}, I₂ {I}, BrCN {Br}, MeCONMe₂ {C(O)Me}, PhCONMe₂ {COPh}; [c] hydrolysis; [d] *Electrophile* {EI}: Ph₂CO {C(OH)Ph₂}, MeCHO {CH(OH)Me}, Me₃SiCl {SiMe₃}, I₂ {I}, C₂Cl₆ {Cl}.

Chloro- and fluoropyrazine were also functionalized at the 6-position using a trick. When treated with 3 equiv. of LTMP in THF at $-100\text{ }^\circ\text{C}$ in the presence of 1 equiv. of chlorotributylstannane, the 3-(tributylstannyl) compounds **76** first formed could be converted to the 6-lithio compound which, *via* migration of the tributylstannyl group, could finally afford 2-halo-6-(tributylstannyl)pyrazines **77** after hydrolysis (Scheme 42).^{52,53}



Scheme 42 Deprotonative functionalization of chloro- and fluoropyrazine. *Reaction conditions:* [a] Bu₃SnCl, LTMP, THF, $-100\text{ }^\circ\text{C}$ to $-40\text{ }^\circ\text{C}$, 2.5 h; [b] hydrolysis.

Similar protocols enabled the metalation of 2-fluoro-6-(tributylstannyl)pyrazine and 2-fluoro-6-arylpyrazines at the 3-position.⁵³ By intercepting the lithio compounds of the latter with iodine, subsequent Sonogashira, Negishi and Suzuki cross-couplings proved possible. Deprotonation of 2-chloro-6-methoxy pyrazine showed incomplete regioselectivity using LDA or LTMP in THF at $-70\text{ }^\circ\text{C}$, with a 15:85 ratio in favor of the 5-position next to the methoxy group.^{55b,c} Recourse to very hindered base lithium *N-tert-butyl-N*-(1-isopropylpentyl)amide (LB₁) lowered the regioselectivity at the position adjacent to the methoxy group.²² Replacing the chloro group with an iodo resulted in a complete regioselectivity when LDA was used in THF at $-70\text{ }^\circ\text{C}$.^{55b}

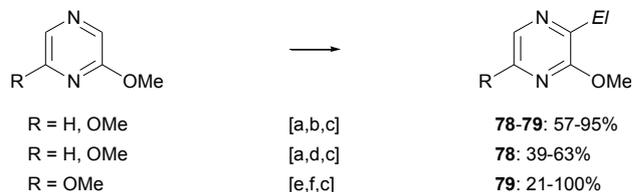
When 2-fluoro-6-methoxy pyrazine was allowed to react with LDA in THF at $-70\text{ }^\circ\text{C}$ for 5 min, trapping with aldehydes showed deprotonation mainly occurred next to the fluoro group (96:4 ratio); LTMP and *N-tert-butyl-N*-(1-isopropylpentyl)amide (LB₁) gave lower selectivities.²²

6-Chloro-2,3-dimethoxyquinoxaline features an interesting case of regioselectivity. Treatment with LTMP (4 equiv.) in THF for 1 h at low temperature followed by reaction with

electrophiles afforded the 5-substituted quinoxalines as major products (85% yield using benzaldehyde as the electrophile). In the absence of directing group on the benzene ring of quinoxaline, *e.g.* with 2-methoxy-3-phenylquinoxaline, the reaction took place at both the 5- and 8-positions.²⁷

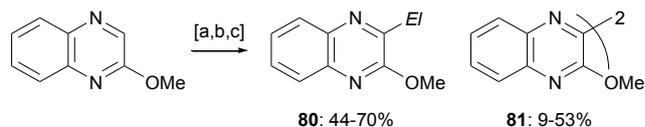
4.4 Metalation of alkoxy- pyrazines and quinoxalines

LTMP-promoted metalation of 2-methoxy and 2,6-dimethoxy pyrazine was carried out in THF at $0\text{ }^\circ\text{C}$ or $-75\text{ }^\circ\text{C}$ to give the compounds **78-79** after electrophilic trapping (Scheme 43).^{25b,28a,29,55b,c,56,60} As previously noted for 3,6-dimethoxy pyridazine, good yields were obtained with electrophiles sufficiently compatible with the base (1 equiv.) to allow *in situ* trapping.^{28a} This statement was confirmed by successive treatment of 2,6-dimethoxy pyrazine with LTMP (1 equiv.) at $0\text{ }^\circ\text{C}$ for 15 min, and deuterated ethanol, which afforded the 3-deuterated compound in a low 32% conversion. Using 2 equiv. of base had a positive effect on the conversion (83% after 15 min and 100% after 30 min).^{56b}



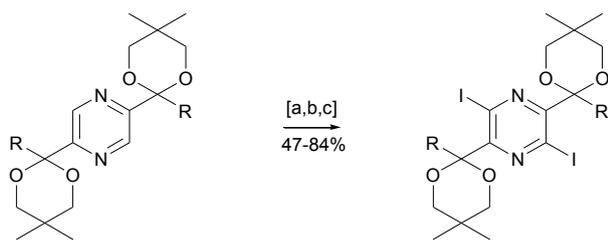
Scheme 43 Deprotonative functionalization of 2-methoxy- and 2,6-dimethoxy pyrazine. *Reaction conditions:* [a] LTMP, THF, $-75\text{ }^\circ\text{C}$; [b] *Electrophile* {EI}: PhCHO {CH(OH)Ph}, MeI {Me}, Me₃SiCl {SiMe₃}; [c] hydrolysis; [d] *Electrophile* {EI}: MeCHO {CH(OH)Me}, PhCHO {CH(OH)Ph}, PhCON(OMe)Me {COPh}, I₂ {I}; [e] LTMP, THF, $0\text{ }^\circ\text{C}$, 45 min; [f] *Electrophile* {EI}: DCl {D}, MeCHO {CH(OH)Me}, PhCHO {CH(OH)Ph}, 2-MeOC₆H₄CHO {CH(OH)(2-MeOC₆H₄)}, HCO₂Et {CHO}, PhCON(OMe)Me {COPh}, I₂ {I}, MeOCOCi {CO₂Me}.

The method using LTMP in THF at $-75\text{ }^\circ\text{C}$ was extended to 2-methoxyquinoxaline (interception of the lithio compound with *N*-methoxy-*N*-methylbenzamide in 43% yield).^{56a} A more complete investigation showed the yields of the 3-substituted derivatives **80** were limited by the competitive formation of the dimer **81** (Scheme 44).⁵⁸



Scheme 44 Deprotonative functionalization of 2-methoxyquinoxaline. *Reaction conditions:* [a] LTMP, THF, $-70\text{ }^\circ\text{C}$, 2 h; [b] *Electrophile* {EI}: DCl/EtOD {D}, MeCHO {CH(OH)Me}, PhCHO {CH(OH)Ph}, 2-MeOC₆H₄CHO {CH(OH)(2-MeOC₆H₄)}, Ph₂CO {C(OH)Ph₂}, I₂ {I}; [c] hydrolysis.

The dideprotonation of several pyrazine-2,5-diketals was achieved using LTMP in THF at $-25\text{ }^\circ\text{C}$ for 4 h, as demonstrated by subsequent reaction with elemental iodine to afford the compounds **82** (Scheme 45).⁶¹ The reagent has to be used in large excess (12 equiv.) which consumes large amounts of the electrophile and limits the scale.



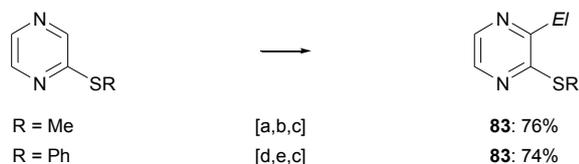
R = Bu, C₁₂H₂₅, 4-^tBuC₆H₄, 4-C₁₂H₂₅C₆H₄

82

Scheme 45 Deprotonative functionalization of pyrazine-2,5-diketals. *Reaction conditions:* [a] LTMP, THF, -25 °C, 4 h; [b] I₂; [c] hydrolysis.

4.5 Metalation of sulfanyl-, sulfinyl- and sulfonyl- pyrazines and quinoxalines

Methylsulfanyl- and phenylsulfanylpyrazine have been deprotonated using LTMP in THF at -75 °C. The reaction occurred at the 3-position, leading to the compound **83** (Scheme 46).^{56a,30} The method was extended to 2-(methylsulfanyl)quinoxaline (interception of the lithio compound with *N*-methoxy-*N*-methylbenzamide in 42% yield).^{56a}



R = Me

[a, b, c]

83: 76%

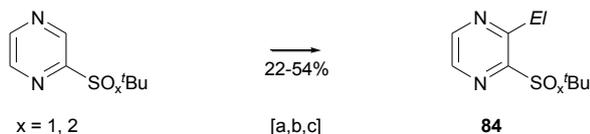
R = Ph

[d, e, c]

83: 74%

Scheme 46 Deprotonative functionalization of methylsulfanyl- and phenylsulfanylpyrazine. *Reaction conditions:* [a] LTMP, THF, -75 °C, 20 min; [b] *Electrophile* {El}: PhCON(OMe)Me {COPh}; [c] hydrolysis; [d] LTMP, THF, -75 °C, 1 h; [e] *Electrophile* {El}: MeCHO {CH(OH)Me}.

Whereas methylsulfinyl- and methylsulfonylpyrazine were mainly deprotonated on the methyl group upon treatment with LTMP, phenylsulfonylpyrazine underwent ring deprotonation using LDA to give after transformation the 3-substituted derivative in 33% yield.³⁰ *Tert*-butylsulfinyl- and *tert*-butylsulfonylpyrazine similarly led to the 3-substituted derivatives **84** in modest yields (Scheme 47).³¹



x = 1, 2

[a, b, c]

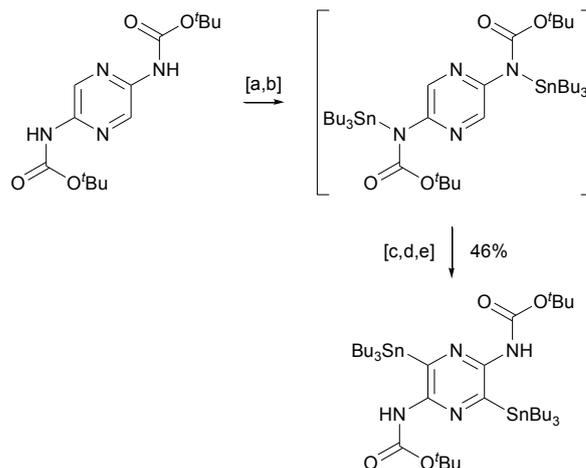
84

Scheme 47 Deprotonative functionalization of sulfinyl- and sulfonylpyrazine. *Reaction conditions:* [a] LTMP or LDA, THF, -75 °C, 30 min; [b] *Electrophile* {El}: MeCHO {CH(OH)Me}, PhCHO {CH(OH)Ph}, I₂ {I}; [c] hydrolysis.

4.6 Metalation of *N*-protected amino- pyrazines and quinoxalines

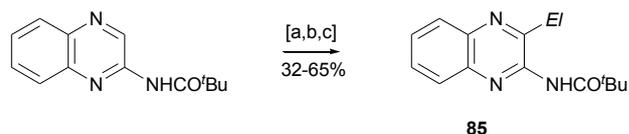
The metalation of *N*-pivaloyl protected aminopyrazine was unsuccessfully attempted using butyl-, *tert*-butyl- and mesityllithium due to easier nucleophilic addition. Recourse to LTMP (2 equiv.) resulted in an incomplete metalation at the 3-position when used in THF at 0 °C, as demonstrated by quenching with benzaldehyde to give after hydrolysis the

expected alcohol in 25% yield.⁶² Deprotonation of *N*-*tert*-butoxycarbonyl diprotected 2,5-diaminopyrazine was achieved using 8 equiv. of the mixed Li-K system obtained by mixing LTMP and potassium *tert*-butoxide, after replacement of the carbamate protons by tributylstannyl groups, as evidenced by interception with chlorotributylstannane (Scheme 48).⁶¹ Subsequent Pd/Cu couplings with diiodopyrazines **82** were utilized to prepare polymers.



Scheme 48 Deprotonative functionalization of *N*-*tert*-butoxycarbonyl diprotected 2,5-diaminopyrazine. *Reaction conditions:* [a] NaH, THF, rt, 1 h; [b] Bu₃SnCl, rt, 15 min; [c] LTMP, ^tBuOK, DEE, rt, 3 h; [d] Bu₃SnCl, rt, overnight; [e] hydrolysis.

Treatment of *N*-pivaloyl protected 2-aminoquinoxaline with LTMP in THF at -70 °C resulted in the regioselective metalation next to the directing group to afford after trapping the 3-substituted derivatives **85** (Scheme 49).⁵⁸



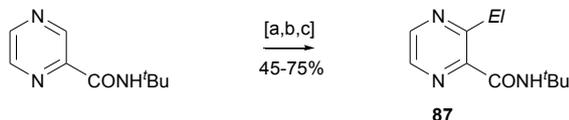
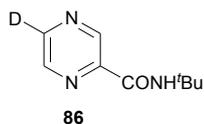
55

85

Scheme 49 Deprotonative functionalization of *N*-pivaloyl 2-aminoquinoxaline. *Reaction conditions:* [a] LTMP, THF, -70 °C, 2.5 h; [b] *Electrophile* {El}: MeCHO {CH(OH)Me}, PhCHO {CH(OH)Ph}, I₂ {I}, CO₂ {CO₂H}; [c] hydrolysis.

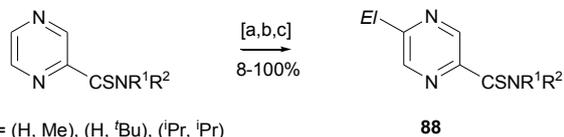
4.7 Metalation of pyrazinecarboxamides and pyrazinethiocarboxamides

Reactions between *N*-(*tert*-butyl)pyrazinecarboxamide and LTMP were conducted in THF at temperatures between -80 °C and 0 °C prior to deuteration. Whereas mixtures where the 5-deuterated derivative **86** predominates were obtained at very low temperatures (45% of **86** against 25% of **87** (El = D) at -80 °C) probably *via* a kinetic lithio compound at C5, the 3-deuterated compound **87** (El = D) was detected at 0 °C (4 equiv. of base) as the only product probably *via* a thermodynamic lithio compound at C3, stabilized by the chelating deprotonated carboxamide function. Subsequent functionalization of the deprotonated site was next considered (Scheme 50).⁶²



Scheme 50 Deprotonative functionalization of *N*-(*tert*-butyl)pyrazine-carboxamide. *Reaction conditions:* [a] LTMP, THF, 0 °C, 1 h; [b] *Electrophile* {*El*}: DCI/EtOD {D}, MeCHO {CH(OH)Me}, PhCHO {CH(OH)Ph}; [c] hydrolysis.

Starting from *N*-methyl-, *N*-(*tert*-butyl)- and *N,N*-diisopropylpyrazinethiocarboxamide, a complete regioselectivity in favor of the kinetic 5-lithio intermediate was observed at low temperature, leading to the compounds **88** (Scheme 51).⁶³



(R¹, R²) = (H, Me), (H, ^tBu), (iPr, iPr)

Scheme 51 Deprotonative functionalization of *N*-methyl-, *N*-(*tert*-butyl)- and *N,N*-diisopropylpyrazinethiocarboxamide. *Reaction conditions:* [a] LTMP, THF, -75 °C, 1.5 h; [b] *Electrophile* {*El*}: DCI/EtOD {D}, MeCHO {CH(OH)Me}, PhCHO {CH(OH)Ph}, Ph₂CO {C(OH)Ph₂}, C₂Cl₆ {Cl}, Bu₃SnCl {SnBu₃}, MeI {Me}, Me₃SiCl {SiMe₃}, I₂ {I}, (PhS)₂ {SPh}; [c] hydrolysis.

5 Conclusions

The methods outlined above allowed the functionalization of numerous diazines, and hence opened an entry to a great variety of building blocks, *e.g.* if combined with other reactions such as cross-couplings.⁶⁴

Despite all the applications so far featured, problems remain. The tendency of the substrates to undergo nucleophilic additions or substitutions limits the scope of the reaction. Recourse to LTMP to perform these reactions reduces nucleophilic attacks of the base to the substrate, but is helpless to prevent reactions from the lithiated substrate. In addition, reactions using LTMP are equilibria, and an excess of base is in general required to ensure satisfying yields.

Recently, new bases such as magnesates and zincates started to emerge, and proved convenient to allow reactions that were not accessible using lithium bases. The scope of these bases for the deprotonation of heterocycles, so far demonstrated with very sensible substrates such as bare diazines and halo pyrimidines deserves to be tested further.

Notes and references

Synthèse et ElectroSynthèse Organiques, Université de Rennes 1, CNRS, Bâtiment 10A, Case 1003, Campus scientifique de Beaulieu, F-35042 Rennes, France.
E-mail: florence.mongin@univ-rennes1.fr; Fax: +33-2-23-23-69-55

- 1 T. Eicher, S. Hauptmann and A. Speicher, *The Chemistry of Heterocycles*, 2nd ed., Wiley-VCH, 2003, Chapter 6.
- 2 (a) M. Tišler and B. Stanovnik, *Comprehensive Heterocyclic Chemistry*, ed. A. R. Katritzky and C. W. Rees, Pergamon Press, Oxford, 1984, Vol. 3, p. 1; (b) W. J. Coates, *Comprehensive Heterocyclic Chemistry*, 2nd ed. A. R. Katritzky, C. W. Rees and E. F. V. Scriven, Pergamon, Oxford, 1996, Vol. 6, p. 1.
- 3 (a) R. A. Carboni and R. V. Lindsey, Jr., *J. Am. Chem. Soc.*, 1959, **81**, 4342–4346; (b) D. L. Boger, *Chem. Rev.*, 1986, **86**, 781–794.
- 4 A. W. Dox and L. Yoder, *J. Am. Chem. Soc.*, 1922, **44**, 361–366.
- 5 P. Molina, A. Arques, V. Vinader, J. Becher and K. Brondum, *Tetrahedron Lett.*, 1987, **28**, 4451–4454.
- 6 H. Bredereck, R. Gompper and H. Herlinger, *Chem. Ber.*, 1958, **91**, 2832–2849.
- 7 (a) G. W. H. Cheeseman and E. S. G. Werstiuk, *Advances in Heterocycles Chemistry*, Academic Press: New York, 1972, Vol. 14, p. 99; (b) G. B. Barlin, *The Chemistry of Heterocyclic Compounds*, Wiley: New York, 1982, Vol. 41.
- 8 G. Büchi and J. Galindo, *J. Org. Chem.*, 1991, **56**, 2605–2606.
- 9 C. Nájera, J. M. Sansano and M. Yus, *Tetrahedron*, 2003, **59**, 9255–9303.
- 10 K. Shen, Y. Fu, J.-N. Li, L. Liu and Q.-X. Guo, *Tetrahedron*, 2007, **63**, 1568–1576.
- 11 T. Imahori and Y. Kondo, *J. Am. Chem. Soc.*, 2003, **125**, 8082–8083.
- 12 (a) G. Quéguiner, F. Marsais, V. Snieckus and J. Epsztajn, *Adv. Heterocycl. Chem.*, 1991, **52**, 187–304; (b) F. Mongin and G. Quéguiner, *Tetrahedron*, 2001, **57**, 4059–4090; (c) M. Schlosser and F. Mongin, *Chem. Soc. Rev.*, 2007, **36**, 1161–1172.
- 13 (a) A. Turck, N. Plé, F. Mongin and G. Quéguiner, *Tetrahedron*, 2001, **57**, 4489–4505; (b) A. Godard, A. Turck, N. Plé, F. Marsais and G. Quéguiner, *Trends Heterocycl. Chem.*, 1993, **3**, 16–29; (c) A. Turck, N. Plé and G. Quéguiner, *Heterocycles*, 1994, **37**, 2149–2172.
- 14 A. J. Clarke, S. McNamara and O. Meth-Cohn, *Tetrahedron Lett.*, 1974, **15**, 2373–2376.
- 15 M. Schlosser, O. Lefebvre and L. Ondi, *Eur. J. Org. Chem.*, 2006, 1593–1598.
- 16 C. Berghian, M. Darabantu, A. Turck and N. Plé, *Tetrahedron*, 2005, **61**, 9637–9644.
- 17 N. Plé, A. Turck, K. Couture and G. Quéguiner, *J. Org. Chem.*, 1995, **60**, 3781–3786.
- 18 A. Seggio, F. Chevallier, M. Vaultier and F. Mongin, *J. Org. Chem.*, 2007, **72**, 6602–6605.
- 19 (a) A. Turck, N. Plé, V. Tallon and G. Quéguiner, *Tetrahedron*, 1995, **51**, 13045–13060; (b) V. Gautheron-Chapoulaud, N. Plé and G. Quéguiner, *Tetrahedron*, 2000, **56**, 5499–5507.
- 20 L. Decrane, N. Plé and A. Turck, *J. Heterocyclic Chem.*, 2005, **42**, 509–513.
- 21 A. Turck, N. Plé, L. Mojovic and G. Quéguiner, *J. Heterocyclic Chem.*, 1990, **27**, 1377–1381.
- 22 F. Toudic, A. Turck, N. Plé, G. Quéguiner, M. Darabantu, T. Lequeux and J. C. Pommelet, *J. Heterocycl. Chem.*, 2003, **40**, 855–860.
- 23 A. Turck, N. Plé, B. Ndzi, G. Quéguiner, N. Haider, H. Schuller and G. Heinisch, *Tetrahedron*, 1993, **49**, 599–606.
- 24 A. Turck, N. Plé, L. Mojovic and G. Quéguiner, *Bull. Soc. Chim. Fr.*, 1993, **130**, 488–492.
- 25 (a) L. Mojovic, A. Turck, N. Plé, M. Dorsy, B. Ndzi and G. Quéguiner, *Tetrahedron*, 1996, **52**, 10417–10426; (b) N. Plé, A. Turck, K. Couture and G. Quéguiner, *Synthesis*, 1996, 838–842.
- 26 F. Trécourt, A. Turck, N. Plé, A. Paris and G. Quéguiner, *J. Heterocycl. Chem.*, 1995, **32**, 1057–1062.
- 27 V. Gautheron-Chapoulaud, I. Salliot, N. Plé, A. Turck and G. Quéguiner, *Tetrahedron*, 1999, **55**, 5389–5404.
- 28 (a) R. J. Mattson and C. P. Sloan, *J. Org. Chem.*, 1990, **55**, 3410–3412; (b) J. J. Lee, S. H. Cho, *Bull. Korean Chem. Soc.*, 1996, **17**, 868–869; *Chem. Abstr.*, 1996, **125**, 300930h.
- 29 A. Turck, N. Plé, A. Leprêtre-Gaquère and G. Quéguiner, *Heterocycles*, 1998, **49**, 205–214.
- 30 A. Turck, N. Plé, P. Pollet, L. Mojovic, J. Duflos and G. Quéguiner, *J. Heterocycl. Chem.*, 1997, **34**, 621–627.

- 31 A. Turck, N. Plé, P. Pollet and G. Quéguiner, *J. Heterocycl. Chem.*, 1998, **35**, 429–436.
- 32 P. Pollet, A. Turck, N. Plé and G. Quéguiner, *J. Org. Chem.*, 1999, **64**, 4512–4515.
- 5 33 N. Le Fur, L. Mojovic, N. Plé, A. Turck, V. Reboul and P. Metzner, *J. Org. Chem.*, 2006, **71**, 2609–2616.
- 34 N. Le Fur, L. Mojovic, N. Plé, A. Turck and F. Marsais, *Tetrahedron*, 2005, **61**, 8924–8931.
- 35 A. Turck, N. Plé, L. Mojovic, B. Ndzi, G. Quéguiner, N. Haider, H. Schuller and G. Heinisch, *J. Heterocycl. Chem.*, 1995, **32**, 841–846.
- 10 36 C. Fruit, A. Turck, N. Plé, L. Mojovic and G. Quéguiner, *Tetrahedron*, 2002, **58**, 2743–2753.
- 37 A. Krasovskiy, V. Krasovskaya and P. Knochel, *Angew. Chem.*, 2006, **118**, 3024–3027; *Angew. Chem. Int. Ed.*, 2006, **45**, 2958–2961.
- 15 38 (a) A. Busch, V. Gautheron-Chapoulaud, J. Audoux, N. Plé and A. Turck, *Tetrahedron*, 2004, **60**, 5373–5382; (b) N. Le Fur, L. Mojovic, A. Turck, N. Plé, G. Quéguiner, V. Reboul, S. Perrio and P. Metzner, *Tetrahedron*, 2004, **60**, 7983–7994.
- 39 T. J. Kress, *J. Org. Chem.*, 1979, **44**, 2081–2082.
- 20 40 (a) R. Radinov, M. Haimova and E. Simova, *Synthesis*, 1986, 886–891; (b) R. Radinov, C. Chanev, M. Haimova, *J. Org. Chem.*, 1991, **56**, 4793–4796.
- 41 N. Plé, A. Turck, P. Martin, S. Barbey and G. Quéguiner, *Tetrahedron Lett.*, 1993, **34**, 1605–1608.
- 25 42 N. Plé, A. Turck, E. Fiquet and G. Quéguiner, *J. Heterocyclic Chem.*, 1991, **28**, 283–287.
- 43 (a) C. Párkányi, N. S. Cho and G. S. Yoo, *J. Organomet. Chem.*, 1988, **342**, 1–7; (b) M. Cushman, J. T. Mihalic, K. Kis, A. Bacher, *J. Org. Chem.*, 1999, **64**, 3838–3845.
- 30 44 N. Plé, A. Turck, A. Heynderickx and G. Quéguiner, *J. Heterocyclic Chem.*, 1994, **31**, 1311–1315.
- 45 N. Plé, A. Turck, A. Heynderickx and G. Quéguiner, *J. Heterocyclic Chem.*, 1997, **34**, 551–556.
- 46 N. Plé, A. Turck, A. Heyndeickx and G. Quéguiner, *Tetrahedron*, 1998, **54**, 9701–9710.
- 35 47 (a) A. Wada, J. Yamamoto and S. Kanatomo, *Heterocycles*, 1987, **26**, 585–589; (b) A. Wada, J. Yamamoto, Y. Hamaoka, K. Ohki, S. Nagai and S. Kanatomo, *J. Heterocycl. Chem.*, 1990, **27**, 1831–1835.
- 48 (a) N. Plé, A. Turck, F. Bardin and G. Quéguiner, *J. Heterocycl. Chem.*, 1992, **29**, 467–470; (b) N. Plé, A. Turck, K. Couture and G. Quéguiner, *Tetrahedron*, 1994, **50**, 10299–10308.
- 40 49 W. Schwaiger and J. P. Ward, *Recl. Trav. Chim. Pays-Bas*, 1971, **90**, 513–515.
- 50 G. P. Rizzi, *J. Org. Chem.*, 1974, **39**, 3598.
- 45 51 (a) C. Fruit, A. Turck, N. Plé, L. Mojovic and G. Quéguiner, *Tetrahedron*, 2001, **57**, 9429–9435; (b) F. Toudic, N. Plé, A. Turck and G. Quéguiner, *Tetrahedron*, 2002, **58**, 283–293.
- 52 F. Buron, N. Plé, A. Turck and G. Quéguiner, *J. Org. Chem.*, 2005, **70**, 2616–2621.
- 50 53 F. Toudic, A. Heynderickx, N. Plé, A. Turck and G. Quéguiner, *Tetrahedron*, 2003, **59**, 6375–6384.
- 54 Y. Aoyagi, A. Maeda, M. Inoue, M. Shiraishi, Y. Sakakibara, Y. Fukui, A. Ohta, K. Kajii and Y. Kodama, *Heterocycles*, 1991, **32**, 735–748.
- 55 55 (a) A. Turck, L. Mojovic and G. Quéguiner, *Synthesis*, 1988, 881–884; (b) A. Turck, N. Plé, D. Dognon, C. Harmoy and G. Quéguiner, *J. Heterocyclic Chem.*, 1994, **31**, 1449–1453; (c) W. Liu, J. A. Walker, J. J. Chen, D. S. Wise, B. L. Townsend, *Tetrahedron Lett.*, 1996, **37**, 5325–5328.
- 60 56 (a) J. S. Ward and L. Merritt, *J. Heterocycl. Chem.*, 1991, **28**, 765–768; (b) A. Turck, D. Trohay, L. Mojovic, N. Plé and G. Quéguiner, *J. Organomet. Chem.*, 1991, **412**, 301–310.
- 57 W. Liu, D. S. Wise, L. B. Townsend, *J. Org. Chem.*, 2001, **66**, 4783–4786.
- 65 58 A. Turck, N. Plé, V. Tallon and G. Quéguiner, *J. Heterocycl. Chem.*, 1993, **30**, 1491–1496.
- 59 N. Plé, A. Turck, A. Heynderickx and G. Quéguiner, *Tetrahedron*, 1998, **54**, 4899–4912.
- 60 C. Berghian, E. Condamine, N. Plé, A. Turck, I. Silaghi-Dumitrescu, 70 C. Maieranu and M. Darabantu, *Tetrahedron*, 2006, **62**, 7339–7354.
- 61 C. Y. Zhang and J. M. Tour, *J. Am. Chem. Soc.*, 1999, **121**, 8783–8790.
- 62 A. Turck, N. Plé, D. Trohay, B. Ndzi and G. Quéguiner, *J. Heterocycl. Chem.*, 1992, **29**, 699–702.
- 75 63 C. Fruit, A. Turck, N. Plé and G. Quéguiner, *Heterocycles*, 1999, **51**, 2349–2365.
- 64 R. Chinchilla, C. Nájera and M. Yus, *Chem. Rev.*, 2004, **104**, 2667–2722.