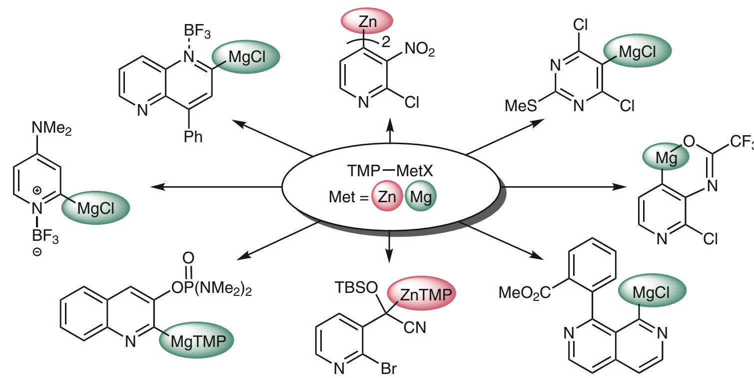
Regioselective C–H Activation of Substituted Pyridines and other Azines using Mg- and Zn-TMP-Bases

Moritz Balkenhohl
Paul Knochel*

Department of Chemistry, Ludwig-Maximilians-Universität München, Butenandtstraße 5-13, Haus F, 81377 München, Germany
Paul.Knochel@cup.uni-muenchen.de



Received: 31.01.2018
Accepted: 04.03.2018
Published online: 19.03.2018
DOI: 10.1055/s-0036-1591966; Art ID: so-2018-d0014-r

Abstract The metalation of substituted pyridines, diazines and related *N*-heterocycles using TMPMgCl·LiCl, $TMP_2Mg \cdot 2LiCl$, TMPZnCl·LiCl or $TMP_2Zn \cdot 2LiCl_2 \cdot 2MgCl_2$ (TMP = 2,2,6,6-tetramethylpiperidyl) in the presence or absence of a Lewis acid is reviewed.

Contents

Key words azines, metalation, *N*-heterocycles, pyridine, TMP bases

1 Introduction

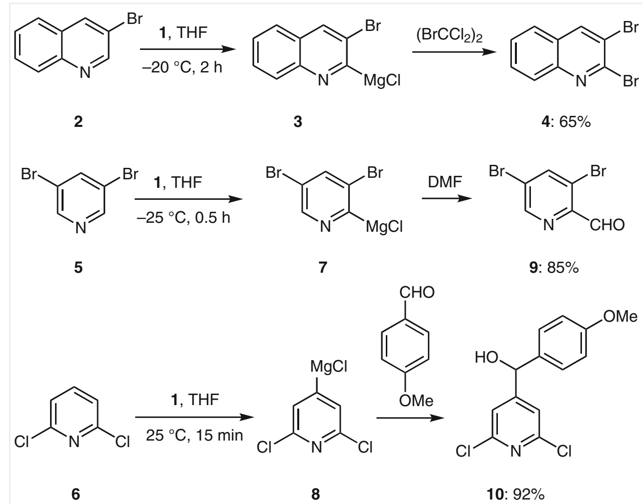
The regioselective functionalization of azines, especially pyridines, is an important synthetic challenge because of the importance of these *N*-heterocycles as pharmaceuticals and agrochemicals.[1] The use of lithium bases for achieving regioselective lithiations has been pioneered by Snieckus,[2] Schlosser,[3] Quéginer[4] and Mongin[4h–j,5] as well as Gros.[6] These powerful bases produce lithiated *N*-heterocycles, which are often only stable at low temperature, although the performance of such metalations in continuous flow may avoid such low temperatures.[7] Furthermore, the use of lithium magnesiate or zincate bases pioneered by Mulvey,[8] Mongin,[8b,9] Uchiyama[8b,9b,e,g,l,10] and Kondo[8b,10a–c,11] has considerably broadened the scope of metalations for the functionalizations of pyridines and other azines. Recently, it became clear that highly reactive magnesium and zinc bases can be obtained by mixing sterically hindered magnesium and zinc bases (derived mostly from 2,2,6,6-tetramethylpiperidine (TMP-H)) with LiCl.[12] The resulting, highly THF-soluble bases[13] are mostly monomeric and kinetically highly active for the magnesiation and zincation of various functionalized pyridines or sensitive azines.[12] Furthermore, in such metalations, only magnesiated or zincated heterocycles are produced, which are compatible with a range of functional groups at moderate to low temperatures. In the case of the zincation of azines, either ambient or elevated temperature (up to 120 °C)[14] can be used, offering considerable potential for industrial applications. Since the metalation of azines using magnesiate or zincate bases has already been reported extensively,[8–11] this review will focus on recent advances describing the most practical and regioselective C–H activations[15] of functionalized pyridines and other azines, using mostly zinc and magnesium TMP-bases.[16]

2 Magnesiation of Pyridines and Related Azines

2.1 Magnesiations using TMPMgCl·LiCl (1)

Usually, magnesium amides of type R_2NMgX or $(R_2N)_2Mg$ are aggregated and relatively slow deprotonation reagents, partially because of their moderate solubility.[17] Mulzer pioneered the use of TMPMgCl for the magnesiation of an azine.[18] A base with higher activity and higher solubility in THF was obtained by using TMPMgCl with LiCl (1 equiv). Thus, mixing of TMP-H with *i*-PrMgCl·LiCl in THF (25 °C, 24 h) provides a ca. 1.4 M soluble base TMPMgCl·LiCl (**1**).[12,13]

This base magnesiates a range of functionalized pyridines and quinolines under mild conditions. Since magnesium reagents are produced, there is no need for low temperatures as it is often the case with corresponding lithiations.[19,20] Thus, the magnesiation of 2-bromoquinoline **2** with TMPMgCl·LiCl (**1**) at –20 °C for 2 h provides the *ortho*-magnesiated product **3** (Scheme 1). After bromolysis, the dibromoquinoline **4** is obtained in 65% yield.[21] Pyridines bearing less sensitive functional groups, such as 3,5-dibromopyridine (**5**) or 2,6-dichloropyridine (**6**), are magnesiated at convenient temperatures (–25 °C or 25 °C), regioselectively providing the pyridylmagnesium derivatives **7** and **8**. Quenching with various electrophiles, such as *N*,*N*-dimethylformamide (DMF) or 4-methoxybenzaldehyde, affords the polyfunctional pyridines **9** and **10** in 85–92% yield (Scheme 1).[12]

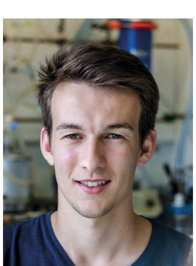


Scheme 1 Regioselective magnesiation of halogenoazines using TMPMgCl·LiCl (**1**)

The last reaction can be readily scaled up to a 100 mmol-scale with no yield loss.[22] Aminopyridines are converted into the corresponding trifluoroacetamides such as **11**. Deprotonation of the amide function with MeMgCl and ring-magnesiation with TMPMgCl·LiCl (**1**) furnishes the Grignard reagent **12**, which, after a transmetalation with $ZnCl_2$ and Negishi cross-coupling,[23,24] affords the 4-arylated pyridine **13** in 80% yield (Scheme 2).[25] The trifluoroacetamido group of **11** is an excellent directing group. Similarly, a sulfoxide function directs a magnesiation in the *ortho*-position with high efficiency. Thus, pyridine **14**, bearing a sulfoxide function at position C4, is magnesiated at –30 °C with TMPMgCl·LiCl (**1**) within 20 min (Scheme 3). Addition of $ZnCl_2$ and Negishi cross-coupling with *p*-iodoanisole catalyzed by 5% $Pd(PPh_3)_4$ (50 °C, 2 h) furnishes the tetrasubstituted pyridine **15** in 68% yield. The sulfoxide group can then be converted into a new magnesium reagent through sulfoxide–magnesium exchange[26] in 2-methyl-THF[27] triggered by *i*-PrMgCl·LiCl (–50 °C, 5 min). Transmetalation with $ZnCl_2$ followed by a Negishi cross-coupling

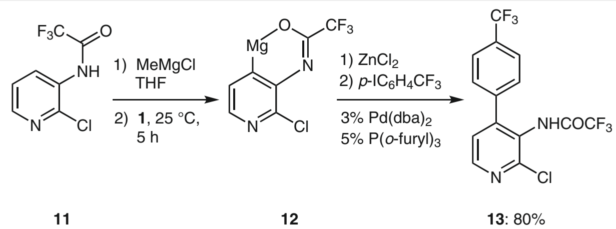
Biographical Sketches

Paul Knochel was born in 1955 in Strasbourg (France). He studied at the University of Strasbourg (France) and did his Ph.D at the ETH-Zürich (D. Seebach). He spent four years at the University Pierre and Marie Curie in Paris (J.-F. Normant) and one year at Princeton University (M. F. Semmelhack). In 1987, he was Professor at the University of Michigan. In 1992, he moved to Philipps-University at Marburg (Germany). In 1999, he then moved to the Chemistry Department of Ludwig-Maximilians-University in Munich (Germany). His research interests include the development of novel organometallic reagents and methods for use in organic synthesis, asymmetric catalysis and natural product synthesis. Prof. Knochel has received many distinguished prizes including the Berthelot Medal of the Academie des Sciences (Paris), the IUPAC Thieme Prize, the Otto-Bayer-Prize, the Leibniz-Prize, the Arthur C. Cope Scholar Award, Karl-Ziegler-Prize, the Nagoya Gold Medal, the H. C. Brown Award and Paul Karrer gold medal. He is member of the Académie des Sciences, the Bavarian Academy of Science, the German Academy of Sciences Leopodina. He is author of over 900 publications.



Moritz Balkenhohl was born in 1992 in Speyer (Germany). He studied chemistry at the Julius-Maximilians-Universität Würzburg and at Imperial College London. In 2015 he joined the group of Prof. Paul Knochel for his Master thesis in Munich and started his PhD thesis in 2016. His research focuses on the functionalization of challenging heterocycles and transition-metal-free amination reactions.

with ethyl 5-bromonicotinate (**16**), catalyzed by 2% $Pd(PPh_3)_4$ (50 °C, 5 h), leads to the complex bis-pyridine **17** in 82% yield (Scheme 3).[28]



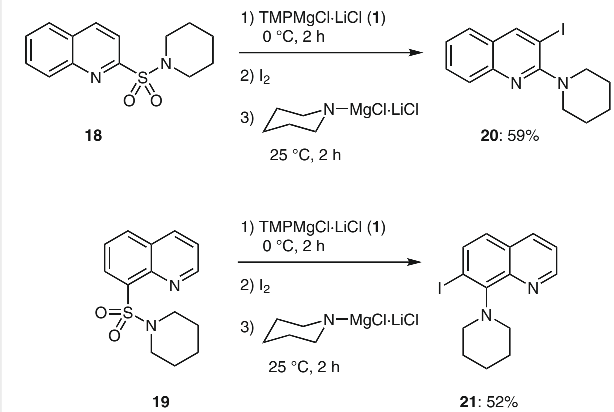
Scheme 2 Magnesiation of a trifluoroamidopyridine using TMPMgCl·LiCl (**1**)

Likewise, sulfonamides are excellent directing groups[2c–d,29] and can undergo amination reactions when treated with an excess of a magnesium amide. Thus, sulfonamides **18** and **19** are magnesiated with TMPMgCl·LiCl (**1**; THF, 0 °C, 2 h). After iodolysis and amination at 25 °C (2 h) with piperidylmagnesium chloride, aminoquinolines **20** and **21** are obtained in 52–59% yield over two steps (Scheme 4).[30]

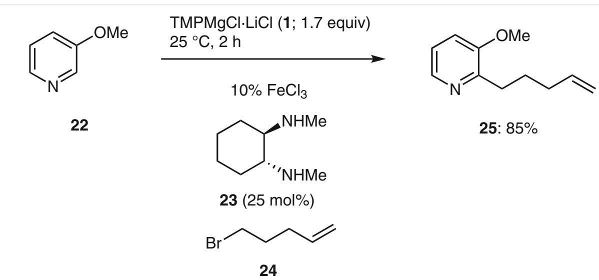
TMPMgCl·LiCl (**1**) also proves to be an excellent base for the C–H activation of 3-methoxypyridine (**22**). Thus, treatment of **22** with 10% $FeCl_3$ and 25% diamine (**23**) and an excess of TMPMgCl·LiCl (**1**) at 25 °C for 2 h allows facile alkylation with various alkyl bromides such as 5-bromopentene (**24**), providing the alkylated product **25** in 85% yield (Scheme 5).[31]

The *N*,*N*,*N*′,*N*′-tetramethylphosphordiamidate group ($OP(O)(NMe_2)_2$) was found to be a more powerful directing group than the methoxy group,[32] which allows efficient magnesiations with TMPMgCl·LiCl (**1**). Thus, the 4-substituted pyridine **26** is magnesiated with **1** (1.5 equiv, 0 °C, 1 h) and subsequently thiolated by reaction with $MeSSO_2Me$, affording the disubstituted pyridine **27** in 88% yield.

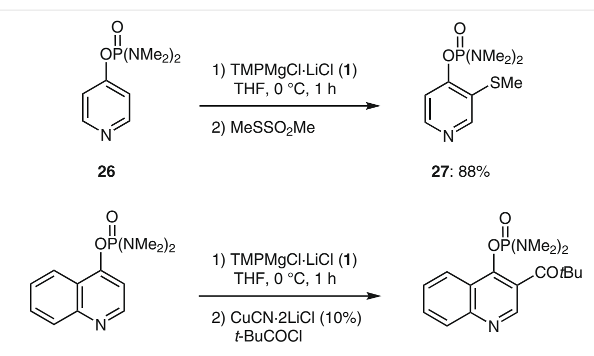
Similarly, quinoline **28** was magnesiated with TMPMgCl·LiCl (**1**) at 0 °C within 1 h and acylated in the presence of a copper(I)-catalyst (CuCN·2LiCl), furnishing the ketone **29** in 62% yield (Scheme 6).[33] This method has been used to prepare the pyridine based COX-2 inhibitor etoricoxib **30**[34] starting from the phosphordiamidate substituted pyridine **31**. Thus, the magnesiation of **31** with TMPMgCl·LiCl (**1**) in THF at 0 °C for 1 h, followed by a transmetalation with $ZnCl_2$ and Negishi cross-coupling with aryl bromide **32** using 1%



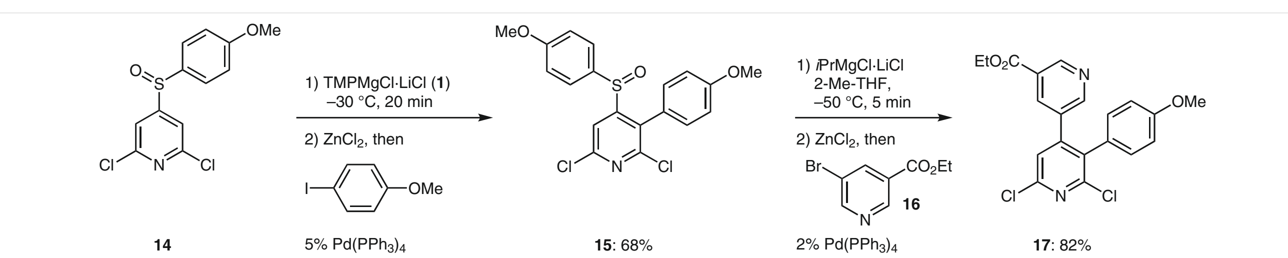
Scheme 4 *ortho*-Metalation, functionalization and amination of quinoline-sulfonamides



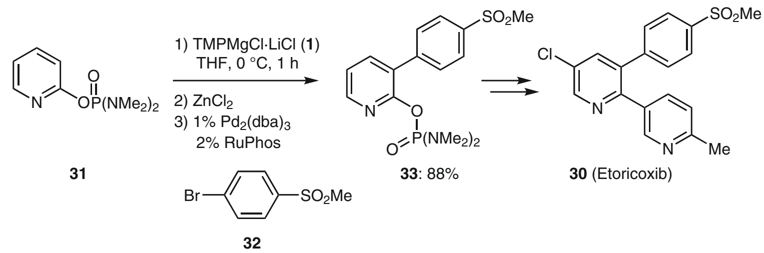
Scheme 5 Iron-catalyzed alkylation of 3-methoxypyridine (**22**)



Scheme 6 *ortho*-Magnesiation of a phosphordiamidate substituted pyridine and quinoline using TMPMgCl·LiCl (**1**)



Scheme 3 *ortho*-Magnesiation of a pyridyl sulfoxide, followed by a sulfoxide–magnesium exchange



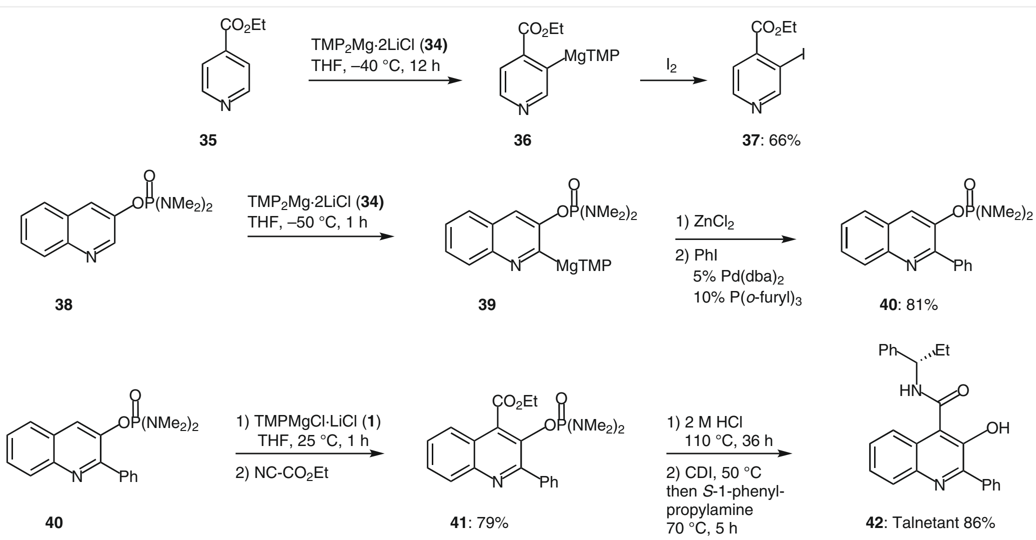
Scheme 7 Synthesis of Etoricoxib (**30**) using TMPMgCl·LiCl (**1**)

$Pd_2(dba)_3$ (dba = dibenzylideneacetone) and 2% RuPhos[35] provides the arylated pyridine **33** in 88% yield. Standard transformations and Stille cross-coupling[36] provides the desired pharmaceutical **30** (Scheme 7).[33]

2.2 Magnesiations using $TMP_2Mg·2LiCl$ (34) and Related Bases

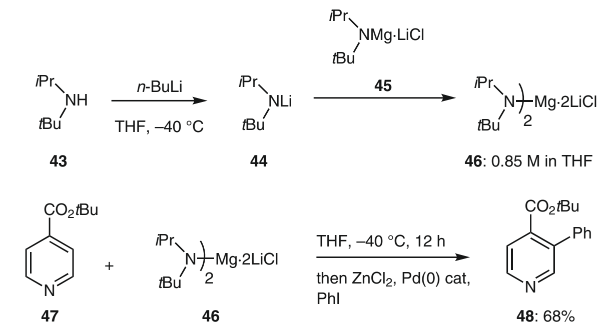
Although TMPMgCl·LiCl (**1**) is a very powerful magnesiation reagent, in the case of substrates bearing weakly acidic or sterically hindered protons, the magnesiation is advantageously performed using $TMP_2Mg·2LiCl$ (**34**).[37] Often, the presence of sensitive functional groups, such as a carboethoxy group, requires low magnesiation temperatures, since higher temperatures lead to considerable side reactions. $TMP_2Mg·2LiCl$ (**34**), which is prepared in quantitative yield by treating TMPLi with **1**, can be stored at 25 °C for several hours. A degradation after several days is however observed. This base readily magnesiates 4-carbethoxypyridine (**35**) at –40 °C for 12 h, leading to **36**, furnishing, after iodolysis, the iodopyridine **37** in 66% yield (Scheme 8).[37] The phosphordiamidate substituted quinoline **38** was magnesiated with **34**, yielding the magnesium reagent **39** (–50 °C, 1 h). After transmetalation with $ZnCl_2$ and Negishi cross-coupling using PhI, 5% $Pd(dba)_2$ and 10% $P(o\text{-furyl})_3$ as catalyst,[38] the arylated quinoline **40** is obtained in 81% yield. Interestingly, the quinoline **40** can now be magnesiated with TMPMgCl·LiCl (**1**) at 25 °C within 1 h. The presence of the phenyl group at position 2 avoids nucleophilic additions to the quinoline ring and allows higher metalation temperatures (25 °C instead of –50 °C). Quenching with $NC\text{-}CO_2Et$ produces the 2,3,4-trisubstituted quinoline **41**, which is further converted into Talnetant (**42**), an NK_3 receptor antagonist, in 86% yield (Scheme 8).[33]

An alternative base with enhanced thermal stability derived from *t*-butyl-isopropylamine (*t*Bu(*i*Pr)NH, **43**) was obtained by treating **43** with *n*-BuLi, giving **44**, followed by the addition of *t*Bu(*i*Pr)NMgCl·LiCl (**45**), affording the



Scheme 8 Azine functionalization using $TMP_2Mg·2LiCl$ (**34**)

magnesium bis-amide **46** in >90% yield (Scheme 9).[39] The metalation of 4-*t*-butoxycarbonylpyridine (**47**) with **46** provides the expected pyridine **48** in 68% yield (Scheme 9).[39]

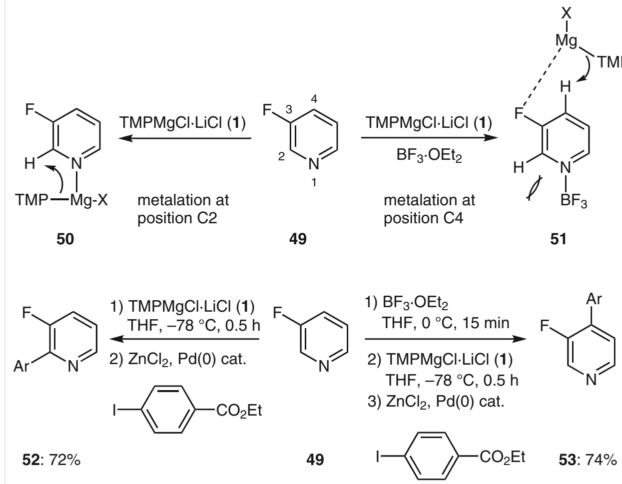


Scheme 9 Preparation of **46** and magnesiation of **47** with $[iPr(tBu)N]_2Mg{\cdot}2LiCl$ (**46**)

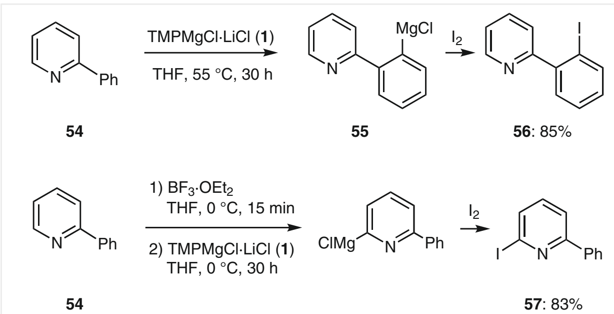
2.3 $BF_3{\cdot}OEt_2$-Promoted Metalations of Pyridines

A typical mono-substituted pyridine, 3-fluoropyridine (**49**), can be metalated in two complementary positions (position C2 or position C4) with TMPMgCl·LiCl (**1**), either in the absence or in the presence of the strong Lewis acid $BF_3{\cdot}OEt_2$ (Scheme 10). Preliminary experiments showed that $BF_3{\cdot}OEt_2$ does not react in an irreversible manner with TMPMgCl·LiCl (**1**) at temperatures below –30 °C. Also, the 3-fluoro substituent considerably acidifies the adjacent positions C2 and C4 of **49**. The position of the metalation is determined by the nature of the complexation with the TMP-base.[40] Thus, by adding TMPMgCl·LiCl (**1**) to **49**, a complexation of **1** to the heterocyclic N-atom takes place, leading to a complex of type **50**, which favors metalation at position C2. On the other hand, in the presence of $BF_3{\cdot}OEt_2$, this strong Lewis acid forms a complex with the N-atom of the pyridine ring and the base **1** may, if at all, only complex the fluorine substituent.

This favors a metalation at position C4 (see **51**). Thus, the presence or absence of $BF_3{\cdot}OEt_2$ allows the arylation of 3-fluoropyridine (**49**) either in position C2 or C4, leading to the expected products **52** and **53** (Scheme 10).[40] The exact nature of the organometallic species obtained after the metalation of **49** in the presence of $BF_3{\cdot}OEt_2$ has been examined by ^{13}C NMR spectroscopy.[40,41] This regioselectivity switch is observed for a range of pyridines. An unexpected regioselectivity is observed in the case of 2-phenylpyridine (**54**). Thus, the treatment of **54** with TMPMgCl·LiCl (**1**) at 55 °C provides the magnesiated pyridine **55**. After iodolysis, pyridine **56** is obtained in 85% yield. Alternatively, the treatment of **54** with $BF_3{\cdot}OEt_2$, followed by TMPMgCl·LiCl (**1**), furnishes, after iodolysis, the 2,6-disubstituted pyridine **57** in 83% yield (Scheme 11).[40]

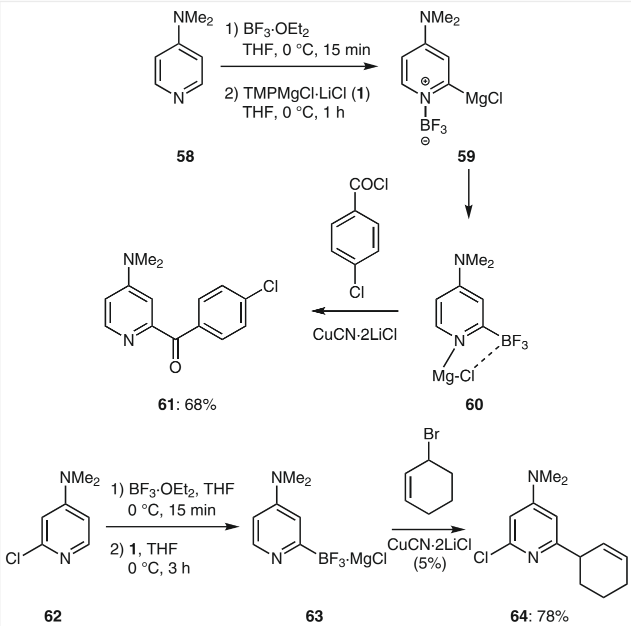


Scheme 10 Regioselective metalation of 3-fluoropyridine **49** in the presence or absence of $BF_3{\cdot}OEt_2$



Scheme 11 Regioselective metalation of 2-phenylpyridine (**54**) with or without $BF_3{\cdot}OEt_2$

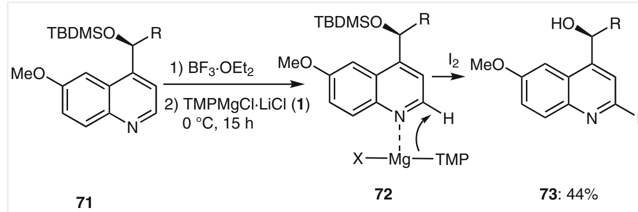
This methodology also allows the functionalization of 4-dimethylaminopyridine (**58**) in position 2. In this case, the coordination with $BF_3{\cdot}OEt_2$ greatly acidifies all the heterocyclic hydrogen atoms, especially those in position C2. Thus, treatment of **58** with $BF_3{\cdot}OEt_2$ in THF, followed by TMPMgCl·LiCl (**1**) at 0 °C for 1 h, furnishes the magnesium derivative **59** or, after metallotropy, the trifluoroborate derivative **60**. After a copper(I)-catalyzed acylation, the 2-ketopyridine **61** is obtained in 68% yield.[42] Similarly, 2-chloro-4-dimethylaminopyridine (**62**) is allylated via the organometallic intermediate **63**, furnishing the trisubstituted pyridine **64** in 78% yield (Scheme 12).[42]



Scheme 12 Functionalization of 4-dimethylaminopyridine (**58**) using TMPMgCl·LiCl (**1**) and BF_3·OEt_2

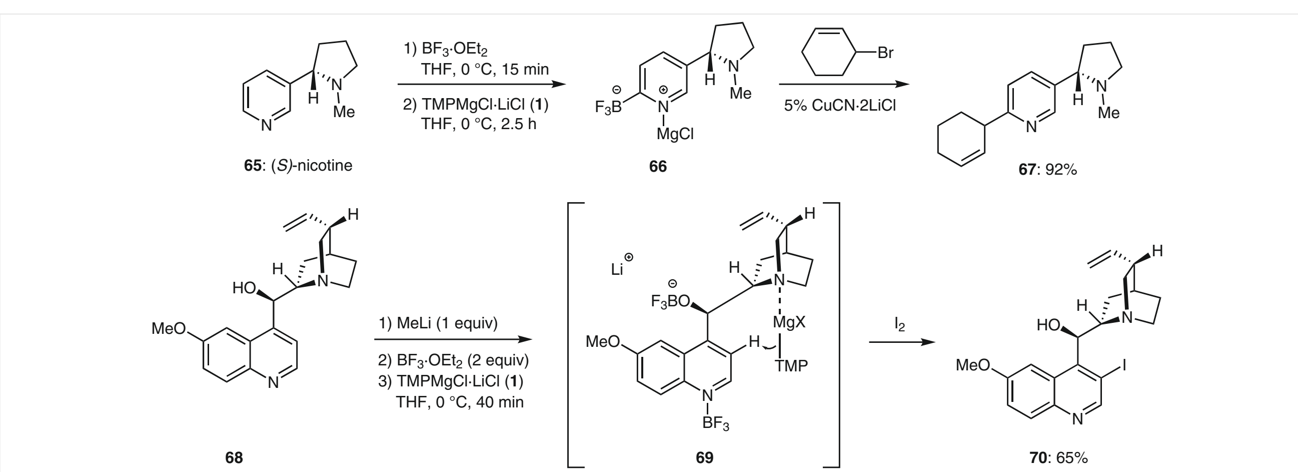
Furthermore a regioselective functionalization of (*S*)-nicotine (**65**) via the organometallic intermediate **66**, leading to 6-functionalized nicotine derivatives, such as **67**, is feasible.[42] Similarly, the metalation of quinine (**68**) can be tuned depending on the reaction conditions used. Thus, the formation of the lithium alcoholate of quinine followed by the addition of BF_3·OEt_2 (2 equiv) is tentatively thought to provide intermediate **69**, which leads to a complexation of **1** at the basic tertiary nitrogen atom and therefore leads to the 3-iodinated quinoline **70** in 65% yield (Scheme 13).[42]

By tuning the protecting groups attached to quinine (**68**), a switch of the metalation is observed. Thus, the conversion of **68** into the TBDMS-silyl enol ether **71** followed by addition of BF_3·OEt_2 (1 equiv) now leads to the BF_3-adduct **72**, which can be metalated with TMPMgCl·LiCl (**1**) exclusively at the position C2, providing, after iodolysis, the 2-iodoquinine derivative **73** in 44% yield (Scheme 14).[42]

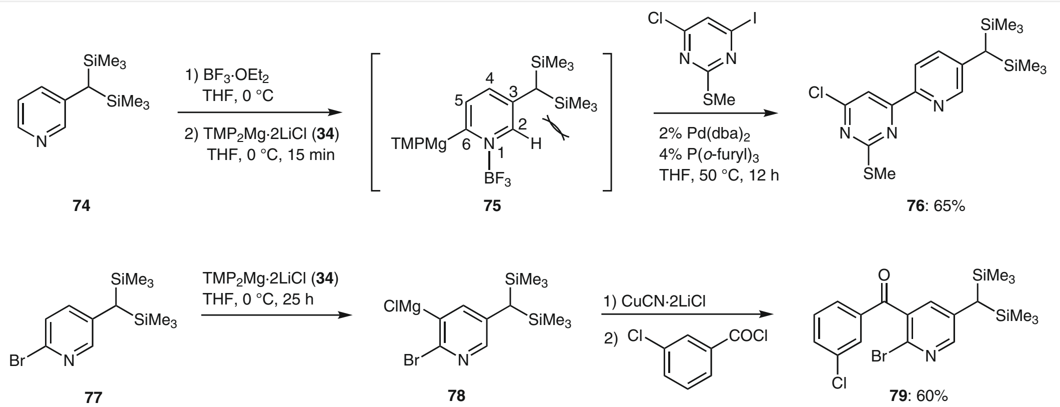


Scheme 14 BF_3·OEt_2-triggered metalation of a silyl-derivative of quinine (**71**)

The regioselectivity of the metalation of pyridines and quinolines is the result of steric and electronic factors, often leading to kinetically controlled products. Thus, the bis-trimethylsilylmethyl group, which is readily attached to the pyridine scaffold, directs the metalation by steric effects. Therefore, the 3-substituted pyridine **74** was activated with BF_3·OEt_2 (0 °C, 15 min) and magnesiated with TMP_2Mg·2LiCl (**34**), since the magnesiation with **1** proved to be ineffective. The BF_3-adduct **75** is exclusively metalated at position C6, providing, after a Negishi cross-coupling with an iodopyrimidine, the bis-azine **76** in 65% yield (Scheme 15).[43] Interestingly, 6-bromo-3-bis(trimethylsilylmethyl)pyridine (**77**) can be directly metalated by TMP_2Mg·2LiCl (**34**) at 0 °C for 25 h, affording the magnesium derivative **78**. Due to the steric hindrance of the silyl-substituent at position C3, no magnesiation occurs at position C2, and only a magnesiation is observed at position C5. Subsequent acylation with an acid chloride, after transmetalation to copper(I) with CuCN·2LiCl, provides ketone **79** in 60% yield (Scheme 15).[43]



Scheme 13 BF_3·OEt_2-triggered metalation of (*S*)-nicotine (**65**) and quinine (**68**) using TMPMgCl·LiCl (**1**)



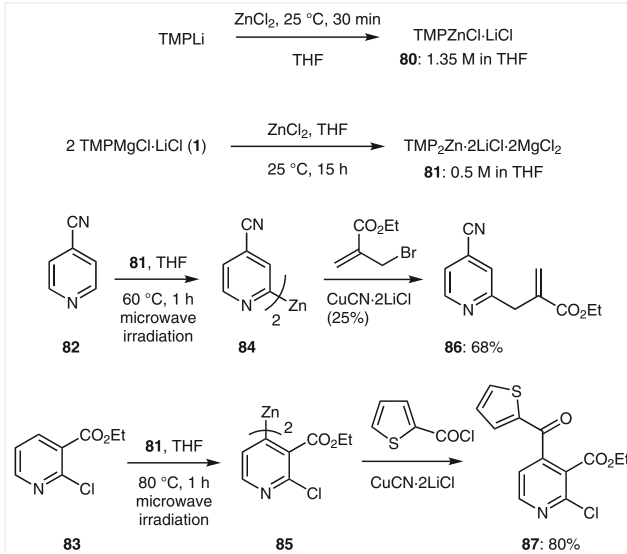
Scheme 15 Metalation of sterically hindered pyridines bearing a bis-trimethylsilylmethyl substituent

3 Zincation of Pyridines and Related Azines using TMPZnCl·LiCl and $TMP_2Zn·2LiCl·2MgCl_2$

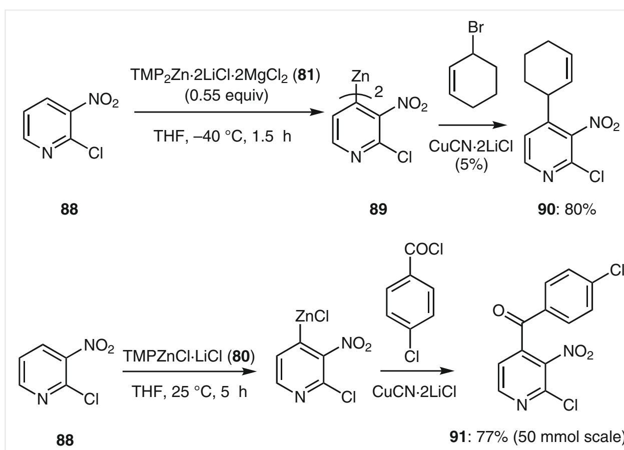
The availability of kinetically active zinc amides further extends the scope of directed metalations of functionalized azines. Two complementary zinc bases TMPZnCl·LiCl (**80**) and $TMP_2Zn·2LiCl·2MgCl_2$ (**81**) are obtained from TMPLi and $ZnCl_2$ or TMPMgCl·LiCl (**1**) and $ZnCl_2$ (Scheme 16).[11,44,45] Since the carbon–zinc bond is much more covalent than the carbon–magnesium bond, electrophilic functional groups are much better tolerated in such zinc organometallics and the directed zincation of various functionalized pyridines such as **82** and **83** is readily achieved.[14] As the carbon–zinc bond in heteroarylzinc reagents is stable up to 100 °C, directed zincations of pyridines **82–83** have been performed under microwave irradiation under elevated temperatures (60–80 °C), providing the corresponding dipyridylzinc reagents **84–85** in high yields. After quenching with electrophiles such as allylic bromides or acyl chlorides in the presence of a copper(I) catalyst, the expected products **86–87** are obtained in 68–80% yield (Scheme 16).[14]

Furthermore, pyridylzinc organometallics do not undergo electron-transfer reactions. Therefore, the electron-deficient nitro group is well tolerated in the zincation of nitro-substituted pyridines such as **88**. In this case, the zincation proceeds at –40 °C within 1.5 h, leading to the bis-pyridylzinc **89**. After a copper-catalyzed allylation with 3-bromocyclohexene, the trisubstituted pyridine **90** is obtained in 80% yield (Scheme 17).[44] Alternatively, the milder zinc base TMPZnCl·LiCl (**80**) can be used to zincate **88** at 25 °C within 5 h and does not require low temperature metalations[45,46] leading to the acylated pyridine **91** in 77% yield on 50 mmol scale (Scheme 17).[46]

Highly oxidized pyridines, such as pyridine *N*-oxides, are smoothly zincated with TMPZnCl·LiCl (**80**) at 25 °C and such functionalizations of pyridines are possible in large scale (20 mmol) in high yields.

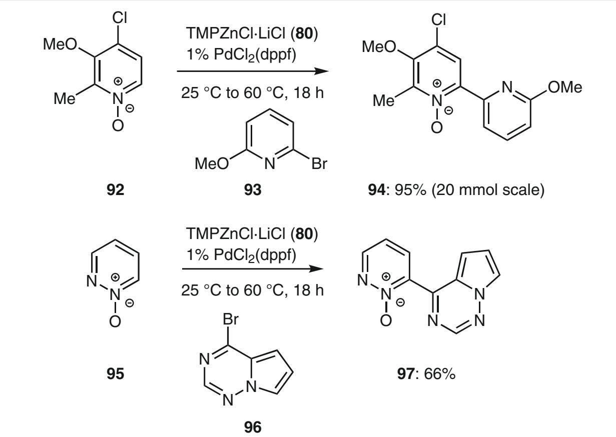


Scheme 16 Preparation of the TMP-zinc bases TMPZnCl·LiCl (**80**) and $TMP_2Zn·2LiCl·2MgCl_2$ (**81**) and of polyfunctional pyridylzinc reagents using **81**



Scheme 17 Zincation of nitro-substituted pyridine **88** using TMPZnCl·LiCl (**80**) or $TMP_2Zn·2LiCl·2MgCl_2$ (**81**)

Thus, a room-temperature zincation of pyridine *N*-oxide **92** with TMPZnCl·LiCl (**80**), and subsequent cross-coupling with the heteroaryl bromide **93**, provides the desired cross-coupling product **94** in 95% yield. Remarkably, this reaction has been extended to diazine *N*-oxides such as pyridazine *N*-oxide **95**, providing, after cross-coupling with the heterocyclic bromide **96**, the complex heterocycle **97** in 66% yield (Scheme 18).[47]

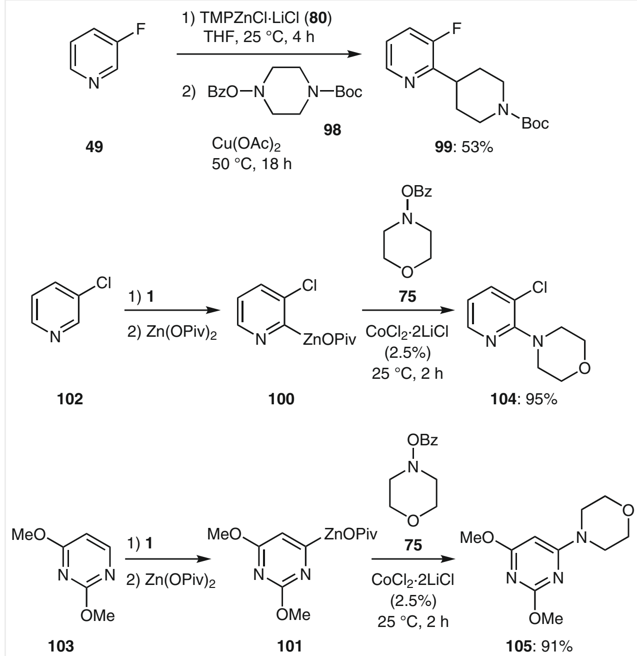


Scheme 18 Metalation of azine *N*-oxides using TMPZnCl·LiCl (**80**)

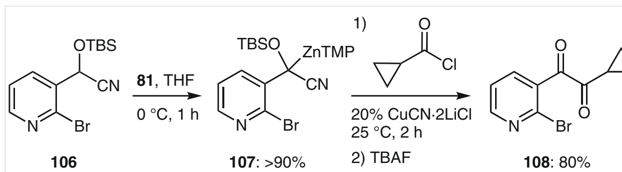
The use of TMPZnCl·LiCl (**80**) is compatible with electrophilic aminations as shown by Wang.[48,49] Thus, TMPZnCl·LiCl (**80**) regioselectively zincates 3-fluoropyridine (**49**) at 25 °C. Addition of a Cu(II)-catalyst (5 mol% $Cu(OAc)_2$) at 50 °C for 18 h in the presence of the electrophilic amination reagent, a benzoyloxypiperazine derivative (**98**), provides the amination product **99** in 53% yield at a 60 mmol scale. A related cobalt(II)-catalyzed amination can be performed under milder conditions using $CoCl_2$·2LiCl as catalyst (2.5%). In this case, the amination proceeds at 25 °C. Thus, pyridylzinc pivalate **100** and **101**,[50] obtained by the magnesiation of the corresponding azine and diazine **102** and **103** with TMPMgCl·LiCl (**1**) followed by the addition of $Zn(OPiv)_2$, are treated with *N*-hydroxymorpholine benzoate in THF at 25 °C for 2 h, furnishing the aminated derivatives **104** and **105** in 91–95% yield (Scheme 19).[51]

The performance of lateral zincations of pyridines has been achieved by using TMP_2Zn·2LiCl·$2MgCl_2$ (**81**). Thus, the treatment of the cyanohydrine derivative **106** with TMP_2Zn·2LiCl·$2MgCl_2$ (**81**) at 0 °C for 1 h provides the benzylic pyridylzinc derivative **107**.

This zinc reagent can be acylated with cyclopropanecarbonyl chloride in the presence of 20% CuCN·2LiCl, affording, after tetrabutylammonium fluoride (TBAF) treatment, ketone **108** in 80% yield (Scheme 20).[52]

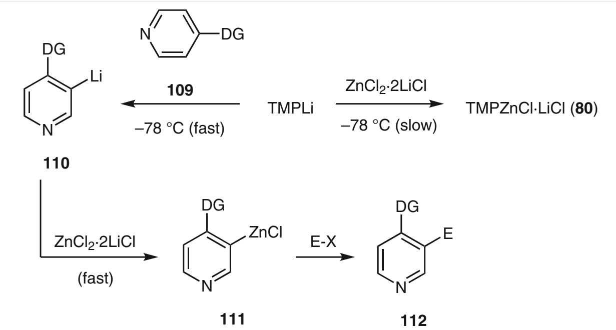


Scheme 19 Electrophilic aminations of zincated azines using TMPZnCl·LiCl (**80**), TMPMgCl·LiCl (**1**) and $Zn(OPiv)_2$



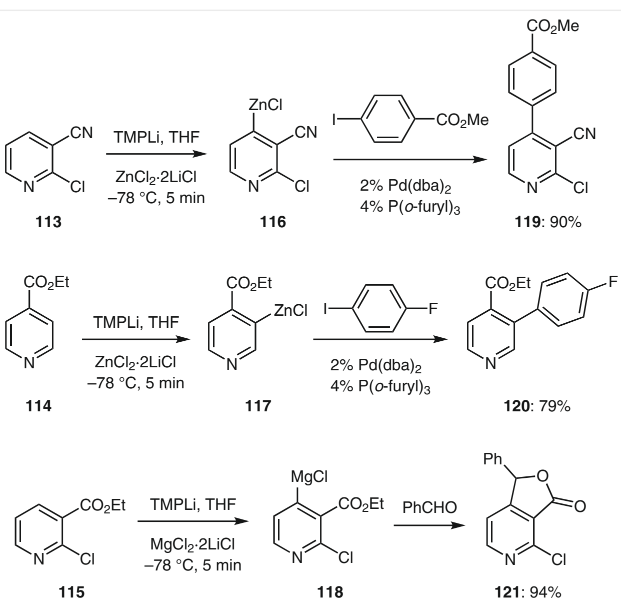
Scheme 20 Lateral zincation of a pyridine cyanohydrine **106** using TMP_2Zn·2LiCl·$2MgCl_2$ (**81**)

The scope of azine zincations has been extended by performing a Barbier type zincation in which the metalation is performed with TMPLi in the presence of $ZnCl_2$·2LiCl at low temperature. Thus, to a mixture of $ZnCl_2$·2LiCl and the substrate pyridine **109**, a THF solution of TMPLi (ca. 1.5 equiv) is added at –78 °C. Under these conditions, the directed lithiation of **109** is fast, producing the *ortho*-lithiated pyridine **110**, which is a highly reactive intermediate, that is transmetalated in situ with the soluble $ZnCl_2$·2LiCl, providing the stable pyridylzinc reagent **111**. Quenching with an electrophile (E-X) under appropriate reaction conditions furnishes then the functionalized pyridine **112** (Scheme 21).[53]



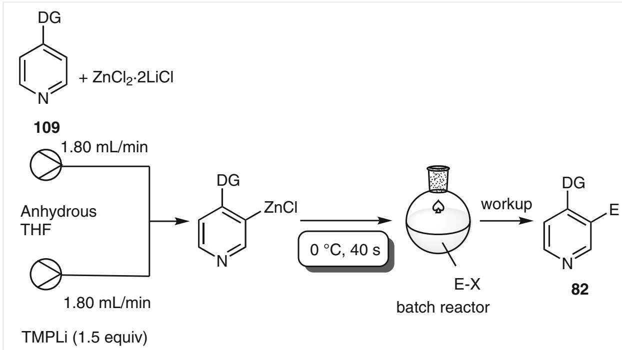
Scheme 21 Barbier type metalation of pyridine **81** using TMPLi in the presence of $ZnCl_2$·2LiCl

That such a Barbier reaction proceeds properly relies on the slow transmetalation between TMPLi and $ZnCl_2$·2LiCl at –78 °C. On the other hand, the directed lithiation and transmetalation steps are required to be fast.[53] This reaction setup has a good reaction scope and the functionalized pyridines **113–115** are smoothly metalated under these in situ trapping conditions, using either $ZnCl_2$·2LiCl or $MgCl_2$·2LiCl as trapping salts, providing the zincated pyridine derivatives **116–118**. After quenching with various electrophiles (aldehydes or aryl halides in the presence of a Pd-catalyst) the polyfunctionalized pyridines **119–121** are obtained in 79–94% yield (Scheme 22).[53]



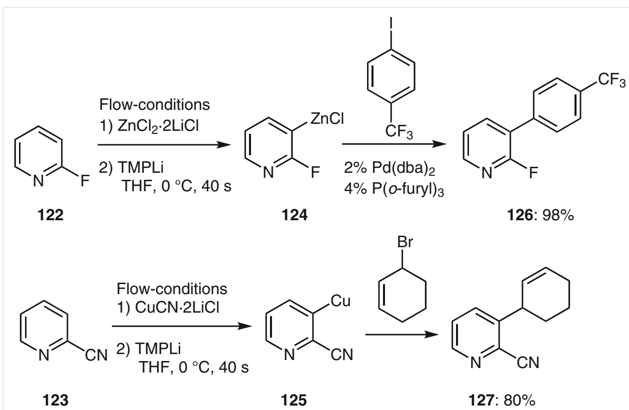
Scheme 22 In situ trapping metalations of polyfunctional pyridines **113–115**

The drawback of these metalations are the required low reaction temperatures. This problem was overcome by using a continuous-flow setup (Scheme 23).[7a] Thus, pyridine substrates bearing a directing group (DG) are mixed with a metallic salt ($ZnCl_2$·2LiCl; $MgCl_2$·2LiCl or CuCN·2LiCl), and added to a TMPLi solution in THF. These solutions were combined in a commercial flow setup from Uniqsis (1.80 mL/min) at 0 °C for 40 s. This continuous-flow setup has several advantages, such as enabling a reaction temperature of 0 °C and a short reaction time of 40 s. Also, the reaction can be readily scaled-up by pumping the solutions longer (Scheme 23).[7a]



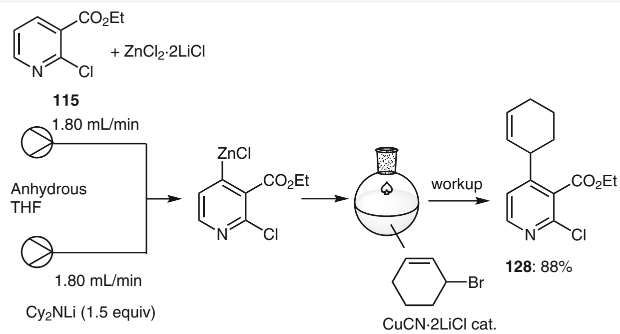
Scheme 23 Continuous-flow setup for in situ trapping metalations

By using this procedure, a range of pyridines such as **122–123** are readily functionalized via the intermediate organometallics **124–125** leading to the expected products **126–127** in 80–98% yield (Scheme 24).[7a]



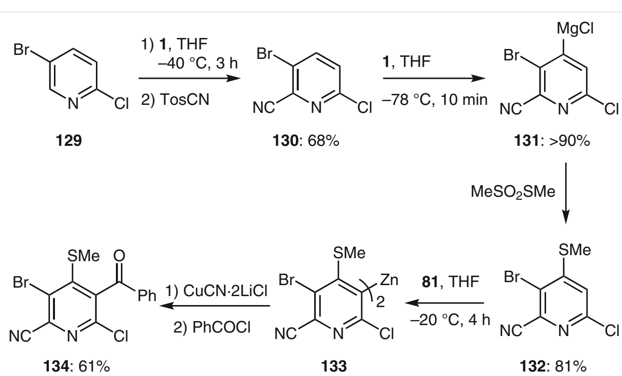
Scheme 24 Continuous-flow metalation of pyridines **122–123** using TMPLi in the presence of a metallic salt

In some cases, this procedure may be performed by replacing TMPLi with the 100 times cheaper lithium biscyclohexylamide (Cy_2NLi).[54] For example, the ethyl nicotinate **115** was metalated with Cy_2NLi (1.5 equiv) at 0 °C within 40 s and further allylated under copper(I)-catalysis in batch, leading to the pyridine **128** in 88% yield (Scheme 25).[54]



Scheme 25 Continuous-flow metalation of pyridine **115** in the presence of $ZnCl_2·2LiCl$ using Cy_2NLi as a cheap lithium amide

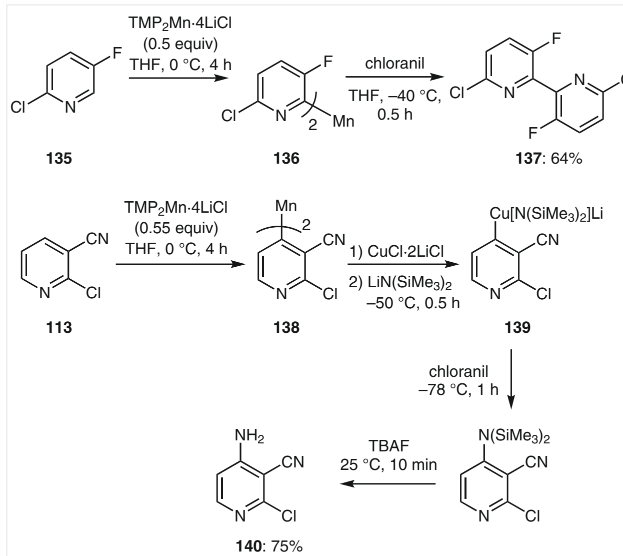
The combined use of TMP-zinc and magnesium bases (TMPMgCl·LiCl (**1**), TMPZnCl·LiCl (**80**) and $TMP_2Zn·2LiCl·2MgCl_2$ (**81**)) in several cases allows a full functionalization of the pyridine scaffold. Thus, the treatment of 5-bromo-2-chloropyridine (**129**) with TMPMgCl·LiCl (**1**) in THF (–40 °C, 3 h), followed by the addition of tosyl cyanide furnishes the regioselective product **130** in 68% yield.[42] Remarkably, the pyridine **130** is magnesiated at low temperature with TMPMgCl·LiCl (**1**), affording the 4-magnesiated pyridine **131**. The regioselectivity of this magnesiation may be explained by a preferential complexation of TMPMgCl·LiCl (**1**) to the bromo-substituent, triggering a metalation in position C4. Quenching with $MeSO_2SMe$ provides thioether **132** in 81% yield. The last metalation is best performed with $TMP_2Zn·2LiCl·2MgCl_2$ (**81**), leading to the bis-pyridylzinc **133**, which was transmetalated to the copper derivative with CuCN·2LiCl and benzoylated with PhCOCl, leading to the pentasubstituted pyridine **134** in 61% yield (Scheme 26).[42]



Scheme 26 Full functionalization of the pyridine scaffold

4 Metalation of Pyridines using other TMP-Bases

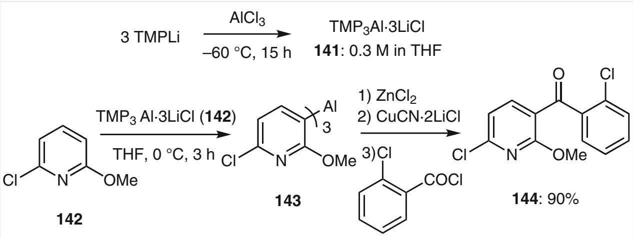
It should be mentioned that related TMP-amide base derivatives from manganese,[55] aluminum,[56] and lanthanum[57] have been reported. Thus, 2-chloro-5-fluoropyridine **135** can be treated with $TMP_2Mn·4LiCl_2$ (THF, 0 °C, 4 h), leading to the bis-pyridylmanganese species **136**. After the addition of chloranil (1 equiv) at –40 °C for 0.5 h, the bis-pyridine **137** is obtained in 64% yield.[55c] The reaction of the 3-cyanopyridine **113** with $TMP_2Mn·4LiCl$ (THF, 0 °C, 0.5 h) affords an intermediate manganese-species **138**, which, after transmetalation with CuCl·2LiCl, followed by the addition of $LiN(SiMe_3)_2$, leads to **139** and oxidative amination with chloranil gives the 4-aminopyridine **140** in 75% yield (Scheme 27).[55a]



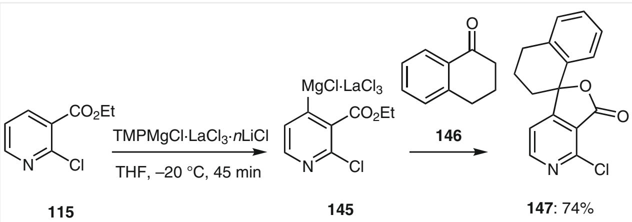
Scheme 27 Magnesiation of pyridine derivatives using $TMP_2Mn·4LiCl$

Aluminum-TMP amides have proven to be especially useful for the metalation of electron-rich pyridines. Thus, the treatment of TMPLi with $AlCl_3$ provides the corresponding $TMP_3Al·3LiCl$ base (**141**) as a 0.3 M solution in THF. This base readily aluminates the 2-methoxypyridine **142** leading to the tris-arylaluminum **143**, which provides, after transmetalation to zinc and to copper, and acylation, the expected ketone **144** in 90% yield (Scheme 28).[56]

The treatment of TMPMgCl·LiCl with $LaCl_3·2LiCl$[58,59] and its addition to a functionalized pyridine such as **115** leads to an organometallic intermediate best represented as **145**. From recent results,[59] the reagent **145** may be better represented as a magnesium reagent complexed with $LaCl_3$, rather than a true aryllanthanum species.[59] However, the reaction of **145** with the sterically hindered ketone **146** leads to the expected addition product **147** in 74% yield (Scheme 29).[57]



Scheme 28 Alumination of an electron-rich pyridine **142** using $TMP_3Al·3LiCl$ (**141**)



Scheme 29 Metalation of the functionalized pyridine **115** using $TMPMgCl·LaCl_3·n$LiCl

5 Magnesiation and Zincation of Diazines

Whereas the metalation of pyridines and quinolones is relatively well explored, the metalation of diazines such as pyrimidine (**148**), pyrazine (**149**), and pyridazine (**150**) is much less studied, and the functionalization of these *N*-heterocycles remains a challenge, as the predictability of the appropriate base for their metalation is still difficult (Figure 1).

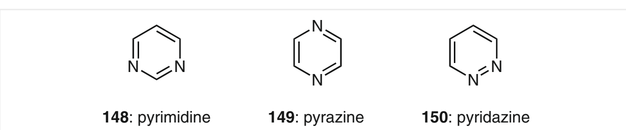
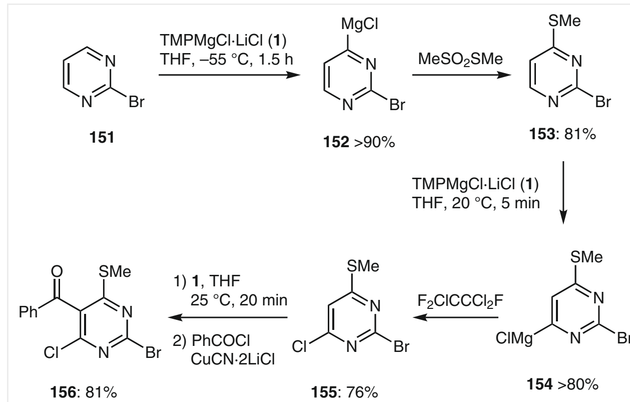


Figure 1 Diazine scaffolds

Nevertheless, the TMP-bases TMPMgCl·LiCl (**1**), $TMP_2Mg·2LiCl$ (**34**), TMPZnCl·LiCl (**80**) and $TMP_2Zn·2LiCl·2MgCl_2$ (**81**) have proven to be a set of very useful metalation reagents, especially well-suited for the functionalization of diazines and annulated analogues. These bases also constitute an automated strong base screening platform, as recently shown by Boga and Christensen.[60] Some recent applications are shown below, as well as guidelines for rationalizing the metalations of various diazines. Whereas pyrimidine itself has a high propensity to add magnesium nucleophiles, substituted pyrimidines are better substrates for metalations. Thus, 2-bromopyrimidine (**151**) undergoes a smooth magnesiation with TMPMgCl·LiCl (**1**) at –55 °C within 1.5 h and produces the 4-magnesiated pyrimidine **152** in >90% yield. After thiolation of **152** with $MeSO_2SMe$, the corresponding thioether **153** is obtained in 81% yield.[61,62] The methylthio substituent has a highly stabilizing effect and considerably stabilizes the pyrimidine towards unwanted nucleophilic additions. Thus, further magnesiation of **153** may now be performed at room temperature and the metalation is complete within 5 min, producing the magnesiated pyrimidine **154**, which, after chlorination, provides the trisubstituted pyrimidine **155** in 76% yield. The last position of the ring is magnesiated under similar conditions furnishing, after copper(I)-mediated benzoylation, the ketone **156** in 81% yield (Scheme 30).[61]

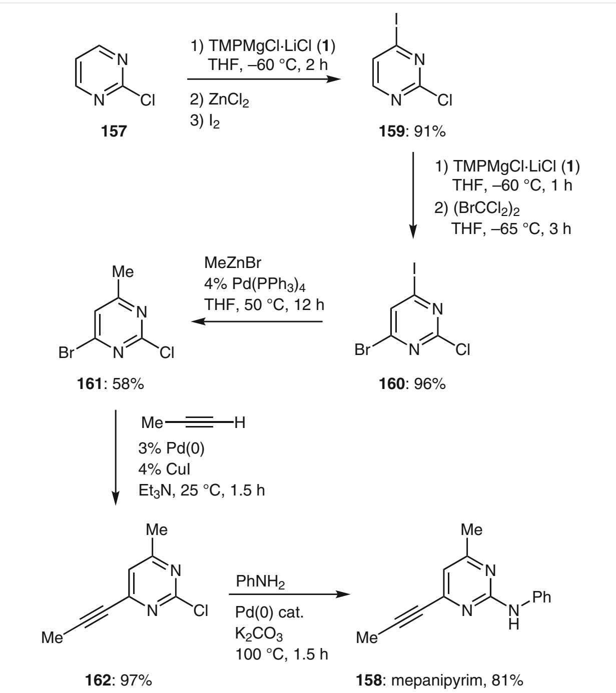


Scheme 30 Regioselective magnesiations of 2-bromopyrimidine (**151**) using TMPMgCl·LiCl (**1**)

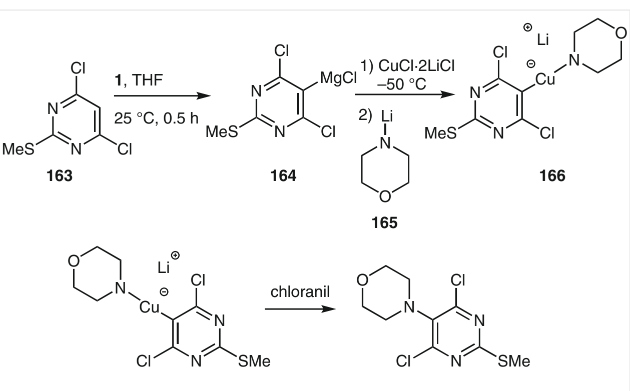
This methodology has been applied to the functionalization of 2-chloropyrimidine (**157**), providing a convenient synthesis of the fungicide mepanipyrim **158**.[63] Thus, the magnesiation of **157** at –60 °C is complete within 2 h using TMPMgCl·LiCl (**1**). Transmetalation with $ZnCl_2$ and iodolysis affords the bis-halogenated pyrimidine **159** in 91% yield. Subsequent magnesiation with TMPMgCl·LiCl (**1**; –60 °C, 1 h) followed by a bromination with 1,2-dibromotetrachloroethane affords the tri-halogenated pyrimidine **160** in almost quantitative yield (96%). Negishi cross-coupling of the most reactive iodine-substituent at **160** using MeZnBr furnishes the pyrimidine **161** in 58% yield. Sonogashira cross-coupling with propyne gives the alkynylpyrimidine **162** in 97% yield. Finally, Pd-catalyzed amination of **162** with aniline furnishes mepanipyrim **158** in 81% yield (Scheme 31).[63]

The amination of the pyrimidine scaffold can also be achieved using TMPMgCl·LiCl (**1**). Thus, the magnesiation of dichloropyrimidine **163** with **1** at 25 °C for 0.5 h produces the magnesium reagent **164**. Its transmetalation with CuCl·2LiCl followed by the addition of *N*-lithiomorpholine (**165**) leads to the lithium amidocuprate **166**, which, after oxidative amination using chloranil, leads to the 5-aminopyrimidine **167** in 68% yield (Scheme 32).[63,64]

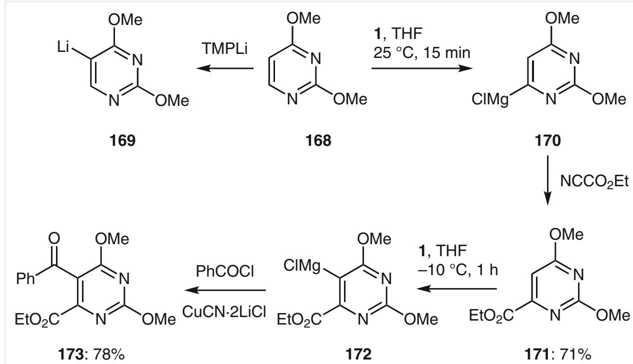
The regioselectivity of the metalation of uracil may be controlled by the bases used.[65–67] Thus, the deprotonation of 2,4-dimethoxypyrimidine **168** with TMPLi proceeds through precomplexation of the lithium base at oxygen and leads to an *ortho*-lithiation (**169**). On the other hand, magnesiation with TMPMgCl·LiCl (**1**) in THF is triggered by a complexation of the magnesium base **1** at the heterocyclic *N*-atom and therefore leads to a magnesiation at the *ortho*-position to nitrogen, providing the magnesium derivative **170**.[57] After quenching with ethyl cyanoformate, the uracil **171** is obtained in 71% yield. Subsequent magnesiation leads to **172** and a copper(I)-mediated benzoylation gives ketone **173** in 78% yield (Scheme 33).[67,68]



Scheme 31 Synthesis of the fungicide mepanipyrim **158** starting from 2-chloropyrimidine (**157**) using TMPMgCl·LiCl (**1**)

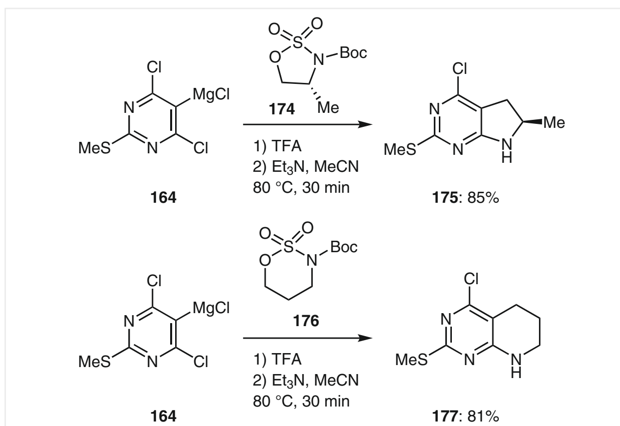


Scheme 32 Amination of the pyrimidine scaffold using TMPMgCl·LiCl (**1**)



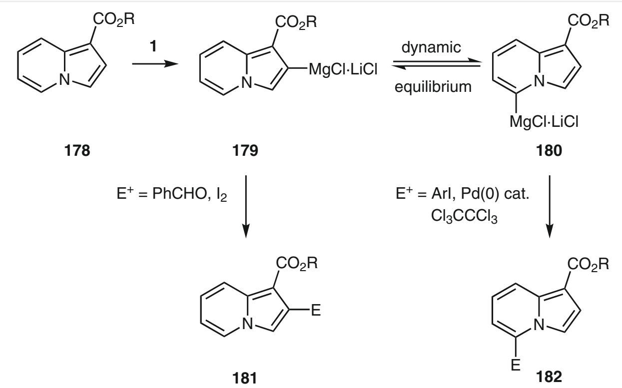
Scheme 33 Selective magnesiation of the protected uracil **168** using TMPMgCl·LiCl (**1**)

The magnesiation of dichloropyrimidine **163** (25 °C, 0.5 h) with TMPMgCl·LiCl (**1**) provides the magnesium derivative **164** as shown in Scheme 32. Its treatment with chiral sulfamidate **174** for 1 h at 25 °C followed by acidification with trifluoroacetic acid (TFA) and heating with Et_3N (4 equiv) in MeCN for 0.5 h at 80 °C leads to the chiral heterocycle **175** in 85% yield. Using the sulfamidate **176** provides tetrahydropyridopyrimidine **177**, which is a precursor for various unsaturated heterocycles (Scheme 34).[69]



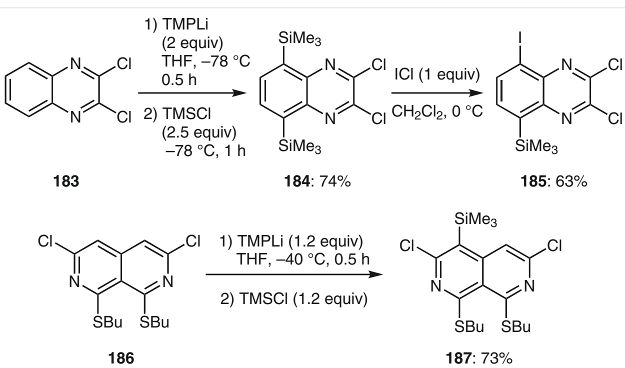
Scheme 34 Preparation of annulated pyrimidine **175** and **177**

The use of magnesium intermediates in some cases leads to rearrangements,[70,71] as shown by the magnesiation of indolizine **178** using TMPMgCl·LiCl (**1**) at 25 °C for 1 h. Under these conditions, a dynamic equilibrium between the two isomeric magnesium species **179** and **180** is observed. Whereas more reactive electrophiles such as iodine and aldehydes provide the products of type **181**, less reactive electrophiles such as Cl_3CCCl_3 or a Negishi cross-coupling provide products of type **182** (Scheme 35).[70]



Scheme 35 Electrophile controlled regioselectivity in the functionalization of indolizine **178** using TMPMgCl·LiCl (**1**)

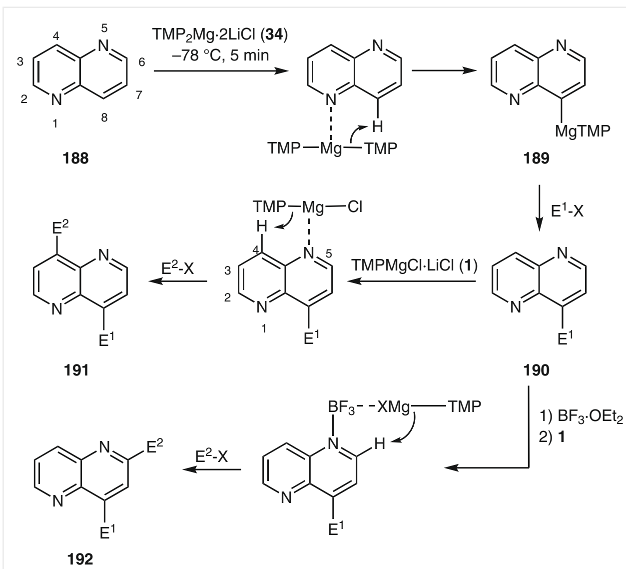
An in situ trapping procedure in several cases avoids side-reactions and provides high yields of products. Thus, the functionalization of the quinoxaline scaffold is possible using TMPLi. The treatment of dichloroquinoxaline **183** with TMPLi (2.4 equiv) in the presence of an excess of TMS-Cl furnishes the bis-silyl derivative **184** in 74% yield. After the addition of ICl (1 equiv) the mono-iodinated quinoxaline derivative **185** is obtained in 63% yield.[72] Similarly, the 2,7-naphthyridine **186** can be converted into silyl derivative **187** in 73% yield (Scheme 36).[73]



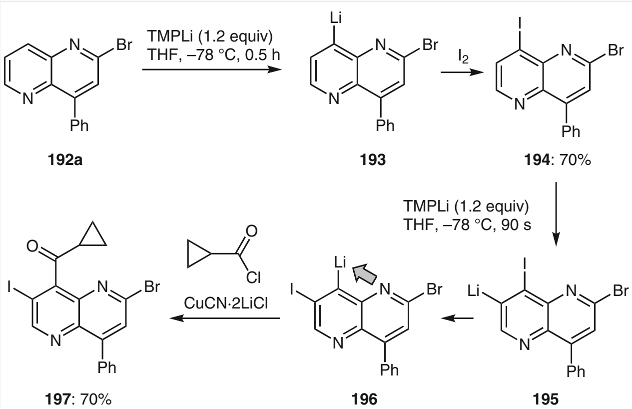
Scheme 36 Functionalization of quinoxalines and 2,7-naphthyridines using TMPLi

The 1,5-naphthyridine scaffold (**188**) has been examined in more detail. Complexation of $TMP_2Mg\cdot 2LiCl$ (**34**) to the nitrogen-atom N1 of **188** leads to a selective metalation in position C8. This magnesiation has to be performed at –78 °C (for 5 min) to avoid decomposition of the metalated species. The resulting magnesium species **189** can be functionalized with various electrophiles E^1-X providing products of type **190**. The mono-substituted naphthyridines **190** can be regioselectively functionalized using either TMPMgCl·LiCl (**1**) or the combination of **1** and $BF_3\cdot OEt_2$. In the first case, complexation of the base **1** occurs at the sterically most accessible N5, leading to a magnesiation and thus functionalization at position C4 (**191**).

On the other hand, the addition of $BF_3\cdot OEt_2$ prior to the addition of **1** blocks a complexation of the magnesium base at N5 and, since N1 is also inaccessible due to the substituent E^1, leads to a complexation of **1** to the BF_3 unit and a deprotonation of the most acidic hydrogen at position C6. After quenching with an electrophile E^2-X the disubstituted 1,5-naphthyridine **192** is obtained (Scheme 37).[74] The products of type **192** may be further metalated, although a very strong lithium base (TMPLi) is required. Thus, the reaction of **192a** with TMPLi at –78 °C for 0.5 h provides the lithium intermediate **193**, which is trapped with iodine, furnishing the adduct **194** in 70% yield. The use of TMPLi also allows a fourth functionalization and the reaction of **194** with TMPLi at –78 °C for 90 s (!) leads to an *ortho*-lithiation, providing the lithium reagent **195**, which gives the more stable lithium derivative **196** through an intramolecular iodine–lithium exchange. After quenching with an electrophile such as an acid chloride in the presence of stoichiometric amounts of CuCN·2LiCl, the corresponding ketone **197** is obtained in 70% yield (Scheme 38).[74] This methodology can be applied for the synthesis of an antibacterial agent such as **198**. Thus, the magnesiation of 1,5-naphthyridine **188** with $TMP_2Mg\cdot 2LiCl$ (**34**) from –40 to –20 °C for 4 h, followed by a transmetalation with $ZnCl_2$ and Pd(0)-catalyzed cross-coupling with 4-*tert*-butylphenyl iodide, provides the arylated naphthyridine **199** in 88% yield. TMPLi-lithiation at position C4 followed by a methylation with methyl triflate affords the disubstituted naphthyridine **200** in 53% yield. This naphthyridine can be converted into the antibacterial drug candidate **198** (Scheme 39).[74,75]



Scheme 37 Regioselective magnesiation and functionalization of 1,5-naphthyridines using $TMP_2Mg\cdot 2LiCl$ (**34**) and TMPMgCl·LiCl (**1**) in the presence or absence of $BF_3\cdot OEt_2$

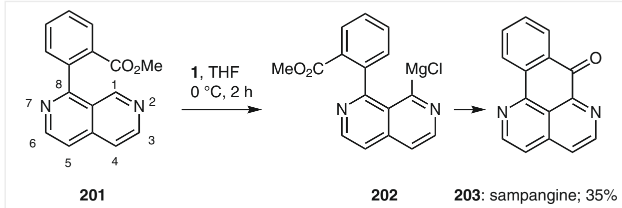


Scheme 38 Tri- and tetra-functionalization of 1,5-naphthyridines using TMPLi

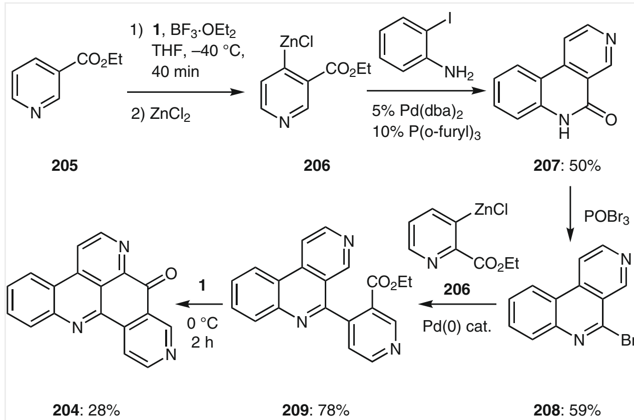
TMPMgCl·LiCl (**1**) can be used to magnesiate highly functionalized 2,7-naphthyridines such as **201**. Thus, the treatment of **201** triggered by a coordination at N2, affords the magnesium derivative **202**, which undergoes an intramolecular addition to the carbethoxy function, providing the alkaloid sampangine **203** in 35% yield (Scheme 40).[76]

Bracher has extended this strategy to a marine pyridoacridine alkaloid demethyldeoxyamphimedine (**204**). Thus, the magnesiation of ethyl nicotinate **205** with TMPMgCl·LiCl (**1**) in the presence of BF_3·OEt_2, followed by transmetalation with $ZnCl_2$, furnishes the zinc reagent **206**, which, after cross-coupling with 2-iodoaniline in the presence of a palladium-catalyst, furnishes the lactam **207** in 50% yield. Conversion into the corresponding bromide **208** using $POBr_3$, followed by a second cross-coupling with the zincated ethyl nicotinate **206**, produces the naphthyridine **209** in 78% yield. Cyclization of **209** with TMPMgCl·LiCl (**1**) furnishes the desired marine pyridoacridine alkaloid **204** in 28% yield (Scheme 41).[77]

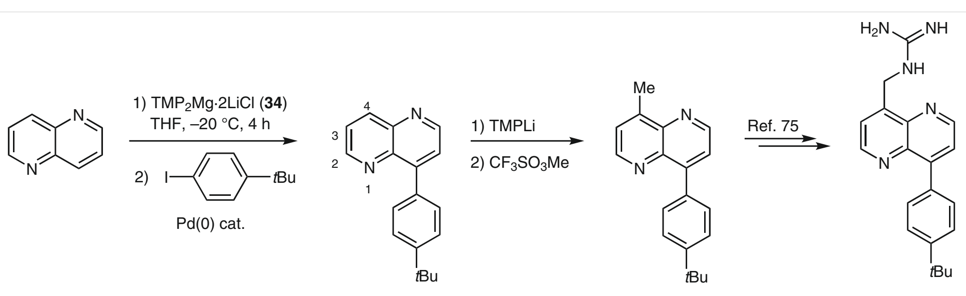
The metalation of the cinnoline scaffold (**210**) can also be realized using TMP_2Mg·2LiCl (**34**). Thus, the reaction of **210** first with BF_3·OEt_2, followed by the addition of TMP_2Mg·2LiCl (**34**) at –78 °C for 10 min, leads to a regioselective magnesiation at C3. This regioselectivity can be explained by assuming that BF_3·OEt_2 complexes at the most readily available nitrogen N2 and that TMP_2Mg·2LiCl coordinates at BF_3 leading to a metalation at C3 (see **211**). After Pd(0)-catalyzed cross-couplings, the desired arylated products of type **212** are obtained. Alternatively, the metalation of **210** with TMP_2Zn·2LiCl·2$MgCl_2$ (**49**) in the presence of $MgCl_2$ leads to a preferential complexation at N1 of the base and at N2 of $MgCl_2$, favoring a zincation at C8 via a transition state of type **213**. After palladium-catalyzed arylation with various aryl iodides, 8-arylated cinnolines of type **214** are obtained (Scheme 42).[78]



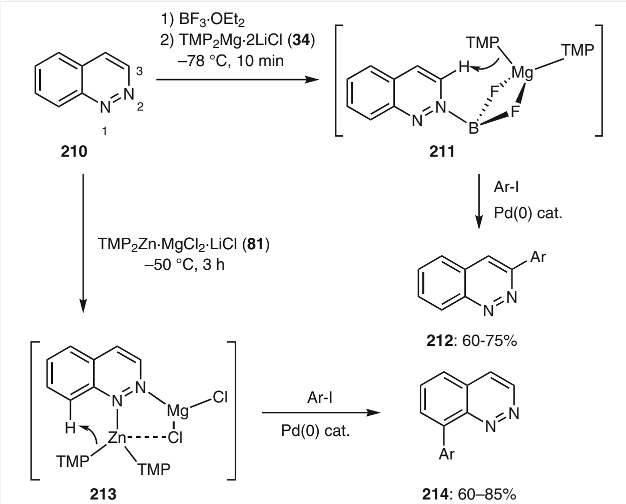
Scheme 40 TMPMgCl·LiCl (**1**) magnesiation of the 2,7-naphthyridine **201** leading to the alkaloid sampangine **203**



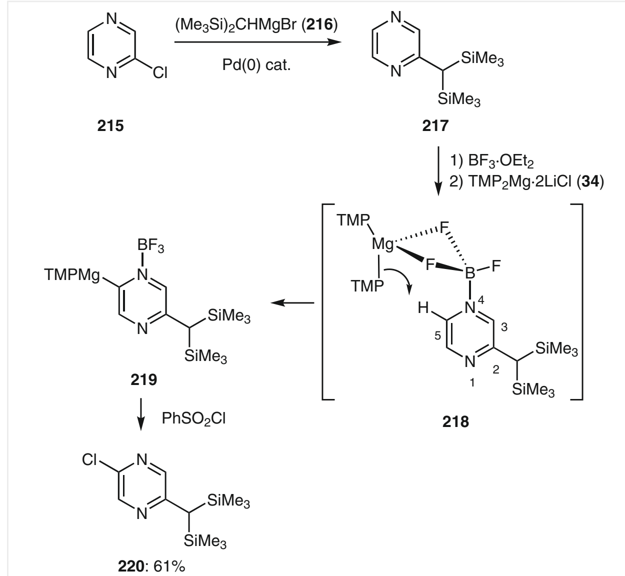
Scheme 41 Preparation of the alkaloid demethyldeoxyamphimedine **204** using TMPMgCl·LiCl (**1**)



Scheme 39 Preparation of the antibacterial agent **198** through successive metalations of 1,5-naphthyridine **188**



Scheme 42 Regioselective metalation of the cinnoline scaffold using $TMP_2Mg{\cdot}2LiCl$ (**34**) and $TMP_2Zn{\cdot}2LiCl{\cdot}2MgCl_2$ (**81**)

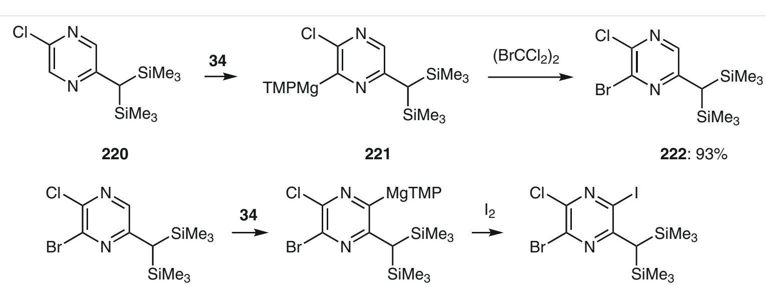


Scheme 43 Regioselective functionalization of the pyrazine scaffold

As shown above, the presence or absence of a Lewis acid such as $BF_3{\cdot}OEt_2$ or $MgCl_2$ is essential for achieving a high regioselectivity in metalations with TMP-bases. This has been demonstrated for various heterocyclic metalations.[79–81] Especially relevant in the frame of this review is the regioselective metalation of the pyrazine scaffold. Thus, the introduction of a bulky bis-trimethylsilylmethyl-substituent to the pyrazine core is readily realized by treating chloropyrazine **215** with the magnesium reagent **216**. The resulting silyl-substituted pyrazine **217** proved to be difficult to magnesiate using TMP-magnesium bases such as **1** or **34**. However, a precomplexation with $BF_3{\cdot}OEt_2$ sufficiently acidifies the ring hydrogen atoms, allowing a regioselective metalation at the least sterically hindered position at C5 (see **218**, Scheme 43).[81]

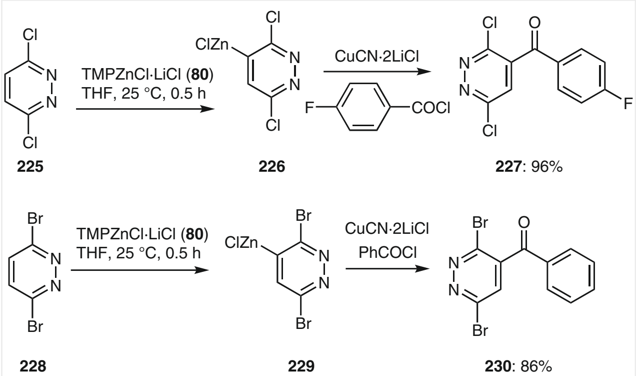
The resulting magnesium reagent **219** reacts with various electrophiles. Chlorination with $PhSO_2Cl$ provides the chloropyrazine **220** in 61% yield. This pyrazine is readily magnesiated in a subsequent step. Remarkably, the inductive effect of the chlorine substituent is sufficient for a magnesiation to be achieved with $TMP_2Mg{\cdot}2LiCl$ (**34**) in the absence of $BF_3{\cdot}OEt_2$. The resulting magnesiated pyrazine **221** can be brominated with 1,2-dibromotetrachloroethane providing the bis-halogenated pyrazine **222** in 93% yield. Finally, the last ring hydrogen of **222** can again be metalated with $TMP_2Mg{\cdot}2LiCl$ (**34**), leading to the magnesium species **223**, which, after iodolysis, provides the tri-halogenated pyrazine **224** in 83% yield (Scheme 44).[81]

The metalation of the pyrazine and the pyridazine scaffolds remains a challenge and usually quite strong bases are required for these metalations. Especially for the pyridazine scaffold, either yields are low or the electrophile scope is narrow.[8f,9a] The presence of two chlorine substituents in 3,6-dichloropyrazine **225** facilitates the metalation and now $TMP_2Zn{\cdot}2LiCl{\cdot}2MgCl_2$ (**81**) leads to a zincation at –78 °C.[82] Also, a more convenient zincation of pyridazine **225** can be realized at 25 °C with $TMPZnCl{\cdot}LiCl$ (**80**). The resulting zinc reagent **226** can be acylated after a transmetalation with $CuCN{\cdot}2LiCl$, leading to the corresponding ketone **227** (Scheme 45).[45] Similarly, the corresponding dibromopyridazine **228** is zincated with $TMPZnCl{\cdot}LiCl$ (**80**) under the same conditions, furnishing the zincated heterocycle



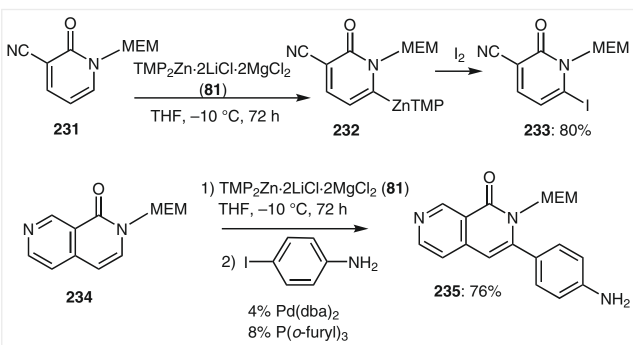
Scheme 44 Successive magnesiation of the pyrazine scaffold using $TMP_2Mg{\cdot}2LiCl$ (**34**)

229, which is benzoated, after transmetalation with CuCN·2LiCl, leading to the ketone **230** in 86% yield (Scheme 45).[46,83]



Scheme 45 Zincations of the halogenopyridazines **225** and **228**

Finally, zinc-TMP-bases are especially efficient for the zincation of 2-pyridones and 2,7-naphthyridones. Thus, treatment of functionalized 2-pyridone **231** with $TMP_2Zn·2LiCl$ (**81**) at –10 °C for 72 h leads to the zincated pyridone **232**, which, after iodolysis, affords the iodopyridone **233** in 80% yield. Similarly, naphthyridone **234** is zincated regioselectively and Pd-catalyzed cross-coupling with 4-iodoaniline provides the cross-coupling product **235** in 76% yield (Scheme 46).[84]



Scheme 46 Functionalization of 2-pyridones and 2-naphthyridones using $TMP_2Zn·2LiCl·2MgCl_2$ (**81**)

6 Conclusion

The functionalization of azines and diazines is an important task for pharmaceutical and agro-chemical research. Herein, we have summarized recent developments in the field of azine metalation using TMPMgCl·LiCl (**1**), $TMP_2Mg·2LiCl$ (**34**), TMPZnCl·LiCl (**80**), and $TMP_2Zn·2LiCl·2MgCl_2$ (**81**), and have shown that they are excellent bases for the functionalization of *N*-heterocycles. The additional use of $BF_3·OEt_2$ or $MgCl_2$ as Lewis acids considerably expands the scope of these bases. Furthermore, the performance of such metalations not in batch, but in continuous flow, allows further tuning of the reaction conditions, so that more convenient reaction temperatures and short reaction times can be achieved. In the future, the combination of these methods will certainly facilitate the functionalization of diazines and benzo-analogues further, since this research is still in its infancy.

Funding Information

We would like to thank the DFG (SFB749) for financial support

Acknowledgment

We would like to thank Albemarle (Hoechst, Germany) for the generous donation of chemicals.

References

(1) (a) Li, X.-Q.; Andersson, T. B.; Ahlström, M.; Weidolf, L. *Drug Metab. Dispos.* **2004**, *32*, 821. (b) Manolikakes, S. M.; Barl, N. M.; Sämann, C.; Knochel, P. *Z. Naturforsch., B* **2013**, *68*, 411. (c) Lamberth, C. *Pest Manage. Sci.* **2013**, *69*, 1106. (d) Dinesh, K.; Subheet, K. J. *Curr. Med. Chem.* **2016**, *23*, 4338. (e) Taylor, A. P.; Robinson, R. P.; Fobian, Y. M.; Blakemore, D. C.; Jones, L. H.; Fadeyi, O. *Org. Biomol. Chem.* **2016**, *14*, 6611.

(2) (a) Beak, P.; Snieckus, V. *Acc. Chem. Res.* **1982**, *15*, 306. (b) Snieckus, V. *Chem. Rev.* **1990**, *90*, 879. (c) Alessi, M.; Larkin, A. L.; Ogilvie, K. A.; Green, L. A.; Lai, S.; Lopez, S.; Snieckus, V. *J. Org. Chem.* **2007**, *72*, 1588. (d) Schneider, C.; Broda, E.; Snieckus, V. *Org. Lett.* **2011**, *13*, 3588. (e) Board, J.; Cosman, J. L.; Rantanen, T.; Singh, S. P.; Snieckus, V. *Platinum Met. Rev.* **2013**, *57*, 234.

(3) (a) Schlosser, M.; Jung, H. C.; Takagishi, S. *Tetrahedron* **1990**, *46*, 5633. (b) Marzi, E.; Bigi, A.; Schlosser, M. *Eur. J. Org. Chem.* **2001**, 1371. (c) Schlosser, M. *Eur. J. Org. Chem.* **2001**, 3975. (d) Schlosser, M.; Rausis, T. *Eur. J. Org. Chem.* **2004**, 1018. (e) Schlosser, M. *Angew. Chem. Int. Ed.* **2005**, *44*, 376.

(4) (a) Marsais, F.; Queguiner, G. *Tetrahedron* **1983**, *39*, 2009. (b) Trécourt, F.; Mallet, M.; Marsais, F.; Queguiner, G. *J. Org. Chem.* **1988**, *53*, 1367. (c) Rocca, P.; Cochennec, C.; Marsais, F.; Thomas-dit-Dumont, L.; Mallet, M.; Godard, A.; Queguiner, G. *J. Org. Chem.* **1993**, *58*, 7832. (d) Trécourt, F.; Mallet, M.; Mongin, O.; Gervais, B.; Quéguiner, G. *Tetrahedron* **1993**, *49*, 8373. (e) Gros, P.; Fort, Y.; Queguiner, G.; Caubère, P. *Tetrahedron Lett.* **1995**, *36*, 4791. (f) Cochennec, C.; Rocca, P.; Marsais, F.; Godard, A.; Quéguiner, G. *Synthesis* **1995**, 321. (g) Arzel, E.; Rocca, P.; Marsais, F.; Godard, A.; Quéguiner, G. *Tetrahedron Lett.* **1998**, *39*, 6465. (h) Mongin, F.; Quéguiner, G. *Tetrahedron* **2001**, *57*, 4059. (i) Turck, A.; Plé, N.; Mongin, F.; Quéguiner, G. *Tetrahedron* **2001**, *57*, 4489. (j) Awad, H.; Mongin, F.; Trécourt, F.; Quéguiner, G.; Marsais, F. *Tetrahedron Lett.* **2004**, *45*, 7873.

(5) (a) Chevallier, F.; Mongin, F. *Chem. Soc. Rev.* **2008**, *37*, 595. (b) Tilly, D.; Chevallier, F.; Mongin, F.; Gros, P. C. *Chem. Rev.* **2014**, *114*, 1207.

(6) Gros, P. C.; Fort, Y. *Eur. J. Org. Chem.* **2009**, 4199.

(7) (a) Becker, M. R.; Knochel, P. *Angew. Chem. Int. Ed.* **2015**, *54*, 12501. (b) Ketels, M.; Konrad, D. B.; Karaghiosoff, K.; Trauner, D.; Knochel, P. *Org. Lett.* **2017**, *19*, 1666.

(8) (a) Mulvey, R. E. *Organometallics* **2006**, *25*, 1060. (b) Mulvey, R. E.; Mongin, F.; Uchiyama, M.; Kondo, Y. *Angew. Chem. Int. Ed.* **2007**, *46*, 3802. (c) Mulvey, R. E. *Acc. Chem. Res.* **2009**, *42*, 743. (d) Armstrong, D. R.; Kennedy, A. R.; Mulvey, R. E.; Parkinson, J. A.; Robertson, S. D. *Chem. Sci.* **2012**, *3*, 2700. (e) Mulvey, R. E. *Dalton Trans.* **2013**, 6676. (f) Uzelac, M.; Kennedy, A. R.; Hevia, E.; Mulvey, R. E. *Angew. Chem. Int. Ed.* **2016**, *55*, 13147.

(9) (a) Seggio, A.; Chevallier, F.; Vaultier, M.; Mongin, F. *J. Org. Chem.* **2007**, *72*, 6602. (b) L'Helgoual'ch, J.-M.; Bentabed-Ababsa, G.; Chevallier, F.; Yonehara, M.; Uchiyama, M.; Derdour, A.; Mongin, F. *Chem. Commun.* **2008**, 5375. (c) Bentabed-Ababsa, G.; Blanco, F.; Derdour, A.; Mongin, F.; Trécourt, F.; Quéguiner, G.; Ballesteros, R.; Abarca, B. *J. Org. Chem.* **2009**, *74*, 163. (d) Nguyen, T. T.; Chevallier, F.; Jouikov, V.; Mongin, F. *Tetrahedron Lett.* **2009**, *50*, 6787. (e) Snégaroff, K.; L'Helgoual'ch, J.-M.; Bentabed-Ababsa, G.; Nguyen, T. T.; Chevallier, F.; Yonehara, M.; Uchiyama, M.; Derdour, A.; Mongin, F. *Chem. Eur. J.* **2009**, *15*, 10280. (f) Dayaker, G.; Chevallier, F.; Gros, P. C.; Mongin, F. *Tetrahedron* **2010**, *66*, 8904. (g) Snégaroff, K.; Komagawa, S.; Chevallier, F.; Gros, P. C.; Golhen, S.; Roisnel, T.; Uchiyama, M.; Mongin, F. *Chem. Eur. J.* **2010**, *16*, 8191. (h) Nguyen, T. T.; Marquise, N.; Chevallier, F.; Mongin, F. *Chem. Eur. J.* **2011**, *17*, 10405. (i) Nagaradja, E.; Chevallier, F.; Roisnel, T.; Jouikov, V.; Mongin, F. *Tetrahedron* **2012**, *68*, 3063. (j) Kadiyala, R. R.; Tilly, D.; Nagaradja, E.; Roisnel, T.; Matulis, V. E.; Ivashkevich, O. A.; Halauko, Y. S.; Chevallier, F.; Gros, P. C.; Mongin, F. *Chem. Eur. J.* **2013**, *19*, 7944. (k) Marquise, N.; Harford, P. J.; Chevallier, F.; Roisnel, T.; Dorcet, V.; Gagez, A.-L.; Sablé, S.; Picot, L.; Thiéry, V.; Wheatley, A. E. H.; Gros, P. C.; Mongin, F. *Tetrahedron* **2013**, *69*, 10123. (l) Harford, P. J.; Peel, A. J.; Chevallier, F.; Takita, R.; Mongin, F.; Uchiyama, M.; Wheatley, A. E. H. *Dalton Trans.* **2014**, 14181. (m) Marquise, N.; Bretel, G.; Lassagne, F.; Chevallier, F.; Roisnel, T.; Dorcet, V.; Halauko, Y. S.; Ivashkevich, O. A.; Matulis, V. E.; Gros, P. C.; Mongin, F. *RSC Adv.* **2014**, *4*, 19602. (n) Messaoud, M. Y. A.; Bentabed-Ababsa, G.; Hedidi, M.; Derdour, A.; Chevallier, F.; Halauko, Y. S.; Ivashkevich, O. A.; Matulis, V. E.; Picot, L.; Thiéry, V.; Roisnel, T.; Dorcet, V.; Mongin, F. *Beilstein J. Org. Chem.* **2015**, *11*, 1475. (o) Nagaradja, E.; Bentabed-Ababsa, G.; Scalabrini, M.; Chevallier, F.; Philippot, S.; Fontanay, S.; Duval, R. E.; Halauko, Y. S.; Ivashkevich, O. A.; Matulis, V. E.; Roisnel, T.; Mongin, F. *Bioorg. Med. Chem.* **2015**, *23*, 6355. (p) Hedidi, M.; Bentabed-Ababsa, G.; Derdour, A.; Halauko, Y. S.; Ivashkevich, O. A.; Matulis, V. E.; Chevallier, F.; Roisnel, T.; Dorcet, V.; Mongin, F. *Tetrahedron* **2016**, *72*, 2196. (q) Hedidi, M.; Erb, W.; Lassagne, F.; Halauko, Y. S.; Ivashkevich, O. A.; Matulis, V. E.; Roisnel, T.; Bentabed-Ababsa, G.; Mongin, F. *RSC Adv.* **2016**, *6*, 63185. (r) Peel, A. J.; Hedidi, M.; Bentabed-Ababsa, G.; Roisnel, T.; Mongin, F.; Wheatley, A. E. H. *Dalton Trans.* **2016**, 6094.

(10) (a) Kondo, Y.; Shilai, M.; Uchiyama, M.; Sakamoto, T. *J. Am. Chem. Soc.* **1999**, *121*, 3539. (b) Imahori, T.; Uchiyama, M.; Sakamoto, T.; Kondo, Y. *Chem. Commun.* **2001**, 2450. (c) Uchiyama, M.; Miyoshi, T.; Kajihara, Y.; Sakamoto, T.; Otani, Y.; Ohwada, T.; Kondo, Y. *J. Am. Chem. Soc.* **2002**, *124*, 8514. (d) Tezuka, N.; Shimojo, K.; Hirano, K.; Komagawa, S.; Yoshida, K.; Wang, C.; Miyamoto, K.; Saito, T.; Takita, R.; Uchiyama, M. *J. Am. Chem. Soc.* **2016**, *138*, 9166.

(11) Imahori, T.; Kondo, Y. *J. Am. Chem. Soc.* **2003**, *125*, 8082.

(12) (a) Haag, B.; Mosrin, M.; Ila, H.; Malakhov, V.; Knochel, P. *Angew. Chem. Int. Ed.* **2011**, *50*, 9794. (b) Krasovskiy, A.; Krasovskaya, V.; Knochel, P. *Angew. Chem. Int. Ed.* **2006**, *45*, 2958. (c) Klatt, T.; Markiewicz, J. T.; Sämann, C.; Knochel, P. *J. Org. Chem.* **2014**, *79*, 4253.

(13) García-Álvarez, P.; Graham, D. V.; Hevia, E.; Kennedy, A. R.; Klett, J.; Mulvey, R. E.; O'Hara, C. T.; Weatherstone, S. *Angew. Chem. Int. Ed.* **2008**, *47*, 8079.

(14) Wunderlich, S.; Knochel, P. *Org. Lett.* **2008**, *10*, 4705.

(15) For recent reviews on C–H activation, see: (a) Chen, Z.; Wang, B.; Zhang, J.; Yu, W.; Liu, Z.; Zhang, Y. *Org. Chem. Front.* **2015**, *2*, 1107. (b) Crabtree, R. H.; Lei, A. *Chem. Rev.* **2017**, *117*, 8481. (c) Murakami, K.; Yamada, S.; Kaneda, T.; Itami, K. *Chem. Rev.* **2017**, *117*, 9302.

(16) For previous reviews, see: (a) Bresser, T.; Mosrin, M.; Monzon, G.; Knochel, P. *J. Org. Chem.* **2010**, *75*, 4686. (b) Knochel, P.; Schade, M. A.; Bernhardt, S.; Manolikakes, G.; Metzger, A.; Piller, F. M.; Rohbogner, C. J.; Mosrin, M. *Beilstein J. Org. Chem.* **2011**, *7*, 1261. (c) Manolikakes, S. M.; Barl, N. M.; Sämann, C.; Knochel, P. *Z. Naturforsch., B* **2013**, *68*, 411. (d) Klatt, T.; Markiewicz, J. T.; Sämann, C.; Knochel, P. *J. Org. Chem.* **2014**, *79*, 4253.

(17) (a) Hauser, C. R.; Walker, H. G. *J. Am. Chem. Soc.* **1947**, *69*, 295. (b) Henderson, K. W.; Kerr, W. J. *Chem. Eur. J.* **2001**, *7*, 3430. (c) Eaton, P. E.; Xiong, Y.; Gilardi, R. *J. Am. Chem. Soc.* **1993**, *115*, 10195. (d) Eaton, P. E.; Lukin, K. A. *J. Am. Chem. Soc.* **1993**, *115*, 11370. (e) Zhang, M.-X.; Eaton, P. E. *Angew. Chem. Int. Ed.* **2002**, *41*, 2169.

(18) (a) Schlecker, W.; Huth, A.; Ottow, E.; Mulzer, J. *J. Org. Chem.* **1995**, *60*, 8414. (b) Schlecker, W.; Huth, A.; Ottow, E.; Mulzer, J. *Liebigs Ann.* **1995**, 1441. (c) Schlecker, W.; Huth, A.; Ottow, E.; Mulzer, J. *Synthesis* **1995**, 1225.

(19) (a) Gribble, G. W.; Saulnier, M. G. *Tetrahedron Lett.* **1980**, *21*, 4137. (b) Verbeek, J.; Brandsma, L. *J. Org. Chem.* **1984**, *49*, 3857. (c) Verbeek, J.; George, A. V. E.; de Jong, R. L. P.; Brandsma, L. *J. Chem. Soc., Chem. Commun.* **1984**, 257. (d) Subota, A. I.; Grygorenko, O. O.; Valter, Y. B.; Tairov, M. A.; Artamonov, O. S.; Volochnyuk, D. M.; Ryabukhin, S. V. *Synlett* **2015**, *26*, 408.

(20) In the case of a stabilized pyridine such as 2-methoxy pyridine, higher temperatures are possible, see: (a) Trecourt, F.; Mallet, M.; Marsais, F.; Queguiner, G. *J. Org. Chem.* **1988**, *53*, 1367. (b) Khartabil, H. K.; Gros, P. C.; Fort, Y.; Ruiz-López, M. F. *J. Am. Chem. Soc.* **2010**, *132*, 2410; and ref. 4d.

(21) Boudet, N.; Lachs, J. R.; Knochel, P. *Org. Lett.* **2007**, *9*, 5525.

(22) Wunderlich, S. H.; Rohbogner, C. J.; Unsinn, A.; Knochel, P. *Org. Process Res. Dev.* **2010**, *14*, 339.

(23) Negishi, E. *Acc. Chem. Res.* **1982**, *15*, 340.

(24) Haas, D.; Hammann, J. M.; Greiner, R.; Knochel, P. *ACS Catal.* **2016**, *6*, 1540.

(25) Monzón, G.; Tirotta, I.; Nishii, Y.; Knochel, P. *Angew. Chem. Int. Ed.* **2012**, *51*, 10624.

(26) (a) Ogawa, S.; Furukawa, N. *J. Org. Chem.* **1991**, *56*, 5723. (b) Capozzi, M. A. M.; Cardellicchio, C.; Naso, F.; Spina, G.; Tortorella, P. *J. Org. Chem.* **2001**, *66*, 5933.

(27) (a) Rauhut, C. B.; Melzig, L.; Knochel, P. *Org. Lett.* **2008**, *10*, 3891. (b) Melzig, L.; Rauhut, C. B.; Knochel, P. *Synthesis* **2009**, 1041. (c) Melzig, L.; Rauhut, C. B.; Knochel, P. *Chem. Commun.* **2009**, 3536.

(28) Melzig, L.; Rauhut, C. B.; Naredi-Rainer, N.; Knochel, P. *Chem. Eur. J.* **2011**, *17*, 5362.

(29) MacNeil, S. L.; Familoni, O. B.; Snieckus, V. *J. Org. Chem.* **2001**, *66*, 3662.

(30) Balkenhohl, M.; François, C.; Sustac, R. D.; Quinio, P.; Knochel, P. *Org. Lett.* **2017**, *19*, 536.

(31) Tran, L. D.; Daugulis, O. *Org. Lett.* **2010**, *12*, 4277.

(32) Rohbogner, C. J.; Clososki, G. C.; Knochel, P. *Angew. Chem. Int. Ed.* **2008**, *47*, 1503.

(33) Rohbogner, C. J.; Wirth, S.; Knochel, P. *Org. Lett.* **2010**, *12*, 1984.

(34) Sorbera, L. A.; Castaner, R. M.; Silvestre, J.; Castaner, J. *Drugs Future* **2001**, *26*, 346.
(35) Milne, J. E.; Buchwald, S. L. *J. Am. Chem. Soc.* **2004**, *126*, 13028.
(36) (a) Milstein, D.; Stille, J. K. *J. Am. Chem. Soc.* **1978**, *100*, 3636. (b) Cordovilla, C.; Bartolomé, C.; Martínez-Ilarduya, J. M.; Espinet, P. *ACS Catal.* **2015**, *5*, 3040.
(37) Clososki, G. C.; Rohbogner, C. J.; Knochel, P. *Angew. Chem. Int. Ed.* **2007**, *46*, 7681.
(38) Farina, V.; Krishnan, B. *J. Am. Chem. Soc.* **1991**, *113*, 9585.
(39) Rohbogner, C. J.; Wunderlich, S. H.; Clososki, G. C.; Knochel, P. *Eur. J. Org. Chem.* **2009**, 1781.
(40) Jaric, M.; Haag, B. A.; Unsinn, A.; Karaghiosoff, K.; Knochel, P. *Angew. Chem. Int. Ed.* **2010**, *49*, 5451.
(41) Manolikakes, S. M.; Jaric, M.; Karaghiosoff, K.; Knochel, P. *Chem. Commun.* **2013**, 2124.
(42) Jaric, M.; Haag, B. A.; Manolikakes, S. M.; Knochel, P. *Org. Lett.* **2011**, *13*, 2306.
(43) Klatt, T.; Werner, V.; Maximova, M. G.; Didier, D.; Apeloig, Y.; Knochel, P. *Chem. Eur. J.* **2015**, *21*, 7830.
(44) Wunderlich, S. H.; Knochel, P. *Angew. Chem. Int. Ed.* **2007**, *46*, 7685.
(45) Mosrin, M.; Knochel, P. *Org. Lett.* **2009**, *11*, 1837.
(46) Bresser, T.; Monzon, G.; Mosrin, M.; Knochel, P. *Org. Process Res. Dev.* **2010**, *14*, 1299.
(47) Gosselin, F.; Savage, S. J.; Blaquiere, N.; Staben, S. T. *Org. Lett.* **2012**, *14*, 862.
(48) McDonald, S. L.; Hendrick, C. E.; Wang, Q. *Angew. Chem. Int. Ed.* **2014**, *53*, 4667.
(49) McDonald, S. L.; Hendrick, C. E.; Bitting, K. J.; Wang, Q. *Org. Synth.* **2015**, *92*, 356.
(50) Manolikakes, S. M.; Ellwart, M.; Stathakis, C. I.; Knochel, P. *Chem. Eur. J.* **2014**, *20*, 12289.
(51) Chen, Y.-H.; Graßl, S.; Knochel, P. *Angew. Chem. Int. Ed.* **2018**, *57*, 1108.
(52) Castelló-Micó, A.; Knochel, P. *Synthesis* **2018**, *50*, 155.
(53) Frischmuth, A.; Fernández, M.; Barl, N. M.; Achrainer, F.; Zipse, H.; Berionni, G.; Mayr, H.; Karaghiosoff, K.; Knochel, P. *Angew. Chem. Int. Ed.* **2014**, *53*, 7928.
(54) Becker, M. R.; Ganiek, M. A.; Knochel, P. *Chem. Sci.* **2015**, *6*, 6649.
(55) (a) Wunderlich, S. H.; Kienle, M.; Knochel, P. *Angew. Chem. Int. Ed.* **2009**, *48*, 7256. (b) Wunderlich, S. H.; Bresser, T.; Dunst, C.; Monzon, G.; Knochel, P. *Synthesis* **2010**, 2670. (c) Haas, D.; Hammann, J. M.; Moyeux, A.; Cahiez, G.; Knochel, P. *Synlett* **2015**, *26*, 1515.
(56) Wunderlich, S. H.; Knochel, P. *Angew. Chem. Int. Ed.* **2009**, *48*, 1501.
(57) Wunderlich, S. H.; Knochel, P. *Chem. Eur. J.* **2010**, *16*, 3304.
(58) Krasovskiy, A.; Kopp, F.; Knochel, P. *Angew. Chem. Int. Ed.* **2006**, *45*, 497.
(59) Benischke, A. D.; Anthore-Dalion, L.; Berionni, G.; Knochel, P. *Angew. Chem. Int. Ed.* **2017**, *56*, 16390.
(60) Boga, S. B.; Christensen, M.; Perrotto, N.; Krska, S. W.; Dreher, S.; Tudge, M. T.; Ashley, E. R.; Poirier, M.; Reibarkh, M.; Liu, Y.; Streckfuss, E.; Campeau, L.-C.; Ruck, R. T.; Davies, I. W.; Vachal, P. *React. Chem. Eng.* **2017**, *2*, 446.
(61) Mosrin, M.; Knochel, P. *Org. Lett.* **2008**, *10*, 2497.
(62) Mosrin, M.; Petrera, M.; Knochel, P. *Synthesis* **2008**, 3697.
(63) Mosrin, M.; Knochel, P. *Chem. Eur. J.* **2009**, *15*, 1468.
(64) Del Amo, V.; Dubbaka, S. R.; Krasovskiy, A.; Knochel, P. *Angew. Chem. Int. Ed.* **2006**, *45*, 7838.
(65) Wada, A.; Yamamoto, J.; Kanatomo, S. *Heterocycles* **1987**, *26*, 585.
(66) Turck, A.; Plé, N.; Quéguiner, G. *Heterocycles* **1994**, *37*, 2149.
(67) Mosrin, M.; Boudet, N.; Knochel, P. *Org. Biomol. Chem.* **2008**, *6*, 3237.
(68) Soorukram, D.; Boudet, N.; Malakhov, V.; Knochel, P. *Synthesis* **2007**, 3915.
(69) Moss, T. A.; Hayter, B. R.; Hollingsworth, I. A.; Nowak, T. *Synlett* **2012**, *23*, 2408.
(70) Amaral, M. F. Z. J.; Baumgartner, A. A.; Vessecchi, R.; Clososki, G. C. *Org. Lett.* **2015**, *17*, 238.
(71) Barl, N. M.; Sansiaume-Dagousset, E.; Karaghiosoff, K.; Knochel, P. *Angew. Chem. Int. Ed.* **2013**, *52*, 10093.
(72) Nafe, J.; Herbert, S.; Auras, F.; Karaghiosoff, K.; Bein, T.; Knochel, P. *Chem. Eur. J.* **2015**, *21*, 1102.
(73) Greiner, R.; Blanc, R.; Petermayer, C.; Karaghiosoff, K.; Knochel, P. *Synlett* **2016**, *27*, 231.
(74) Balkenhohl, M.; Greiner, R.; Makarov, I. S.; Heinz, B.; Karaghiosoff, K.; Zipse, H.; Knochel, P. *Chem. Eur. J.* **2017**, *23*, 13046.
(75) Ioannidou, H. A.; Martin, A.; Gollner, A.; Koutentis, P. A. *J. Org. Chem.* **2011**, *76*, 5113.
(76) Plodek, A.; König, M.; Bracher, F. *Eur. J. Org. Chem.* **2015**, 1302.
(77) Melzer, B.; Plodek, A.; Bracher, F. *J. Org. Chem.* **2014**, *79*, 7239.
(78) Klatt, T.; Roman, D. S.; León, T.; Knochel, P. *Org. Lett.* **2014**, *16*, 1232.
(79) Klier, L.; Aranzamendi, E.; Ziegler, D.; Nickel, J.; Karaghiosoff, K.; Carell, T.; Knochel, P. *Org. Lett.* **2016**, *18*, 1068.
(80) Klier, L.; Bresser, T.; Nigst, T. A.; Karaghiosoff, K.; Knochel, P. *J. Am. Chem. Soc.* **2012**, *134*, 13584.
(81) Groll, K.; Manolikakes, S. M.; du Jourdin, X. M.; Jaric, M.; Bredihhin, A.; Karaghiosoff, K.; Carell, T.; Knochel, P. *Angew. Chem. Int. Ed.* **2013**, *52*, 6776.
(82) Wunderlich, S.; Knochel, P. *Chem. Commun.* **2008**, 6387.
(83) Unsinn, A.; Ford, M. J.; Knochel, P. *Org. Lett.* **2013**, *15*, 1128.
(84) Ziegler, D. S.; Greiner, R.; Lumpe, H.; Kqiku, L.; Karaghiosoff, K.; Knochel, P. *Org. Lett.* **2017**, *19*, 5760.