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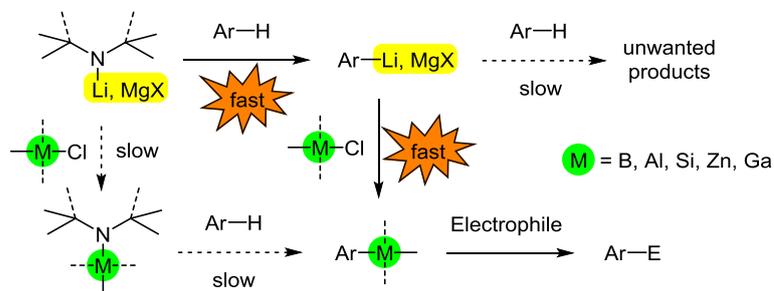
Abstract Deprotometalation is an efficient method to functionalize regioselectively aromatic compounds including heterocycles. This short review shows how it is possible to intercept aryllithiums (and other polar arylmetals) as soon as they are formed by *in situ* 'trans-metal trapping'. The approach avoids long contact between aryllithiums and sensitive substrates. In addition, it allows less activated substrates to be deprotonated by non-nucleophilic lithium amides. While using chlorosilanes and borates still arouses the interest of chemists, methods based on zinc, aluminum and gallium more recently appeared, enabling this chemistry to grow dramatically.

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1 Introduction

Deprotometalation followed by electrophilic trapping is a powerful method to functionalize aromatic compounds.[1] Regioselectively is in general ensured through the use of directing groups that (i) stabilize the generated arylmetals by intramolecular coordination and/or electron-withdrawing effect (under thermodynamic control), or (ii) favor the reaction by coordination to the base and/or hydrogen acidification (under kinetic control).

The limits of deprotolithiation and -magnesation result from the high ionic character of the carbon-metal bond. Consequently, the aromatic substrates can be weakly compatible with the generated arylmetals, e.g. in case of sensitive directing groups or heterocycles prone to nucleophilic attacks. The arylmetals can

also be unstable, e.g. in the presence of adjacent halogens to release metal halides. In addition, from activated or sensitive aromatics including heterocycles, classical deprotolithiation followed (after a contact time) by electrophilic quenching in general affords the most stable lithio compounds; therefore, there is a need for tools to access other regioselectivities resulting from the kinetic ones.

Besides using low temperatures or monometallic bases containing softer metals,[2] more recent studies have shown that lithium -ate bases (e.g. zincates) and Turbo bases can be more efficiently employed to achieve chemoselective deprotonative metalations.[3] Nevertheless, these bimetallic deprotonating agents can imply either the presence of additives that may be unwanted for the following reactions, or the generation of arylmetal species unsuitable for subsequent trappings. They can also fail in affording the required regioisomers.

In situ 'trans-metal trapping' is a way to address these issues by intercepting the arylmetals with an electrophilic trap as soon as they are formed. In addition, by pushing the reaction to completion, it is an efficient alternative to external quench for reversible reactions not benefiting from the required difference of four pK_a units between the base and the substrate.[4]
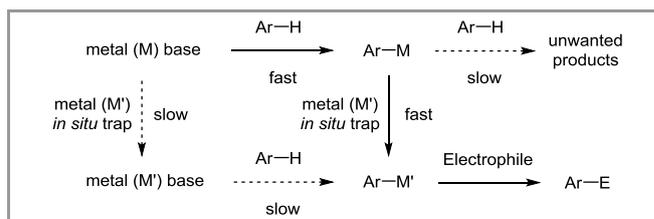
Scheme 1 Principle of *in situ* trapping metalation (dashed arrows indicate unwanted pathways)

The method applies if the base (metal M) rather reacts with the substrate (Ar-H) than with the *in situ* trap (metal or semi-metal

M'), and if the arylmetal (Ar-M) is quenched by the *in situ* trap rather than by unwanted reactions (Scheme 1).[5] In practice, sterically encumbered bases such as lithium diisopropylamide (LiDA) or lithium 2,2,6,6-tetramethylpiperidide (LiTMP) can in general be used.[6]

As regards the electrophilic traps, whereas chlorosilanes and borates have been employed since the eighties, more recent studies have identified zinc, aluminum and gallium species as appropriate to this purpose.[7] In this Short Review, our goal is to focus on examples using this method and thus display its applications to the functionalization of aromatics including heterocycles.

2 Silicon-based *in situ* traps

That chlorotrimethylsilane could accelerate deprotometalation was already noticed in 1982 by reacting 2-bromopyridine with LiDA in tetrahydrofuran (THF) at low temperatures.[8] Although LiDA is not a conventional base for benzene proton abstraction, it turns out to be one in the presence of such a trap capable of intercepting the aryllithium as soon as it is formed.

The first complete study on *in situ* trapping (here, using chlorotrimethylsilane) as a way to allow sensitive aromatic compounds to be deprotolithiated was reported in 1983.[9] Without *in situ* trap, benzonitrile cannot be lithiated by LiDA at temperatures below –90 °C whereas LiTMP gave average yields at –78 °C (2-(trimethylsilyl)benzonitrile: 53%; 2-iodobenzonitrile: 35%; 3-phenylphthalide: 40% after warming with diluted aqueous HCl) and degradation at higher temperatures.[9] As regards alkyl benzoates, deprotolithiation using LiTMP takes place at –78 °C, but leads to self-condensation products in the absence of *in situ* trap.[10] Krizan and Martin relied on the LiTMP-chlorotrimethylsilane tandem to functionalize benzonitrile, benzene esters and pivalophenone (Table 1).[9]

Table 1 Functionalization of benzonitrile, isopropyl and ethyl benzoate, and pivalophenone using the LiTMP-chlorotrimethylsilane pair

| R	x / y / T	Yield(s) (%)
CN	3 / 6 / −78	86 (R' = SiMe$_3$)
CN	2.2 / 10 / 0	65 (R' = SiMe$_3$), 35 (R' = H)
CO$_2$iPr	1.2 / 10 / −78	90 (R' = H)
CO$_2$Et	1.2 / 10 / −78	38 (R' = H)
COtBu	2.2 / 10 / −78	59 (R' = H)

By adding benzonitrile to an excess of LiTMP and chlorotrimethylsilane in THF at –78 °C, 2-(trimethylsilyl)- and 2,6-bis(trimethylsilyl)benzonitrile formed. By controlling the amount of base, monofunctionalization was observed from isopropyl and, to a lesser extent, sterically less hindered ethyl benzoate; it could be even extended to pivalophenone. By starting from diphenylsulfone, dichlorodimethylsilane also worked as *in situ* trap to provide the cyclic silane (Scheme 2).[9]

The polyfunctionalization observed above (Table 1; R = CN), and also evidenced from 1,3-dicyanobenzene and tetraisopropyl

1,2,4,5-benzenetetracarboxylate (Scheme 3),[9] is probably due to *in situ* metalation-trapping of an initially formed monosilane.
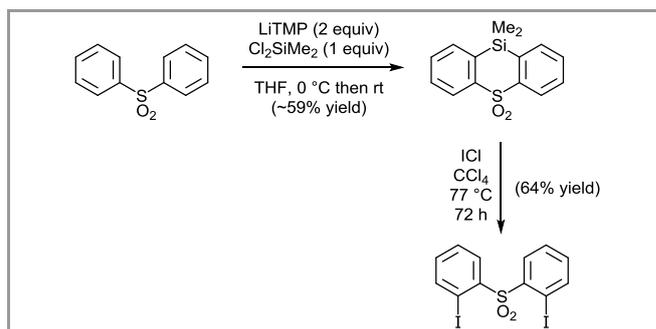
Scheme 2 Functionalization of diphenylsulfone using the LiTMP-dichlorodimethylsilane tandem
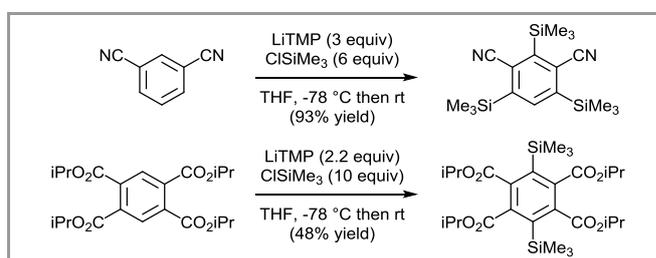
**Scheme 3** Functionalization of 1,3-dicyanobenzene and tetraisopropyl 1,2,4,5-benzenetetracarboxylate using the LiTMP-chlorotrimethylsilane pair

Similarly, Luliński and Serwatowski documented in 2003 the double metalation-silylation of 1,4- and 1,2-dibromobenzene by using LiDA in the presence of chlorotrimethylsilane (2 equiv each; Scheme 4).[11] It is worth noting that, once functionalized at C2, the 6-position of 1,4-dibromobenzene is somewhat protected toward deprotometalation owing to the buttressing effect[12] exerted by the trimethylsilyl group next to the bromine atom.[13] Similarly, the lower yield noticed in the double functionalization of 1,2-dibromobenzene is not related to competitive benzyne formation[14] or halogen 'dance' reaction,[15] these possibilities being here prevented under *in situ* trapping. A reaction unfavored at C6 due to the buttressing effect exerted by the trimethylsilyl present at C3 is more likely to occur.
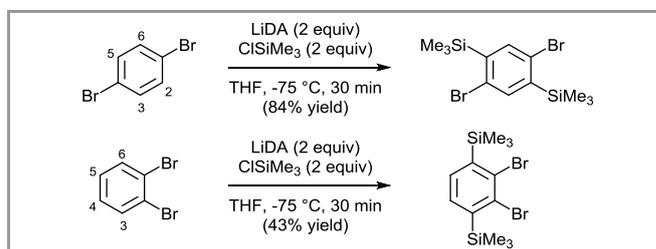
Scheme 4 Double metalation-*in situ* silylation of 1,4- and 1,2-dibromobenzene using the LiDA-chlorotrimethylsilane tandem

In the above examples, if the amount of base is reduced, clean monofunctionalizations are not yet obvious since both the substrates and the monosilylated products share a similar reactivity.[11] However, the use of an additional bulky substituent can help to control the reaction outcome. Indeed, from 1,2-dibromobenzene, a second deprotonation can be completely suppressed in the presence of a substituent at C4. In addition,

LiTMP was identified as a better base than LiDA to this purpose (Scheme 5).
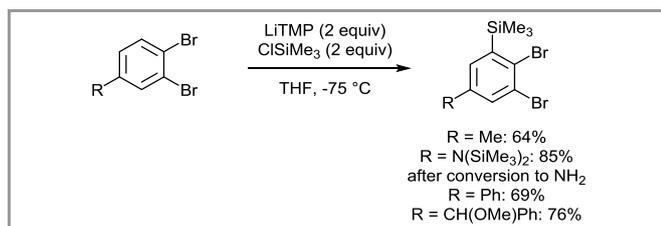
Scheme 5 Single metalation-*in situ* silylation of 4-substituted 1,2-dibromobenzenes using the LiTMP-chlorotrimethylsilane tandem

In the example below reported by Widhalm and co-workers in 2009, dideprotonation is employed to generate a symmetrical 2,2'-dibromo-3,3'-disilylated binaphthyl from which four different 2,2',3,3'-tetrahalogenated derivatives can be prepared (Scheme 6).[16]
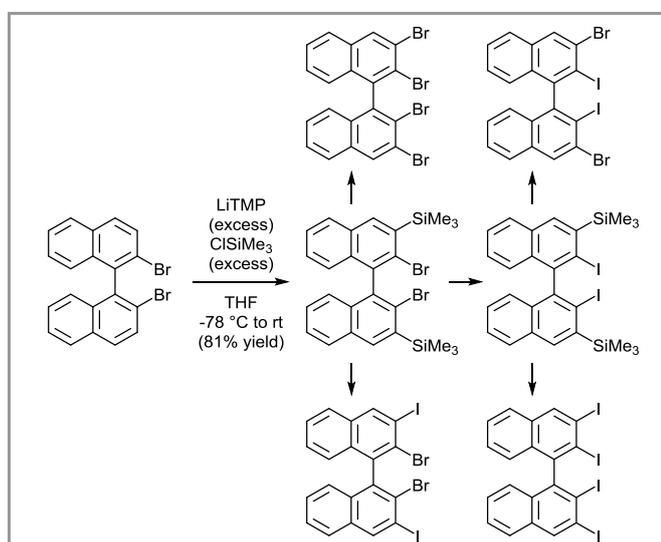

Scheme 6 Synthesis of 2,2',3,3'-tetrahalogenated derivatives from 2,2'-dibromo-1,1'-biphenyl using the LiTMP-chlorotrimethylsilane pair

If elimination of lithium bromide is prevented by *in situ* trapping in the above examples, it is not a universal rule. For example, bromoanisoles cannot undergo LiDA-mediated deprotonation in THF at low temperatures using chlorotrimethylsilane, the insufficient stability of the intermediate 2-bromophenyllithiums leading to benzyne formation.[17] One possible trick consists of using a remote bromine, which stabilizes the lithio product by electron-withdrawing effect,[18] but the issue is not entirely solved.

In the course of the synthesis of aryne precursors, Mesgar and Daugulis observed in 2016 that chlorodimethylsilane, sterically smaller and more electrophilic than chlorotrimethylsilane, is a more efficient *in situ* trap for unstable 2-halogenated phenyllithiums. The best results were recorded by mixing the reagents at –110 °C before warming (Table 2).[19]

As reported before with esters, there is no need to protect the carboxylic acid function if the chlorotrimethylsilane *in situ* quench is applied to the deprotolithiation of *meta*-anisic acid using LiTMP (3 equiv) in THF under cryogenic conditions. The trimethylsilyl group thus introduced can act as a protecting group, enabling subsequent functionalization at the 6-position (Scheme 7).[20] Unlike chlorotrimethylsilane and -triethylsilane, which allowed *ortho*-phthalic acids to be difunctionalized in the presence of LiTMP (Scheme 8), chlorotriisopropylsilane and -*tert*-butyldimethylsilane are not suitable *in situ* traps.[21]

Table 2 Functionalization of halogenated benzenes using the LiTMP-chlorodimethylsilane tandem

Substrate	Product	Yield (%)
		94
		55
		94
		51
		76
		76
		95
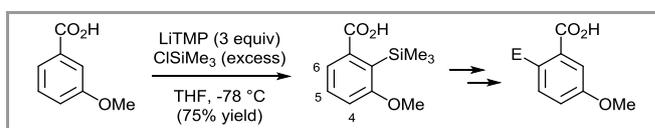
Scheme 7 Functionalization of *meta*-anisic acid using the LiTMP-chlorotrimethylsilane tandem
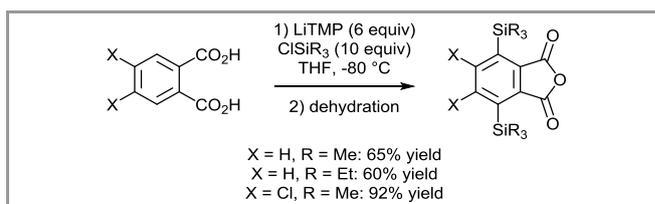
Scheme 8 Difunctionalization of phthalic acids using LiTMP-ClSiR₃ pairs

Nitro group is hardly compatible with deprotolithiation due to its possible reduction by electron transfer from the base or the arylmetal. In order to minimize the contact time between nitro

aromatics and carbon-centered anions, Black and co-workers employed metal amide-chlorotrimethylsilane pairs to attempt the functionalization of 2,4-difluoro-1-nitrobenzene. As shown in Table 3, the best results were observed by using sodium and potassium amides.[22] The reaction using sodium bis(trimethylsilyl)amide (NaHMDS) was further extended to other sensitive substrates (Table 4). The results show very electron-deficient aromatics are required, suggesting for these substrates a mechanism based on inductive acidification of the adjacent hydrogen rather than on coordination of the base by the directing group.[22]

Base	Yield(s) (%)
LiDA	36
LiTMP	33
LiBSBA[a]	70 (75)[b]
LiHMDS	78
NaHMDS	100
KHMDS	91

[a] Lithium (*tert*-butyldimethylsilyl)-*tert*-butylamide. [b] Using chlorotrimethylstannane as *in situ* trap.

Table 4 Functionalization of nitrobenzenes using the NaHMDS-chlorotrimethylsilane tandem

Substrate	Product	Yield (%)
		100
		100
		100
		61
		10

Beside its usefulness to avoid side reactions of sensitive substrates, *in situ* trapping can also be at the origin of an altered regioselectivity. For example, whereas 2-bromopyridine is selectively functionalized at C3 upon treatment with LiDA in

THF at low temperatures before electrophilic trapping,[23] mixtures of 3-silylated (thermodynamic, main) and 4-silylated (kinetic, minor) products are obtained in the presence of chlorotrimethylsilane.[24] A kinetic lithio compound at C6 is even intercepted by the *in situ* trap (65% yield) when LiTMP is employed in diethyl ether at –78 °C.[25]

In the same vein, Snieckus, Mortier and co-workers documented an optional site selectivity for the functionalization of *N,N*-dialkylated biphenyl-2-carboxamides depending on if the electrophile is *in situ* or not. For example, *N,N*-diethylbiphenyl-2-carboxamide is silylated *ortho* to the functional group by using the *in situ* quench protocol whereas the initially formed lithio compound equilibrates with the 2'-lithiobiphenyl-2-carboxamide without. The latter is rapidly intercepted by the carboxamide, here also playing the role of internal trap (Scheme 9).[26]
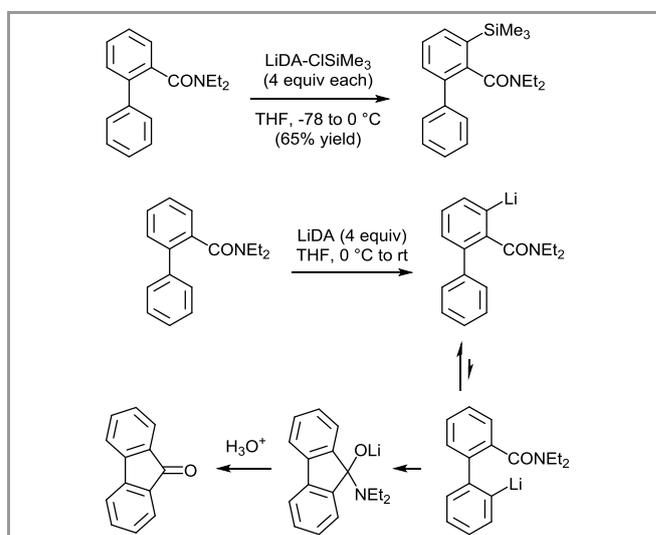
Scheme 9 Functionalization of *N,N*-diethylbiphenyl-2-carboxamide using LiDA with and without *in situ* chlorotrimethylsilane

Simpkins and co-workers used in 1994 a chiral lithium amide to attempt the enantioselective deprotonation of tricarbonyl(η^6-arene)chromium complexes (Table 5).[27] The higher levels of asymmetric induction were recorded by using chlorotrimethylsilane as internal quench (0.04 M). The lower enantioselectivities noticed with external quench reactions (73% ee if the trapping is performed after 0.5 min, 52% after 1 h, 25% after 3 h) were rationalized by an intermolecular equilibration between substrate and lithiated derivative. *In situ* trapping here helped in achieving a kinetically controlled reaction giving chiral, nonracemic tricarbonyl(η^6-arene)chromium complexes.[27-28]

This study was extended to substituted ferrocenes. Although diphenylphosphinylferrocene proved to be the best candidate, the silylated derivative was isolated in 95% yield but only 54% ee by using the method depicted in Table 5.[29]

Finally, because it provides irreversible conditions, the LiTMP-chlorotrimethylsilane pair was used to evaluate the relative reaction rates (kinetic acidities) of different substituted benzenes, and thus the ability of the substituents to enhance the proton mobility at the transition state.[30]

Table 5 Enantioselective functionalization of tricarbonyl(η^6-arene)chromium complexes using a chiral lithium amide under kinetic control
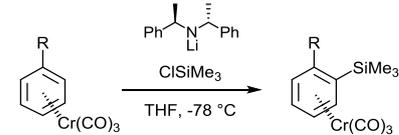
R	Yield (%)	ee (%)
OMe	83	84
OEt	82	81
OiPr	65	90
OtBu	0	-
OCH$_2$OMe	76	80
CH(OCH$_2$CH$_2$O)	36	84
Cl	27	51
F	57	16
CONiPr$_2$	87	48
N(Me)COtBu	65	44

3 Boron-based *in situ* traps

Esters are considered as better directing groups than amides in deprotometalations; nevertheless, their use was delayed because of their low compatibility with organolithiums.[10] Smooth bases such as Mg(TMP)$_2$ were first evaluated in THF for the functionalization of methyl benzoate, but the reactions required an excess of reagent.[2] Inspired by the study of Krizan and Martin (Table 1),[9] Caron and Hawkins demonstrated in 1998 that LiDA can be an efficient kinetic base, compatible with both chlorotrimethylsilane and triisopropylborate.[31] In the presence of the latter, various neopentyl benzoates were converted into the corresponding 2-boronyl derivatives (isolated as their diethanolamine complexes) upon treatment with LiDA in THF (Table 6). Except in the case of the 4-fluoro derivative, the function was introduced regioselectively at the position adjacent to the ester.[31]

Table 6 Functionalization of neopentyl benzoate using the LiDA-triisopropylborate tandem
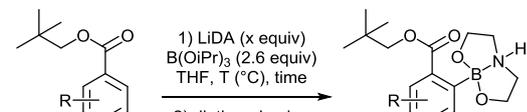
R	x	T (°C), time (min)	Yield (%)
4-Br	1.1	−78, 5	84
4-CF$_3$	1.1	0, 30	74
4-OMe	1.6	0, 180	70
4-F	1.1	−78, 15	52[a]
4-Cl	1.2	−78, 10	90
2-Br	1.2	−78, 10	88
2-CF$_3$	1.2	−78, 60	93
3-F	1.2	−78 to −40, 180	90

[a] Competitive metalation next to fluorine was noticed.

By switching from LiDA to LiTMP, Vedsø and co-workers accessed a large range of 2-substituted arylboronic esters, appropriate partners in Suzuki-type cross-coupling. The reaction using hindered and more basic LiTMP (pK_a = 37.3 for 2,2,6,6-tetramethylpiperidine against 35.7 for diisopropylamine)[32] is no more limited to the neopentyl ester function, but works with simpler ethyl benzoate, as well as benzonitrile, fluorobenzene and even the less activated chlorobenzene (Table 7).[33] It is worth noting that although 2-chlorophenyllithium can only be accumulated at –100 °C,[34] *in situ* trapping at higher temperature bypasses subsequent elimination giving benzyne.[14]

That LiTMP is more powerful than LiDA was also demonstrated by Kristensen and co-workers for the lithiation-*in situ* borylation of cyanopyridines (Figure 1)[35] and in the course of a study on the deprotometalation of substituted benzonitriles.[4] By this way, nitrile was compared to different directing groups (DG) already used in deprotometalation reactions (Table 8).[4]

Table 7 Functionalization of ethyl benzoate, benzonitrile, fluorobenzene and chlorobenzene using lithium amide-triisopropylborate tandems
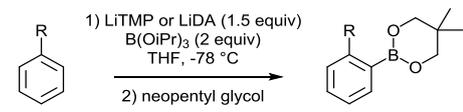
R	Yield using LiTMP(%)	Yield using LiDA (%)
CO$_2$Et	92	0[a]
CN	61[b]	0[a]
F	98	87
Cl	96	<30[c]

[a] Only *N,N*-diisopropylbenzamide formed. [b] Benzamide resulting from the addition of LiTMP to benzonitrile formed in 20-25% yield. [c] Numerous impurities present.

80% yield	52% yield	94% yield
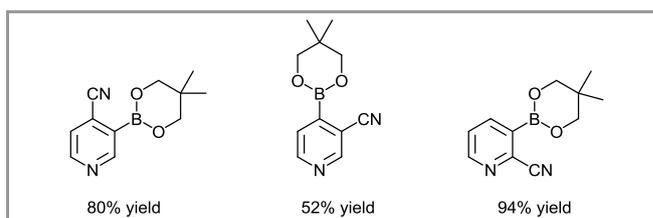
Figure 1 Borylated cyanopyridines synthesized by using (i) LiTMP-B(OiPr)$_3$ (1.2 equiv) in THF at -78 °C and (ii) neopentylglycol

Table 8 Comparison of CN to other metalation directing groups (DG) using *in situ* trapping
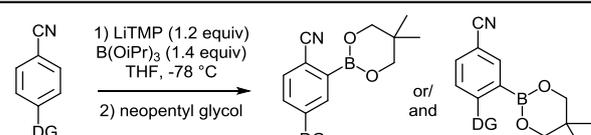
DG	Ratio[a]	Yield (%)
OMe	30/70 (25/25)[b]	96
CF$_3$	100/0 (40/0)[b]	99
F	40/60 (35/45)[b]	94
Cl	93/7 (60/35)[b]	99
Br	90/10 (70/25)[b]	98

DG	Ratio	Yield (%)
OMe	100/0	96
CF$_3$	0/100	98
F	100/0	96
Cl	100/0	[c]
Br	100/0	96

DG	Ratio	Yield (%)
OMe	100/0	96
CF₃	100/0	99
F	40/60	99
Cl	95/5	96
Br	98/2	97

DG	Ratio	Yield (%)
OMe	100/0	96
CF_3	100/0	99
F	40/60	99
Cl	95/5	96
Br	98/2	97

[a] The values in brackets are those using LiDA instead of LiTMP. [b] The rest is the 4-substituted *N,N*-diisopropylcarboxamide. [c] Impossible to isolate as a single entity.

Snieckus and co-workers reported in 2007 a one-pot deprotometalation-*in situ* boronation-oxidation to generate hydroxy derivatives of sensitive *N,N*-diethylpicolinamides. The process does not require cryogenic temperatures and works in high yields (Scheme 10). Pinacolate and boroxazine derivatives of the different *N,N*-diethylpyridinecarboxamides, *N,N*-diethyl-3-pyridinesulfonamide and -carbamate, and 3-fluoropyridine were similarly prepared and converted by Suzuki coupling.[36]
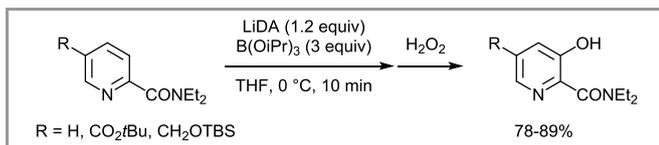
Scheme 10 Picolinamide deprotonation-*in situ* boronation-oxidation

Morpholine amides are safer and less expensive alternatives to Weinreb amides, which are known as acylation reagents of organometallic compounds. Kristensen and co-workers documented in 2017 the functionalization of various aromatic morpholine amides by using *in situ* borylation. When combined with triisopropyl borate, LiTMP proved superior than LiDA for this purpose (Table 9).[37]

Table 9 Borylation of morpholine amides using the tandem LiTMP (1.2 equiv)-B(OiPr)₃ (1.4 equiv)

DG	Ratio[a]	Yield (%)
OMe	93/7	78
CF_3	100/0	68
F	43/14[a]	-
Cl	95/5	86
Br	100/0	93
CN	84/16	63

| DG	Ratio	Yield (%)
OMe	70/0[a]	-
CF_3	1/92	68
F	5/5[a]	-
Cl	100/0	72
CN	50/50	67

DG	Ratio	Yield (%)
OMe	0/0[a]	-
CF_3	95/0	84
F	73/27	59
Cl	100/0	78
Br	100/0	90
CN	100/0	80

[a] The rest is starting material.

In the azine series, boron-based *in situ* traps can also activate the substrates toward deprotonation and even control the regioselectivity. In this way, Knochel and co-workers employed in 2010 ClMgTMP·LiCl in the presence of boron trifluoride etherate in THF to chemo- and regioselectively deprotonate pyridines and related *N*-heterocycles (e.g. quinoline, Scheme 11) which are substrates prone to nucleophilic attacks.[38] Interestingly, optional site selectivity could be reached from various nitrogen-containing substrates depending on if boron trifluoride is present or absent from the reaction mixture (Figure 2).[38a,38c]
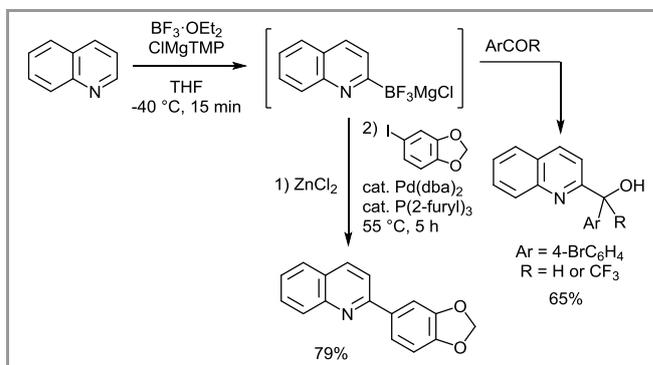
Scheme 11 Functionalization of quinoline using ClMgTMP·LiCl in the presence of BF₃·Et₂O
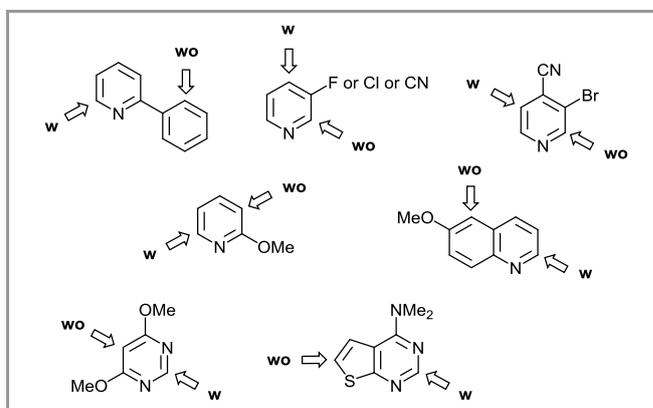
Figure 2 Regioselectivity of the functionalization of azines and diazines using ClMgTMP·LiCl in the presence (**w**) or absence (**wo**) of BF₃·Et₂O

4 Zinc-based *in situ* traps

In the course of the search of new lithium-zinc bases, Mongin and co-workers generated 1:1 LiTMP-Zn(TMP)$_2$ by reacting ZnCl$_2$·TMEDA (TMEDA = *N,N,N',N'*-tetramethylethylenediamine) with LiTMP (3 equiv).[39] Due to steric incompatibility, formation of the lithium zincate LiZn(TMP)$_3$ is prohibited. This lack of cocomplexation between both amides is of interest, the combination working as a base, LiTMP, in the presence of an *in situ* trap, (Zn(TMP)$_2$).[40] This basic mixture is thus capable of deprotonating chemoselectively a large range of sensitive aromatic substrates including heterocycles.

Lithiation of bare diazines represents a difficult task due to the low LUMO levels of these substrates, and thus their sensitivity to nucleophilic attacks. With pyrazine and pyridazine, the reaction is possible using LiTMP in excess, as long as very short reaction times at very low temperatures are respected. In contrast, metalation of pyrimidine can only be accomplished using the *in situ* trapping technique.[41] 1:1 LiTMP-Zn(TMP)$_2$ could be used in THF at room temperature or above to lead, after iodolysis, to the expected iodides in medium yields (Scheme 12).[42]
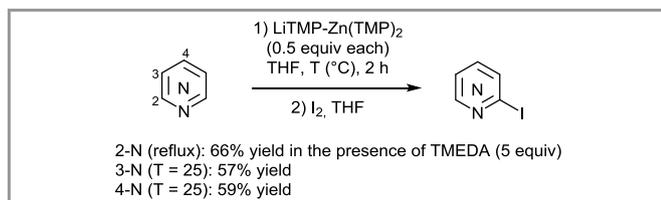
Scheme 12 Deprotonation-iodolysis of bare diazines using 1:1 LiTMP-Zn(TMP)$_2$ (generated from ZnCl$_2$·TMEDA and LiTMP in a 1:3 ratio)

Similarly, deprotolithiation of 3-bromo- and 3-chloropyridine using lithium amides have to be carried out at –78 °C in order to avoid nucleophilic attacks onto the π-deficient ring and elimination of lithium halide giving pyridyne.[23] In the presence of Zn(TMP)$_2$, LiTMP can be used at room temperature; the kinetic 2-metalated compounds can be intercepted by iodolysis whereas they equilibrate to afford the more stable 4-lithio derivatives in the absence of *in situ* trap (Scheme 13).[43]
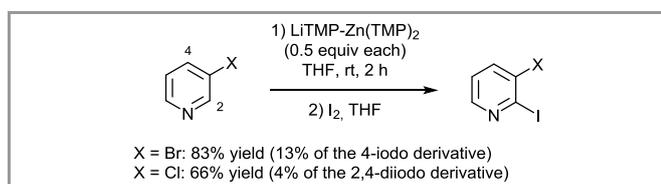
Scheme 13 Deprotonation-iodolysis of 3-bromo- and 3-chloropyridine using 1:1 LiTMP-Zn(TMP)$_2$ (generated from ZnCl$_2$·TMEDA and LiTMP in a 1:3 ratio)

The kinetic deprotonation sites are in general next to heteroatoms able to coordinate metals (lowering the pK_a values upon coordination by nitrogen). As a consequence, *N*-(3-pyridyl)pyrrole and -indole are for example deprotolithiated next to the pyridine nitrogen before interception by Zn(TMP)$_2$ (Scheme 14).[44]

Whereas LiTMP is barely employed to deprotometalate benzenes, 1:1 LiTMP-Zn(TMP)$_2$ can be used for both aromatic heterocycles benefiting from relatively acidic hydrogens (Scheme 12 and 13; Figure 3, top) and less activated substrates such as anisole and naphthalenes (Figure 3, bottom).[45]
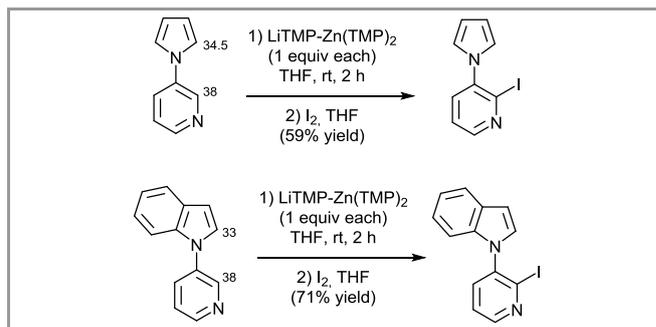
Scheme 14 Deprotonation-iodolysis of *N*-(3-pyridyl)pyrrole and -indole (selected pK_a values are given) using 1:1 LiTMP-Zn(TMP)$_2$ (generated from ZnCl$_2$·TMEDA and LiTMP in a 1:3 ratio)
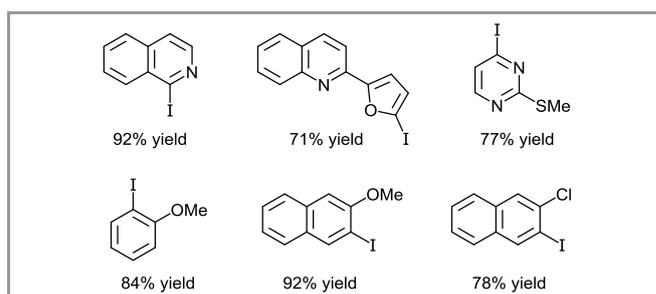
Figure 3 Iodinated products synthesized by using 1:1 LiTMP-Zn(TMP)$_2$ (generated from ZnCl$_2$·TMEDA and LiTMP in a 1:3 ratio)

Ferrocenes bearing electrophilic functional groups such as carboxamides, nitrile and esters can undergo a similar treatment at room temperature to provide, after subsequent trapping, either the 2-iodo derivatives or the Negishi-type coupling products. From bromoferrocene, the recorded result evidenced a competitive halogen 'dance'[15] at this temperature (Table 10).[46]

Table 10 Deprotonation followed by iodolysis or Negishi-type coupling of ferrocenes bearing functional groups (FG) using 1:1 LiTMP-Zn(TMP)$_2$ (generated from ZnCl$_2$·TMEDA and LiTMP in a 1:3 ratio)

FG	Yield of iodide (%)	Yield of pyridyl (%)
CONEt$_2$	91	80
CONMe$_2$	78	a
CON[(CH$_2$)$_2$O(CH$_2$)$_2$]	84	a
CN	87	67
CO$_2$Me	83	a
Br	64[b]	a

[a] Reaction not attempted. [b] 1-Bromo-3-iodoferrocene also isolated in 7% yield.

In an attempt to enantioselectively prepare 2-functionalized methyl ferrocenecarboxylates, Mongin and co-workers mixed in THF the substrate with the putative zinc diamide (used as *in situ* trap) coming from bis[(*S*)-1-phenylethyl]amine before adding lithium bis[(*S*)-1-phenylethyl]amide. When the reaction was

page

carried out at −78 °C for 24 h before iodolysis, the expected iodide was obtained in a moderate 50% yield (due to remaining starting material) but with an 80% ee (Scheme 15).[47] Recourse to sugar-derived ferrocene esters possessing chiral directing groups, either combined to chiral lithium amides as above or with 1:1 LiTMP-Zn(TMP)$_2$, proved to be more promising.[48]
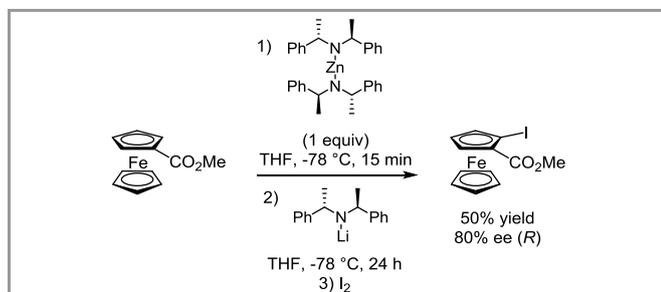
Scheme 15 Enantioselective functionalization of methyl ferrocenecarboxylate by metalation and *in situ* 'trans-metal trapping' using chiral metal amides

Eaton and co-workers showed in the eighties that LiTMP can be used in the presence of mercury chloride to more efficiently perform amide-directed cubane[49] and cyclopropane[50] deprotonation. The idea was to make use of the small amount of organolithium in equilibrium with the starting material, and to use mercury salts as *in situ* trap to shift the lithiation equilibrium toward the aryllithium. It is worth noting that the obtained organomercury chloride can be converted either to an organolithium (using methyllithium) or -magnesium (using methylmagnesium bromide) by reverse transmetalation.[51]

The presence of zinc chloride, cadmium chloride, chlorotrimethylstannane or chlorotrimethylsilane also allows cubanes to react (mono- or dideprotonation), but less efficiently than mercury chloride (dideprotonation).[49b] However, reactions to access less toxic organometals such as organozincs can be envisaged from more reactive substrates such as activated benzenes and aromatic heterocycles. In this way, Knochel and co-workers performed in 2009 Mg(TMP)$_2$·2LiCl-triggered room temperature deprotonations using zinc chloride as *in situ* trap to functionalize numerous substrates prone to nucleophilic attacks (e.g. quinoxalines; Scheme 16). In addition to its *in situ* trap role, zinc chloride can activate the aromatic substrate toward metalation by coordination.[52] The protocol also avoided aryne formation in the course of the deprotometalation of 1,4-dibromobenzene.[53]

The same authors evidenced in 2013 a more efficient pair. By combining ClMgTMP·LiCl with zinc chloride in the presence of lithium chloride (more soluble), they observed a metalation up to 50 times faster than using single ClMgTMP·LiCl for 10-15 °C temperature increase. The procedure tolerates the presence of highly sensitive functional groups such as an aldehyde or electron-deficient heterocycles (Table 11).[54]

Toward indazoles, this combination proved more powerful than 1:1 LiTMP-Zn(TMP)$_2$ as the competitive ring opening reaction noticed with the latter[55] can be avoided using the former.[54]
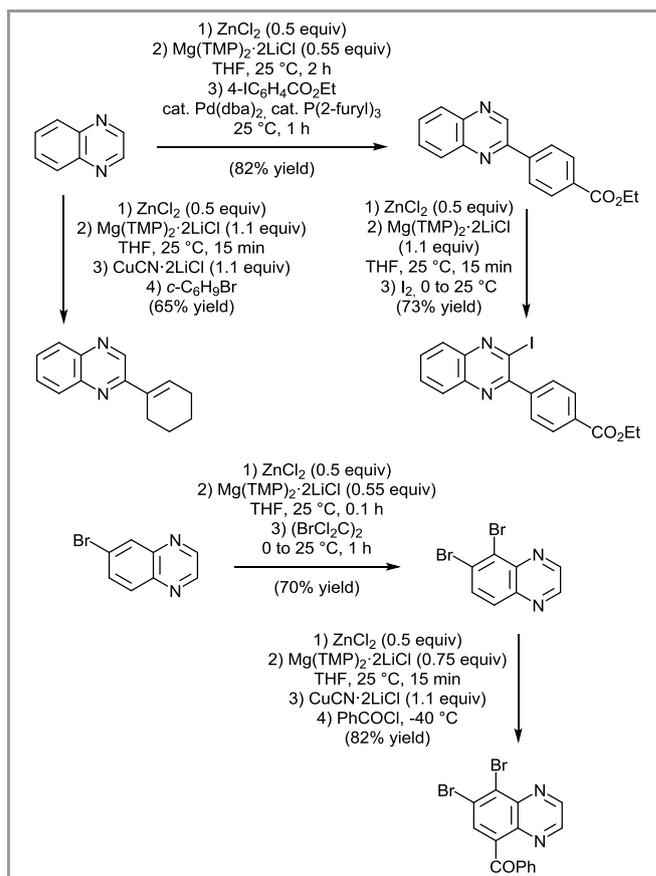
Scheme 16 Functionalization of quinoxalines using Mg(TMP)$_2$·LiCl in the presence of zinc chloride

Table 11 Functionalization of sensitive aromatic substrates (Ar-H) using ClMgTMP·LiCl in the presence of ZnCl$_2$·LiCl or ZnCl$_2$·2LiCl

n	time	Electrophile, conditions	Ar-E	Yield (%)
1	0.1 h	1) CuCN·2LiCl 2) PhCOCl		82
1	1 h	4-MeOC$_6$H$_4$I cat. Pd(dba)2 cat. P(2-furyl)$_3$		57
1	2 h	I$_2$		78
2	0.1 h	1) CuCN·2LiCl 2) 4-ClC$_6$H$_4$COCl		74

In 2014, optional site selectivity proved possible from various activated aromatic compounds by using either ClM(TMP)·LiCl (M = Zn or Mg; deprotonation at the most acidic site) or LiTMP (1.5 equiv) in tandem with ZnCl$_2$·2LiCl (1.1 equiv) at low temperatures (kinetic metalation). The method can be applied to substrates not metalated by ClMgTMP·LiCl at low temperatures, and for which metalation with LiTMP is faster than the transmetalation of LiTMP to ClZnTMP·LiCl. A few examples are given in Scheme 17. According to the authors, deprotolithiation proceeds at least six times faster than the transmetalation of the base by the metal salt.[56]
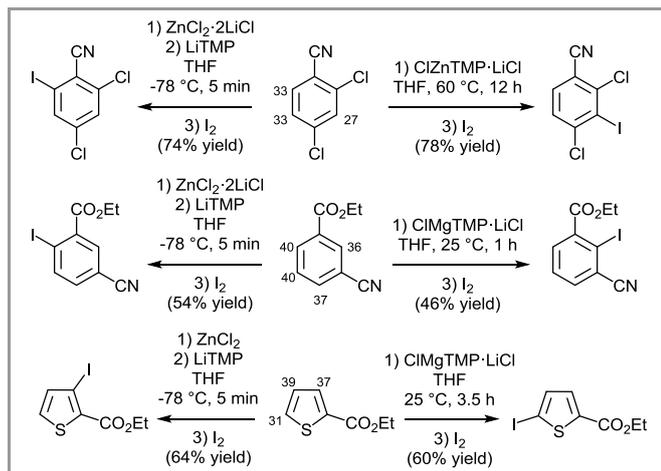
Scheme 17 Regioselectivity of the functionalization of aromatic compounds (pK_a values are given) by using either ClM(TMP)·LiCl (M = Zn or Mg) or LiTMP in tandem with ZnCl$_2$·2LiCl at low temperatures

The good solubility of ZnCl$_2$·TMEDA in THF led Erb, Mongin and co-workers to employ it as *in situ* trap in tandem with LiTMP. Except from 2-benzoylthiophene, performing the reactions in THF at −55 °C allowed various aromatic ketones to be regioselectively functionalized next to the functional group (Table 12).[57] Although ZnCl$_2$·TMEDA is an efficient *in situ* trap for most of the substrates, it shows limitations in the LiTMP-mediated deprotonation of fluorenone. Indeed, in this case, the corresponding iodide is isolated in a moderate 52% yield due to the concomitant formation of the alcohol resulting from the intermolecular addition of the lithio compound to the ketone (which acts as *in situ* trap) (Scheme 18). This alcohol becomes the only isolated product by carrying out the reaction using 1:1 LiTMP-Zn(TMP)$_2$ at room temperature.[57-58]

Eaton and Martin showed in 2008 that the LiTMP-HgCl$_2$ pair can be employed to obtain the 2,6-dimercurated derivatives of *N,N*-diethylbenzamide, isopropyl benzoate, benzonitrile and chlorobenzene, the intermediate 2-mercurated also being a suitable candidate for deprotolithiation-*in situ* trapping. Because the mercurated aromatics can be intercepted by a limited number of electrophiles (e.g. bromine and iodine), the authors converted the 2,6-dimercurated *N,N*-diethylbenzamide into the corresponding dilithio compound by using butyllithium (reverse transmetalation) and made by this way the quenching possible with deuterated methanol and iodomethane.[59]

Table 12 Functionalization of aromatic ketones using LiTMP in the presence of ZnCl$_2$·TMEDA

Ar—H	1) ZnCl$_2$·TMEDA (1 equiv) 2) LiTMP (1.5 equiv) THF, -55 °C, 15 min ——————————— 3) Electrophile, conditions	Ar—E

Electrophile, conditions	Ar-E	Yield (%)
I$_2$, rt		X = O: 72 X = S: 53 (80)[a]
2-chloropyridine, cat. PdCl$_2$, cat. dppf THF, reflux, 16 h		76
I$_2$, rt		R = H: 30 (37)[b] R = F, 63 R = Cl, 73 R = OMe, 88
I$_2$, rt		X = O: 60 X = S: 60
I$_2$, rt		80

[a] Reaction performed at −30 °C. [b] Reaction performed at −70 °C.
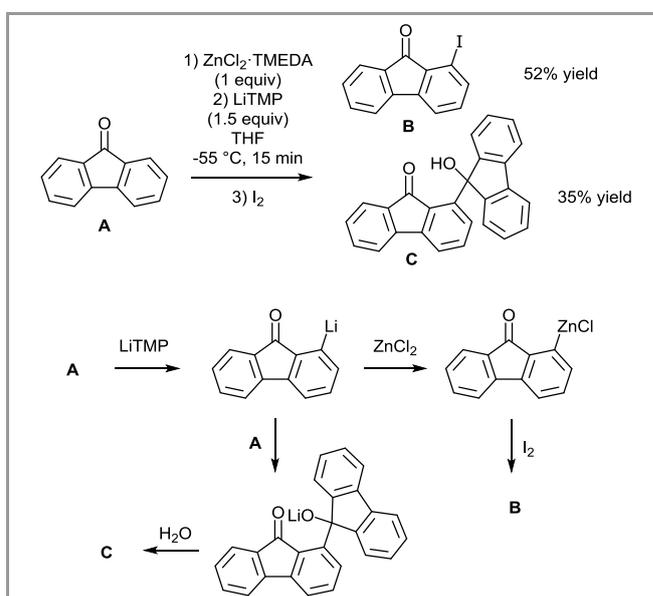
Scheme 18 Limitations of the ZnCl$_2$·TMEDA *in situ* trap

Dideprotonation (and sometimes more) has been observed in azole series by Chevallier and co-workers by increasing the amount of *in situ* generated 1:1 LiTMP-Zn(TMP)$_2$.[60] Interestingly, the lithium-zinc combination was employed to functionalize 2-arylated 1,2,3-triazoles. Indeed, whereas 2-substituted 4-lithio-1,2,3-triazoles are unstable due to facile ring opening, here they can be trapped by the present zinc species and a second metalation can operate as exemplified in Scheme 19.[61]
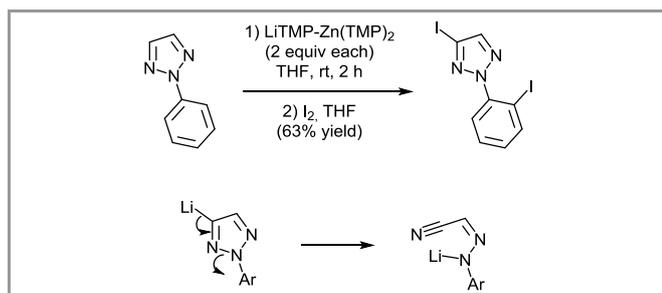
Scheme 19 Dideprotonation-iodolysis of 2-phenyl-1,2,3-triazole using 1:1 LiTMP-Zn(TMP)$_2$ (generated from ZnCl$_2$·TMEDA and LiTMP in a 1:3 ratio) and comparison with deprotolithiation

Benzotriazoles arylated on their terminal nitrogen were similarly difunctionalized by Mongin and co-workers. From 1-phenyl-1H-benzotriazole, the first deprotonation presumably occurs on the benzo ring, next to a coordinating triazole nitrogen that favors the approach of the base (position greatly favored using less base), and the second deprotonation on the phenyl ring, next to the second coordinating triazole nitrogen.[55] Mulvey and co-workers studied the reaction without zinc trap, and deduced that deprotolithiation of the benzo ring is followed by benzyne formation with N$_2$ extrusion, and addition of a second lithiobenzotriazole to the triple bond.[62] The advantage of *in situ* 'trans-metal trapping' is once more evidenced (Scheme 20).
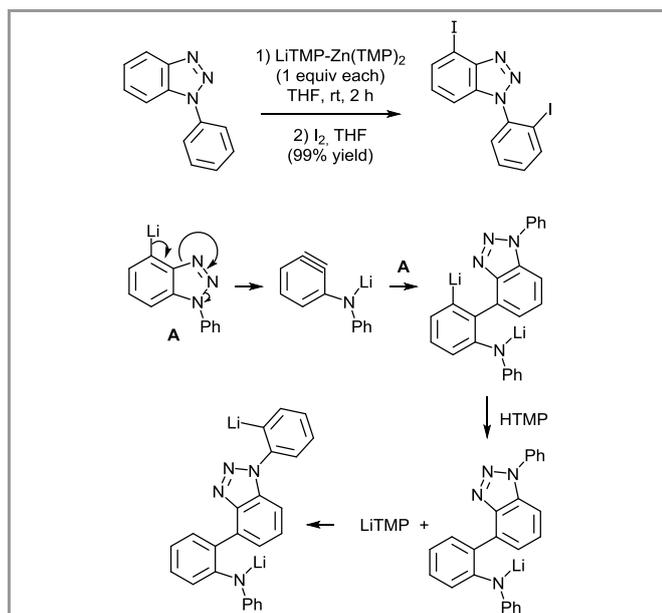
Scheme 20 Dideprotonation-iodolysis of 1-phenyl-1H-benzotriazole using 1:1 LiTMP-Zn(TMP)$_2$ (generated from ZnCl$_2$·TMEDA and LiTMP in a 1:3 ratio) and comparison with deprotolithiation using LiTMP

In the pyridine series, various substrates are prone to dimetalation (e.g. 3-fluoro- and 2,6-difluoropyridine; Scheme 21) whereas others are not (e.g. 2-fluoropyridine, 2- and 4-methoxypyridine) in the presence of an excess of base. This ability seems to be related to the acidity of the different pyridine substrates.[63]
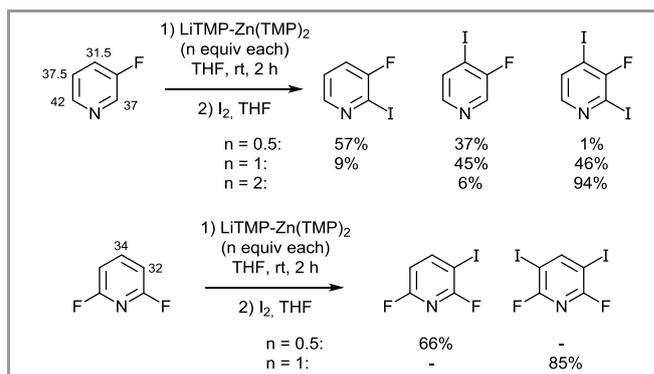
Scheme 21 Dideprotonation-iodolysis of 3-fluoro- and 2,6-difluoropyridine (pK$_a$ values) using 1:1 LiTMP-Zn(TMP)$_2$ (generated from ZnCl$_2$·TMEDA and LiTMP in a 1:3 ratio)

5 Aluminum- and gallium-based *in situ* traps

Mulvey, Robertson and co-workers documented in 2012 the different pathways exhibited by the LiAl(TMP)iBu$_3$ and LiAl(TMP)$_2$iBu$_2$ bases. Unlike the former, which allows 3-halogenated anisoles to be easily deprotonated at their 2-position, the latter makes the generated arylmetal species more reactive toward benzyne formation (due to the presence of the remaining TMP ligand). As regards the formation of this more reactive arylmetal, LiTMP-triggered deprotolithiation followed by *in situ* trapping with iBu$_2$Al(TMP) was proposed (Scheme 22).[64] Similarly, 3-fluoroanisole was converted to 3-(2,2,6,6-tetramethyl-N-piperidinyl)anisole in hexane or deuterated benzene.[65]
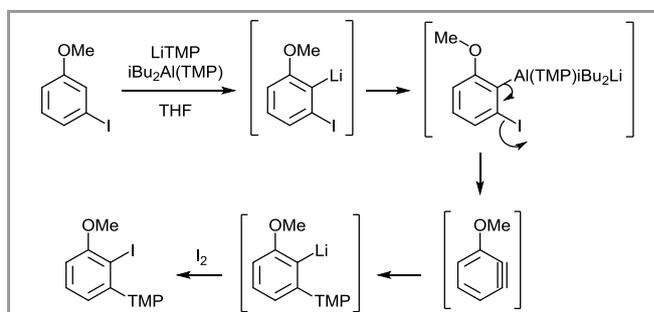

Scheme 22 Outcome of 3-iodoanisole deprotonation using LiTMP-iBu$_2$Al(TMP)

An extended study published in 2014 on the structure of LiAl(TMP)$_2$iBu$_2$ led to the existence of two homometallic species, LiTMP·THF and iBu$_2$Al(TMP)·THF, in THF solution.[66] Thus, whereas LiTMP is responsible from deprotometalation, the reaction is driven by carbophilic and bulky iBu$_2$Al(TMP); as a consequence, *ortho*-metalation of anisole works much more efficiently in the presence of the *in situ* trap (aluminated product produced in 99% yield) than without (5% of lithiated anisole).[67] The tandem LiTMP-iBu$_2$Al(TMP) can be employed in hexane at room temperature; when the reactions do not take place next to halogen, deprotonation occurs in high yields, as shown by subsequent iodolysis (Table 13).[68]

Table 13 Functionalization of aromatic compounds using LiTMP-iBu$_2$Al(TMP)		
Ar—H → (1) LiTMP-iBu$_2$Al(TMP), hexane, rt; 3) I$_2$) → Ar—I		
Substrate	Product	Yield (%)
(OMe, phenol ether)	(OMe, 2-iodo)	77
(OMe, OMe meta)	(OMe, OMe, I)	81
(OMe naphthalene)	(OMe, I naphthalene)	70
(CONiPr$_2$)	(CONiPr$_2$, 2-I)	88
(OMe, I)	(I, OMe, I)	96

When ferrocene was treated by the 1:1 mixture of LiTMP and iBu$_2$Al(TMP) in the presence of stoichiometric THF, either mono- or 1,1-dimetalation took place, depending on the amount of base.[69]

Hevia, Mulvey and co-workers evidenced in 2016 bulky and soluble Ga(CH$_2$SiMe$_3$)$_3$ as new *in situ* trap for LiTMP-mediated deprotometalations. The tandem can be used in hexane at room temperature for pyrazine, pyridazine and pyrimidine monodeprotonation (base-trap-substrate ratio: 1:1:1). Pyrazine dideprotonation also takes place under stoichiometric control (base-trap-substrate ratio: 2:2:1) but not regioselectively, giving both the 2,5- and 2,6-gallated products in a 62:38 ratio.[70]

When compared with iBu$_2$Al(TMP), Ga(CH$_2$SiMe$_3$)$_3$ *in situ* trap gives more stable 2-metalated fluorobenzenes upon LiTMP-induced deprotometalation in hexane at low temperature.[65]

6 Other *in situ* traps

In the frame of this Short Review, we focused on the most commonly encountered *in situ* traps. We will here mention a few examples that show other species can be used to intercept polar arylmetals as soon as they are formed.

Deprotonations using Mg(TMP)$_2$·2LiCl can be carried out in the presence of chlorotributylstannane or copper salt, as depicted in Scheme 23.[52]

More recently, MgCl$_2$·2LiCl and CuCN·2LiCl were more simply combined with LiTMP in order to diversify the further trapping steps (Scheme 24).[56]

Scheme 23 — Quinoxaline: 1) ClSnBu$_3$ (1.1 equiv); 2) Mg(TMP)$_2$·2LiCl (1.1 equiv), THF, -78 °C, 0.5 h → 2-SnBu$_3$ quinoxaline (73% yield).

Ethyl 4-chlorobenzoate: 1) CuCN·2LiCl (1.1 equiv); 2) Mg(TMP)$_2$·2LiCl (1.1 equiv), THF, -20 °C, 12 h; 3) PhCOCl, -20 °C, 2 h → product (CO$_2$Et, COPh, Cl) (71% yield).
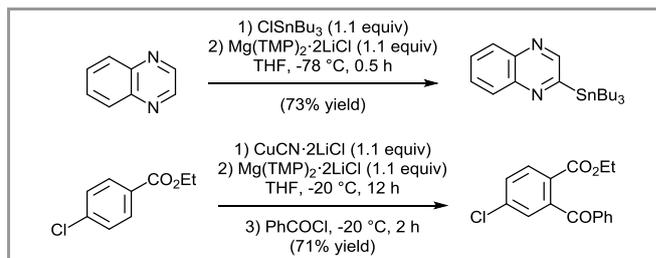
Scheme 23 Use of ClSnBu$_3$ and CuCN·2LiCl as *in situ* traps in combination with Mg(TMP)$_2$·2LiCl

Scheme 24 — 2,4-dichlorobenzonitrile (CN, Cl, Cl): 1) MgCl$_2$·2LiCl (1.1 equiv); 2) LiTMP (1.5 equiv), THF, -78 °C, 5 min; 3) 4-FC$_6$H$_4$SSO$_2$Ph → product (75% yield).

Same substrate: 1) CuCN·2LiCl (1.1 equiv); 2) LiTMP (1.5 equiv), THF, -78 °C, 5 min; 3) 3-bromocyclohexene → product (89% yield).
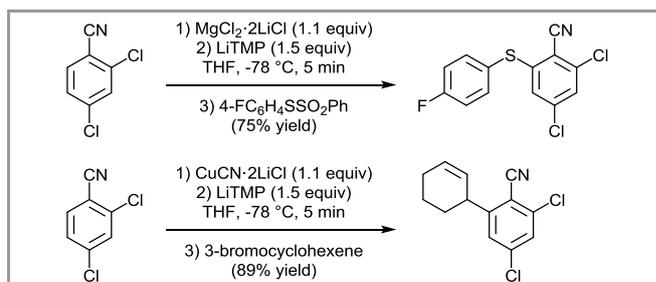
Scheme 24 Use of MgCl$_2$·2LiCl and CuCN·2LiCl as *in situ* traps in combination with LiTMP

7 Continuous-flow *in situ* 'trans-metal trapping'

In 2015, Becker and Knochel managed the flow deprotolithiation of various aromatic compounds including heterocycles in the presence of different metal salts, the obtained arylmetals being quenched in subsequent batch reactions (Table 14). The reaction scope under flow conditions is broader than that of the corresponding batch procedures. The reaction kinetics under continuous-flow mode differ significantly from those of the batch reactions, and contact times < 1 min are enough to ensure high yields. Importantly, cryogenic temperatures are no more required with the former since the reaction components are rapidly mixed, thus avoiding hot spots. Moreover, scale-up (from 1.7 to 12 mmol in the present paper) can be performed without further optimization, just by using a longer time in the flow reactor. Interestingly, unusual kinetically controlled regioselectivities were noticed in several cases (e.g. deprotonation of ethyl 3-fluorobenzoate at C6 in spite of a more acidic hydrogen at C2).[71]

Table 14 Flow deprotometalation of aromatic compounds using LiTMP in the presence of metal salts (**A** = ZnCl$_2$·2LiCl; **B** = MgCl$_2$; **C** = CuCN·2LiCl; **D** = LaCl$_3$·2LiCl) followed by batch electrophilic trapping

Ar—H → 1) **A**, **B**, **C** or **D** (n equiv); 2) LiTMP (1.5 equiv), THF, 0 °C, 40 s; 3) Electrophile, conditions → Ar—E

Metal salt (n)	Electrophile, conditions	Ar-**E**	Yield (%)
A (0.5)	4-MeOC$_6$H$_4$I, cat. Pd(dba)$_2$, cat. P(2-furyl)$_3$	(EtO$_2$C, NC, OMe biaryl)	73
A (0.5)	PhCOCl (Cu-mediated acylation)	(EtO$_2$C, F, COPh)	70

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B (0.5)	NC-CO$_2$Et	(aryl with CO$_2$Et, Br, F)	84
A (0.5-1.1)	4-F$_3$CC$_6$H$_4$I cat. Pd(dba)$_2$ cat. P(2-furyl)$_3$	(pyridine with CF$_3$, F)	98
A (0.5-1.1)	3-bromocyclohexene (Cu-catalyzed allylation)	(pyridine with CN, cyclohexenyl)	80
C (1.1)	BrCH$_2$C(CO$_2$Et)=CH$_2$	(pyridine with CO$_2$Et and CH$_2$C(CO$_2$Et)=CH$_2$)	79
A (0.5-1.1)	4-MeOC$_6$H$_4$I cat. Pd(dba)$_2$ cat. P(2-furyl)$_3$	(pyridine with CN, OMe-phenyl)	88
A (0.5-1.1)	4-MeOC$_6$H$_4$I cat. Pd(PPh$_3$)$_4$	(nitro-benzothiazole with OMe-phenyl, O$_2$N)	63
D (0.5)	Et$_2$CO	(dibromothiophene with C(OH)(Et)$_2$)	64

B	ClSiMe$_3$	(Ph-N=N, SiMe$_3$, F, Br)	92
A	ClCOcPr, after transmetalation with CuCN·2LiCl	(NC, CN, cyclopropyl ketone)	78
A	4-EtO$_2$CC$_6$H$_4$I cat. Pd(OAc)$_2$ cat. SPhos	(CN, NC, CO$_2$Et-phenyl)	82
A^a	I$_2$	(NC, I, CN)	79
A	BrCH$_2$C(CO$_2$Et)=CH$_2$ cat. CuCN·2LiCl	(CO$_2$Et, MeO, CN)	58

[a] Reaction performed at −70 °C instead of 0 °C

More recent studies performed on sensitive unsymmetrical azobenzenes, compounds of interest to access elaborated pharmaceuticals, and benzonitriles clearly evidence a large scope for *in situ* trapping metalations under continuous flow conditions (Table 15).[72] Compared with the corresponding batch procedures, less equivalents of base of metal salt are required for the flow ones.

Dicyclohexylamine (Cy$_2$NH) being far less expensive than 2,2,6,6-tetramethylpiperidine, the replacement of LiTMP by LiNCy$_2$ was examined by Knochel and co-workers in 2015, and gave similar yields than LiTMP (Table 16).[73]

Table 15 Flow deprotometalation of unsymmetrical azobenzenes and benzonitriles using LiTMP in the presence of metal salts (**A** = ZnCl$_2$; **B** = MgCl$_2$·LiCl) followed by batch electrophilic trapping

1) **A** or **B** (0.5 equiv)
2) LiTMP (1.5 equiv)
THF, 0 °C, 20-45 s
Ar—H $\longrightarrow$ Ar—E
3) Electrophile, conditions

Metal salt	Electrophile, conditions	Ar-E	Yield (%)
A	4-O$_2$NC$_6$H$_4$I cat. Pd(OAc)$_2$ cat. SPhos	(Ph-N=N, NO$_2$, F)	69
A	4-EtO$_2$CC$_6$H$_4$I cat. Pd(OAc)$_2$ cat. SPhos	(Ph-N=N, CO$_2$Et, CN)	67

Table 16 Flow deprotometalation of aromatic compounds using LiNCy$_2$ in the presence of metal salts (**A** = ZnCl$_2$·2LiCl; **B** = MgCl$_2$; **D** = LaCl$_3$·2LiCl) followed by batch electrophilic trapping

1) **A**, **B**, **C** or **D** (0.5 equiv)
2) LiTMP (1.5 equiv)
THF, 0 °C, 40 s
Ar—H $\longrightarrow$ Ar—E
3) Electrophile, conditions

Metal salt	Electrophile, conditions	Ar-E	Yield (%)
B	PhSO$_2$SPh	(F, SPh, Cl)	75
A	4-EtO$_2$CC$_6$H$_4$I cat. Pd(dba)$_2$ cat. P(2-furyl)$_3$	(EtO$_2$C, CO$_2$Et, Br, CO$_2$Et-phenyl)	72
A	RC$_6$H$_4$I cat. Pd(dba)$_2$ cat. P(2-furyl)$_3$	(Cl, CN, F, R-phenyl)	97 (3-OMe) 73 (4-CN)
A	4-EtO$_2$CC$_6$H$_4$I cat. Pd(dba)$_2$ cat. P(2-furyl)$_3$	(pyridine with CO$_2$Et-phenyl, Br, Br)	67
A	3-MeOC$_6$H$_4$I cat. Pd(dba)$_2$ cat. P(2-furyl)$_3$	(pyrazine with Cl, Cl, OMe-phenyl)	77
D	4-ClC$_6$H$_4$CHO	(pyrazole with Cl-phenyl, Me, OH)	62
A	3-bromocyclohexene (Cu-catalyzed allylation)	(furan with Br, CO$_2$Et, cyclohexenyl)	76

8 Conclusion

The development of *in situ* 'trans-metal trapping' allowed the limits of aromatic deprotometalation to be extended (tolerance toward functional group, soft conditions to deprotonate less activated substrates), and the method is now used in multistep syntheses, such as that of the natural product 2,6-dichloro-3-phenethylphenol below (3 steps, 63% overall yield; Scheme 25).[53] In addition, *in situ* 'trans-metal trapping' allowed unexpected regioselectivities to be reached (e.g. far from fluorine) as well as aromatic polymetalations.
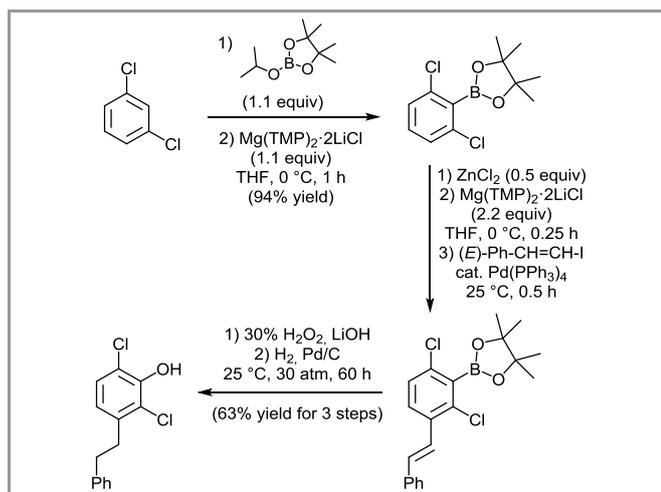
Scheme 25 Synthesis of the natural product 2,6-dichloro-3-phenethylphenol using *in situ* 'trans-metal trapping'

As shown in this short review, main group organometallics play a crucial role in organic synthesis. It is expected to continue to growth with the use of the methods presented in the synthesis of elaborated scaffolds. The increased compatibility gained by employing continuous flow reactions, as well as the low price and toxicity of the metal salts used here should contribute to this development.

References

(1) (a) Gschwend, H. W.; Rodriguez, H. R. *Org. React. (N.Y.)* **1979**, *26*, 1. (b) Gant, T. G.; Meyers, A. I. *Tetrahedron* **1994**, *50*, 2297. (c) Schlosser, M. *Organoalkali Chemistry*, In *Organometallics in Synthesis: A Manual*, 2nd ed.; Schlosser, M., Ed.; John Wiley & Sons: Hoboken, **2002**, Chap. 1, 1. (d) Hartung, C. G.; Snieckus, V. *The Directed ortho Metalation of Aromatic Compounds*, In *Modern Arene Chemistry*; Astruc, D., Ed.; **2002**, 330. (e) Clayden, J. *Directed Metalation of Aromatic Compounds*, In *Chemistry of Organolithium Compounds*; Rappoport, Z.; Marek, I., Eds.; **2004**, *1*, 495. (f) Tilly, D.; Magolan, J.; Mortier, J. *Chem. Eur. J.* **2012**, *18*, 3804.

(2) See for example: Eaton, P. E.; Lee, C. H.; Xiong, Y. *J. Am. Chem. Soc.* **1989**, *111*, 8016.

(3) (a) Mulvey, R. E.; Mongin, F.; Uchiyama, M.; Kondo, Y. *Angew. Chem. Int. Ed.* **2007**, *46*, 3802. (b) Mulvey, R. E. *Acc. Chem. Res.* **2009**, *42*, 743. (c) Haag, B.; Mosrin, M.; Ila, H.; Malakhov, V.; Knochel, P. *Angew. Chem. Int. Ed.* **2011**, *50*, 9794. (d) Mongin, F.; Harrison-Marchand, A. *Chem. Rev.* **2013**, *113*, 7563. (e) Mulvey, R. E. *Dalton Trans.* **2013**, *42*, 6676. (f) Harford, P. J.; Peel, A. J.; Chevallier, F.; Takita, R.; Mongin, F.; Uchiyama, M.; Wheatley, A. E. H. *Dalton Trans.* **2014**, *43*, 14181.

(4) Lysén, M.; Hansen, H. M.; Begtrup, M.; Kristensen, J. L. *J. Org. Chem.* **2006**, *71*, 2518.

(5) Benischke, A. D.; Ellwart, M.; Becker, M. R.; Knochel, P. *Synthesis* **2016**, *48*, 1101.

(6) Note that lithium chloride, formed by using *in situ* traps such as chlorotrimethylsilane and zinc chloride, can also impact the reaction rate. See for example: (a) Lipshutz, B. H.; Wood, M. R.; Lindsley, C. W. *Tetrahedron Lett.* **1995**, *36*, 4385. (b) Gupta, L.; Hoepker, A. C.; Singh, K. J.; Collum, D. B. *J. Org. Chem.* **2009**, *74*, 2231. (c) Hevia, E.; Mulvey, R. E. *Angew. Chem., Int. Ed.* **2011**, *50*, 6448. (d) Liang, J.; Hoepker, A. C.; Algera, R. F.; Ma, Y.; Collum, D. B. *J. Am. Chem. Soc.* **2015**, *137*, 6292.

(7) In the frame of this Short Review, we discarded studies on the lithium-cadmium base "(TMP)$_3$CdLi" in spite of a probably similar behavior: (a) Mongin, F.; Uchiyama, M. *Curr. Org. Chem.* **2011**, *15*, 2340. (b) Armstrong, D. R.; Kennedy, A. R.; Mulvey, R. E.; Parkinson, J. A.; Robertson, S. D. *Chem. Sci.* **2012**, *3*, 2700.

(8) Marsais, F.; Laperdrix, B.; Güngör, T.; Mallet, M.; Queguiner, G. *J. Chem. Res. (S)* **1982**, 278.

(9) Krizan, T. D.; Martin, J. C. *J. Am. Chem. Soc.* **1983**, *105*, 6155.

(10) Upton, C. J.; Beak, P. *J. Org. Chem.* **1975**, *40*, 1094.

(11) (a) Luliński, S.; Serwatowski, J. *J. Org. Chem.* **2003**, *68*, 5384. (b) Luliński, S.; Serwatowski, J. *J. Org. Chem.* **2003**, *68*, 9384.

(12) Decouzon, M.; Ertl, P.; Exner, O.; Gal, J.-F.; Maria, P.-C. *J. Am. Chem. Soc.* **1993**, *115*, 12071.

(13) Heiss, C.; Marzi, E.; Schlosser, M. *Eur. J. Org. Chem.* **2003**, 4625.

(14) Gilman, H.; Gorsich, R. D. *J. Am. Chem. Soc.* **1956**, *78*, 2217.

(15) Erb, W.; Mongin, F. *Tetrahedron* **2016**, *72*, 4973.

(16) Widhalm, M.; Aichinger, C.; Mereiter, K. *Tetrahedron Lett.* **2009**, *50*, 2425.

(17) Dąbrowski, M.; Kubicka, J.; Luliński, S.; Serwatowski, J. *Tetrahedron Lett.* **2005**, *46*, 4175.

(18) (a) Luliński, S.; Serwatowski, J.; Zaczek, A. *Eur. J. Org. Chem.* **2006**, 5167. (b) Mongin, F. *Chimia* **2016**, *70*, 48.

(19) Mesgar, M.; Daugulis, O. *Org. Lett.* **2016**, *18*, 3910.

(20) (a) Nguyen, T.-H.; Chau, N. T. T.; Castanet, A.-S.; Nguyen, K. P. P.; Mortier, J. *Org. Lett.* **2005**, *7*, 2445. See also: (b) Chau, N. T. T.; Nguyen, T. H.; Castanet, A.-S.; Nguyen, K. P. P.; Mortier, J. *Tetrahedron* **2008**, *64*, 10552.

(21) Michaux, J.; Bessières, B.; Einhorn, J. *Tetrahedron Lett.* **2012**, *53*, 48.

(22) Black, W. C.; Guay, B.; Scheuermeyer, F. *J. Org. Chem.* **1997**, *62*, 758.

(23) (a) Gribble, G. W.; Saulnier, M. G. *Tetrahedron Lett.* **1980**, *21*, 4137. (b) Gribble, G. W.; Saulnier, M. G. *Heterocycles* **1993**, *35*, 151.

(24) Effenberger, F.; Daub, W. *Chem. Ber.* **1991**, *124*, 2119.

(25) Imahori, T.; Uchiyama, M.; Sakamoto, T.; Kondo, Y. *Chem. Commun.* **2001**, 2450.

(26) Tilly, D.; Fu, J.-m.; Zhao, B.-p.; Alessi, M.; Castanet, A.-S.; Snieckus, V.; Mortier, J. *Org. Lett.* **2010**, *12*, 68.

(27) (a) Price, D. A.; Simpkins, N. S.; MacLeod, A. M.; Watt, A. P. *J. Org. Chem.* **1994**, *59*, 1961. (b) Ewin, R. A.; MacLeod, A. M.; Price, D. A.; Simpkins, N. S.; Watt, A. P. *J. Chem. Soc., Perkin Trans. 1* **1997**, 401.

(28) See also: Schmalz, H.-G.; Schellhaas, K. *Tetrahedron Lett.* **1995**, *36*, 5515.

(29) Price, D.; Simpkins, N. S. *Tetrahedron Lett.* **1995**, *36*, 6135.

(30) Mongin, F.; Curty, C.; Marzi, E.; Leroux, F. R.; Schlosser, M. *ARKIVOC* **2015**, 48.

(31) Caron, S.; Hawkins, J. M. *J. Org. Chem.* **1998**, *63*, 2054.

(32) Fraser, R. R.; Mansour, T. S.; Savard, S. *J. Org. Chem.* **1985**, *50*, 3232.

(33) Kristensen, J.; Lysen, M.; Vedsø, P.; Begtrup, M. *Org. Lett.* **2001**, *3*, 1435.

(34) Iwao, M. *J. Org. Chem.* **1990**, *55*, 3622.

(35) Hansen, H. M.; Lysén, M.; Begtrup, M.; Kristensen, J. L. *Tetrahedron* **2005**, *61*, 9955.

(36) Alessi, M.; Larkin, A. L.; Ogilvie, K. A.; Green, L. A.; Lai, S.; Lopez, S.; Snieckus, V. *J. Org. Chem.* **2007**, *72*, 1588.

(37) Cederbalk, A.; Lysén, M.; Kehler, J.; Kristensen, J. L. *Tetrahedron* **2017**, *73*, 1576.

(38) (a) Jaric, M.; Haag, B. A.; Unsinn, A.; Karaghiosoff, K.; Knochel, P. *Angew. Chem. Int. Ed.* **2010**, *49*, 5451. (b) Jaric, M.; Haag, B. A.; Manolikakes, S. M.; Knochel, P. *Org. Lett.* **2011**, *13*, 2306. (c) Groll, K.; Manolikakes, S. M.; Mollat du Jourdin, X.; Jaric, M.; Bredihhin, A.; Karaghiosoff, K.; Carell, T.; Knochel, P. *Angew. Chem., Int. Ed.* **2013**, *52*, 6776.

(39) Seggio, A.; Lannou, M.-I.; Chevallier, F.; Nobuto, D.; Uchiyama, M.; Golhen, S.; Roisnel, T.; Mongin, F. *Chem. Eur. J.* **2007**, *13*, 9982.

(40) (a) L'Helgoual'ch, J. M.; Seggio, A.; Chevallier, F.; Yonehara, M.; Jeanneau, E.; Uchiyama, M.; Mongin, F. *J. Org. Chem.* **2008**, *73*, 177. (b) Snégaroff, K.; Komagawa, S.; Chevallier, F.; Gros, P. C.; Golhen, S.; Roisnel, T.; Uchiyama, M.; Mongin, F. *Chem. Eur. J.* **2010**, *16*, 8191. (c) García-Álvarez, P.; Mulvey, R. E.; Parkinson, J. A. *Angew. Chem. Int. Ed.* **2011**, *50*, 9668.

(41) Plé, N.; Turck, A.; Couture, K.; Quéguiner, G. *J. Org. Chem.* **1995**, *60*, 3781.

(42) Seggio, A.; Chevallier, F.; Vaultier, M.; Mongin, F. *J. Org. Chem.* **2007**, *72*, 6602.

(43) Snégaroff, K.; Nguyen, T. T.; Marquise, N.; Halauko, Y. S.; Harford, P. J.; Roisnel, T.; Matulis, V. E.; Ivashkevich, O. A.; Chevallier, F.; Wheatley, A. E. H.; Gros, P. C.; Mongin, F. *Chem. Eur. J.* **2011**, *17*, 13284.

(44) Ameur Messaoud, M. Y.; 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.

(45) (a) 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. (b) 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. (c) Marquise, N.; Nguyen, T. T.; Chevallier, F.; Picot, L.; Thiery, V.; Lozach, O.; Bach, S.; Ruchaud, S.; Mongin, F. *Synlett* **2015**, *26*, 2811.

(46) (a) Dayaker, G.; Sreeshailam, A.; Chevallier, F.; Roisnel, T.; Radha Krishna, P.; Mongin, F. *Chem. Commun.* **2010**, *46*, 2862. (b) Tazi, M.; Erb, W.; Halauko, Y. S.; Ivashkevich, O. A.; Matulis, V. E.; Roisnel, T.; Dorcet, V.; Mongin, F. *Organometallics* **2017**, *36*, 4770.

(47) Dayaker, G.; Tilly, D.; Chevallier, F.; Hilmersson, G.; Gros, P. C.; Mongin, F. *Eur. J. Org. Chem.* **2012**, 6051.

(48) (a) Sreeshailam, A.; Dayaker, G.; Ramana, D. V.; Chevallier, F.; Roisnel, T.; Komagawa, S.; Takita, R.; Uchiyama, M.; Radha Krishna, P.; Mongin, F. *RSC Adv.* **2012**, *2*, 7030. (b) Dayaker, G.; Sreeshailam, A.; Ramana, D. V.; Chevallier, F.; Roisnel, T.; Komagawa, S.; Takita, R.; Uchiyama, M.; Krishna, P. R.; Mongin, F. *Tetrahedron* **2014**, *70*, 2102.

(49) (a) Eaton, P. E.; Castaldi, G. *J. Am. Chem. Soc.* **1985**, *107*, 724. (b) Eaton, P. E.; Higuchi, H.; Millikan, R. *Tetrahedron Lett.* **1987**, *28*, 1055.

(50) Eaton, P. E.; Daniels, R. G.; Casucci, D.; Cunkle, G. T.; Engel, P. *J. Org. Chem.* **1987**, *52*, 2100.

(51) Eaton, P. E.; Cunkle, G. T.; Marchioro, G.; Martin, R. M. *J. Am. Chem. Soc.* **1987**, *109*, 948.

(52) Dong, Z.; Clososki, G. C.; Wunderlich, S. H.; Unsinn, A.; Li, J.; Knochel, P. *Chem. Eur. J.* **2009**, *15*, 457.

(53) Unsinn, A.; Rohbogner, C. J.; Knochel, P. *Adv. Synth. Catal.* **2013**, *355*, 1553.

(54) Unsinn, A.; Wunderlich, S. H.; Knochel, P. *Adv. Synth. Catal.* **2013**, *355*, 989.

(55) Nagaradja, E.; Chevallier, F.; Roisnel, T.; Dorcet, V.; Halauko, Y. S.; Ivashkevich, O. A.; Matulis, V. E.; Mongin, F. *Org. Biomol. Chem.* **2014**, 1475.

(56) 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.

(57) (a) 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. (b) Hedidi, M.; Maillard, J.; Erb, W.; Lassagne, F.; Halauko, Y. S.; Ivashkevich, O. A.; Matulis, V. E.; Roisnel, T.; Dorcet, V.; Hamze, M.; Fajloun, Z.; Baratte, B.; Ruchaud, S.; Bach, S.; Bentabed-Ababsa, G.; Mongin, F. *Eur. J. Org. Chem.* **2017**, 5903.

(58) Amara, R.; Bentabed-Ababsa, G.; Hedidi, M.; Khoury, J.; Awad, H.; Nassar, E.; Roisnel, T.; Dorcet, V.; Chevallier, F.; Fajloun, Z.; Mongin, F. *Synthesis* **2017**, *49*, 4500.

(59) Eaton, P. E.; Martin, R. M. *J. Org. Chem.* **1988**, *53*, 2728.

(60) (a) Chevallier, F.; Halauko, Y. S.; Pecceu, C.; Nassar, I. F.; Dam, T. U.; Roisnel, T.; Matulis, V. E.; Ivashkevich, O. A.; Mongin, F. *Org. Biomol. Chem.* **2011**, *9*, 4671. (b) 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.

(61) Chevallier, F.; Blin, T.; Nagaradja, E.; Lassagne, F.; Roisnel, T.; Halauko, Y. S.; Matulis, V. E.; Ivashkevich, O. A.; Mongin, F. *Org. Biomol. Chem.* **2012**, *10*, 4878.

(62) Fuentes, M. A.; Kennedy, A. R.; Mulvey, R. E.; Parkinson, J. A.; Rantanen, T.; Robertson, S. D.; Snieckus, V. *Chem. Eur. J.* **2015**, *21*, 14812.

(63) 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.

(64) Crosbie, E.; Kennedy, A. R.; Mulvey, R. E.; Robertson, S. D. *Dalton Trans.* **2012**, *41*, 1832.

(65) McLellan, R.; Uzelac, M.; Kennedy, A. R.; Hevia, E.; Mulvey, R. E. *Angew. Chem., Int. Ed.* **2017**, *56*, 9566.

(66) Armstrong, D. R.; Crosbie, E.; Hevia, E.; Mulvey, R. E.; Ramsay, D. L.; Robertson, S. D. *Chem. Sci.* **2014**, *5*, 3031.

(67) Uzelac, M.; Kennedy, A. R.; Hevia, E. *Inorg. Chem.* **2017**, *56*, 8615.

(68) Mulvey, R. E.; Armstrong, D. R.; Conway, B.; Crosbie, E.; Kennedy, A. R.; Robertson, S. D. *Inorg. Chem.* **2011**, *50*, 12241.

(69) Clegg, W.; Crosbie, E.; Dale-Black, S. H.; Hevia, E.; Honeyman, G. W.; Kennedy, A. R.; Mulvey, R. E.; Ramsay, D. L.; Robertson, S. D. *Organometallics* **2015**, *34*, 2580.

(70) Uzelac, M.; Kennedy, A. R.; Hevia, E.; Mulvey, R. E. *Angew. Chem., Int. Ed.* **2016**, *55*, 13147.

(71) Becker, M. R.; Knochel, P. *Angew. Chem. Int. Ed.* **2015**, *54*, 12501.

(72) (a) Ketels, M.; Konrad, D. B.; Karaghiosoff, K.; Trauner, D.; Knochel, P. *Org. Lett.* **2017**, *19*, 1666. (b) Ketels, M.; Ziegler, D. S.; Knochel, P. *Synlett* **2017**, *28*, 2817.

(73) Becker, M. R.; Ganiek, M. A.; Knochel, P. *Chem. Sci.* **2015**, *6*, 6649.

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