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Deprotonative Metalation of Chloro- and Bromopyridines Using Amido-Based Bimetallic Species and Regioselectivity-Computed CH Acidity Relationships

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Abstract: A series of chloro- and bromopyridines have been deprotometalated by using a range of 2,2,6,6-tetramethylpiperidino-based mixed lithium–metal combinations. Whereas lithium–zinc and lithium–cadmium bases afforded different mono- and diiodides after subsequent interception with iodine, complete regioselectivities were observed with the corresponding lithium–copper combination, as demonstrated by subsequent trapping with benzoyl chlorides. The obtained selectivities have been discussed in light of the CH acidities of the substrates, determined both in the gas phase and as a solution in THF by using the DFT B3LYP method.

Keywords: acidity · bimetallic bases · deprotonation · lithium · pyridines

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Introduction

The deprotonative metalation of aromatic compounds has great synthetic potential. The methodology that uses alkyllithiums and lithium dialkylamides has been largely employed for this purpose.[1] Applications to π-deficient heteroaromatics such as pyridines have been delayed, with one complication being that the alkyllithiums used as base or the heteroaryllithiums generated by deprotonation using hindered lithium amides can easily add to the C=N bond of the azine.[2]

Other possible complications that arise after deprotonation of chloro- and bromopyridines are heteroaryne formation, ring opening, and halogen scrambling.[2a] Most of these side reactions have now been circumvented with the use of alkyllithiums and hindered lithium dialkylamides at very low temperatures. Nevertheless, these conditions can be prohibitive, and there is need for alternative methods. The use of metal additives to obtain more chemoselective bases is a challenging field. Pioneering methods carried out in the pyridine series with BuLi– or Me_3SiCH_2Li–(DMAE)Li (DMAE = 2-dimethylaminoethoxide) merge alkyllithiums and lithium alkoxides.[3] More recently, other $[(R)_n(R')_nMLi]$-type bases, in which metal M is not an alkali metal (for example, M = Mg,[4] Zn,[4a,c,5] and Cu[6]), have been described by different groups for their ability to deprotonate sensitive heterocycles and notably pyridines.

We recently accomplished the room-temperature deprotometalation of a large range of substrates including sensitive heterocycles by using newly developed lithium–zinc,[7] lithium–cadmium,[8] and lithium–copper(I)[9] combinations, prepared in situ from MCl_2·TMEDA (M = Zn, Cd, or Cu;

TMEDA = *N*,*N*,*N*′,*N*′-tetramethylethylenediamine) and lithium reagents (alkyllithiums or lithium amides). The studies performed have notably shown that the most efficient [$(R)_n(R')_n$MLi] bases were obtained with R = R′ = TMP (TMP = 2,2,6,6-tetramethylpiperidido). Herein we report our investigation on the deprotometalation of the synthetically useful chloro- and bromopyridines by using such reagents and a further development with [$(TMP)_2$CuLi], which allowed isolated, crystalline, Gilman-type reagent to be applied in deprotonative metalation. Additionally, since most related investigations only describe the synthetic outcome of reactions, and since the regioselectivity is partly determined by the acidity of the different hydrogen atoms in the substrate molecule, we tried to rationalize the reaction results by using the CH acidities in THF of the pyridine substrates. The pK_a values of azines were calculated within the density functional theory (DFT) framework by using the homodesmic reaction approach developed earlier for azoles.[10]

Results and Discussion

As the number of substances investigated is rather large and their chemical identity diverse enough, we decided that a traditional literature review followed by an all-in-one experiment description would be a tedious and ineffective approach. Instead, we decided to present general trends in computed CH acidity first. Then experimental results for particular azine derivatives are discussed in connection with their acidities and literature data. And, finally, the conclusions on reaction regioselectivity control are given.

Computational aspects: A brief review of papers devoted to experimental and theoretical investigation of CH acidity in azoles is presented in our previous publications;[10] however, data on CH acidity in azines are scanty. The main reasons are stated above, namely, the necessity of using very strong bases at very low temperatures and the side reactions observed with azine carbanions. Among the reported experimental studies, CH acidity measurements on alkylated pyridines in THF[11] and carbon acidities in the gas phase on heteroaromatic compounds, including azines,[12] should be mentioned. The CH acidity of some unsubstituted azines have also been studied by quantum chemical calculations by using semiempirical Austin Model 1 (AM1)[12a,13] and DFT[14] methods.

In the present work, gas-phase acidity and pK_a values of solutions in THF were calculated within the DFT framework as thoroughly described earlier.[10a] Namely, gas-phase acidity was associated with the Gibbs energy ($\Delta_{acid}G$) of deprotonation of the substance [Eq. (1)]:

$$R{-}H_{(g)} \rightarrow R^-_{(g)} + H^+_{(g)} \quad (1)$$

By using calculated values of Gibbs energy of species in the gas phase, $\Delta_{acid}G$ was calculated by the following formula [Eq. (2)]:

$$\Delta_{acid}G = G^0_{298}(R^-) + G^0_{298}(H^+) - G^0_{298}(RH) \quad (2)$$

The pK_a values were calculated by means of isodesmic reaction method. We considered the following isodesmic reaction [Eq. (3)]:

$$R{-}H_{(s)} + Het^-_{(s)} \rightarrow R^-_{(s)} + Het{-}H_{(s)} \quad (3)$$

in which Het−H is an appropriate six-membered heterocycle with an experimentally known pK_a value. In this work, we chose unsubstituted pyridine as a reference compound. The main reasons for such a choice are structural and pK_a range proximity.

The isodesmic reaction Gibbs energy was calculated using Equation (4):

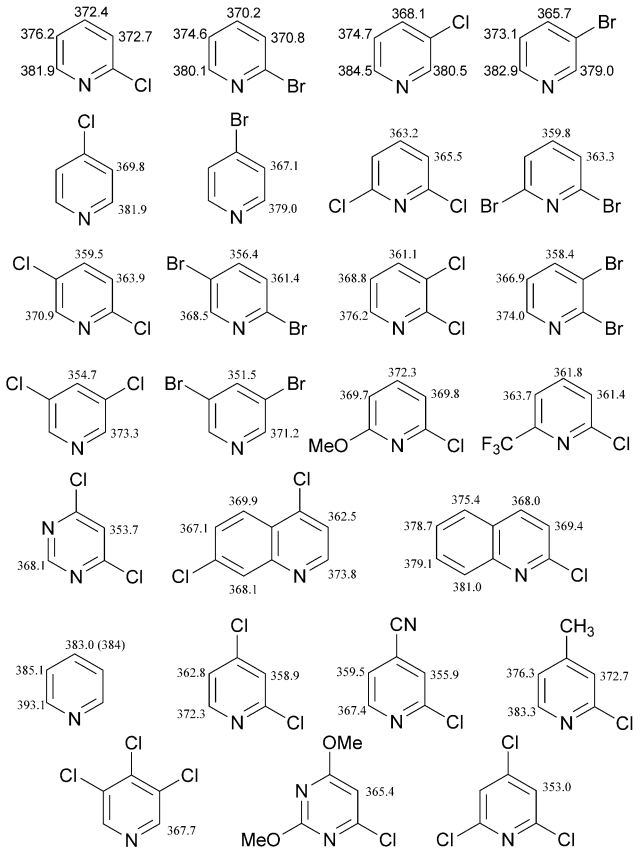
$$\Delta_r G_s = \sum_{\text{products}} G_s - \sum_{\text{reactants}} G_s \quad (4)$$

Further, it can be proved that [Eq. (5)]:

$$pK_a(RH) = pK_a(HetH) + \frac{\Delta_r G_s}{RT}\frac{1}{\ln 10} \quad (5)$$

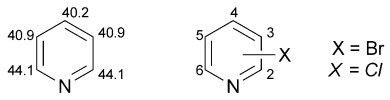
Theoretically related approaches have previously been used for NH acidity determination of pyridinium salts[15] and for pK_a calculation of azines together with quantitative structure–property relationships (QSPR) modeling.[16]

Investigation of gas-phase CH acidity (Scheme 1) is of great importance for the development of an acidity scale free of solvent influence. The calculated values of the gas-phase acidity of investigated compounds lie within the range of 351.5 (for 3,5-dibromopyridine) to 393.1 kcal mol^{-1} (for unsubstituted pyridine) and are in excellent agreement with the available experimental data.[12] The insertion of halogens into azine leads to a significant $\Delta_{acid}G$ decrease (10–12 kcal mol^{-1} for the first atom and another 8–10 kcal mol^{-1} for the second one, on average). In all cases, bromine exhibits a stronger acidifying effect than chlorine, which is in agreement with the electronic effects of the substituents.[17] One can see that deprotonation α to nitrogen must be thermodynamically unfavorable due to destabilization of the carbanion formed by repulsion of two neighboring lone electron pairs (this effect was thoroughly discussed earlier[10a]). On the contrary, the sites α to halogens are the most acidified. When switching from isolated molecules to their solution in THF, the trends in CH acidity of halogenoazines remain the same (Tables 1–9). Insertion of a halogen into an azine ring leads to a decrease in pK_a values by 4–8 units for the first atom and by 3–6 units for the subsequent one (Table 1). The calculated pK_a values of investigated compounds in THF lie in a wide range from 23.6 (for 4,6-dichloropyrimidine) to 44.1 (for pyridine). Bromine also exhibits a stronger acidifying effect than chlorine, including long range action (see 2,6-



Scheme 1. Calculated values of $\Delta_{acid}G$ [kcal mol^{-1}] of the investigated azines (experimental value[12a] given in brackets).

Table 1. pK_a(THF) decrease for pyridine caused by halogen substituents.

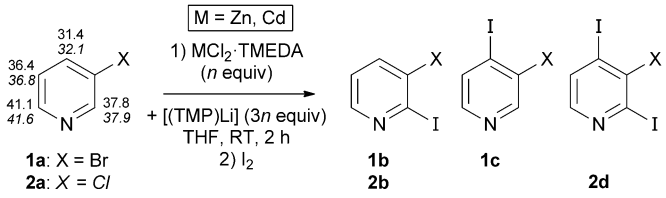


X	ΔpK_a(THF)				
	C2	C3	C4	C5	C6
2-Br (2-Cl)	–	7.4 (6.9)	5.2 (4.5)	3.5 (3.1)	4.4 (3.9)
3-Br (3-Cl)	6.3 (6.2)	–	8.8 (8.1)	4.5 (4.1)	3.0 (2.5)
4-Br (4-Cl)	4.3 (3.7)	8.8 (7.9)	–	8.8 (7.9)	4.3 (3.7)
2,6-diBr (2,6-diCl)	–	9.9 (9.3)	9.7 (8.4)	9.9 (9.3)	–
2,5-diBr (2,5-diCl)	–	11.1 (10.4)	12.6 (11.7)	–	10.5 (10.1)
(2,4-diCl)	–	(14.2)	–	(10.5)	(7.9)
2,3-diBr (2,3-diCl)	–	–	12.2 (11.3)	7.0 (6.4)	6.8 (6.2)
3,5-diBr (3,5-diCl)	9.1 (8.7)	-	16.3 (15.5)	-	9.1 (8.7)
(2,4,6-triCl)	–	(16.3)	–	(16.3)	–
(3,4,5-triCl)	(11.4)	–	–	–	(11.4)

dichloropyridine and 2,6-dibromopyridine). When compared with the gas phase, the halogen effect on the adjacent sites becomes even stronger, thereby leading to the most acidic position switching for 2-halogenopyridine, 2,6-dichloropyridine, and 2-chloroquinoline. The most evident acidifying effect takes place in molecules with concordant halogen or/and nitrogen interactions (see 3-halogenopyridine, 2,5-dihalogenopyridine, 3,5-dihalogenopyridine, and 4,6-dichloropyrimidine).

Synthetic aspects: We first focused on the deprotometalation of 3-bromo- and 3-chloropyridine (**1a** and **2a**) (Table 2). The literature reveals a high level of flexibility over the regioselectivity with which metalation occurs in 3-bromopyridine. (DA)Li (DA = diisopropylamido) at −78 °C[18] or [tBu$_2$Zn(DA)Li] at room temperature[19] abstracts its C4 hydrogen when the reaction is conducted in THF. Treatment of a solution of 3-bromopyridine in THF by

Table 2. Calculated pK_a(THF) values for the 3-halogenopyridines **1a** and **2a**, and deprotonative metalation followed by trapping with I_2.



Entry	Substrate [X]	M, n [equiv]	Products, yields [%]		
1	**1a** (Br)	Zn, 0.5	**1b**, 83[a]	**1c**, 13[a]	–
2	**2a** (Cl)	Zn, 0.5	**2b**, 66[a]	–	**2d**, 4[a,b]
3		Cd, 0.5	**2b**, 50[a]	–	**2d**, 8[a,b]
4		Cd, 1.0	**2b**, –	–	**2d**, 69[a,c]

[a] Yields after isolation by column chromatography. [b] Traces of 3-chloro-2,5-diiodopyridine (**2e**) were also observed. [c] 3-Chloro-2,4,5-triiodopyridine (**2f**) and 3-chloro-2,4,6-triiodopyridine (**2g**) were also isolated in 3 and 2% yield, respectively.

tBuLi at −78 °C followed by quenching with chlorotrimethylsilane also leads to the 4-substituted derivative.[20] The use of (DA)Li in THF at −60 to −50 °C promotes bromine migration, thereby affording 4-bromo-3-substituted pyridines as the major products after interception with electrophiles.[2a] This result is proved by quantum chemical calculations, which predict for such a rearrangement close to zero Gibbs energy (1.9 kJ mol^{-1}) in THF. Conducting the reactions in THF at −100 °C, or using chlorotrimethylsilane as an in situ trap, gives rise to mixtures of 2- and 4-substituted 3-bromopyridines.[21] In contrast, the reaction exclusively occurs at the 2-position when using [tBu$_2$Zn(TMP)Li] in Et$_2$O at room temperature[19] or [(TMP)$_4$Zr] in THF at −10 °C.[22]

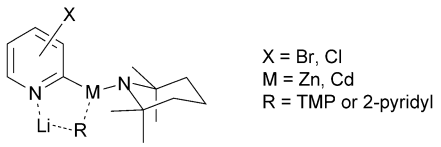
The 1:1 mixture of [(TMP)Li] and [(TMP)$_2$Zn],[7c] easily generated in situ by adding 1.5 equiv of [(TMP)Li] to 0.5 equiv of ZnCl$_2$·TMEDA,[23] was chosen to develop a new

approach to the room temperature deprotometalation of 3-bromopyridine (**1a**). Upon treatment by the basic mixture in THF for 2 h and subsequent interception with iodine, the halogenopyridine was converted to a mixture of the 2- and 4-iodo derivatives **1b** and **1c**, which could be isolated in 83 and 13% yields, respectively (Table 2, entry 1).

As observed with 3-bromopyridine, 3-chloropyridine (**2a**) is regioselectively lithiated at the 4-position by using hindered lithium amides at very low temperatures in THF.[18] The TMP-based lithium magnesiates can also be employed at −10°C for the same purpose.[24] In contrast, metalation takes place at the 2-position by using BuLi–TMEDA in Et_2O at −60°C,[25] BuLi–(DMAE)Li in hexane at −60°C,[26] 2:1 Me_3SiCH_2Li–(DMAE)Li in hexane at 0°C,[27] [(TMP)MgCl]·LiCl in THF at −78°C,[4c] and [$(TMP)_4Zr$] in THF at 0°C.[22]

The use of 1:1 [(TMP)Li]/[$(TMP)_2Zn$] was attempted in the metalation of 3-chloropyridine (**2a**). Under the conditions employed for the 3-bromo substrate, reaction occurred similarly at C2 to afford the 2-iodo derivative **2b** in 66% yield after subsequent trapping (Table 2, entry 2). Upon treatment with [$(TMP)_3CdLi$], easily generated in situ by adding 1.5 equiv of [(TMP)Li] to 0.5 equiv of $CdCl_2$·TMEDA,[28] the iodide **2b** was obtained in a lower 50% yield due to the competitive formation of other iodides such as the 2,4-diiodo derivative **2d** (entry 3). The formation of the latter species could be favored by using 1 equiv of base instead of 0.5, thereby affording the diiodide **2d** in 69% yield (entry 4).

From these different data, it is possible to draw some conclusions. The use of hindered lithium amides in THF allows reversible reactions, and the 4-lithio species is thus the thermodynamic monometal product (combined electron-withdrawing effects of the halogen[29] and nitrogen; no electron repulsion with the lone pair of the azine nitrogen).[2] The reaction using *t*BuLi in THF also leads to the 4-substituted derivative. In this case, there is no equilibrium, and the compound results from an abstraction of the most acidic hydrogen, as *t*BuLi is not very prone to nitrogen complexation in the presence of THF.[2] Under kinetic conditions (low temperatures or in situ trap), the reaction takes place at both the 4 (most acidic hydrogen) and 2 (approach of the base favored by complexation to the ring nitrogen) positions as a result of effects that stabilize the transition state.[30] The ability of the ring nitrogen to complex the metal of the base is reinforced by using Et_2O and, to a greater extent, hexane as the solvent. In addition, compared with the monometallic bases, the bimetallic ones could be more easily directed to the 2-position through metal complexation by the ring nitrogen. More importantly, whereas the 4-metalated derivative is more stable than the 2-metalated one (which suffers from electron repulsion with the lone pair of the azine nitrogen) in the case of monometal bases, it could be different with bimetal bases. Indeed, for the latter, the lone pair of the azine nitrogen could be involved in a complexation of the second metal (lithium), thereby stabilizing the structure.[31] By using 1:1 [(TMP)Li]/[$(TMP)_2Zn$], or [$(TMP)_3CdLi$], a shift in equilibrium to the 4-metalated species from the initially formed 2-metalated pyridine could thus be prevented by stabilization through lithium complexation as depicted in Scheme 2.

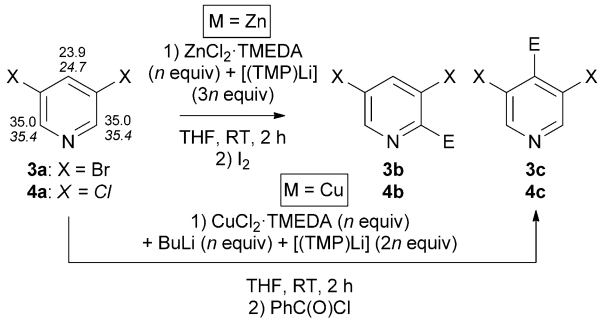


Scheme 2. Proposed stabilization through lithium complexation.

This could explain why the second metalation, when it takes place, occurs at the most acidic 4-position, the pyridine nitrogen not being more available for lithium complexation.

We next studied the behavior of 3,5-dibromo- and 3,5-dichloropyridine (**3a** and **4a**; Table 3). 3,5-Dibromo-[32] and 3,5-dichloropyridine[33] are regioselectively lithiated at their 4-position when treated with (DA)Li at low temperatures in THF. The TMP-based lithium magnesiates at −10°C[24] and BuLi at −75°C[34] behave similarly when used in THF in the case of the dichloride. In contrast, metalation of 3,5-dibromopyridine occurs at the 2-position when using [(TMP)MgCl]·LiCl in THF at 25°C.[35]

Table 3. Calculated pK_a(THF) values for the 3,5-dihalogenopyridines **3a** and **4a**, and deprotonative metalation followed by electrophilic trapping.



Entry	Substrate [X]	M, *n* [equiv]	Products [E], yields [%]	
1	**3a** (Br)	Zn, 0.5	**3b** (I), 22[a]	**3c** (I), 8[b]
2	**4a** (Cl)	Zn, 0.3	**4b** (I), 3[a]	**4c1** (I), 16[a]
3		Cu, 1	–	**4c2** (C(O)Ph), 33[a]

[a] Yields after isolation by column chromatography. [b] Yield estimated by ^{1}H NMR spectroscopy for a nonseparable mixture with starting material.

The use of 1:1 [(TMP)Li]/[$(TMP)_2Zn$] with the 3,5-dihalogenopyridines **3a** and **4a** resulted in mixtures with predominant metalation next to nitrogen in the case of the dibromide **3a** (Table 3, entry 1) and favored reaction at the 4-position in the case of the dichloride **4a** (entry 2). Complete regioselectivity at C4 was obtained when using [$(TMP)_2CuLi$] prepared in situ by successively adding 1 equiv of BuLi (causing reduction of copper(II) to copper(I)), and 2 equiv of [(TMP)Li] to 1 equiv of

$CuCl_2$·TMEDA.[36] Due to easy oxidation of copper(I), the use of iodine as the electrophile is prohibited. Indeed, it has previously been shown to promote oxidative homocoupling in addition to the expected iodides.[9b] We thus turned to aroyl chlorides to intercept the intermediate aryl cuprates.[6,37] Under the same deprotonation conditions, and after trapping with benzoyl chloride, the ketone **4c2** was isolated in a modest 33% yield (entry 3). It is important to note that, whatever the reaction conditions tested, it proved impossible to functionalize 3-chloropyridine by using [$(TMP)_2CuLi$].

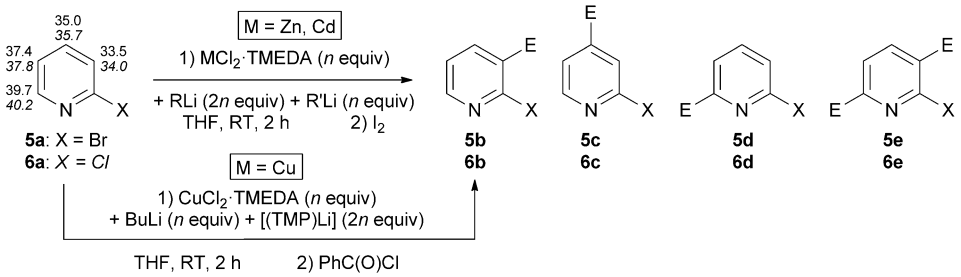
The combination of two adjacent acidifying halogens makes the pyridine 4-position easy to attack; as a consequence, different bases can be employed for this purpose under several reaction conditions. Deprotometalation at the 2-position can nevertheless be observed by employing bimetallic bases such as [(TMP)MgCl]·LiCl or 1:1 [(TMP)Li]/[$(TMP)_2Zn$], for reasons similar to those given for 3-halogenopyridines, but also provided that the pyridine bears bulky halogens such as bromines. Indeed, with smaller chloro groups, the combined acidifying effects of the halogens overcome the ability of the ring nitrogen to complex the base.

2-Bromo- and 2-chloropyridine (**5a** and **6a**) were next considered (Table 4). With 2-bromopyridine, the (DA)Li-promoted reaction occurs at the 3-position in THF at −78°C.[38] The 3-position is also preferentially attacked by using [tBu_2Zn(DA)Li] in Et_2O at −20°C.[19] Employing chlorotrimethylsilane as an in situ trap results in major lithiation at the 3-position, with minor lithiation at the 4-position.[21] [(TMP)Li] in Et_2O at −78°C in the presence of chlorotrimethylsilane and [tBu_2Zn(TMP)Li] in THF at room temperature both lead to functionalization at the 6-position.[19]

When treated with 1:1 [(TMP)Li]/[$(TMP)_2Zn$] (0.5 equiv each) in THF at room temperature for 2 h, metalation of 2-bromopyridine (**5a**) took place, but unregioselectively at the 3-, 4-, and 6-position, and some dimetalation was noted (Table 4, entry 1). The reaction repeated by using 1:1 [(TMP)Li]/[$(TMP)_2Zn$] (0.3 equiv each) allowed to us discard the dimetalation reaction, but no regioselectivity improvement was observed (entry 2). We thus decided to attempt the use of other lithium–zinc combinations.

[$Bu(TMP)_2ZnLi$][7e] (0.7 equiv) was employed under the same reaction conditions, and furnished a 67:33 mixture of the 3- and 4-iodo derivatives **5b1** and **5c** (Table 4, entry 3). Surprisingly, when 1 equiv of [$Bu(TMP)_2ZnLi$] was used, the three iodides **5b1**, **5c**, and **5d** were obtained in a 43:17:40 ratio, together with the diiodide **5e** (entry 4). [Bu_2-(TMP)ZnLi][7e] proved much less efficient than the previous bases. Using 0.7 or 1 equiv of this less hindered base allowed us to avoid the formation of the 6-iodo derivative **5d**, thereby leading to mixtures of **5b1** and **5c** (entries 5 and 6). The deprotometalation reaction was not observed any more

Table 4. Calculated pK_a(THF) values for the 2-halogenopyridines **5a** and **6a**, and deprotonative metalation followed by electrophilic trapping.



Entry	Substrate [X]	M, *n* [equiv]	R, R′	Products [E], yields [%]			
1	**5a** (Br)	Zn, 0.5	TMP, TMP	**5b1** (I), 36[a]	**5c** (I), 16[a]	**5d** (I), 22[a]	**5e** (I), 8[a]
2		Zn, 0.3	TMP, Bu	**5b1** (I), 42[a]	**5c** (I), 13[a]	**5d** (I), 35[a]	**5e** (I), 1[a]
3		Zn, 0.7	Bu, TMP	**5b1** (I), 65[a]	**5c** (I), 32[a]	**5d** (I), traces[a]	**5e** (I), –
4[b]		Zn, 1	Bu, Bu	**5b1** (I), 37[a]	**5c** (I), 15[a]	**5d** (I), 34[a]	**5e** (I), 7[a]
5		Zn, 0.7	–	**5b1** (I), 20[a]	**5c** (I), 18[a]	**5d** (I), –	**5e** (I), –
6		Zn, 1		**5b1** (I), 34[a]	**5c** (I), 23[a]	**5d** (I), –	**5e** (I), –
7[c]		Zn, 1		**5b1** (I), –	**5c** (I), –	**5d** (I), –	**5e** (I), –
8		Cu, 1		**5b2** (C(O)Ph), 20[d]	–	–	–
9	**6a** (Cl)	Zn, 0.5	TMP, TMP	**6b1** (I), 43[a]	**6c** (I), 9[a]	**6d** (I), 30[d]	**6e** (I), 15[d]
10		Zn, 0.7	TMP, Bu	**6b1** (I), 63[a]	**6c** (I), 11[a]	**6d** (I), 4[d]	**6e** (I), –
11[e]		Zn, 1		**6b1** (I), 41[a]	**6c** (I), 6[a]	**6d** (I), 10[d]	**6e** (I), 3[d]
12		Zn, 0.7	Bu, TMP	**6b1** (I), 58[a]	**6c** (I), 19[a]	**6d** (I), –	**6e** (I), –
13		Zn, 1		**6b1** (I), 66[a]	**6c** (I), 17[a]	**6d** (I), –	**6e** (I), –
14		Cd, 0.5	TMP, TMP	**6b1** (I), 52[a]	**6c** (I), 4[a]	**6d** (I), 41[d]	**6e** (I), 3[d]
15[f]		Cd, 1		**6b1** (I), 21[a]	**6c** (I), 4[a]	**6d** (I), –	**6e** (I), 35[d]
16		Cu, 1	–	**6b2** (C(O)Ph), 83[d]	–	–	–
17		Cu, 1	–	**6b3** ($C(O)C_6H_4$-4-Cl), 79[d]	–	–	–

[a] Yields estimated by ^{1}H NMR spectroscopy for inseparable mixtures. [b] 2-Bromo-5-iodopyridine (**5f**) was also isolated in 1% yield. [c] 2-Iodopyridine (**5g**) was isolated in 72% yield. [d] Yields after isolation by column chromatography. [e] 2,5-Diiodopyridine (**6f**) was also isolated in 4% yield. [f] 2-Chloro-5,6-diiodopyridine (**6g**) and 2-chloro-3,4,6-triiodopyridine (**6h**) were also isolated in 7 and 5% yield, respectively.

when using [Bu_3ZnLi]; bromine–zinc exchange took place instead, as described recently,[31] to afford 2-iodopyridine (**5g**) in 72% yield (entry 7).

Complete regioselectivity at C3 could be obtained using [$(TMP)_2CuLi$], as evidenced by trapping with benzoyl chloride. Nevertheless, due to the sensitivity of the metalated species under the reaction conditions, the ketone **5b2** was isolated in a modest 20% yield (Table 4, entry 8). Performing the reaction at lower temperatures did not allow this result to be improved due to the competitive formation of regioisomers.

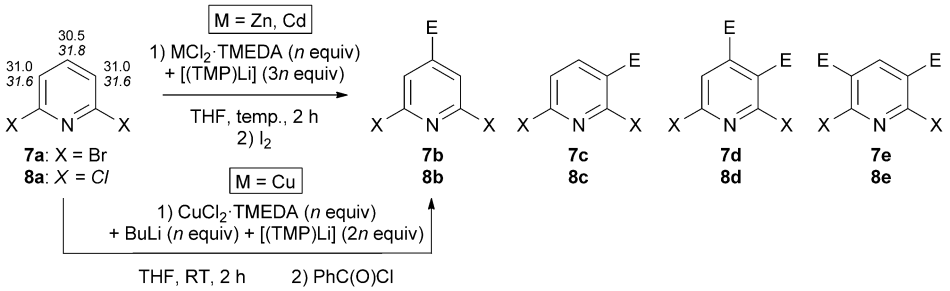
2-Chloropyridine can be lithiated at C3 using either (DA)Li,[18,39] or PhLi in the presence of a catalytic amount of diisopropylamine,[40] in THF at low temperatures. TMP-based lithium magnesates can also be employed at −10°C in THF.[24] By contrast, BuLi–(DMAE)Li[41] and 2:1 Me_3SiCH_2Li–(DMAE)Li[27] regioselectively abstract the proton at C6 when employed in hexane at −78 and 0°C, respectively.

As previously noted for 2-bromopyridine, 2-chloropyridine (**6a**) was converted into a mixture of the 3-, 4-, and 6-iodo derivatives **6b1**, **6c**, and **6d** as well as the 3,6-diiodo derivative **6e** when successively treated with 1:1 [(TMP)Li]/[$(TMP)_2Zn$] (0.5 equiv each) in THF at room temperature for 2 h and I_2 (Table 4, entry 9). [$Bu(TMP)_2ZnLi$][7e] (0.7 equiv and, to a lesser extent, 1 equiv) favored the formation of the iodide **6b1** (entries 10 and 11). As observed with 2-bromopyridine, the formation of the 6-iodo derivative **6d** was discarded when using [$Bu_2(TMP)ZnLi$][7e] (entries 12 and 13). [$(TMP)_3CdLi$] (0.5 equiv) gave results similar to those obtained using 1:1 [(TMP)Li]/[$(TMP)_2Zn$] (0.5 equiv each) (entry 14); its higher ability to dideprotonate was evidenced using 1 equiv of base, the diiodide **6e** being isolated in 35% yield with cadmium (entry 15), against 3% with zinc (entry 11). Both high efficiency and regioselectivity for the C3 site were obtained by using [$(TMP)_2CuLi$] as a base, a result demonstrated by trapping with benzoyl chlorides to give the ketones **6b2** and **6b3** in 83 and 79% yield, respectively (entries 16 and 17).

Some conclusions can be drawn. As shown using hindered lithium amides, the thermodynamic monometal product is the 3-metalated species (due to electron-withdrawing effects of the halogen and absence of electron repulsion by the lone pair of nitrogen). Under kinetic conditions (in situ trap), the reaction takes place at the 6-position (the approach of the base is favored by complexation to the ring nitrogen, in particular when using solvents less polar than THF).[2] As for 3-substituted pyridines, the bimetallic bases could be more easily directed to the 6-position through metal complexation by the ring nitrogen, and the bimetallic species thus generated could have the advantage of better stabilization through ring nitrogen complexation to the second metal (lithium) (Scheme 2). Relative to the 3-halogenopyridines, lower acidities of the most acidic hydrogen (pK_a of 33.5–34.0 instead of 31.4–32.1), and the resulting lower acidity differences, are responsible for the mixtures obtained in the case of the 2-halogenopyridines. The formation of the products **5e** and **6e** combines two trends, namely, equilibrium deprotometalation (at the most acidic 3-position), and those driven by base coordination (at the 6-position).

We next turned to 2,6-dibromo- and 2,6-dichloropyridine (**7a** and **8a**) (Table 5). 2,6-Dichloropyridine can be lithiated at C3 by using PhLi at −40°C in THF in the presence of a catalytic amount of diisopropylamine.[40] (DA)Li in THF at −80°C leads to the formation of 3-substituted derivatives contaminated with their 4-substituted isomers; by contrast, BuLi in general favors the formation of 4-substituted derivatives but without discarding the 3-substituted regioisomers.[42] TMP-based lithium magnesates also lead to mixtures.[24] A clean C4 deprotonation of 2,6-dibromo- and 2,6-

Table 5. Calculated pK_a(THF) values for the 2,6-dihalogenopyridines **7a** and **8a**, and deprotonative metalation followed by electrophilic trapping.



Entry	Substrate (X)	M, *n* [equiv]	*T*	Products [E], yields [%]			
1	**7a** (Br)	Zn, 0.5	RT	**7b** (I), 87[a]	**7c** (I), 12[a]	**7d** (I), <1[a]	**7e** (I), <1[a]
2		Zn, 0.5	0°C	**7b** (I), 85[a]	**7c** (I), 15[a]	–	–
3		Zn, 0.5	40°C	**7b** (I), 87[a]	**7c** (I), 11[a]	**7d** (I), 2[a]	-
4		Zn, 0.3	RT	**7b** (I), 65[a]	**7c** (I), 29[a]	–	–
5		Cd, 0.5	RT	**7b** (I), 71[a]	**7c** (I), 15[a]	**7d** (I), 11[a]	**7e** (I), 4[a]
6	**8a** (Cl)	Zn, 0.5	RT	**8b1** (I), 38[b]	**8c1** (I), 6[b]	**8d** (I), 19[b]	**8e** (I), 5[b]
7		Cd, 0.5	RT	**8b1** (I), 51[b]	**8c1** (I), 27[b]	**8d** (I), 13[b]	**8e** (I), 5[b]
8		Cu, 1	RT	**8b2** (C(O)Ph), 24	**8c2** (C(O)Ph), 41	–	–

[a] Yields after isolation by column chromatography. [b] Yields estimated by ^1H NMR spectroscopy for inseparable mixtures.

dichloropyridine can be performed by using [(TMP)MgCl]·LiCl in THF at −30 and 25 °C, respectively.[43]

The reaction of 2,6-dibromopyridine (**7a**) with 1:1 [(TMP)Li]/[(TMP)$_2$Zn] (0.5 equiv each) afforded the 4-iodo derivative **7b** in 87% yield (Table 5, entry 1). This regioselectivity could result from combined acidifying and congesting effects of the bromo groups. To reduce the formation of the 3-iodo derivative **7c**, isolated in 12% yield, the reaction was performed at 0 and 40 °C, but without significant change to the outcome (entries 2 and 3). Reduction of the amount of 1:1 [(TMP)Li]/[(TMP)$_2$Zn] to 0.3 equiv each led to increased formation of the 3-iodo derivative **7c** (entry 4), as observed to a lesser extent from 2-bromopyridine (Table 4, entry 2). Turning to cadmium instead of zinc resulted in the concomitant formation of the diiodides **7d** and **7e**, isolated in 11 and 4% yield, respectively (entry 5). The reactions that involved 2,6-dichloropyridine (**8a**) only gave mixtures of mono- and diiodides when using either 1:1 [(TMP)Li]/[(TMP)$_2$Zn] (0.5 equiv each) or [(TMP)$_3$CdLi] (0.5 equiv; entries 6 and 7). Using [(TMP)$_2$CuLi] allowed us to avoid the formation of disubstituted derivatives. It proved nevertheless impossible to avoid the formation of the 4-substituted regioisomer **8b2**, a result that could be related to the similar acidities of the hydrogen atoms at C3 and C4 (entry 8).

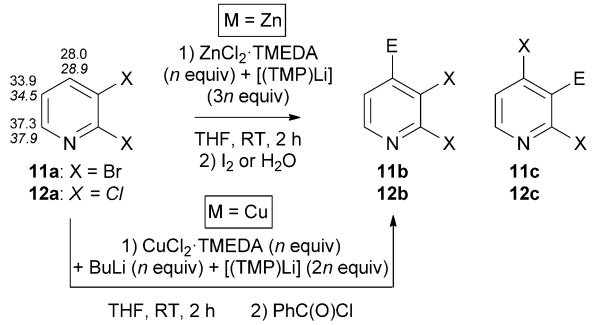
2,5-Dibromo- and 2,5-dichloropyridine (**9a** and **10a**) were next considered (Table 6). To our knowledge, the deprotometalation of 2,5-dibromopyridine has never been the subject of studies. The corresponding dichloride can be lithiated at C4 in THF upon exposure to (DA)Li[44] or to BuLi–TMEDA[45] at −75 °C, or even to TMP-based lithium magnesates at −10 °C.[24] As for the C6 site, it is attacked by using *tert*-butyllithium in Et$_2$O at −75 °C.[45]

Upon treatment with 1:1 [(TMP)Li]/[(TMP)$_2$Zn] (0.5 equiv each), 2,5-dibromopyridine (**9a**) was converted to a mixture of mono- and diiodides from which the 4-iodo derivative **9b** was isolated in 46% yield (structure confirmed by X-ray structure analysis). Metalation at C6 also occurred significantly, as indicated by interception with iodine giving **9c** (Table 6, entry 1).

Using 1:1 [(TMP)Li]/[(TMP)$_2$Zn] (0.3 equiv each) with 2,5-dichloropyridine (**10a**) led to a 1:1 mixture of 4- and 6-substituted derivatives **10b1** (structure confirmed by X-ray structure analysis) and **10c** in addition to small amounts of the 3-iodo and the 4,6-diiodo derivatives **10f** and **10d** (structure confirmed by X-ray structure analysis) (Table 6, entry 2). The reaction that employed [(TMP)$_2$CuLi] furnished the ketone **10b2** in 42% yield after trapping with benzoyl chloride under similar conditions (entry 3). Low acidity differences, as well as low acidities, seem to be responsible for the mixtures obtained using 1:1 [(TMP)Li]/[(TMP)$_2$Zn].

The behavior of 2,3-dibromo- and 2,3-dichloropyridine was finally examined (**11a** and **12a**) (Table 7). It is known that 2,3-dibromopyridine can be converted into 3-substituted 2,4-dibromopyridines upon treatment with (DA)Li in THF at −70 °C in the presence of a catalytic amount of bromine followed by electrophilic trapping.[46]

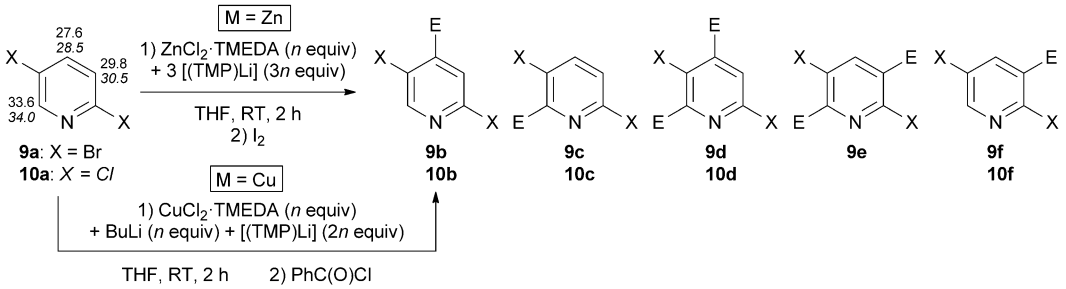
Table 7. Calculated pK_a(THF) values for the 2,3-dihalogenopyridines **11a** and **12a**, and deprotonative metalation followed by electrophilic trapping.



Entry	Substrate [X]	M, *n*	Products [E], yields [%]	
1	**11a** (Br)	Zn, 0.5	**11b** (I), 27[a]	**11c1** (I), 19[a]
2			**11a**, 65[b]	**11c2** (H), 25[b]
3	**12a** (Cl)	Zn, 0.3	**12b1** (I), 52[b]	–
4		Cu, 1	**12b2** (C(O)Ph), 70[b]	–

[a] Yield estimated by ^{1}H NMR spectroscopy for a nonseparable mixture with starting material. [b] Yields after isolation by column chromatography.

Table 6. Calculated pK_a(THF) values for the 2,5-dihalogenopyridines **9a** and **10a**, and deprotonative metalation followed by electrophilic trapping.



Entry	Substrate (X)	M, *n* [equiv]	Products [E], Yields [%]				
1	**9a** (Br)	Zn, 0.5	**9b** (I), 46[a]	**9c** (I), 23[b]	**9d** (I), 8[b]	**9e** (I), 4[b]	**9f** (I), 2[b]
2	**10a** (Cl)	Zn, 0.3	**10b1** (I), 34[b]	**10c** (I), 34[b]	**10d** (I), 3[b]	–	**10f** (I), 6[b]
3		Cu, 1	**10b2** (C(O)Ph), 42[a]	–	–	–	–

[a] Yields after isolation by column chromatography. [b] Yields estimated by ^{1}H NMR spectroscopy for inseparable mixtures.

By using 1:1 [(TMP)Li]/[(TMP)$_2$Zn] (0.5 equiv each) with 2,3-dibromopyridine (**11a**), the expected 4-iodo derivative **11b** was obtained, but in a mixture from which 2,4-dibromo-3-iodopyridine (**11c**) was also identified (Table 7, entry 1). A bromine migration (from the 3- to the 4-position) thus took place, as observed when using lithium amides as metalating agents.[46] It was confirmed by using water instead of iodine to quench the reaction mixture after the deprotonation step (entry 2), and could be here explained by the presence of (TMP)Li in the basic mixture. Again, according to DFT calculations, such rearrangement (bromine migration) is highly thermodynamically favored ($\Delta_r G = -19.3$ kJ mol^{-1}).

2,3-Dichloropyridine (**12a**) has previously been lithiated in THF at the 4-position by using either (DA)Li or BuLi at −75 °C.[45] By using 1:1 [(TMP)Li]/[(TMP)$_2$Zn] (0.3 equiv each to avoid the competitive formation of diiodides), the 4-iodo derivative **12b1** was the only compound isolated (Table 7, entry 3). The ketone **12b2** was prepared in 70% yield by employing [(TMP)$_2$CuLi] as before (entry 4). It is the CH acidity that could be the reason why most of the reagents tested deprotonate 2,3-dihalogenopyridines at their 4-position. This acidity results from the presence of the ring nitrogen, but also from the presence of both adjacent and more distant halogeno groups, which exert their acidifying effects.

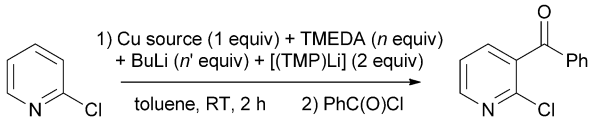
The above set of experiments points out a peculiarity of the lithium–copper base inasmuch as it tends to act like a monometal base. We next performed a number of experiments to get a better understanding of such reactivity. To identify the parameters responsible for the deprotometalation when using [(TMP)$_2$CuLi], we performed further experiments with 2-chloropyridine (**6a**) (Table 8). First, starting from CuCl as copper source (only 1 equiv of LiCl is formed in the course of the base preparation), reactions were carried out in THF, a solvent that is able to dissolve LiCl in the presence or absence of TMEDA to afford the ketone **6b2** in 90 and 86% yield, respectively (Table 8, entries 1 and 2).

We next attempted reactions in toluene, a solvent in which LiCl is not soluble. By employing [(TMP)$_2$CuLi] (1 equiv), which was prepared in situ from CuCl$_2$·TMEDA by successively adding 1 equiv of BuLi and 2 equiv of [(TMP)Li], in toluene at room temperature for 2 h, the ketone **6b2** was isolated after interception with benzoyl chloride in 60% yield (Table 8, entry 3). Under these conditions, the presence of LiCl (2 equiv) and TMEDA (1 equiv) can have an impact on the structure of the metalated species, and thus on the course of the reaction. Starting from CuCl$_2$ (2 equiv of LiCl are present as before), a reaction performed without TMEDA led to the ketone **6b2** in 19% yield (entry 4).

To further investigate whether the presence of LiCl in the reaction mixture influenced the effectiveness with which deprotonative metalation occurred, two strategies for preparing unambiguously Gilman-type base were adopted. First, reaction mixtures were filtered (removing LiCl precipitate formed in situ) after the preparation of the base in hydrocarbon media and the presence or absence of TMEDA (which could inhibit LiCl precipitation). Reactions with 2-chloropyridine (**6a**) were then performed, and these conditions both furnished the ketone **6b2** in 37% yield (Table 8, entries 5 and 6). The corresponding reactions performed in the presence of higher levels of LiCl (that is, omitting the filtration step) gave 61 and 50% yield, respectively (entries 7 and 8). These results show that TMEDA has a slight positive effect on the course of the reaction in toluene when LiCl is present; this effect could be related to more LiCl kept in solution and, as would be expected, the effect is most significant when filtration is not used to remove solid LiCl. The reason why entries 5 and 7 (as well as entries 6 and 8) do not give similar yields could therefore be related to higher levels of LiCl in the system in the second case(s).

The second strategy was to crystallize, isolate, and use [(TMP)$_2$CuLi]. The structure of a representative homoleptic bis(amido)cuprate known to promote highly selective deprotonative metalation has previously been examined by a combination of X-ray diffraction and DFT techniques.[6] Thus, crystallography showed the prototype Lipshutz-type cuprate [(TMP)$_2$Cu(CN)Li$_2$]·THF to be a dimer in the solid state with each CN moiety coordinated by two lithium centers and remote from copper. However, more recent work has suggested the ready interconversion of Gilman-type and Lipshutz-type structures.[47] More recently, the competitive formation of [(TMP)$_2$Cu(X)Li$_2$] (X = halide) and [(TMP)$_2$CuLi] has been studied and the ability to isolate the latter compound noted.[48] The observed structure of this species compared with those previously seen for bis(organyl)-[49] and organyl(amido)-[50] cuprates[51] but contrasted with other known TMP-containing Gilman-type cup-

Table 8. Deprotonative metalation of 2-chloropyridine (**6a**) in toluene followed by benzoylation.



6a **6b2**

Entry	Solvent	Cu source	*n* [equiv] TMEDA, *n'* [equiv] BuLi	TMEDA [equiv] present	LiCl [equiv] present	Yield [%][a]
1	THF	CuCl	1, 0	1	1	90
2		CuCl	0, 0	0	1	86
3	toluene	CuCl$_2$[b]	0, 1	1	2	60
4		CuCl$_2$	0, 1	0	2	19
5	toluene	CuCl	1, 0	1	[c]	37
6		CuCl	0, 0	0	[c]	37
7		CuCl	1, 0	1	1	61
8		CuCl	0, 0	0	1	50
9[d]	THF	CuCl	0, 0	0	0	25
10[d]	toluene	CuCl	0, 0	0	0	15

[a] Yields after isolation by column chromatography. [b] Chelate CuCl$_2$·TMEDA was employed. [c] Insoluble LiCl removed by filtration. [d] Reactions performed using a base prepared from CuCl in toluene containing 1 equiv of THF, and isolated by filtration.

rates.[47] Importantly, the ability to prepare solid [(TMP)$_2$CuLi] maximizes our chances of carrying out deprotonative metalations with a Gilman-type lithiocuprate base. In the present case, using THF or toluene as solvent for the deprotometalation of **6a** with pre-isolated [(TMP)$_2$CuLi] furnished the expected ketone **6b2** in 25 and 15% yield, respectively (Table 8, entries 9 and 10).

The difference between the results of entries 6 and 10 in Table 8 could be due to some LiCl remaining in solution in the case of entry 6, thereby allowing the presence of some Lipshutz cuprate. The yields obtained depend strongly on the choice of solvent (entries 9 and 10), a result that could be related to different structures that pertain to the Gilman base in THF and toluene.

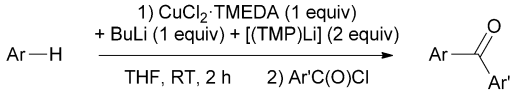
From these studies, we can deduce that the best solvent for the reaction is THF, maybe because it dissolves LiCl, thus favoring the formation of a Lipshutz cuprate, and/or it enables the formation of a base structure more suitable for an efficient deprotonation step. In nonpolar solvents such as toluene, TMEDA can be used to increase the yields for a reason that could be similar.

Due to the ability of [(TMP)$_2$CuLi] to promote regioselective deprotometalation reactions in THF at RT, we decided to extend its use to other pyridine substrates (Table 9). The directing ability of the chloro group was compared with those of methoxy and trifluoromethyl groups in the metalation of the 2,6-disubstituted pyridines **13a** and **14a**; it proved to have a stronger acidifying effect, thus allowing a major formation of the derivatives **13b1** and **14b1** (Table 9, entries 1–3). The presence of groups sensitive to nucleophilic or basic reagents is not tolerated, as demonstrated with the attempted reactions from the 4-substituted 2-chloropyridines **15a** and **16a** (entries 4 and 5).

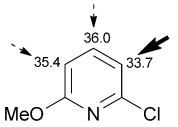
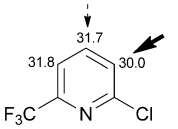
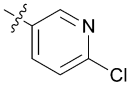
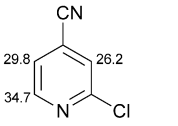
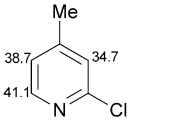
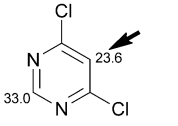
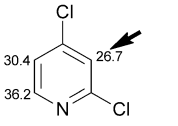
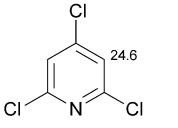
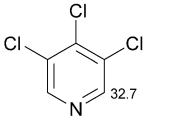
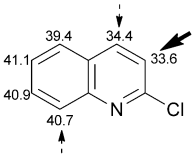
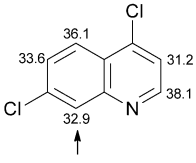
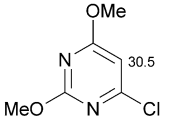
The dichloro substrates **17a** and **18a** were logically functionalized at the site flanked by both halogens (most acidic hydrogen) to afford the ketones **17b** and **18b** in moderate to medium yields (Table 9, entries 6 and 7). The trichloropyridine **19a** that benefits from a symmetry was converted to the benzoyl derivative in 80% yield (entry 8). As previously observed with other chloropyridines unsubstituted at their 2- and 6-positions such as 3- and 4-chloropyridine, the trichloropyridine **20a** did not furnish any expected ketone (entry 9).

Things occurred similarly in the quinoline series. Indeed, chloroquinolines could be functionalized, provided a substituent is present at the position adjacent to the nitrogen atom, albeit in a lower regioselectivity due to lower acidity differences, and to nitrogen complexation also activating the 8-position (Table 9, entries 10 and 11). Sensitivity to nucleophilic attacks was no more a limit to functionalize 6-chloro-2,4-dimethoxypyrimidine (**23a**), and the expected ketone **23b** was isolated in 78% yield (entry 12).

Table 9. Calculated pK_a(THF) values for the different halogenoazines **13a–23a**, and deprotonative cupration followed by electrophilic trapping.



a **b**

Entry	Ar—H	Ar′	Yields [%][a]
1	 **13a**	Ph	at C3: **13b1**, 37[b] at C4: **13c**, 16 at C5: **13d**, 16[b]
2		C_6H_4-2-Cl	at C3: **13b2**, 54
3	 **14a**		at C3: **14b1**, 33 at C4: **14b2**, 13
4	 **15a**	Ph	–
5	 **16a**	Ph	–
6	 **17a**	Ph	at C5: **17b**, 21
7[c]	 **18a**	Ph	at C3: **18b**, 55
8	 **19a**	Ph	**19b**, 80
9	 **20a**	Ph	–
10	 **21a**	Ph	at C3: **21b1**, 44 at C4: **21b2**, 11 at both C3 and C8: **21b3**, 19
11	 **22a**	Ph	at C8: **22b**, 10
12[c]	 **23a**	Ph	**23b**, 78

[a] Yields after isolation by column chromatography. [b] Yields estimated by ^{1}H NMR spectroscopy for inseparable mixtures. [c] Using the base prepared from CuCl in the presence of TMEDA (1 equiv).

Conclusion

Undoubtedly, the results here obtained show that the room-temperature deprotonative metalation that uses amido-based bimetallic species, and in particular lithium cuprates, opens up new possibilities for the functionalization of halogenoazines. To use wisely the numerous methods available, one should take into account the following aspects.

The reactions described provide flexible synthetic methods since their regioselectivity depends on either kinetics or thermodynamics, therefore they can be controlled by base, media and temperature choice. In the case of the monohalogenoazines (**1a**, **2a**, **5a**, and **6a**), the use of lithium amides in polar solvents (THF) at moderately low temperatures favors reaction at the most acidic site (thermodynamic control). Such a position can easily be predicted when taking into account two opposite trends: a strong halogen *ortho*-acidifying effect and the detriment of the α position to the azine nitrogen (which originates from electron repulsion of carbanion with the lone pair of nitrogen).

On the contrary, the bimetallic bases in general drive the substitution into the position next to the ring nitrogen through metal complexation. In this case, the course of the reaction can be enhanced by using nonpolar solvents at low temperatures. The lithium cuprate is an exception since it looks more like a lithium reagent, not tolerating reactive functional groups, and thus leading to deprotonation of the most acidic hydrogen atoms. This could be rationalized by considering the thermodynamic unfavorability of the 2-metalated species.

Experimental Section

Metalation reactions were performed under an argon atmosphere. THF was distilled over sodium/benzophenone. Column chromatography separations were achieved on silica gel (40–63 μm). Melting points were measured using a Kofler apparatus. ^{1}H and ^{13}C NMR spectra were recorded using a Bruker Avance III spectrometer at 300 and 75 MHz, respectively. ^{1}H chemical shifts (δ) are given in ppm relative to the solvent residual peak, and ^{13}C chemical shifts relative to the central peak of the solvent signal;[52] coupling constants (J) are given in Hz. Mass spectra (HRMS) measurements were performed at the CRMPO (Centre Régional de Mesures Physiques de l'Ouest) of Rennes using either a Waters Q-TOF 2 (positive electrospray CI mode) or a Bruker micrOTOF Q II (positive ElectroSpray Ionisation mode or positive Atmospheric Pressure CI mode) instrument.

General procedure for the metalation with the in situ prepared mixture of MCl_2·TMEDA (M = Zn or Cd, 0.5 equiv) and [Li(TMP)] (1.5 equiv) followed by iodination: BuLi (1.6 M hexanes solution, 6.0 mmol) and MCl_2·TMEDA (M = Zn or Cd, 2.0 mmol) were successively added to a stirred, cooled (0 °C) solution of 2,2,6,6-tetramethylpiperidine (1.0 mL, 6.0 mmol) in THF (5 mL). The mixture was stirred for 15 min at 0 °C before the introduction of the bromopyridine (4.0 mmol). After 2 h at room temperature, a solution of I_2 (1.5 g, 6.0 mmol) in THF (5 mL) was added. The mixture was stirred overnight before the addition of an aqueous saturated solution of $Na_2S_2O_3$ (20 mL) and extraction with CH_2Cl_2 (3 × 20 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification by flash chromatography on silica gel gave the iodo derivative.

Metalation of 3-bromopyridine (1a): Using the general procedure (M = Zn), a separable mixture of 3-bromo-2-iodopyridine (**1b**) and 3-bromo-4-iodopyridine (**1c**) was obtained.

3-Bromo-2-iodopyridine (1b): White solid. M.p. 51 °C; ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.11 (dd, J = 4.6 and 7.9 Hz, 1H), 7.76 (dd, J = 1.7, 7.9 Hz, 1H), 8.24 ppm (dd, J = 1.7, 4.6 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 123.8, 124.1, 129.9, 139.7, 148.3 ppm. These data are consistent with those reported in the literature.[53]

3-Bromo-4-iodopyridine (1c): White solid. M.p. 110–111 °C; ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.81 (d, J = 5.1 Hz, 1H), 8.11 (brd, J = 5.1 Hz, 1H), 8.69 ppm (brs, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 112.4, 129.1, 135.2, 147.8, 151.0 ppm. These data are consistent with those reported in the literature.[54]

Metalation of 3-chloropyridine (2a): Using the general procedure (M = Zn), a separable mixture of 3-chloro-2-iodopyridine (**2b**), 3-chloro-2,4-diiodopyridine (**2d**), and 3-chloro-2,5-diiodopyridine (**2e**) was obtained. Using the general procedure (M = Cd), a separable mixture of 3-chloro-2-iodopyridine (**2b**), and 3-chloro-2,4-diiodopyridine (**2d**) was obtained. Using the general procedure (M = Cd) with 1 equiv of base instead of 0.5 equiv, a separable mixture of 3-chloro-2,4-diiodopyridine (**2d**), 3-chloro-2,4,5-triiodopyridine (**2f**), and 3-chloro-2,4,6-triiodopyridine (**2g**) was obtained.

3-Chloro-2-iodopyridine (2b): Colorless prisms. M.p. 47 °C; ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.19 (dd, J = 4.6, 7.9 Hz, 1H), 7.61 (dd, J = 1.7, 7.9 Hz, 1H), 8.21 ppm (dd, J = 1.7, 4.6 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 121.4, 123.5, 136.1, 138.0, 147.8 ppm. These data are consistent with those reported in the literature.[55]

3-Chloro-2,4-diiodopyridine (2d):[56] White solid. M.p. 157 °C; ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.74 (d, J = 5.0 Hz, 1H), 7.81 ppm (d, J = 5.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 107.7, 119.5, 134.5, 142.0, 147.6 ppm.

3-Chloro-2,4,5-triiodopyridine (2f): ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 8.46 ppm (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 108.5, 117.0, 122.1, 142.8, 153.3 ppm.

3-Chloro-2,4,6-triiodopyridine (2g): ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 8.14 ppm (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 108.5, 112.1, 117.9, 142.7, 144.0 ppm.

Metalation of 3,5-dibromopyridine (3a): Using the general procedure (M = Zn), a nonseparable mixture of 3,5-dibromo-2-iodopyridine (**3b**), 3,5-dibromo-4-iodopyridine (**3c**), and starting material were obtained.

3,5-Dibromo-2-iodopyridine (3b): White solid. M.p. 66–68 °C; ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.95 (d, J = 2.2 Hz, 1H), 8.38 ppm (d, J = 2.2 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 120.3, 121.7, 130.5, 141.8, 149.5 ppm. These data are consistent with those reported in the literature.[35]

3,5-Dibromo-4-iodopyridine (3c): ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 8.55 ppm (s, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 120.3, 129.8 (2C), 148.4 ppm (2C).

Metalation of 3,5-dichloropyridine (4a): Using the general procedure (M = Zn) with 0.33 equiv of base instead of 0.5 equiv, a separable mixture of 3,5-dichloro-2-iodopyridine (**4b**) and 3,5-dichloro-4-iodopyridine (**4c1**) was obtained.

3,5-Dichloro-2-iodopyridine (4b): White solid. M.p. 68 °C; ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.68 (d, J = 2.3 Hz, 1H), 8.27 ppm (d, J = 2.3 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 118.2, 132.0, 135.8, 138.7, 146.9 ppm. The structure was identified unequivocally by X-ray structure analysis.

3,5-Dichloro-4-iodopyridine (4c1): White solid. M.p. 183 °C; ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 8.39 ppm (s, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 114.6, 138.3 (2C), 145.6 ppm (2C). These data are consistent with those reported in the literature.[24] The structure was identified unequivocally by X-ray structure analysis.

Metalation of 2-bromopyridine (5a): Using the general procedure (M = Zn), a nonseparable mixture of 2-bromo-3-iodopyridine (**5b1**) and 2-bromo-4-iodopyridine (**5c**), and a partially separable mixture of 2-

bromo-6-iodopyridine (**5d**) and 2-bromo-3,6-diodopyridine (**5e**) were obtained.

2-Bromo-3-iodopyridine (5b1): ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 6.97 (dd, J = 4.6, 7.8 Hz, 1H), 8.08 (dd, J = 1.7, 7.8 Hz, 1H), 8.32 ppm (dd, J = 1.7, 4.6 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 99.6, 123.5, 148.2, 148.5, 148.9 ppm. These data are consistent with those reported in the literature.[57]

2-Bromo-4-iodopyridine (5c): ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.60 (d, J = 5.2 Hz, 1H), 7.88 (s, 1H), 8.02 ppm (d, J = 5.2 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 106.6, 132.0, 136.6, 142.4, 150.2 ppm. These data are consistent with those reported in the literature.[58]

2-Bromo-6-iodopyridine (5d): ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.14 (t, J = 7.7 Hz, 1H), 7.46 (dd, J = 0.8, 7.7 Hz, 1H), 7.69 ppm (dd, J = 0.8, 7.7 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 115.9, 127.5, 134.0, 139.4, 141.1 ppm. These data are consistent with those reported in the literature.[57]

2-Bromo-3,6-diodopyridine (5e): ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.36 (d, J = 8.0 Hz, 1H), 7.71 ppm (d, J = 8.0 Hz, 1H).

2-Bromo-5-iodopyridine (5f): ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 7.29 (d, J = 8.3 Hz, 1H), 7.82 (dd, J = 2.2, 8.3 Hz, 1H), 8.59 ppm (s, 1H). These data are consistent with those reported in the literature.[57]

2-Iodopyridine (5g): BuLi (1.6 M hexanes solution, 6.0 mmol) was added to a stirred, cooled (0 °C) solution of $ZnCl_2$·TMEDA (0.50 g, 2.0 mmol) in THF (5 mL). The mixture was stirred for 15 min at 0 °C before introduction of the bromopyridine (4.0 mmol). After 2 h at room temperature, a solution of I_2 (1.5 g, 6.0 mmol) in THF (5 mL) was added. The mixture was stirred overnight before the addition of an aqueous saturated solution of $Na_2S_2O_3$ (20 mL) and extraction with CH_2Cl_2 (3×20 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification by flash chromatography on silica gel gave 2-iodopyridine. Yellow oil. ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 7.24–7.38 (m, 2H), 7.73 (d, J = 7.6 Hz, 1H), 8.37 ppm (s, 1H); ^{13}C NMR ($CDCl_3$, 63 MHz): δ = 118.0, 122.8, 134.8, 137.4, 150.6 ppm. These data are consistent with those obtained from a commercial sample (Acros).

Metalation of 2-chloropyridine (6a): Using the general procedure (M = Zn), a nonseparable mixture of 2-chloro-3-iodopyridine (**6b1**), 2-chloro-4-iodopyridine (**6c**), 2-chloro-6-iodopyridine (**6d**), and 2-chloro-3,6-diiodopyridine (**6e**) were obtained. Using the general procedure (M = Cd), a nonseparable mixture of 2-chloro-3-iodopyridine (**6b1**), 2-chloro-4-iodopyridine (**6c**), 2-chloro-6-iodopyridine (**6d**), and 2-chloro-3,6-diiodopyridine (**6e**) were obtained. Using the general procedure (M = Cd) with 1 equiv of base instead of 0.5 equiv, a nonseparable mixture of 2-chloro-3-iodopyridine (**6b1**), 2-chloro-4-iodopyridine (**6c**), 2-chloro-3,6-diiodopyridine (**6e**), 6-chloro-2,3-diiodopyridine (**6g**), and 2-chloro-3,4,6-triiodopyridine (**6h**) were obtained.

2-Chloro-3-iodopyridine (6b1): ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 6.92 (dd, J = 4.7, 7.8 Hz, 1H), 8.10 (dd, J = 1.8, 7.8 Hz, 1H), 8.32 ppm (dd, J = 1.7, 4.7 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 94.8, 123.2, 148.6, 148.7, 154.3 ppm. These data are consistent with those reported in the literature.[8e]

2-Chloro-4-iodopyridine (6c): ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.55 (dd, J = 1.3, 5.2 Hz, 1H), 7.70 (d, J = 1.3 Hz, 1H), 8.02 ppm (d, J = 5.2 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 106.6, 131.4, 132.9, 149.5, 151.5 ppm. These data are consistent with those reported in the literature.[59]

2-Chloro-6-iodopyridine (6d): White solid. M.p. 84 °C; ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.50 (dd, J = 1.2, 7.9 Hz, 1H), 7.55 (dd, J = 7.2, 7.9 Hz, 1H), 7.86 ppm (dd, J = 1.2, 7.2 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 115.5, 123.5, 133.5, 139.5, 150.6 ppm. These data are consistent with those reported in the literature.[60]

2-Chloro-3,6-diiodopyridine (6e): ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.36 (d, J = 8.0 Hz, 1H), 7.71 ppm (d, J = 8.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 94.7, 114.3, 134.5, 149.4, 154.0 ppm.

2,5-Diiodopyridine (6f): M.p. 152 °C; ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.50 (dd, J = 0.7, 8.2 Hz, 1H), 7.60 (dd, J = 2.4, 8.2 Hz, 1H), 8.58 ppm (dd, J = 0.6, 2.4 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 93.0, 116.4, 136.6, 145.8, 156.7 ppm. These data are consistent with those reported in the literature.[31] The structure was identified unequivocally by X-ray structure analysis.

6-Chloro-2,3-diiodopyridine (6g): ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.23 (d, J = 8.0 Hz, 1H), 7.75 ppm (d, J = 8.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 106.9, 114.1, 133.2, 148.7, 161.9 ppm.

2-Chloro-3,4,6-triiodopyridine (6h): ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 8.10 ppm (s, 1H).

Metalation of 2,6-dibromopyridine (7a): Using the general procedure (M = Zn), a nonseparable mixture of 2,6-dibromo-4-iodopyridine (**7b**) and 2,6-dibromo-3-iodopyridine (**7c**) was obtained. Using the general procedure (M = Cd), a nonseparable mixture of 2,6-dibromo-4-iodopyridine (**7b**), 2,6-dibromo-3-iodopyridine (**7c**), 2,6-dibromo-3,4-diiodopyridine (**7d**), and 2,6-dibromo-3,5-diiodopyridine (**7e**) was obtained.

2,6-Dibromo-4-iodopyridine (7b): ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.84 ppm (s, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 107.5, 135.5 (2C), 141.0 ppm (2C). These data are consistent with those reported in the literature.[43]

2,6-Dibromo-3-iodopyridine (7c): ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.18 (d, J = 8.0 Hz, 1H), 7.90 ppm (d, J = 8.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 98.2, 128.1, 140.0, 147.4, 150.0 ppm. These data are consistent with those reported in the literature.[61]

2,6-Dibromo-3,4-diiodopyridine (7d): ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.92 ppm (s, 1H).

2,6-Dibromo-3,5-diiodopyridine (7e): ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 8.39 ppm (s, 1H).

Metalation of 2,6-dichloropyridine (8a): Using the general procedure (M = Zn or Cd), nonseparable mixtures of 2,6-dichloro-4-iodopyridine (**8b**), 2,6-dichloro-3-iodopyridine (**8c**), 2,6-dichloro-3,4-diiodopyridine (**8d**), and 3,6-dichloro-3,5-diiodopyridine (**8e**) were obtained.

2,6-Dichloro-4-iodopyridine (8b1): ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.64 ppm (s, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 107.6, 131.4 (2C), 150.6 ppm (2C). These data are consistent with those reported in the literature.[43]

2,6-Dichloro-3-iodopyridine (8c1): ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.01 (d, J = 8.1 Hz, 1H), 8.05 ppm (d, J = 8.1 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 92.5, 124.0, 150.2, 150.5, 153.8 ppm. These data are consistent with those reported in the literature.[61]

2,6-Dichloro-3,4-diiodopyridine (8d): ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.74 ppm (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 108.3, 123.7, 132.7, 150.0, 153.5 ppm. These data are consistent with those reported in the literature.[62]

2,6-Dichloro-3,5-diiodopyridine (8e): ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 8.50 ppm (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 93.0 (2C), 149.9, 158.8 ppm (2C).

Metalation of 2,5-dibromopyridine (9a): Using the general procedure (M = Zn), 2,5-dibromo-4-iodopyridine (**9b**) and a nonseparable mixture of 3,6-dibromo-2-iodopyridine (**9c**), 3,6-dibromo-2,4-diiodopyridine (**9d**), 2,5-dibromo-3,6-diiodopyridine (**9e**), and 2,5-dibromo-3-iodopyridine (**9f**) were obtained.

2,5-Dibromo-4-iodopyridine (9b):[63] White solid. M.p. 142–144 °C; ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 8.00 (s, 1H), 8.45 ppm (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 114.3, 128.3, 138.5, 140.0, 150.5 ppm. The structure was identified unequivocally by X-ray structure analysis.

3,6-Dibromo-2-iodopyridine (9c): ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.32 (d, J = 8.2 Hz, 1H), 7.62 ppm (d, J = 8.2 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 122.4, 128.1, 129.4, 138.3, 141.1 ppm.

3,6-Dibromo-2,4-diiodopyridine (9d): ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.92 ppm (s, 1H).

2,5-Dibromo-3,6-diiodopyridine (9e): ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 8.12 ppm (s, 1H).

2,5-Dibromo-3-iodopyridine (9f): ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 8.22 (d, J = 2.3 Hz, 1H), 8.39 ppm (d, J = 2.3 Hz, 1H).

Metalation of 2,5-dichloropyridine (10a): Using the general procedure (M=Zn) with 0.33 equiv of base instead of 0.5 equiv, a nonseparable mixture of 2,5-dichloro-4-iodopyridine (**10b1**), 3,6-dichloro-2-iodopyridine (**10c**), 3,6-dichloro-2,4-diiodopyridine (**10d**), 2,5-dichloro-3-iodopyridine (**10f**), and starting material was obtained.

2,5-Dichloro-4-iodopyridine (10b1): ^{1}H NMR ($CDCl_3$, 300 MHz): δ= 7.84 (s, 1H), 8.33 ppm (s, 1H). These data are consistent with those reported in the literature.[24] The structure was identified unequivocally by X-ray structure analysis.

3,6-Dichloro-2-iodopyridine (10c): ^{1}H NMR ($CDCl_3$, 300 MHz): δ=7.24 (d, J=8.3 Hz, 1H), 7.58 ppm (d, J=8.3, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ=119.3, 124.1, 137.4, 137.9, 147.8 ppm.

3,6-Dichloro-2,4-diiodopyridine (10d): ^{1}H NMR ($CDCl_3$, 300 MHz): δ= 7.78 ppm (s, 1H). The structure was identified unequivocally by X-ray structure analysis.

2,5-Dichloro-3-iodopyridine (10f): ^{1}H NMR ($CDCl_3$, 300 MHz): δ=8.13 (d, J=2.4 Hz, 1H), 8.31 ppm (d, J=2.4 Hz, 1H).

Metalation of 2,3-dibromopyridine (11a): Using the general procedure (M=Zn), a nonseparable mixture of 2,3-dibromo-4-iodopyridine (**11b**), 2,4-dibromo-3-iodopyridine (**11c1**), and starting material was obtained.

2,3-Dibromo-4-iodopyridine (11b): ^{1}H NMR ($CDCl_3$, 300 MHz): δ=7.73 (d, J=5.0 Hz, 1H), 7.90 ppm (d, J=2.3 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ=113.9, 131.5, 134.3, 142.8, 147.5 ppm.

2,4-Dibromo-3-iodopyridine (11c1): ^{1}H NMR ($CDCl_3$, 300 MHz): δ= 7.49 (d, J=5.1 Hz, 1H), 8.12 ppm (d, J=5.1 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ=108.2, 126.6, 142.1, 148.7, 149.7 ppm.

2,4-Dibromopyridine (11c2): This compound was obtained using the general procedure (M=Zn), but trapping with water instead of I_2. ^{1}H NMR ($CDCl_3$, 300 MHz): δ=7.41 (dd, J=1.6 and 5.3 Hz, 1H), 7.68 (d, J= 1.5 Hz, 1H), 8.19 ppm (d, J=5.3 Hz, 1H). These data are consistent with those obtained from a commercial sample (Alfa).

Metalation of 2,3-dichloropyridine (12a): Using the general procedure (M=Zn) with 0.33 equiv of base instead of 0.5 equiv, 2,3-dichloro-4-iodopyridine (**12b1**) was obtained.

2,3-Dichloro-4-iodopyridine (12b1): White solid. M.p. 111°C; ^{1}H NMR ($CDCl_3$, 300 MHz): δ=7.73 (d, J=5.1 Hz, 1H), 7.89 ppm (d, J=5.1 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ=111.2, 134.0, 135.4, 146.6, 148.5 ppm. The structure was identified unequivocally by X-ray structure analysis.

General procedure for the cupration (using $(TMP)_2CuLi$) followed by benzoylation: BuLi (1.6 M hexanes solution, 2.0 mmol) and, 15 min later, a solution of Li(TMP) prepared in THF (2 mL) at 0°C from 2,2,6,6-tetramethylpiperidine (0.68 mL, 4.0 mmol) and BuLi (1.6 m hexanes solution, 4.0 mmol) were successively added to a stirred, cooled (0°C) suspension of $CuCl_2$·TMEDA (0.5 g, 2.0 mmol) in THF (5 mL). The mixture was stirred for 15 min at this temperature before introduction of the substrate (2.0 mmol). After 2 h at room temperature, the electrophile (4.0 mmol) was added at 0°C. The mixture was stirred for 16 h at the required temperature before addition of brine (5 mL) and extraction with Et_2O (3× 10 mL). The combined organic layers were washed with brine (10 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure before purification by column chromatography on silica gel (the eluent is given in the product description).

3,5-Dichloropyridin-4-yl phenyl ketone (4c2):[64] Eluent: heptane/EtOAc (90:10). Yellow powder. M.p. 51°C; ^{1}H NMR ($CDCl_3$, 300 MHz): δ= 7.46–7.54 (m, 2H), 7.66 (tt, J=7.4, 1.3 Hz, 1H), 7.76–7.82 (m, 2H), 8.58 ppm (s, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ=128.8 (2C), 129.3 (2C), 129.6 (2C), 134.3, 135.1, 144.7, 147.8 (2C), 190.2 ppm. These data are consistent with those reported in the literature.

4-Chlorophenyl 2-chloropyridin-3-yl ketone (6b3): Eluent: heptane/EtOAc (80:20). Orange powder. M.p. 56°C; ^{1}H NMR ($CDCl_3$, 300 MHz): δ=7.40 (dd, J=4.8, 7.5 Hz, 1H), 7.47 (m, 2H), 7.75 (m, 3H), 8.57 ppm (dd, J=1.9, 4.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ=122.5, 129.4 (2C), 131.4 (2C), 134.2, 134.6, 138.1, 141.0, 147.8, 151.2, 192.3 ppm. These data are consistent with those reported in the literature.[65]

2,6-Dichloropyridin-4-yl phenyl ketone (8b2): Eluent: heptane/EtOAc (90:10). White powder. M.p. 88°C; ^{1}H NMR ($CDCl_3$, 300 MHz): δ=7.51 (s, 2H), 7.51–7.58 (m, 2H), 7.68 (tt, J=7.4, 1.3 Hz, 1H), 7.75–7.82 ppm (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ=122.5 (2C), 129.1 (2C), 130.2 (2C), 134.4, 135.0, 149.8, 151.3 (2C), 192.2 ppm; HRMS (ESI): m/z calcd for $C_{12}H_8{}^{35}L_2NO$ $[M+H^+]$: 251.9983; found: 251.9980.

2,6-Dichloropyridin-3-yl phenyl ketone (8c2): Eluent: heptane/EtOAc (90:10). Yellow powder. M.p. 67°C (lit.[66] 67–68°C); ^{1}H NMR ($CDCl_3$, 300 MHz): δ=7.41 (d, J=7.9 Hz, 1H), 7.44–7.54 (m, 2H), 7.64 (tt, J= 7.4, 1.3 Hz, 1H), 7.71 (d, J=7.9 Hz, 1H), 7.75–7.81 ppm (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ=123.1, 129.0 (2C), 130.0 (2C), 133.5, 134.5, 135.6, 140.3, 147.3, 151.8, 192.6 ppm.

2,5-Dichloropyridin-4-yl phenyl ketone (10b2): Eluent: heptane/EtOAc (90:10). White powder. M.p. 131°C; ^{1}H NMR ($CDCl_3$, 500 MHz): δ= 7.32 (s, 1H), 7.49–7.53 (m, 2H), 7.67 (tt, J=1.2, 7.4 Hz, 1H), 7.77–7.81 (m, 2H), 8.48 ppm (s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ=123.1, 127.4, 129.2 (2C), 130.1 (2C), 134.7, 135.0, 148.4, 149.9, 150.0, 191.5 ppm; HRMS (ESI): m/z calcd for $C_{12}H_7{}^{35}L_2NNaO$ $[M+Na]^+$: 273.9802; found: 273.9801.

2,3-Dichloropyridin-4-yl phenyl ketone (12b2): Eluent: heptane/EtOAc (80:20). Beige powder. M.p. 112°C; ^{1}H NMR ($CDCl_3$, 300 MHz): δ= 7.22 (d, J=4.8 Hz, 1H), 7.46–7.55 (m, 2H), 7.66 (tt, J=1.3, 7.4 Hz, 1H), 7.74–7.82 (m, 2H), 8.42 ppm (d, J=4.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ=121.4, 127.0, 129.2 (2C), 130.1 (2C), 134.6, 134.9, 147.3, 148.8, 150.6, 192.0 ppm; HRMS (ESI): m/z calcd for $C_{12}H_7{}^{35}L_2NNaO$ $[M+Na]^+$: 273.9802; found: 273.9803.

2-Chloro-6-methoxypyridin-3-yl phenyl ketone (13b1): This compound was identified in the crude by ^{1}H NMR spectroscopy. ^{1}H NMR ($CDCl_3$, 300 MHz): δ=3.89 (s, 3H), 7.04 (d, J=7.7 Hz, 1H), 7.71 ppm (d, J= 7.7 Hz, 1H).

2-Chloro-6-methoxypyridin-4-yl phenyl ketone (13c): Eluent: heptane/EtOAc (80:20). Yellow powder. M.p. 94°C; ^{1}H NMR ($CDCl_3$, 300 MHz): δ=4.00 (s, 3H), 6.91 (d, J=1.1 Hz, 1H), 7.18 (d, J=1.1 Hz, 1H), 7.46–7.55 (m, 2H); 7.65 (tt, J=1.3, 7.4 Hz, 1H), 7.77–7.85 ppm (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ=54.7, 109.6, 115.7, 128.9 (2C), 130.3 (2C), 133.9, 135.6, 149.2, 149.8, 164.1, 193.8 ppm; HRMS (ESI): m/z calcd for $C_{13}H_{10}{}^{35}ClNNaO_2$ $[M+Na]^+$: 270.0298; found: 270.0299.

2-Chloro-6-methoxypyridin-5-yl phenyl ketone (13d): This compound was identified in the crude by ^{1}H NMR spectroscopy. ^{1}H NMR ($CDCl_3$, 300 MHz): δ=4.02 (s, 3H), 6.79 (d, J=8.3 Hz, 1H), 7.68 ppm (d, J= 8.3 Hz, 1H).

2-Chloro-6-methoxypyridin-3-yl 2-chlorophenyl ketone (13b2): Eluent: heptane/EtOAc (80:20). Yellow powder. M.p. 44°C; ^{1}H NMR ($CDCl_3$, 300 MHz): δ=3.81 (s, 3H), 7.02 (d, J=7.9 Hz, 1H), 7.31–7.47 (m, 4H), 7.96 ppm (d, J=7.9 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ=54.8, 117.1, 120.1, 127.0, 129.7, 129.9, 131.4, 131.8, 139.4, 142.9, 152.9, 161.8, 192.5 ppm; HRMS (ESI): m/z calcd for $C_{13}H_9{}^{35}L_2NNaO_2$ $[M+Na]^+$: 303.9908; found: 303.9909.

2-Chloro-6-(trifluoromethyl)pyridin-3-yl 2-chloropyridin-5-yl ketone (14b1): Eluent: heptane/EtOAc (80:20). Yellow powder. M.p. 110°C; ^{1}H NMR ($CDCl_3$, 300 MHz): δ=7.52 (dd, J=0.7, 8.4 Hz, 1H), 7.82 (d, J=7.8 Hz, 1H), 7.98 (dd, J=0.6, 7.8 Hz, 1H), 8.11 (dd, J=2.5, 8.4 Hz, 1H), 8.70 ppm (dd, J=0.7, 2.5 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ= 119.7 (q, J=2.8 Hz), 120.3 (q, J=275 Hz), 125.2, 129.8, 136.5, 139.3, 139.9, 148.3, 150.0 (q, J=37 Hz), 151.6, 157.3, 190.0 ppm; HRMS (APCI): m/z calcd for $C_{12}H_5{}^{35}L_2F_3N_2O$ $[M]^+$: 319.97255, m/z calcd for $C_{12}H_5{}^{35}L_2F_3N_2O$ $[M+H]^+$: 320.98038; found: 319.9726 and 320.9803, respectively.

2-Chloro-6-(trifluoromethyl)pyridin-4-yl 2-chloropyridin-5-yl ketone (14b2): Eluent: heptane/EtOAc (80:20). Beige powder. M.p. 105°C; ^{1}H NMR ($CDCl_3$, 300 MHz): δ=7.57 (d, J=8.3 Hz, 1H), 7.79 (d, J= 0.6 Hz, 1H), 7.89 (d, J=1.1 Hz, 1H), 8.13 (dd, J=2.4, 8.3 Hz, 1H), 8.77 ppm (d, J=2.2 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ=118.3 (q, J=2.8 Hz), 120.3 (q, J=275 Hz), 125.3, 126.9, 129.5, 139.7, 147.4, 149,7 (q, J=37 Hz), 151.3, 153.4, 157.2, 189.7 ppm; HRMS (APCI): m/z calcd for $C_{12}H_5{}^{35}L_2F_3N_2O$ $[M]^+$: 319.97255, m/z calcd for $C_{12}H_5{}^{35}L_2F_3N_2O$:

320.98038 $[M+H]^+$ and 285.0037 $[M-Cl]^+$; found: 319.9726, 320.9801, and 285.0044, respectively.

5-Benzoyl-4,6-dichloropyrimidine (17b): Eluent: heptane/EtOAc (80:20). Yellow powder. M.p. 113 °C (lit.[67] 106–109 °C); ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.48–7.53 (m, 2H), 7.64–7.69 (m, 1H), 7.80 (d, J = 7.5 Hz, 2H), 8.88 ppm (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 129.4 (2C), 129.6 (2C), 132.0, 134.4, 135.3, 158.3, 158.7, 188.8 ppm. These data are consistent with those reported in the literature.[67]

3-Benzoyl-2,4-dichloropyridine (18b): Eluent: heptane/EtOAc (90:10). Yellow powder. M.p. 70 °C (lit.[42] 79–80 °C); ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.41 (d, J = 5.4 Hz, 1H), 7.52 (t, J = 7.7 Hz, 2H), 7.67 (tt, J = 1.2, 7.5 Hz, 1H), 7.81–7.84 (m, 2H), 8.43 ppm (d, J = 5.4 Hz, 1H) (these data are consistent with those reported in the literature[42]); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 123.9, 129.3 (2C), 129.7 (2C), 134.2, 134.9, 135.0, 143.1, 148.6, 150.3, 190.7 ppm.

Phenyl 2,4,6-trichloropyridin-3-yl ketone (19b): Eluent: heptane/EtOAc (90:10). White powder. M.p. 92 °C; ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.46 (s, 1H), 7.48–7.56 (m, 2H), 7.68 (tt, J = 7.4, 1.3 Hz, 1H), 7.78–7.86 ppm (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 124.0, 129.4 (2C), 129.7 (2C), 132.9, 134.8, 135.1, 144.7, 147.7, 151.3, 190.0 ppm; HRMS (ESI): m/z calcd for $C_{12}H_6{}^{35}L_3NNaO$ $[M+Na)^{+\cdot}]$: 307.9413; found 307.9412.

2-Chloro-3-benzoylquinoline (21b1): Eluent: heptane/EtOAc (70:30). Beige powder. M.p. 98 °C (lit.[68] 96 °C). ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 7.43–7.48 (m, 2H), 7.55–7.61 (m, 2H), 7.77–7.84 (m, 4H), 8.05 (d, J = 8.5 Hz, 1H), 8.18 ppm (s, 1H) (these data are consistent with those reported in the literature[68]); ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 126.0, 127.9, 128.1, 128.5, 128.8 (2C), 130.1 (2C), 131.9, 132.4, 134.1, 136.2, 138.5, 146.5, 147.9, 193.3 ppm; HRMS (ESI): m/z calcd for $C_{16}H_{11}{}^{35}ClNO$ $[M+H]^+$: 268.0529, m/z calcd for $C_{16}H_{10}{}^{35}ClNNaO$ $[M+Na]^+$: 290.0349; found: 268.0529 and 290.0349, respectively.

2-Chloro-4-benzoylquinoline (21b2): Eluent: heptane/EtOAc (70:30). Beige powder. M.p. 105 °C (lit.[69] 105–107 °C); ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 7.38 (s, 1H), 7.47–7.55 (m, 3H), 7.65 (tt, J = 1.2 and 7.5 Hz, 1H), 7.75–7.80 (m, 2H), 7.83–7.85 (m, 2H), 8.10 ppm (d, J = 8.4 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 120.8, 124.0, 125.5, 128.0, 129.1 (2C), 129,2, 130.4 (2C), 131.3, 134.7, 136.1, 147.7, 148.4, 150.0, 194.6 ppm; HRMS (ESI): m/z calcd for $C_{16}H_{11}{}^{35}ClNO$ $[M+H]^+$: 268.0529; found: 268.0531.

2-Chloro-3,8-dibenzoylquinoline (21b3): Eluent: heptane/EtOAc (70:30). Beige powder. M.p. 201 °C; ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 7.49 (t, J = 7.5 Hz, 2H), 7.44 (t, J = 7.4 Hz, 2H), 7.59 (t, J = 7.4 Hz, 1H), 7.64 (t, J = 7.4 Hz, 1H), 7.72 (t, J = 7.6 Hz, 1H), 7.81–7.87 (m, 5H), 8.01 (dd, J = 0.8, 8.1 Hz, 1H), 8.26 ppm (s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 126.2, 127.3, 128.5 (2C), 129.0 (2C), 130.1, 130.2 (2C), 130.3 (2C), 130.8, 133.5, 133.6, 134.4, 136.1, 137.6, 138.1, 138.6, 145.6, 147.1, 193.3, 196.4 ppm; HRMS (ESI): m/z calcd for $C_{23}H_{15}{}^{35}ClNO$ $[M+H]^+$: 372.0791, m/z calcd for $C_{23}H_{14}{}^{35}ClNNaO_2$ $[M+Na]^+$: 394.0611; found: 372.0802 and 394.0612, respectively.

8-Benzoyl-4,7-dichloroquinoline (22b): Eluent: heptane/EtOAc (90:10). Yellow powder. M.p. 98 °C; ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.40–7.48 (m, 2H), 7.51 (d, J = 4.7 Hz, 1H), 7.60 (tt, J = 1.3, 7.4 Hz, 1H), 7.71 (d, J = 4.7 Hz, 1H), 7.80–7.86 (m, 2H), 8.31 (d, J = 9.0 Hz, 1H), 8.69 ppm (d, J = 4.7 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 122.0, 125.2, 126.2, 128.9 (2C), 129.1, 129.8 (2C), 133.0, 134.0, 136.7, 137.8, 142.8, 147.8, 151.4, 194.6 ppm; HRMS (APCI): m/z calcd for $C_{16}H_{10}{}^{35}L_2NO$ $[M+H]^+$: 302.01339, m/z calcd for $C_{16}H_9{}^{35}L_2NO$ $[M]^+$: 301.00557; found: 302.0133 and 301.0059, respectively.

5-Benzoyl-6-chloro-2,4-dimethoxypyrimidine (23b): Eluent: heptane/EtOAc (90:10). White powder. M.p. 112 °C; ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 3.94 (s, 3H), 4.07 (s, 3H), 7.46–7.51 (m, 2H), 7.63 (tt, J = 1.5, 7.4 Hz, 1H), 7.82–7.86 ppm (m, 2H) (these data are consistent with those reported in the literature[70]); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 55.3, 55.9, 112.9, 129.0 (2C), 129.6 (2C), 134.4, 136.3, 158.2, 164.4, 169.6, 190.9 ppm.

2-Bromopyridin-3-yl phenyl ketone (**5b2**) and 2-chloropyridin-3-yl phenyl ketone (**6b2**) have previously been described.[9b]

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