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Functionalization of pyridyl ketones using deprotolithiation-*in situ* zincation

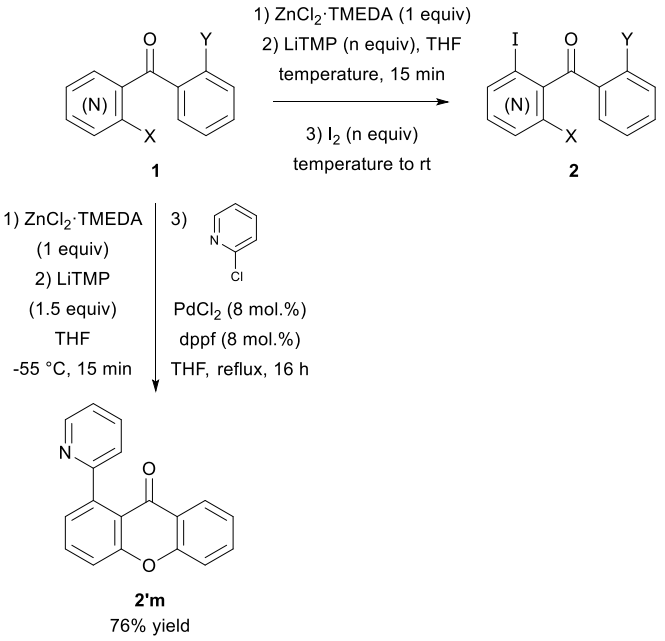
Madani Hedidi,[a,b,c] William Erb,[a,*] Frédéric Lassagne,[a] Yury S. Halauko,[d,*] Oleg A. Ivashkevich,[d] Vadim E. Matulis,[e] Thierry Roisnel,[f] Ghenia Bentabed-Ababsa[b,*] and Florence Mongin[a]

The metallation of aryl ketones was achieved by using LiTMP in the presence of $ZnCl_2$·TMEDA, as evidenced by subsequent interception with iodine or by palladium-catalysed cross-coupling reaction. One of the synthesized iodo ketones has been further elaborated to reach derivatives of biological interest.

Pyridines play a large part in biological processes (nicotine, niacin, NADP, vitamin B_6…), in pharmaceuticals and agrochemicals,[1] as well as in organic materials.[2] In addition, pyridyl ketones bearing a halogen at the position adjacent to the carbonyl function are key intermediates to access heterocyclic scaffolds of interest such as azafluorenones,[3] azaxanthones,[4] naphthyridones,[5] and thieno-,[6] pyrazolo-[7] and isoxazolo-pyridines.[8]

Even if deprotonative lithiation[9] has been largely used to regioselectively functionalize pyridines,[10] the method has never been extended to pyridyl ketones due to their low compatibility with organolithiums. Mixed lithium-nonalkali metal combinations have been developed to achieve chemoselective deprotometallation of aromatics.[11] In this context, the 1:1 mixture of homometallic amides LiTMP (TMP = 2,2,6,6-tetramethylpiperidino) and $Zn(TMP)_2$,[12] obtained by mixing in a 3:1 ratio LiTMP and $ZnCl_2$·TMEDA (TMEDA = *N*,*N*,*N'*,*N'*-tetramethylethylenediamine) in THF (THF = tetrahydrofuran), was successfully employed with a large range of sensitive substrates.[13] Such a synergy, attributed to reversible deprotolithiation shifted by zinc-mediated transmetallation[12] (or 'trans-metal trapping'[14]), has since been extended to the use of LiTMP in the presence of $ZnCl_2$·2LiCl, $MgCl_2$ or CuCN·2LiCl.[15]

Herein, we report the efficiency of aryl ketones as directing groups for LiTMP-mediated deprotometallation of pyridines and other arenes in the presence of $ZnCl_2$·TMEDA as *in situ* trap (Scheme 1, Table 1).



Scheme 1 Zincation of aryl ketones **1** using LiTMP in the presence of $ZnCl_2$·TMEDA followed by iodolysis or palladium-catalysed cross-coupling to afford ketones **2** and **2'**.

Thus, after optimization of the reaction conditions (using four different reaction temperatures from -70 to -10 °C and different amounts of LiTMP from 1 to 3 equiv), treatment of 2-benzoylpyridine (**1a**) in THF containing $ZnCl_2$·TMEDA (1 equiv) with LiTMP (1.5 equiv) at -30 °C for 15 min and then iodine led to the 3-iodo derivative **2a** in 50% yield (entry 1). Similarly, 4-benzoylpyridine (**1b**) was converted to the 3-iodo derivative **2b** by using LiTMP (2 equiv); with this substrate benefiting from two free positions adjacent to the benzoyl group, a second deprotonation was observed to some extent, as evidenced by the competitive formation of the diiodo **2b'** (entry 2).

3-Benzoylpyridine (**1c**) is more prone to nucleophilic attack onto the ring than its 2- and 4-isomers.[16] As a consequence, deprotolithiation-zincation could only be evidenced by subsequent iodolysis at temperatures below -50 °C. Using LiTMP (1.5 equiv) at -55 or -70 °C for 15 min and then iodine provided the 4-iodo derivative **2c** in 30 or 37% yield, respectively (entry 3).

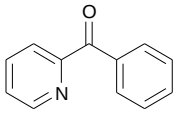
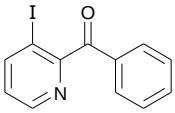
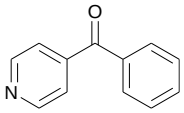
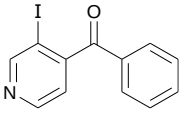
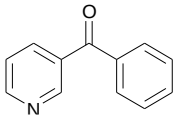
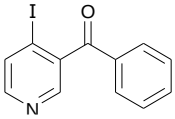
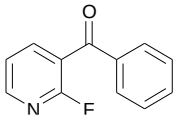
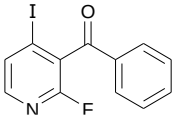
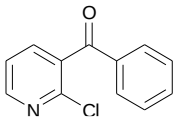
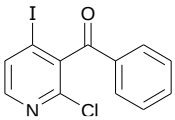
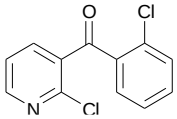
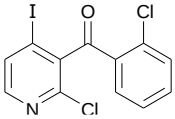
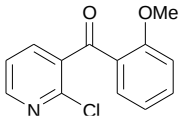
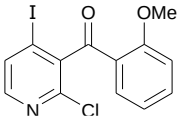
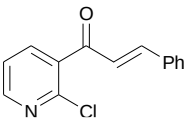
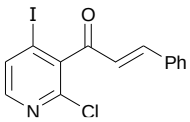
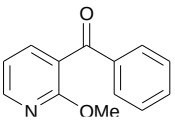
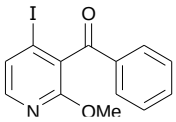
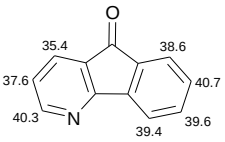
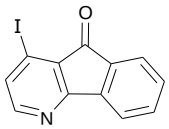
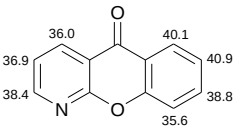
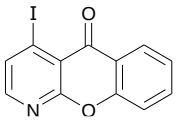
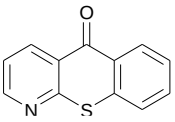
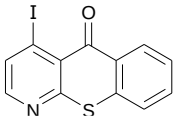
When present at pyridine 2-position, halogens are known to acidify the 4-position, as shown by pK_a values calculated in THF.[13a] The 2-halogeno 3-benzoylpyridines **1d**-**h** were thus prepared.[17] Accordingly, when similarly reacted by using LiTMP at -55 °C, the iodo derivatives **2d**-**g** were isolated in improved yields, in line with the long range effects of fluorine and chlorine (entries 4-7). In contrast, the reaction from **1h** proved more complex, giving the iodide **2h** in a modest yield (entry 8).

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† Electronic supplementary information (ESI) available: General procedures, experimental procedures and compound characterizations, ^{1}H and ^{13}C NMR spectra of the new compounds, and X-ray crystallographic data. CCDC 1475309 (**2j'**), 1475009 (**2k'**) and 1475010 (**2n'**). For ESI and crystallographic data in CIF see DOI: 10.1039/x0xx00000x

The presence of a methoxy group at 2-position of 3-benzoylpyridine also had a positive impact on the course of the reaction since involving **1i** in the sequence furnished the iodo derivative **2i** in 88% yield (entry 9). Whereas this group does not acidify remote pyridine 4-position,[13b] it acts by making the pyridine ring less sensitive towards competitive nucleophilic attack. Indeed, based on the ^{1}H NMR chemical shifts in $CDCl_3$ of **1c** (8.12 and 8.82 ppm for H4 and H6, respectively) and **1i** (7.72 and 8.32 ppm for H4 and H6, respectively), one can predict as shown by Handy and Zhang[18] that the partial positive charges at C4 and C6 will be reduced for **1i**.

Table 1 Substrates **1a-l**, calculated pK_a(THF) values for **1j** and **1k**, conditions used for the deprotolithiation-zincation, and iodinated aryl ketones **2a-l** obtained.

Entry	Substrate/n/temperature	Product/yield[a] (%)
1	 **1a**: 1.5 equiv, -30 °C	 **2a**: 50%
2	 **1b**: 2 equiv, -30 °C	 **2b**: 45%[b]
3	 **1c**: 1.5 equiv, -55 °C **1c**: 1.5 equiv, -70 °C	 **2c**: 30% **2c**: 37%
4	 **1d**: 1.5 equiv, -55 °C	 **2d**: 63%
5	 **1e**: 1.5 equiv, -55 °C	 **2e**: 73%
6	 **1f**: 1.5 equiv, -55 °C	 **2f**: 78%
7	 **1g**: 1.5 equiv, -55 °C	 **2g**: 70%
8	 **1h**: 1.5 equiv, -55 °C	 **2h**: 27%
9	 **1i**: 1.5 equiv, -55 °C	 **2i**: 88%
10	 **1j**: 1.5 equiv, -55 °C	 **2j**: 33%[c]
11	 **1k**: 1.5 equiv, -55 °C	 **2k**: 60%[d]
12	 **1l**: 1.5 equiv, -55 °C	 **2l**: 60%

[a] Yield after purification by column chromatography. [b] 4-Benzoyl-3,5-diiodopyridine (**2b'**) was also obtained in 10% yield. [c] 1,5-Diiodo-4-azafluorenone (**2j'**) was also obtained in 20% yield. [d] 1,6-Diiodo-4-azaxanthone (**2k'**) was also obtained in 10% yield.

The behaviour of the ketones **1j-l**, possessing reduced flexibility on carbonyl direction, was similarly examined. 4-azafluorenone (**1j**) was converted to the 1-iodo derivative **2j** in a moderate yield, similar to that obtained from 3-benzoylpyridine (**1c**). In the case of **1j**, the phenyl ring was also attacked to a lesser extent at a position facing the pyridine nitrogen to afford the diiodide **2j'** (entry 10, Figure 1). In contrast with the reaction from **1j**, the sequence using 4-azaxanthone (**1k**) and 4-azathioxanthone (**1l**) provided the iodides **2k** and **2l** in higher 60% yields (entries 11 and 12).

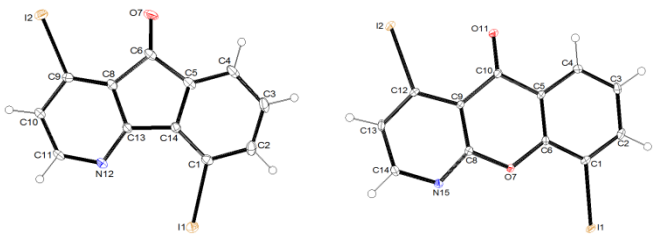


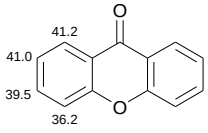
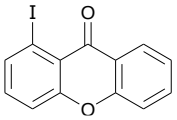
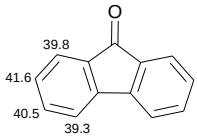
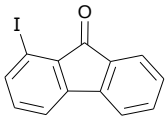
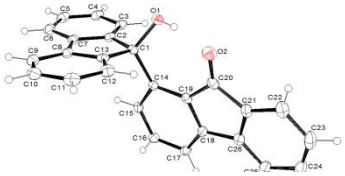
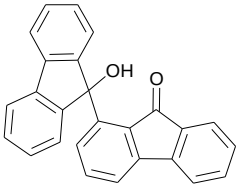
Figure 1 ORTEP diagrams (30% probability) of compounds **2j'** and **2k'**.

In order to evaluate the scope of the method, we chose other aromatic substrates.[19] When compared with its 4-aza analogue **1k**, xanthone (**1m**) similarly led to the 1-iodo **2m** in 72% yield. On the contrary, as previously noted between **1j**

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and **1k**, the reaction from **1n** was less efficient than from **1m**. Indeed, 1-iodofluorenone (**2n**) was obtained in 52% yield, but together with the ketone **2n'** (35% yield) resulting from an addition of the metallated product to **1n** (Scheme 1, Table 2). As organozincs hardly react with ketones, the product **2n'** could rather result from an addition of 1-lithiofluorenone to **1n** more rapid than its trapping by the zinc species. These results suggest that the carbonyl direction in the metallated derivative coming from **1n** is less prone to stabilize a 1-lithio compound than that from **1m**.

Table 2 Substrates **1m** and **1n** and their calculated pK_a(THF) values, conditions used for the deprotolithiation-zincation, iodinated aryl ketones **2m** and **2n** obtained, and ORTEP diagram (30% probability) of compound **2n'**.

Entry	Substrate/n/temperature	Product/yield[a] (%)
1	 **1m**: 1.5 equiv, -55 °C	 **2m**: 72%
2	 **1n**: 1.5 equiv, -55 °C	 **2n**: 52%
		 **2n'**: 35%

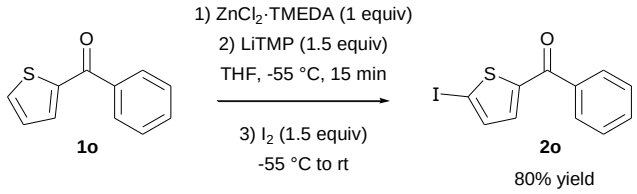
[a] Yield after purification by column chromatography.

Interestingly, the deprotolithiation-*in situ* zincation could be combined with a subsequent Negishi cross-coupling reaction.[20] Thus, using catalytic amounts of $PdCl_2$ as palladium source and 1,1'-diphenylphosphinoferrocene (dppf) as ligand with 2-chloropyridine[12a] allowed **2'm** to be formed from 9-xanthone (**1m**) in 76% yield (Scheme 1).

CH acidities are in general useful data to better understand deprotometallation outcomes, in particular regarding regioselectivity issues. We thus calculated selected pK_a values in THF solution by means of quantum chemistry at the DFT B3LYP level of theory.[13] After geometry optimization and calculation of the vibrational frequencies by using the 6-31G(d) basis set, the single point energies were obtained using the 6-311+G(d,p) basis set. The solvent influence was treated through the polarized continuum model (PCM) with the default parameters for THF. Finally, the pK_a values were reached from the Gibbs energy of the homodesmic reaction between the studied and probe heterocycles.

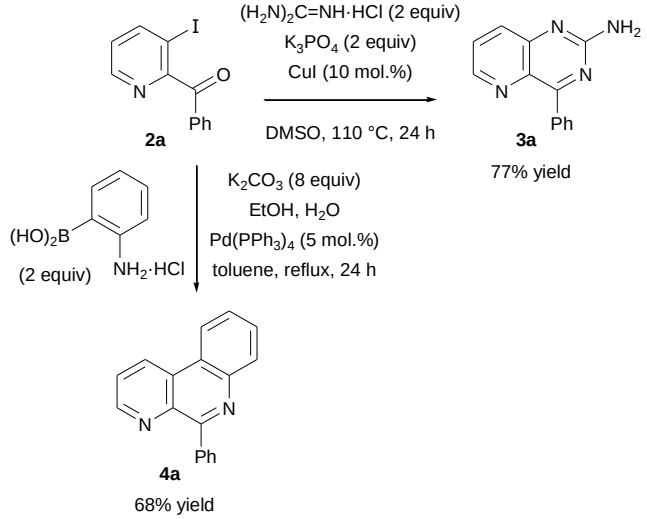
That both sets of CH acidity values for **1m** and **1n** are rather similar (Table 2) supports the role of the carbonyl direction on the course of the reaction through coordination. Analogously, the difference observed between the pK_a values of **1j** and **1k** is not significant enough to allow for a rationalization of the distinct yields noted, rather suggesting a more efficient stabilization of the metallated compound by the carbonyl group in the case of **1k** at the origin of the higher yield. Besides, the formation of dimetallated products from **1j** and **1k**, as demonstrated by isolation of **2j'** and **2k'** (Figure 1), could be favoured for the former by a nitrogen assistance and, for the latter, by a relatively low pK_a value (35.6) at the 6-position (Table 1).

Finally, when 2-benzoylthiophene (**1o**) was submitted to LiTMP in the presence of $ZnCl_2$·TMEDA as before, the reaction took place next to sulphur to afford after iodolysis the iodo derivative **2o** in 80% yield (Scheme 2).



Scheme 2 Zincation of phenyl 2-thienyl ketone (**1o**) using LiTMP in the presence of $ZnCl_2$·TMEDA followed by iodolysis to afford the iodinated 2-thienyl ketone **2o**.

To move towards nitrogen-containing derivatives of biological interest, 2-benzoyl-3-iodopyridine (**2a**) was involved in further reactions (Scheme 3). A catalyst-base system was first optimized to perform guanidine copper-catalysed *N*-arylation.[21] Upon treatment with K_3PO_4 as base and CuI as catalyst source in the presence of DMSO, the iodide **2a** was converted to the pyrido[3,2-*d*]pyrimidine **3a** in 77% yield. Besides, cyclizing Suzuki coupling[22] was performed from the ketone **2a** and 2-aminophenylboronic acid under palladium catalysis to provide 5-phenylbenzo[*f*][1,7]naphthyridine (**4a**)[23] in 68% yield.



Scheme 3 Conversion of 2-benzoyl-3-iodopyridine (**2a**) to derivatives of biological interest.

Please do not adjust margins

In summary, we have reported a short and simple access to iodinated aryl ketones. Additionally, transition metal-mediated reactions occurring with cyclization led to elaborated scaffolds. Applications towards the synthesis of libraries of compounds for biological evaluation are currently under investigation in our laboratory.

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