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Aromatic Iodides: Synthesis and Conversion to Heterocycles †

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Abstract: Aromatic heterocycles can be found in many molecules endowed with specific properties, in particular for applications in the fields of medicinal chemistry and materials science. In the group, we notably develop synthetic methodologies to selectively introduce iodine onto aromatic compounds and to use this heavy halogen in order to build heterocycles of interest. While we sometimes employed direct iodinations on electron-enriched aromatic compounds, we mainly optimized deprotometallation-iodolysis sequences to functionalize substrates sensitive to nucleophilic attacks. In particular, hindered lithium amide-metal trap tandems have been designed to overcome the low tolerance of some functional groups (e.g., ketones or sensitive diazines) toward organolithiums. The aromatic iodides generated these ways have been involved in transition metal-catalyzed cross-couplings to access original scaffolds (oxazoloquinoxalines, pyrazinoisatins, pyrazinocarbazoles...). We especially developed the use of aromatic iodides in copper-mediated *N*-arylation of anilines, e.g., to reach triarylamines. Combined with subsequent cyclizations, these reactions allowed an access to numerous heterocyclic compounds (such as acridones, acridines, other aza-aromatic polycycles and helicene-like structures) with potential applications. From some of the scaffolds obtained, biological evaluation in the frame of collaborations allowed properties of interest to be discovered (e.g., specific inhibition of protein kinases GSK-3 or PIM, related to cancer development).

Keywords: organic synthesis; methodology; aromatic iodide; heterocycle; biological activity

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1. Introduction

Aromatic iodides are particularly useful substrates for a wide range of reactions including cross-coupling reactions catalyzed by transition metals.

In this mini-review, our goal is to highlight the contributions of our group in this field, whether to rationalize the regioselectivity of direct iodination reactions, to implement deprotometallation-iodolysis sequences from sensitive aromatic compounds in order to reach other iodinated derivatives, and finally to use these iodinated derivatives as partners in the *N*-arylation of anilines.

Whenever possible, we sought to show the usefulness of the synthesized iodinated derivatives as well as the compounds obtained by *N*-arylation. Thus, the potential applications of the synthesized molecules, especially their biological activity, have been discussed.

2. Selective Introduction of Iodine onto Aromatic Compounds

In this paragraph, we will present through selected examples the two ways that we have considered to introduce an iodine on aromatic compounds, direct iodination and deprotometalation followed by iodolysis.

2.1. Direct Iodination and Application to the Synthesis of Heterocycles of Interest

Direct iodination generally concerns electron-rich aromatic compounds, and the reaction often takes place at the carbon site possessing the most negative atomic carbon charge. Another way to predict the outcome of aromatic electrophilic substitution (S_EAr) reactions [1] such as iodination relies on Fukui's concept (in a reaction with an electrophile, an aromatic compound reacts at its carbon having the highest amplitudes of the highest occupied molecular orbital (HOMO) coefficient—in absolute value) [2]. For example, calculating the amplitudes of these coefficients for 1-(3,5-dimethylphenyl)-7-azaindole and 1-(2-thienyl)-7-azaindole by applying Hückel's theory [3,4] indicated a favored reaction at C3 and C5′, respectively, in accordance with the experimental results [5] (products **1** and **2**; Figure 1).

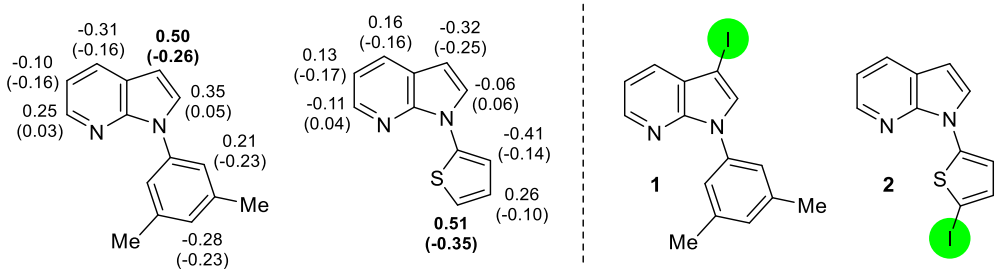


Figure 1. (Left) HOMO coefficients (obtained by using the HuLiS calculator [4]) and calculated C charges (in brackets) for 1-(3,5-dimethylphenyl)-7-azaindole and 1-(2-thienyl)-7-azaindole. (**Right**) Halogenated products **1** and **2** obtained after treatment with iodine.

From various 6-aminoquinoxalines [6], iodination similarly occurred at C5, as predicted by the amplitudes of the HOMO coefficients (see examples in Figure 2). The 6-amino-5-iodoquinoxalines **3–5** thus obtained in high yields are particularly interesting substrates for subsequent functionalization. Indeed, inspired by Verma and co-workers [7], a derivative of **3** was converted into the corresponding 6-thioureido derivative by reaction with benzoyl isothiocyanate (Scheme 1, top). Subsequent cyclization led to an original thiazolo[5,4-*f*]quinoxaline (Scheme 1, right) that was identified as a selective CK1 kinase inhibitor and showed a promising antiproliferative activity on melanoma cells (66% inhibition at 10 μM). From the same derivative of **3**, reaction with phenylacetylene and sulfur under the conditions of Wu and Jiang (tripotassium phosphate, and catalytic copper(I) iodide and 1,10-phenanthroline, in hot dimethylsulfoxide (DMSO) under oxygen) [8] led to another original member of the thiazolo[5,4-*f*]quinoxaline family [9] (Scheme 1, bottom left).

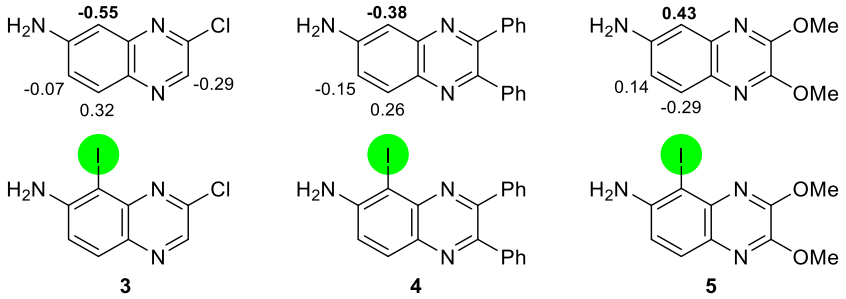
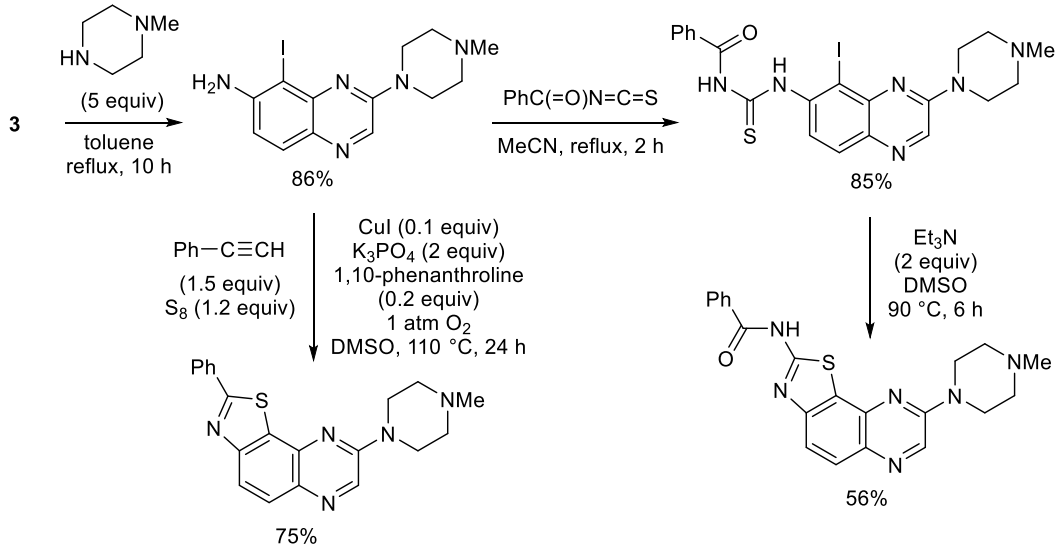
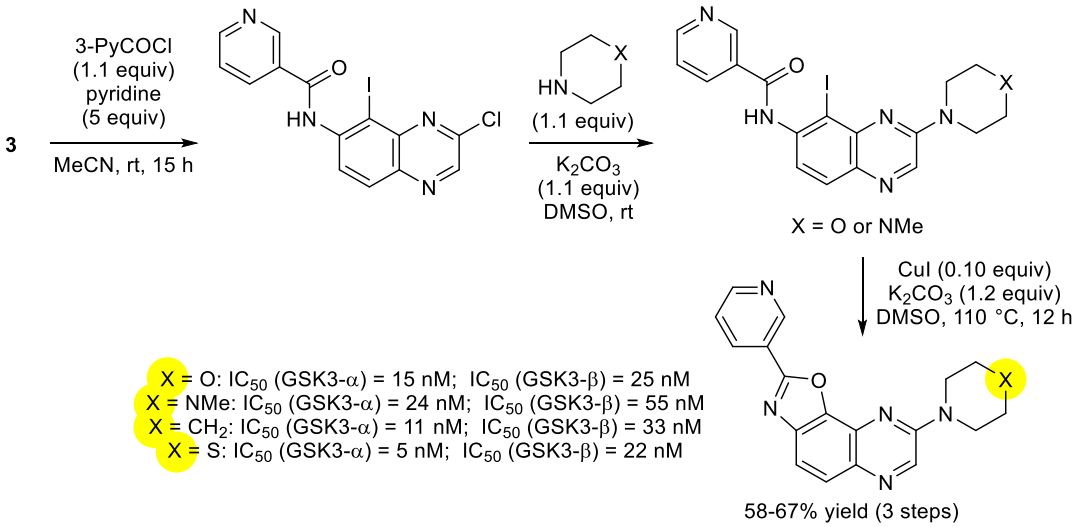


Figure 2. HOMO coefficients (obtained by using the HuLiS calculator [4]) for substituted 6-aminoquinoxalines and products **3–5** resulting from their iodination.



Scheme 1. Conversion of **3** into thiazolo[5,4-*f*]quinoxalines.

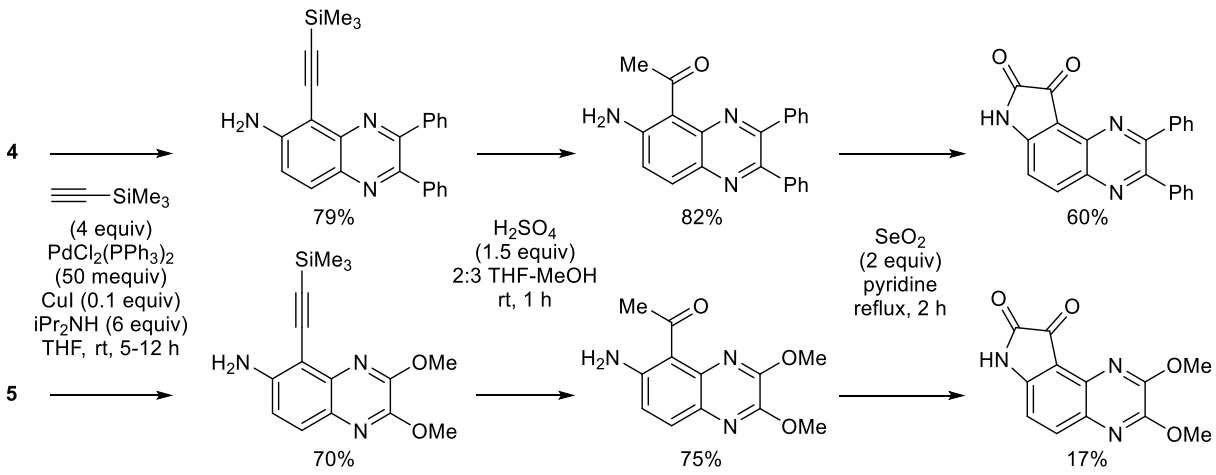
To access oxazolo[5,4-*f*]quinoxalines, which were at that time unknown heterocycles of interest [10], 6-amino-5-iodoquinoxaline **3** was first converted to carboxamides (here, *N*-aroylation with nicotinoyl chloride; Scheme 2, top left). After substitution of the chlorine atom by a secondary amine, the oxazole ring was finally built by using a copper-catalyzed cyclization [11] (potassium carbonate, and catalytic copper(I) iodide in DMSO at 110 °C). The synthesized compounds were tested on a panel of disease-related protein kinases, and some of them proved to be strong, ATP-competitive inhibitors of GSK3, with a preference for the isoform α [12] (Scheme 2, right).



Scheme 2. Conversion of **3** into oxazolo[5,4-*f*]quinoxalines and activity on GSK3 kinases.

An access to new pyrazino[*b*,*e*]isatins was in parallel developed from the 6-aminoquinoxalines **4** and **5**. After introduction of the required two carbons by a Sonogashira coupling with trimethylsilylacetylene [13], under conditions already reported (diisopropylamine, and catalytic palladium(II) chloride bis(triphenylphosphine) and copper(I) iodide in tetrahydrofuran (THF) at room temperature) [14], the alkynes were hydrated toward the 5-acetyl-6-amino derivatives (Scheme 3, left). The original pyrazino-fused isatins were finally formed by oxidative cyclization in the presence of selenium oxide (Scheme 3,

right). When tested on melanoma cells, the dimethoxylated derivative exhibited a significant activity (41% inhibition at 10 μM) [9].



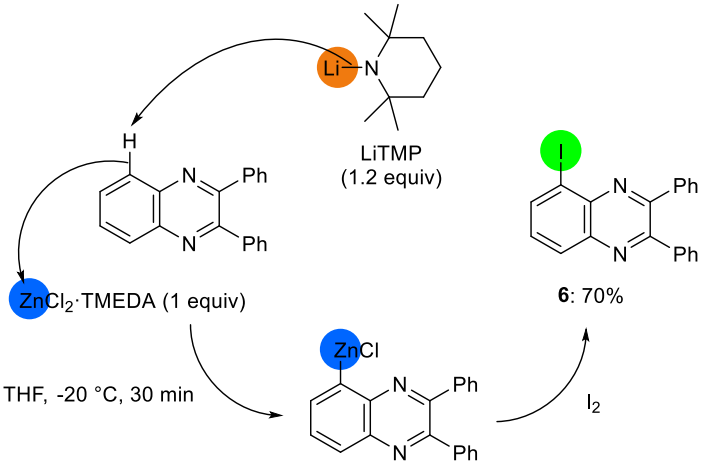
Scheme 3. Conversion of **4** and **5** into pyrazino[*b*,*e*]isatins.

2.2. Deprotometalation with In Situ Trapping-Iodolysis as an Alternative to Direct Iodination

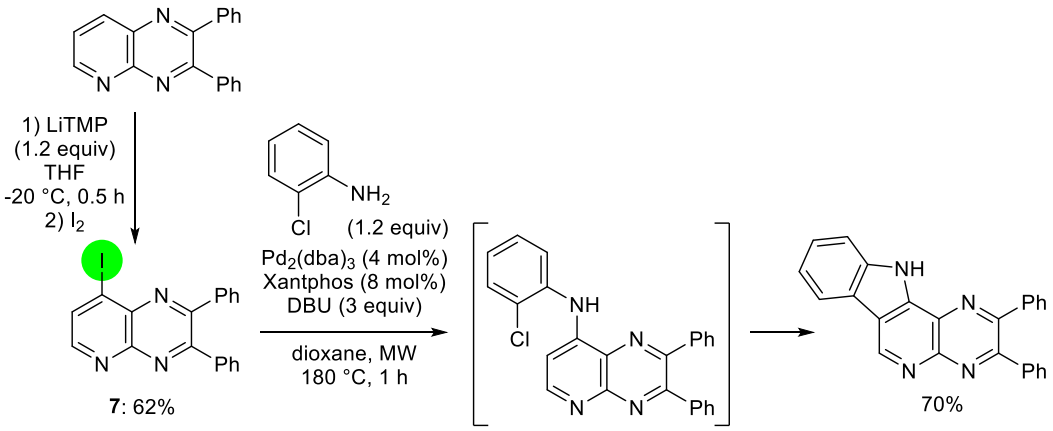
Deprotolithiation followed by electrophilic trapping is an elegant way to functionalize aromatic compounds for which direct iodination is ineffective, either because it does not work or because it does not achieve the desired regioselectivity [15–20]. However, due to the high ionic character of the carbon-metal bond, sensitive aromatic substrates (e.g., heterocycles) and aryllithiums of low stability might not be tolerated. In this case, alternative approaches such as the use of lithium -ate bases (e.g., lithium zincates) and Turbo bases (e.g., LiCl-containing zinc amides) prepared from hindered secondary amines such as 2,2,6,6-tetramethylpiperidine (H-TMP) have been developed [21–26].

A complementary approach consists in carrying out the deprotolithiation in the presence of an electrophilic trap capable of intercepting the aryllithium as soon as it is generated, thus avoiding side reactions. This was made possible by using the lithium amides LiDA (lithium diisopropylamide) and LiTMP (lithium 2,2,6,6-tetramethylpiperidide) as bases, and chlorotrimethylsilane and triisopropyl borate as electrophiles. Moreover, for reversible reactions that do not benefit from the difference of four pK_a units between the base and the substrate, in situ trapping is a way to push the reaction to completion [27]. This strategy has been developed from the 1980s by using silicon-based and boron-based electrophiles, and more recently by using metal-based in situ traps [28].

In the group, we have been especially interested in the use of $ZnCl_2$·TMEDA (TMEDA = *N*,*N*,*N*′,*N*′-tetramethylethylenediamine) as in situ trap to intercept aryllithiums that could otherwise either attack the aromatic substrate or undergo degradation. The thus generated arylzinc compounds can then be easily converted to the corresponding iodides [28]. This was for example performed on 2,3-diphenylquinoxaline, affording the iodide **6** in good yield [29] (Scheme 4). A similar approach was successfully applied to pyrido[2,3-*b*]pyrazine for which the lithiated derivative has a low stability. The iodide **7** thus obtained was next involved in a palladium-catalyzed *N*-arylation/C-H activation sequence with 2-chloroaniline. Under conditions inspired by those of Maes, [30] Pieters [31] and co-workers for related reactions (diazabicyclo[5.4.0]undec-7-ene, and catalytic dipalladium(0) tris(dibenzylideneacetone) and Xantphos, in dioxane), using a high 180 °C temperature for 10 min under microwave irradiation led to an original heterocycle in 70% yield [29] (Scheme 5).

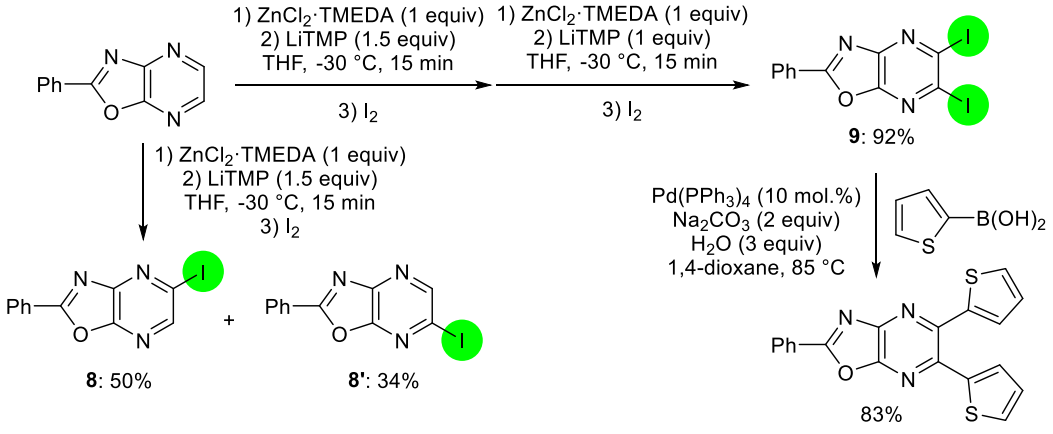


Scheme 4. Conversion of 2,3-diphenylquinoxaline into the 5-iodinated derivative **6**.



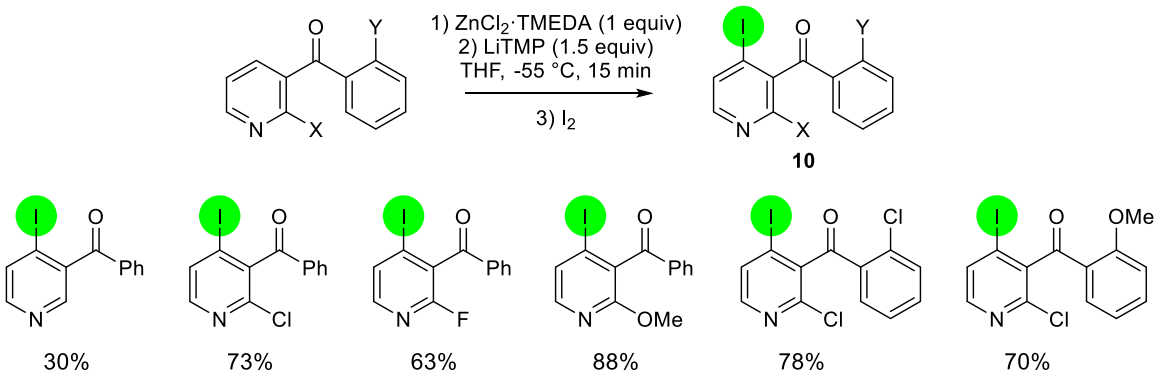
Scheme 5. Conversion of pyrido[2,3-*b*]pyrazine into the 5-iodinated derivative **7** and application to the synthesis of a pyrazino-fused azacarbazole.

Due to their low LUMO levels, pyrazines are prone to nucleophilic attacks [32–34]. From 2-phenyloxazolo[4,5-*b*]pyrazine, the use of LiTMP in the presence of $ZnCl_2$·TMEDA (in order to intercept the formed aryllithium before competitive reactions) allowed a chemoselective reaction to take place. However, due to the small reactivity difference between the two positions next to the pyrazine nitrogens, two iodides **8** and **8'** were formed. However, by repeating the reaction, it proved possible to prepare diiodide **9** from which a double Suzuki coupling was achieved using 2-thienylboronic acid [35] (Scheme 6).



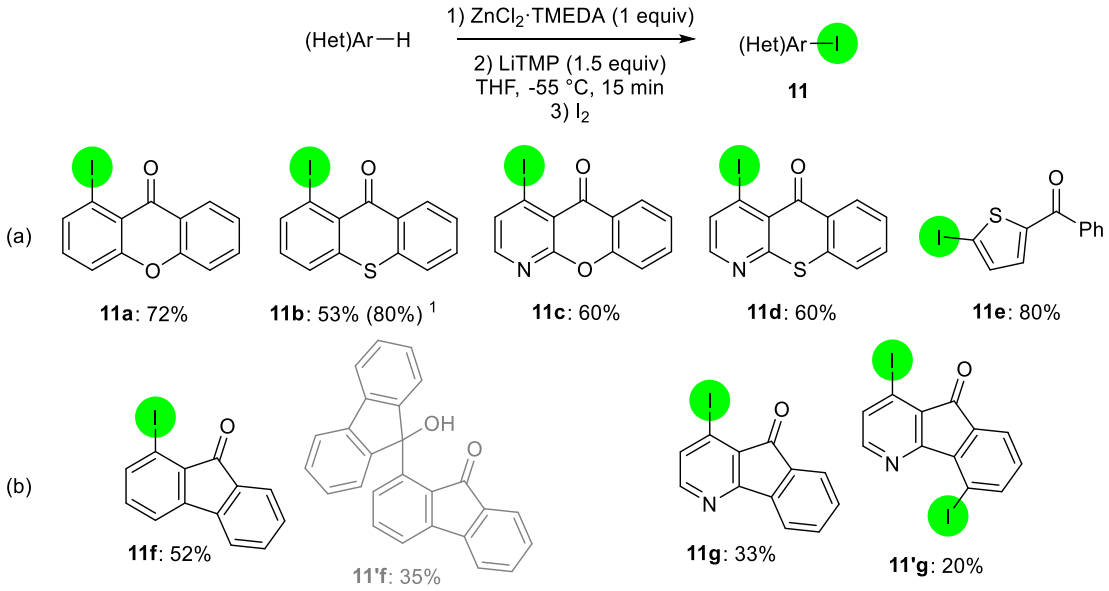
Scheme 6. Conversion of 2-phenyloxazolo[4,5-*b*]pyrazine into monoiodinated derivatives **8** and **8′**, or diiodinated derivative **9**, and application to the synthesis of a pyrazino-fused azacarbazole.

Due to our interest in the synthesis of diarylketones by deprotocupration using TMP-based lithium cuprates [26], we were eager to functionalize such compounds by using the tandem reagents LiTMP and $ZnCl_2$·TMEDA. The protocol was successfully applied to 3-aroylpyridines, but required low temperatures given the sensitivity of these substrates to nucleophiles. It was observed that the presence of a heteroatom-containing substituent at the 2-position of the pyridine ring favored the reaction, allowing the iodides **10** to be obtained in higher yields [36] (Scheme 7).



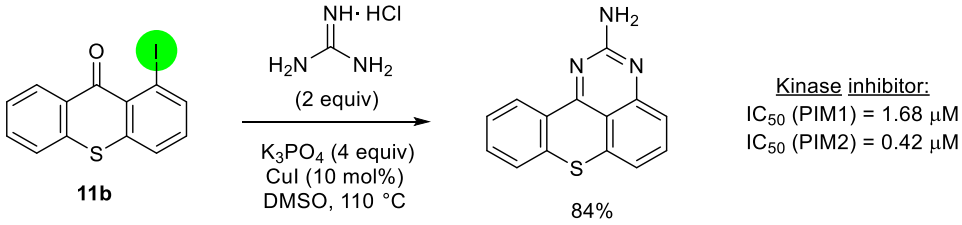
Scheme 7. Functionalization of 3-benzoylpyridines toward the iodides **10** by deprotometalation with in situ trapping followed by iodolysis.

Pleasingly, this functionalization was not limited to pyridine ketones as the iodides **11a-d** were also provided from (thio)xanthones and nitrogen analogs. In the particular case of 2-benzoylthiophene, the reaction did not take place next to the carbonyl group, but this time next to the sulfur (product **11e**; Scheme 8a). From fluorenone, the reaction proved to be less efficient (52% yield for product **11f**) than from xanthone due to a competitive addition of the lithiated intermediate on the carbonyl function of the substrate (**11′f** isolated in 35% yield) before interception by $ZnCl_2$·TMEDA. This could be due either to a less stabilization of the lithiated intermediate or to a greater sensitivity of the fluorenone ketone function. The presence of a nitrogen at the 4-position of the fluorenone made the reaction more complex (only 33% yield of product **11g**), because a second remote deprotometalation was also observed (**11′g** obtained in 20% yield) [36,37] (Scheme 8b).



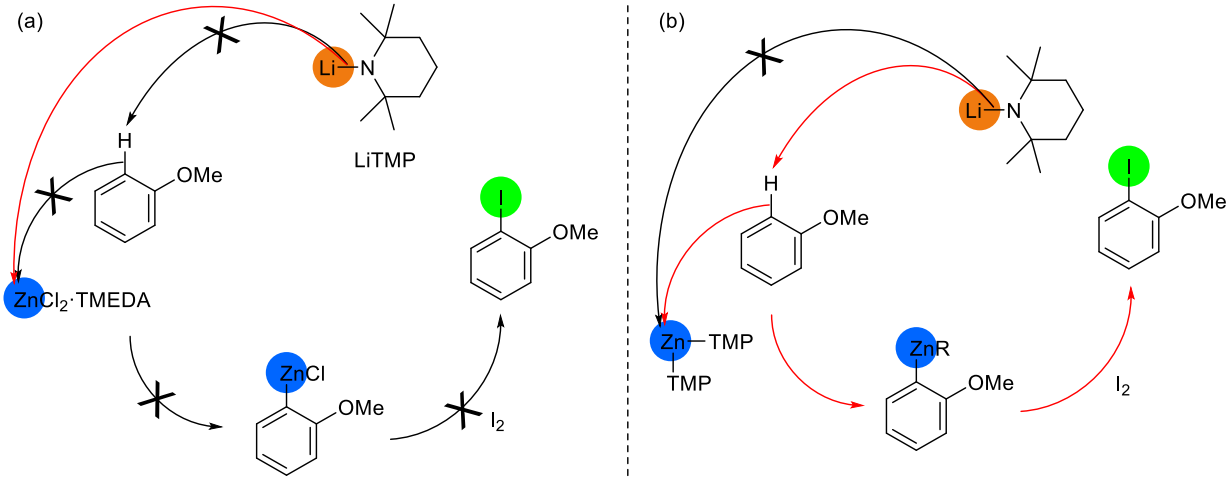
Scheme 8. Functionalization of various (hetero)aromatic ketones toward the monoiodides **11** and the by-products **11′**. [1] Reaction carried out at −30 °C.

This approach is of particular interest as aromatic ketones bearing an iodine next to the carbonyl group are key intermediates to access larger heterocycles. For example, reacting 1-iodothioxanthone (**11b**) with guanidine hydrochloride, in the presence of tripotassium phosphate [38], catalytic copper(I) iodide [39], in DMSO (solvent/ligand) [40] at 110 °C, furnished an original benzothiopyrano[4,3,2-*de*]quinazoline. Due to the widespread biological properties of quinazolines, biological studies were performed from the latter, revealing a broad spectrum of activity on the microbial growth of strains of bacteria (not shown). Moreover, the bioactivity of this tetracycle was evaluated against serine/threonine protein kinases, and a promising ability to inhibit PIM kinases (involved in signaling pathways fundamental to cancer development and progression) was revealed by dose-dependent effect [37] (Scheme 9).



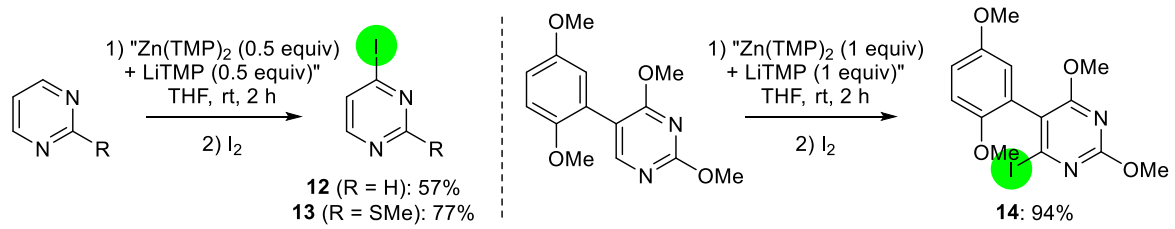
Scheme 9. Conversion of the aromatic iodide **11b** into a benzothiopyrano[4,3,2-*de*]quinazoline promising as PIM kinase inhibitor.

The ability of $ZnCl_2$·TMEDA and LiTMP to act in tandem and thus promote deprotometalation reaction largely depends on the acidity of the aromatic substrate. While LiTMP can deprotonate the (hetero)aromatic compound before being quenched with $ZnCl_2$·TMEDA in the example above, things are different with less activated substrates like anisole [41] (Scheme 10a). However, if $Zn(TMP)_2$ (prepared from 2 equivalents of LiTMP and $ZnCl_2$·TMEDA) is used instead of $ZnCl_2$·TMEDA, similar behavior can be restored [28,41] (Scheme 10b).



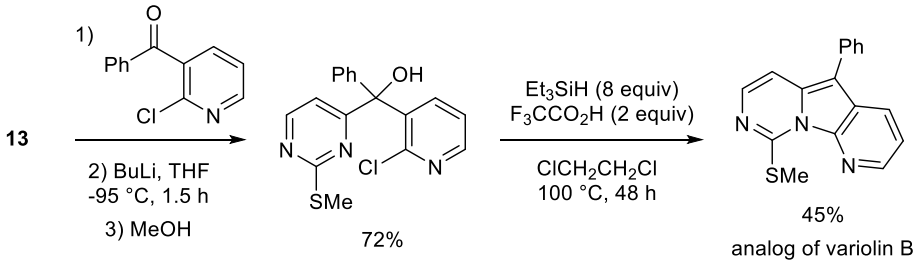
Scheme 10. (**a**) Unsuccessful use of LiTMP-$ZnCl_2$·TMEDA for the deprotometalation with in situ trapping-iodolysis of unactivated aromatic substrates. (**b**) Successful use of LiTMP-$Zn(TMP)_2$ for the deprotometalation with in situ trapping-iodolysis of unactivated aromatic substrates.

This variant has been applied to the functionalization of bare diazines, and in particular of pyrimidine which is especially prone to nucleophilic attacks [42]. While the use of LiTMP at low temperature mainly led to the formation of 4,4′-bipyrimidine from this substrate, the 4-lithiated pyrimidine could be trapped in situ by transmetalation to provide, after iodolysis, the expected product **12** in 57% yield [43]. The presence of substituents on the diazine generally favors the reaction, as observed from 2-(methylthio)pyrimidine (product **13**) and 2,4-dimethoxy-5-(2,5-dimethoxyphenyl)pyrimidine (product **14**; Scheme 11).



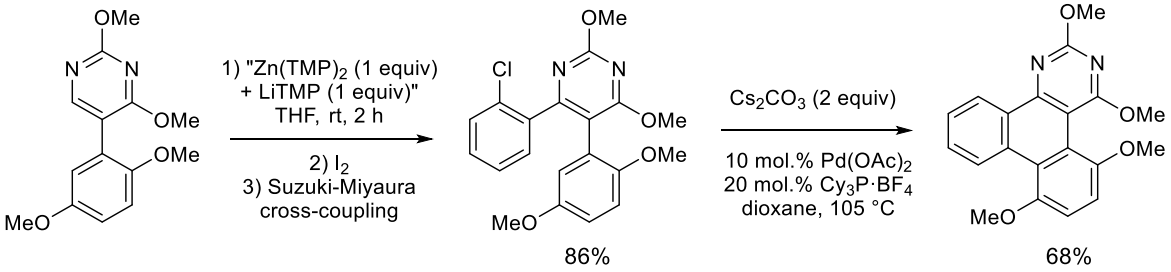
Scheme 11. Functionalization of pyrimidine, 2-(methylthio)pyrimidine (**left**) and 2,4-dimethoxy-5-(2,5-dimethoxyphenyl)pyrimidine (**right**) toward the iodides **12–14**, respectively, by deprotometalation with in situ trapping followed by iodolysis.

Iodopyrimidines are also precursors of heterocycles of potential interest. As an example, the iodide **13** was easily converted to a triarylmethanol, by iodine/lithium exchange in the presence of a ketone [44–46] to intercept the lithiated intermediate. Cyclization of this tertiary alcohol finally led to an analog of variolin B [47] (Scheme 12).



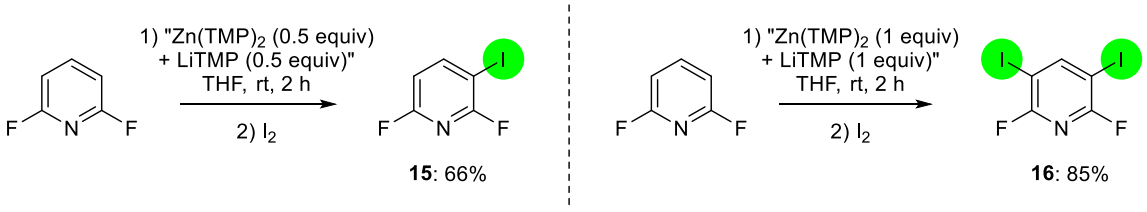
Scheme 12. Conversion of the iodide **13** into an analog of variolin B.

Aromatic iodides are also substrates of choice for performing Suzuki-Miyaura cross-coupling reactions [48,49]. As shown in Scheme 13, there is no need to isolate the iodide **14**, as it could be easily transformed by in situ reaction with 2-chlorophenylboronic acid under reported conditions [50] to afford a precursor of diazatriphenylene. Intramolecular C-H arylation [51–53] conditions were finally found to reach this tetracycle [54].



Scheme 13. Formation of the iodide **14** and in situ conversion to a diazatriphenylene.

While the variant LiTMP-Zn(TMP)$_2$ is able to deprotonate less activated substrates, it is also able to dideprotonate substrates that benefit from two activated positions. As a consequence, diiodides can be formed, as exemplified below from 2,6-difluoropyridine. In this case using LiTMP (0.5 equiv) and Zn(TMP)$_2$ (0.5 equiv) led to the 3-iodinated **15** (66% yield) while simply increasing these amounts to LiTMP (1 equiv) and Zn(TMP)$_2$ (1 equiv) in the reaction furnished the 3,5-diiodinated **16** in 85% yield [55] (Scheme 14).



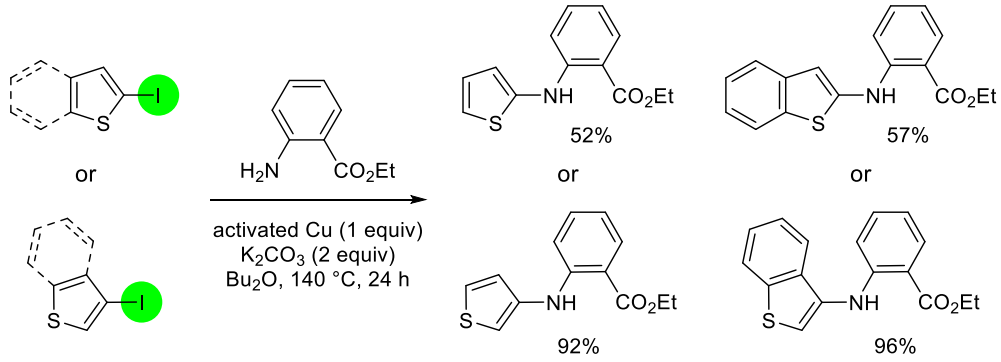
Scheme 14. Functionalization of 2,6-difluoropyridine, either at C3 (**left**) or at C3 and C5 (**right**) toward the iodides **15** and **16**, respectively, by deprotometalation with in situ trapping followed by iodolysis.

3. Aromatic Iodides in Copper-Mediated *N*-Arylation of Anilines

In the last years, we have been interested in the copper-mediated *N*-arylation of anilines which represents a way to reach new scaffolds from the various aromatic iodides we could prepare. Among the halogenated aromatics used as partners in such *N*-arylation of anilines, thiophenes are poorly represented. When treated with 3-bromothiophene in the presence of *N*-ethylmorpholine and copper(II) bromide (dimethylformamide, reflux, 2 h), it has been shown that potassium anthranilate was only *N*-arylated in a moderate 32% yield [56]. A better result was observed by reacting aniline with 3-bromothiophene in water containing potassium hydroxide, tetrabutylammonium bromide, and catalytic chitosan and copper(I) oxide (80% monoarylation yield after 12 h at 70 °C) [57]. 2-Bromobenzothiophene appears to be even less reactive because its cross-coupling with aniline in *N*,*N*-dimethylethanolamine containing potassium phosphate and catalytic copper/copper(I) iodide at 85 °C for 2 days failed [58].

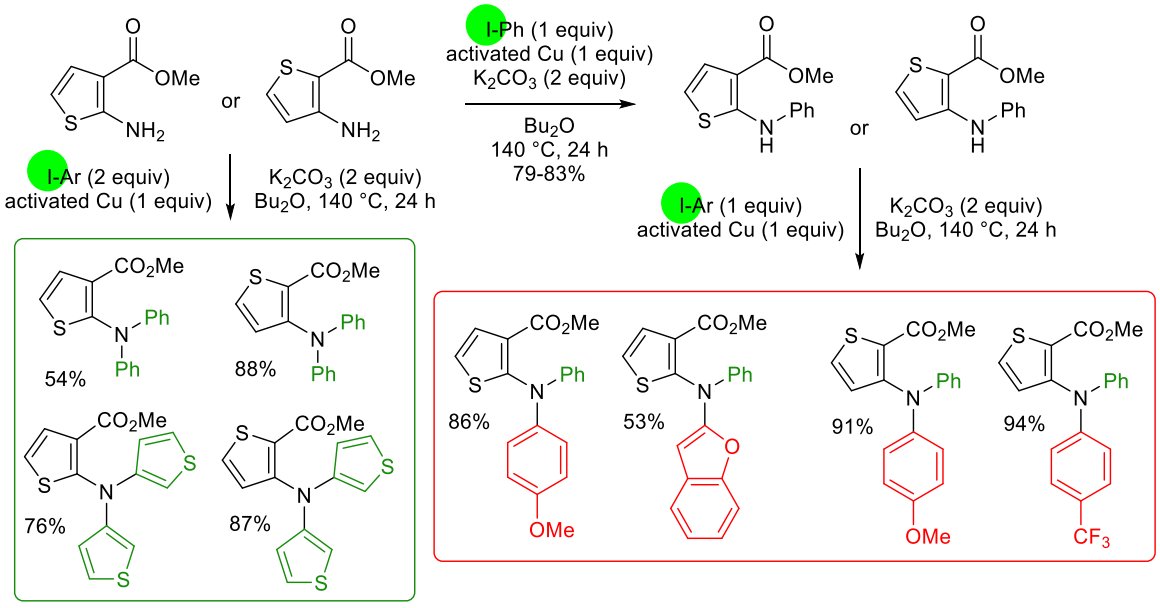
In view of the absence of results relating to the *N*-arylations of anilines with iodothiophenes, and inspired by the conditions reported by Hellwinkel and Ittemann in the benzene series [59], we selected ethyl anthranilate as the coupling partner. While using 2-iodothiophene only gave the expected product in 52% yield under our optimized conditions (1 equiv activated copper and 2 equiv potassium carbonate in dibutyl ether at 140 °C for 24 h), 3-iodothiophene proved much more reactive, giving the product in 92% yield. Similarly, using 2- and 3-iodobenzothiophene led to the *N*-arylated products in 57% and

96% yield, respectively (Scheme 15). This trend was attributed to less electron-rich 3-thienyl or benzothienyl groups (facilitating reductive elimination) when compared with 2-thienyls or benzothienyls [60].



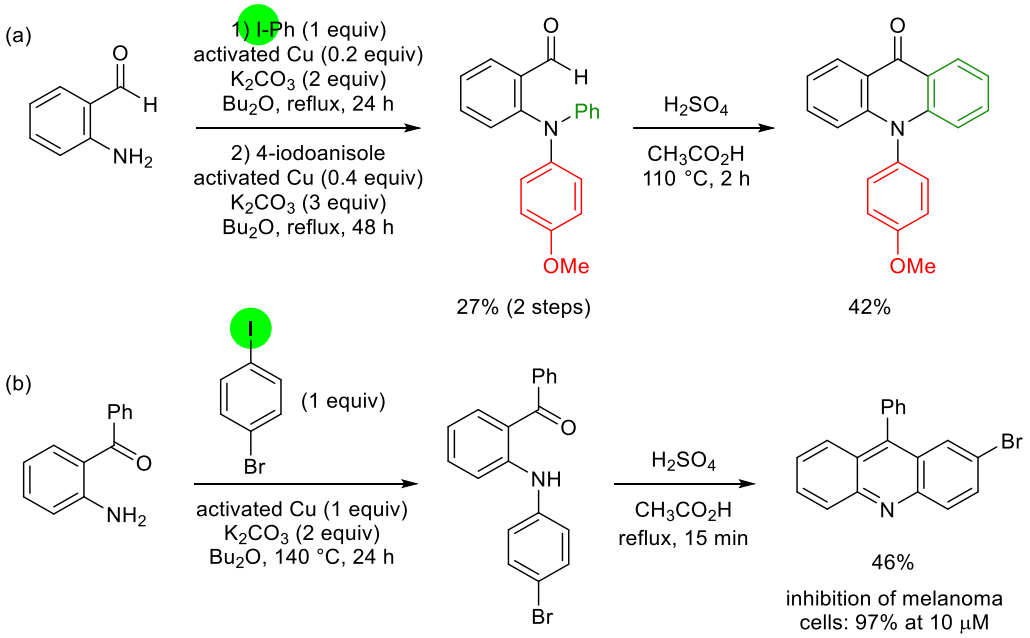
Scheme 15. *N*-Arylation of ethyl anthranilate using 2- or 3-iodothiophene, and 2- or 3-iodobenzothiophene.

Provided that 3-iodothiophene is selected as reaction partner and not the 2-iodinated isomer, both methyl 2-amino-3-thiophenecarboxylate and methyl 3-amino-2-thiophenecarboxylate could be *N*,*N*-diarylated in yields similar to those recorded when using iodobenzene (Scheme 16, left). Pleasingly, these aminothiophenes can also be involved in two successive *N*-arylation reactions with different aromatic or heteroaromatic iodides, affording various triarylamines in moderate to excellent yields (Scheme 16, right) [61].



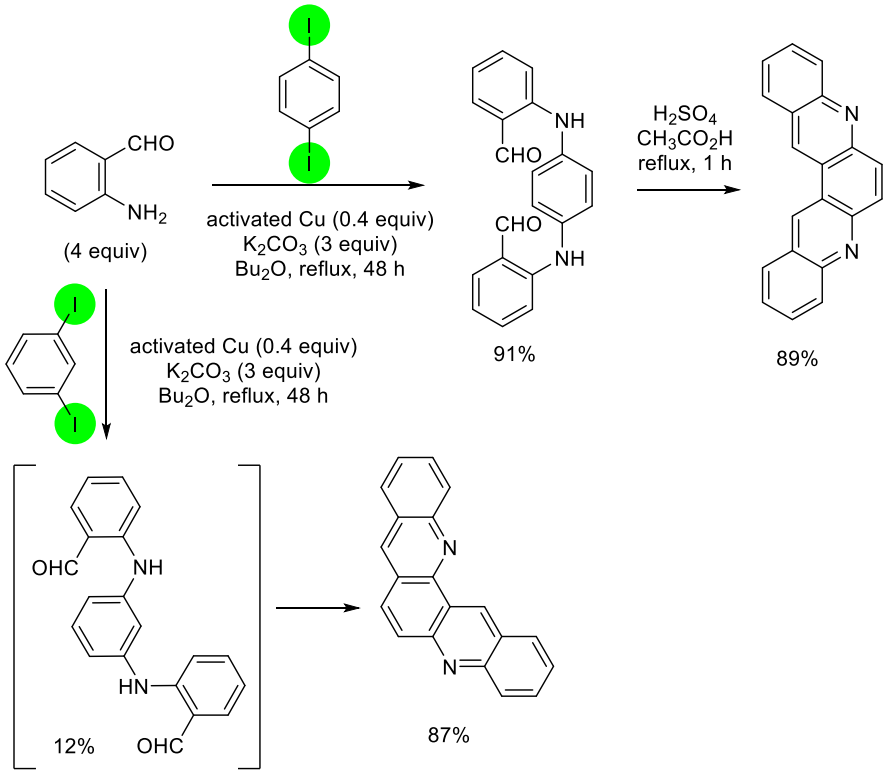
Scheme 16. Single (**top**) and double (**bottom**) *N*-arylation of methyl 2-amino-3-thiophenecarboxylate and methyl 3-amino-2-thiophenecarboxylate toward triarylamines.

If the ester function of ethyl anthranilate is replaced by an aldehyde or a ketone, the *N*-arylation reactions can be followed by ring formations toward fused tricyclic products. If the cyclization, under acidic conditions, is performed after two *N*-arylation steps, acridones can be reached (the one depicted in Scheme 17a occurred selectively with the phenyl group). On the contrary, if it is carried out after a single *N*-arylation, acridines are rather obtained as illustrated in Scheme 17b, leading to a molecule endowed with a significant antiproliferative activity against melanoma cells [62].



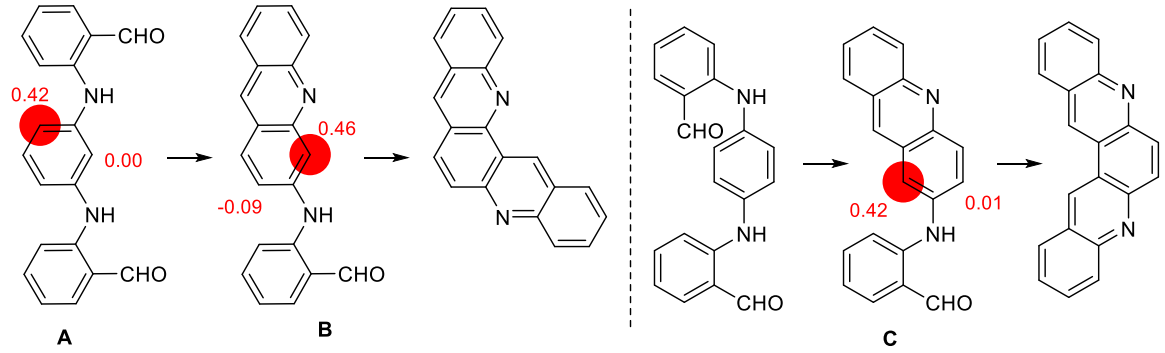
Scheme 17. Access to acridone and acridine scaffolds by double and single *N*-arylation, respectively, followed by cyclization.

Interestingly, double *N*-arylation reactions can also be achieved by using a diiodide as coupling partner. Thus, reaction of 2-aminobenzaldehyde with 1,4-diiodobenzene under the above conditions led to the expected *N*,*N*′-disubstituted 1,4-phenylenediamine which, upon acidic treatment, cyclized to afford a diaza-pentacycle in high yield. However, when 1,3-diiodobenzene is used instead, the intermediate *N*,*N*′-disubstituted 1,3-phenylenediamine is isolated in a low 12% yield due to its easy cyclization under the coupling conditions (Scheme 18) [62].



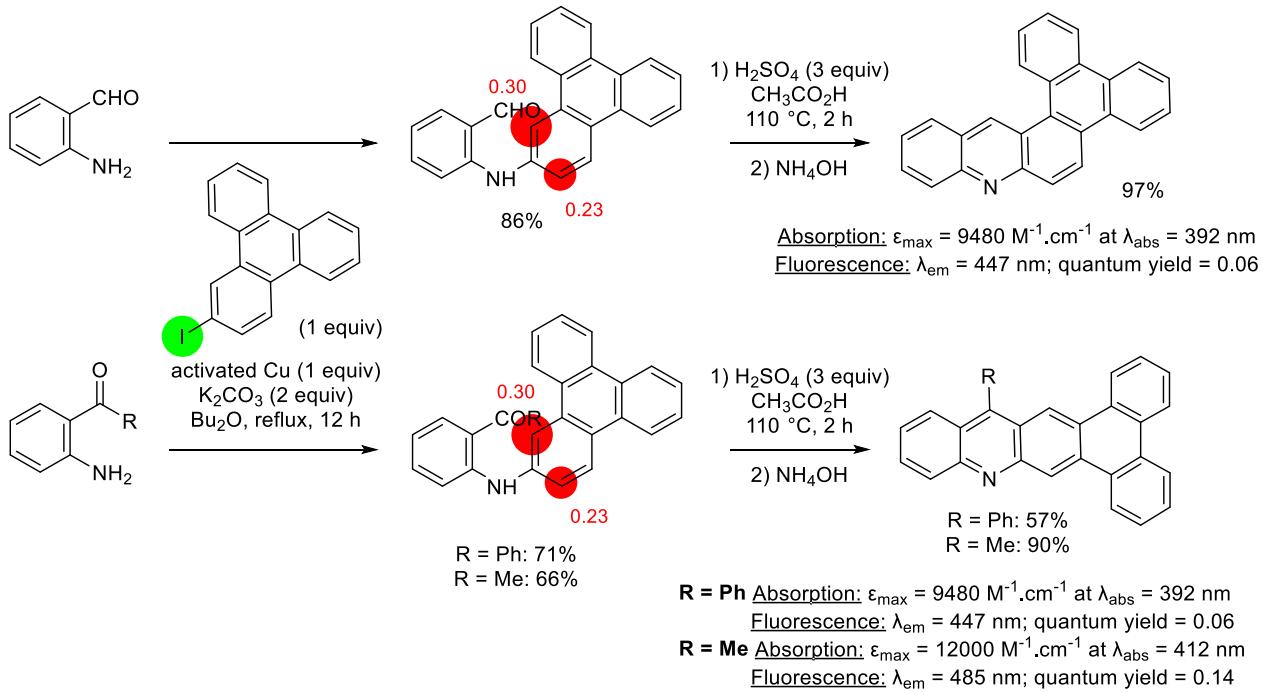
Scheme 18. Access to diaza-pentacycles by double *N*-arylation followed by cyclization.

To rationalize the regioselectivity of these cyclizations which are aromatic electrophilic substitutions, we calculated the amplitudes of the HOMO coefficients [3,4] of the *N*,*N*′-disubstituted 1,3-phenylenediamine intermediate **A** and the putative intermediates **B** and **C**. Pleasingly, the experimental regioselectivities matched those predicted, with all cyclizations occurring at the carbon site with the highest coefficient (Scheme 19) [63].



Scheme 19. HOMO coefficients (obtained by using the HuLiS calculator [4]) of the *N*,*N*′-disubstituted 1,3-phenylenediamine intermediate **A** and of the putative intermediates **B** and **C**.

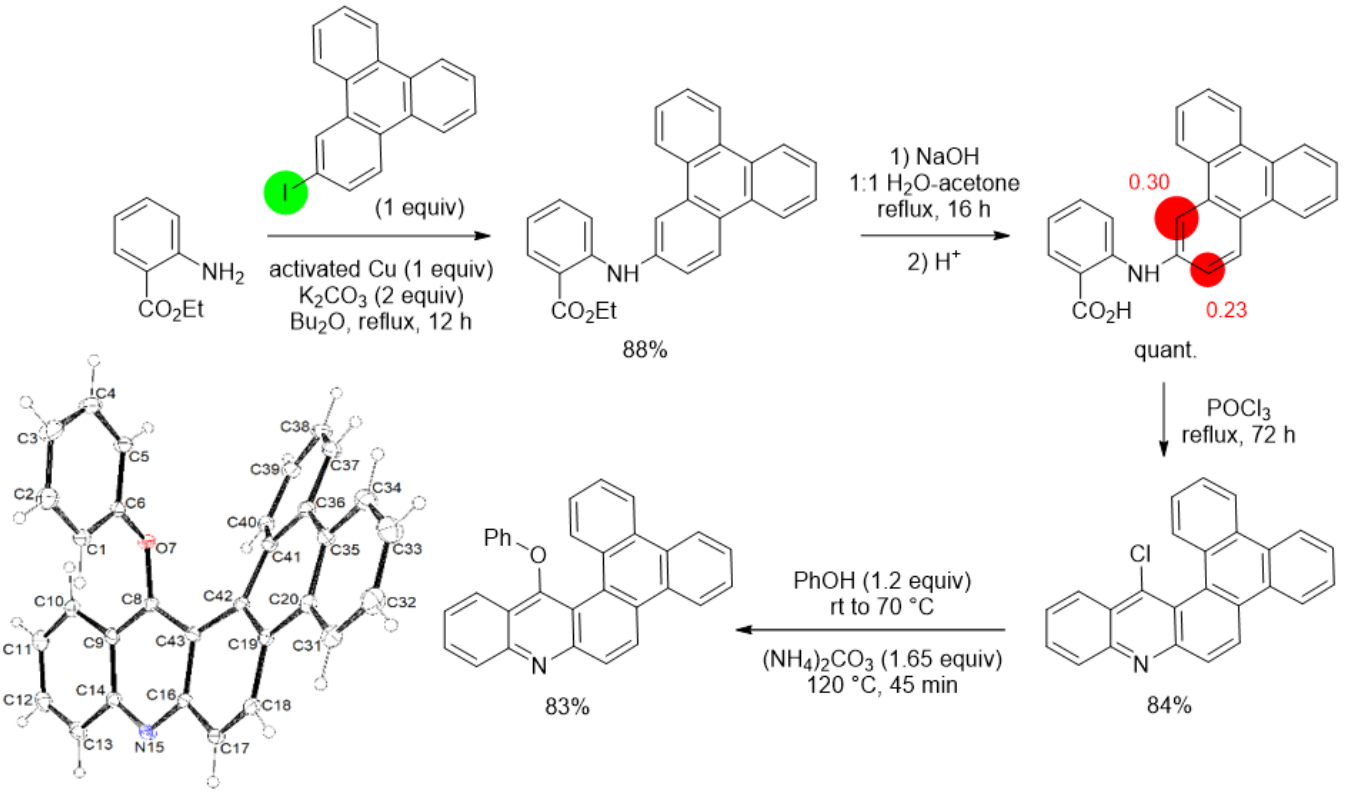
Larger aza-aromatic polycycles have been similarly obtained using 2-iodotriphenylene as a coupling partner for the *N*-arylation of 2-aminobenzaldehyde or 2-aminophenones. The amplitudes of the HOMO coefficients showed a cyclization slightly in favor of the most hindered position. However, this has only been verified experimentally from the aldehyde and not from the ketones, probably for steric reasons. The aza-hexacycles thus obtained showed a significant fluorescence (Scheme 20) [63].



Scheme 20. Formation of aza-aromatic hexacycles by coupling 2-aminobenzaldehyde or 2-aminophenones with 2-iodotriphenylene.

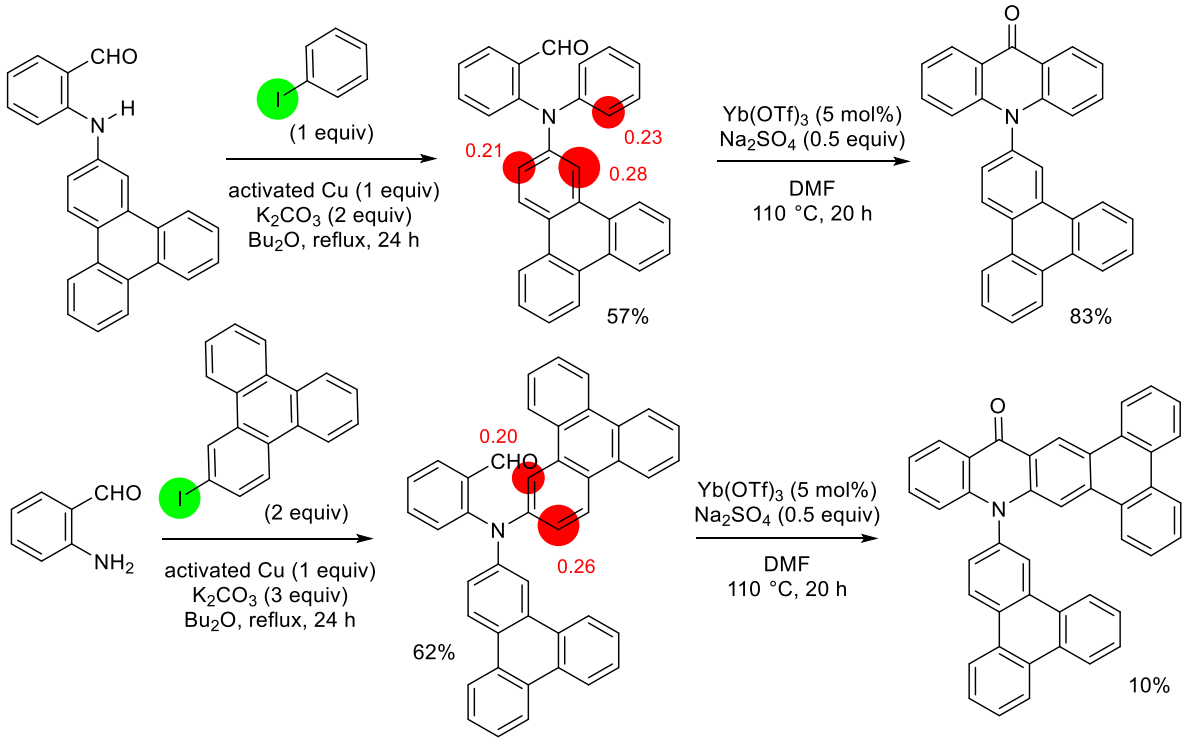
In order to prepare a helicene-like structure with a substituent opposite the nitrogen, we coupled ethyl anthranilate with 2-iodotriphenylene. The ester function was next hydrolyzed, and the corresponding 4-chloroacridine skeleton was built in the presence of

phosphorus oxychloride. Finally, the chloro group was replaced to afford the expected target (Scheme 21) [63].



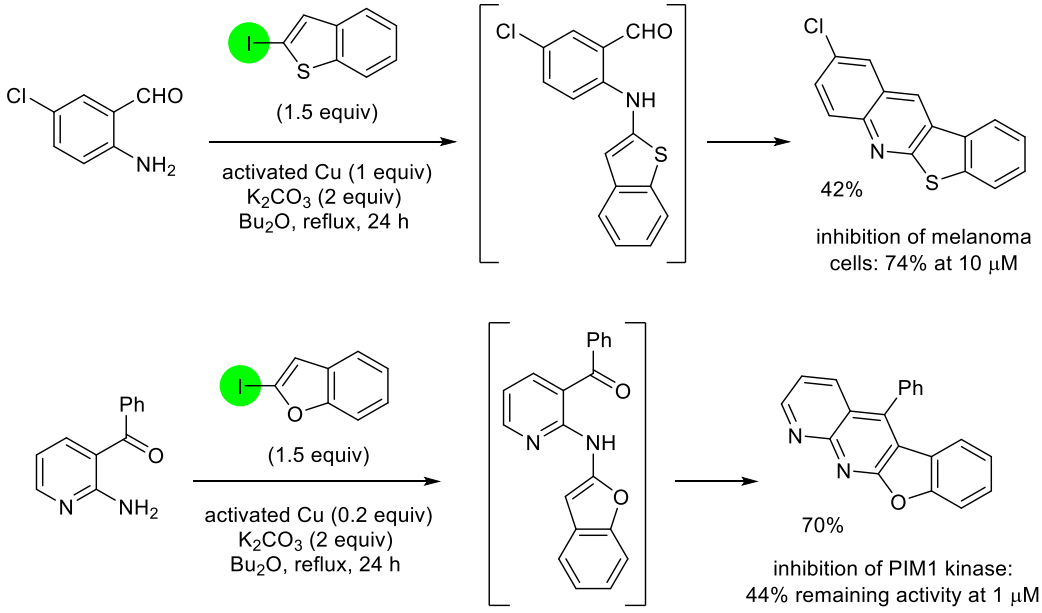
Scheme 21. Synthesis of a helicene-like aza-aromatic hexacycle.

As before, we prepared original acridones from 2-aminobenzaldehyde by introducing aryl groups, either different or similar, before cyclization under conditions using ytterbium(III) triflate reported by Yang and co-workers [64]. As before, our regioselectivity predictions applied when steric hindrance was not predominant (Scheme 22) [63].



Scheme 22. Synthesis of polycyclic acridones.

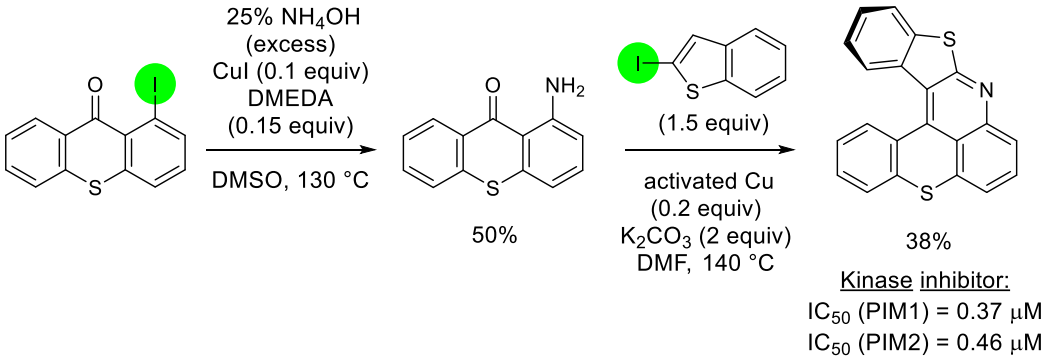
As already observed by coupling 2-aminobenzaldehyde with 1,3-diiodobenzene (Scheme 18), using 2-iodobenzothiophene or 2-iodobenzofuran as coupling partner directly leads to polycycles; indeed, cyclization of the *N*-arylated product directly takes place under the coupling conditions. As illustrated in Scheme 23, this was employed to access tetracycles of biological interest such as benzothieno[2,3-*b*]quinolines and benzofuro[2,3-*b*][1,8]naphthyridines [60,65].



Scheme 23. Synthesis of a benzothieno[2,3-*b*]quinoline and a benzofuro[2,3-*b*][1,8]naphthyridine.

Interestingly, this *N*-arylation-cyclization sequence was applied to access helicene-like benzo(thio)pyrano[4,3,2-*de*]benzothieno[2,3-*b*]quinolines which are heterocycles of

biological interest. In this context, the hexacycle depicted in Scheme 24 was prepared in two steps from the 1-iodothioxanthone (**11b**). This iodide was first converted to the corresponding aniline which was engaged in the *N*-arylation reaction with 2-iodobenzothiophene. The formed hexacycle proved to be a promising inhibitor of PIM protein kinases which are related to cancer development [66].



Scheme 24. Synthesis of a benzothiopyrano[4,3,2-*de*]benzothieno[2,3-*b*]quinoline.

4. Conclusions

The many examples presented throughout this mini-review demonstrate the interest of direct iodination reactions and deprotometallation-trapping sequences to access iodinated aromatics. The latter are relevant substrates for many reactions, and in particular for copper-catalyzed couplings, which make it possible to develop original heterocyclic structures.

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Conflict of Interest: The authors declare no conflict of interest.

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