Synthesis of α- and β-Carbolines by a Metalation/Negishi Cross-Coupling/S_NAr Reaction Sequence

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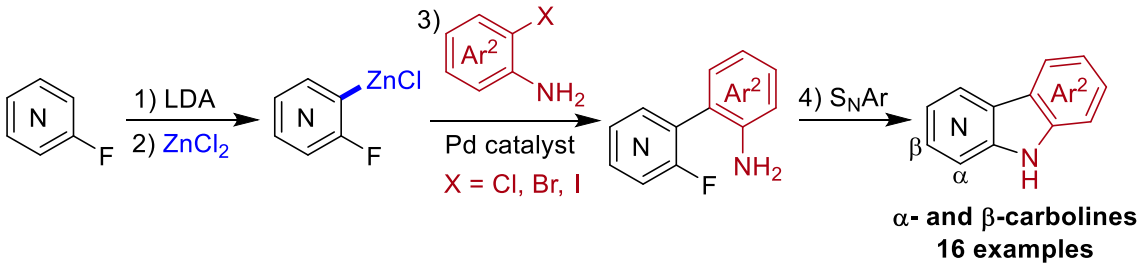
Carbolines are privileged scaffolds in medicinal chemistry, and therefore, novel and efficient approaches to their synthesis are in high demand. An efficient method for the synthesis of α- and β-carbolines from fluoropyridines and 2-haloanilines is reported. This streamlined procedure consists of a four-step directed ortho-lithiation, zincation, Negishi cross-coupling, and intramolecular nucleophilic aromatic substitution, providing access to a diverse set of functionalised carbolines. While the procedure is applicable to batch conditions, the generation of arylzinc intermediates in continuous flow has been demonstrated.



While β-carbolines (pyrido[3,4-*b*]indoles) are found in numerous natural products, which are widely distributed among plants, marine organisms, insects, mammalians, and human tissues,[1] α-carbolines (pyrido[2,3-*b*]indoles) are considerably less well investigated.[2] However, the significance of both classes of molecules is exemplified by their bioactivity in various disease-related pathways, thus meriting them as anticancer, neuropharmacological, anti-inflammatory, antibacterial and antiviral agents. Specific examples include the neuro-protective alkaloid mescengricin,[3] the cytotoxic marine natural products grossularine-1 and -2,[4] and the naturally occurring anticancer agent harmine (Figure 1).[5] In addition to their diverse biological activity,

carbolines have found interesting applications in material science.[6] Thus, the efficient preparation of this class of alkaloids from readily available starting materials is of considerable interest.

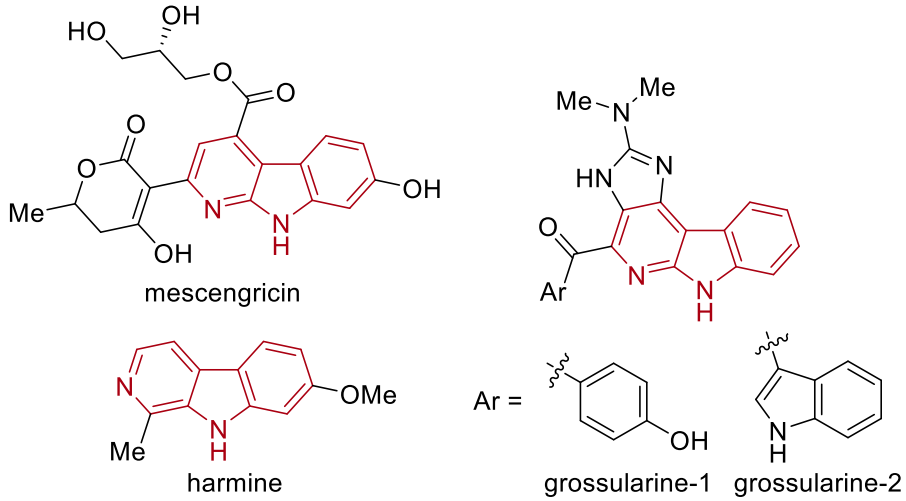
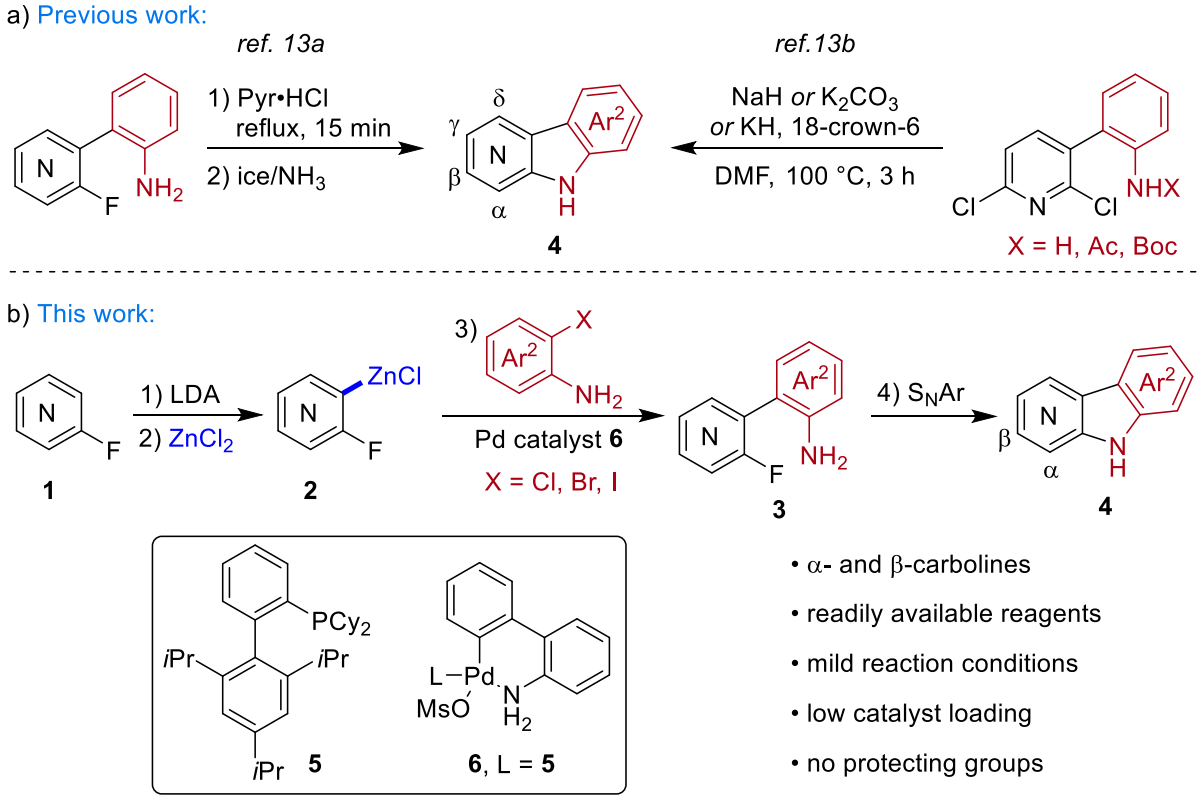


Figure 1. Examples of naturally occurring bioactive α- and β-carbolines.

Among common synthetic approaches towards the preparation of carbolines,[7] several cross-coupling procedures have been developed, including methods that utilise sequential palladium-catalysed aryl amination followed by intramolecular arylation.[8] Complementary procedures have been reported that generate first the C–C bond followed by Buchwald-Hartwig amination,[9] condensation,[10] thermal[11] or metal-catalysed[12] nitrene insertion, or nucleophilic aromatic substitution.[13] Typically, these reactions employ harsh reaction conditions and high catalyst loadings while often relying on elaborated, not readily available reagents.

In light of these challenges, a complementary approach towards the synthesis of α- and β-carbolines was envisaged. Some of us have previously demonstrated a valuable methodology for the synthesis of 2-fluorobiaryls under continuous flow conditions.[14] Building up on this experience and inspired by Queguiner's and Achab's approaches towards the synthesis of carbolines (Scheme 1a),[13] a reaction sequence comprising four synthetic operations was envisioned (Scheme 1b): 1) Directed *ortho*-lithiation of fluoropyridine **1**; 2) zincation of the aryllithium species; 3) Negishi cross-coupling of arylzinc **2** with 2-haloanilines to generate 2-aminobiaryl **3**; 4) intramolecular nucleophilic aromatic substitution (S_NAr) of **3** to provide tricyclic carboline **4**. We anticipated that XPhos-based precatalyst **6**, which has previously been shown to facilitate efficient C(sp^2)–C(sp^2) Negishi cross-coupling reactions, would allow for rapid activation and high reactivity even at low catalyst loading.[15] Furthermore, we were confident that the first two steps for the generation of arylzinc **2** would be suitable to be

conducted under continuous flow conditions, enabling rapid generation and safe handling of thermally unstable organolithium intermediates.[16] A comparable procedure for the formation of (hetero)aryl zincates in flow followed by Negishi cross-coupling under batch conditions has been reported by Knochel and co-workers.[17] The synthesis of *ortho–ortho* substituted biaryl compounds **3** is interesting in its own right, as it has been reported that these structurally diverse species are currently underrepresented in medicinal chemistry.[18] The intramolecular S_NAr would finally provide access to different classes of carbolines. Herein, we describe the protection group-free preparation of α- and β-carbolines via a telescoped metalation/cross-coupling/S_NAr reaction sequence.

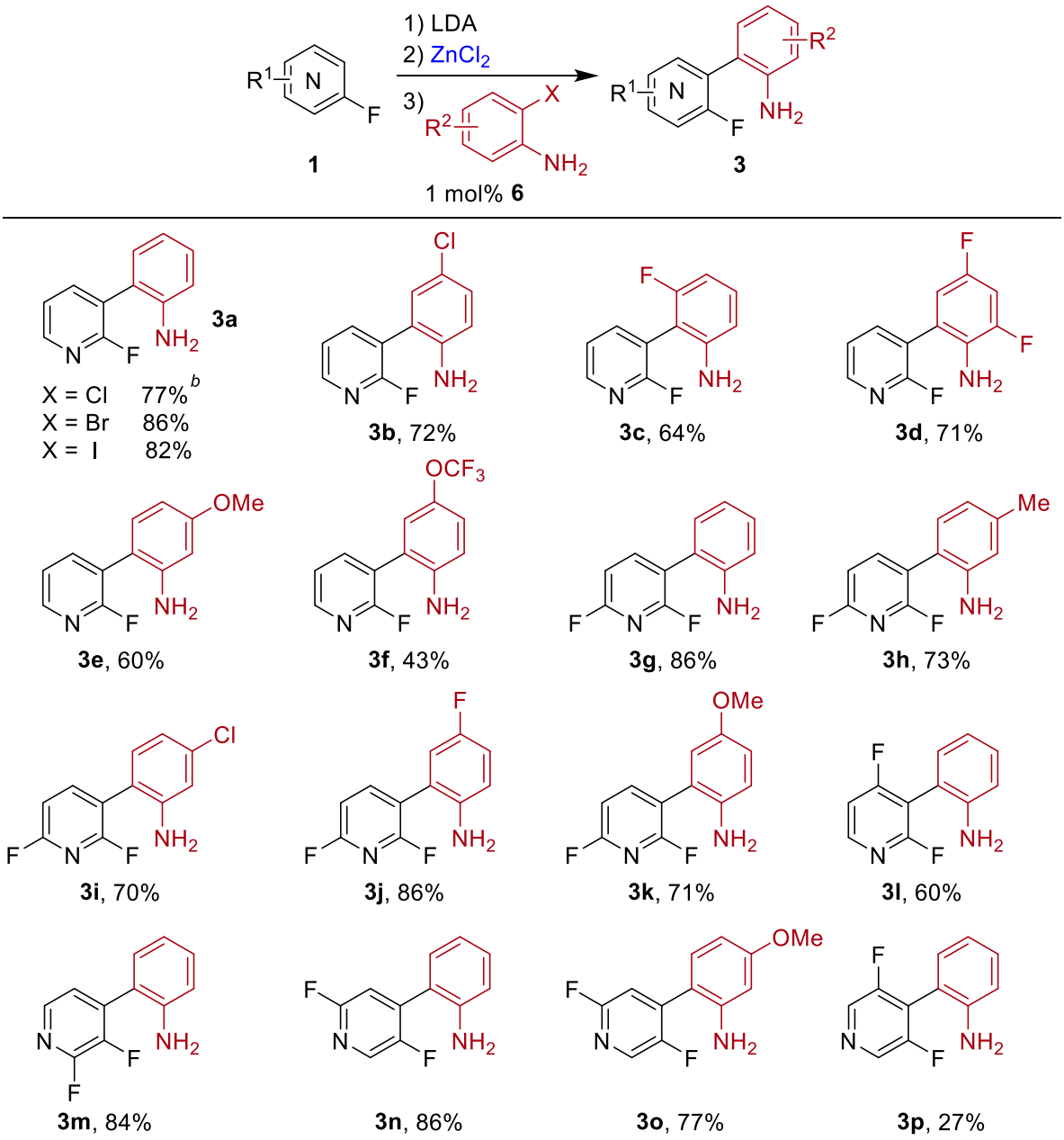


Scheme 1. a) Previously reported S_NAr conditions for the synthesis of carbolines. b) Synthesis of carbolines by a lithiation/zincation/Negishi cross-coupling/S_NAr reaction sequence; XPhos ligand **5** and third generation palladium precatalyst **6**.

We initiated our studies by generating a diverse set of 2-aminobiaryls **3** as precursors for **4**. The directed lithiation of various fluoropyridines (**1**) with lithium diisopropylamide (LDA) has previously been described to occur with high regioselectivity in *ortho*-position to the fluorine directing group at the most acidic proton.[19] For the directed lithiation of **1** under batch conditions with LDA, we found that 5 min at –25 ºC was an excellent compromise between reaction time and temperature. Increasing the lithiation temperature above –25 ºC led to a dark

brown discolouration of the reaction mixture, which indicated the decomposition of the aryllithium species to the corresponding undesired benzyne. Instead of commercially available LDA solution, the amide base could also be generated *in situ* via the addition of *n*-butyllithium to a mixture of **1** and diisopropylamine in THF to provide comparable results.

Table 1. Scope of 2-aminobiaryls **3**.[a]

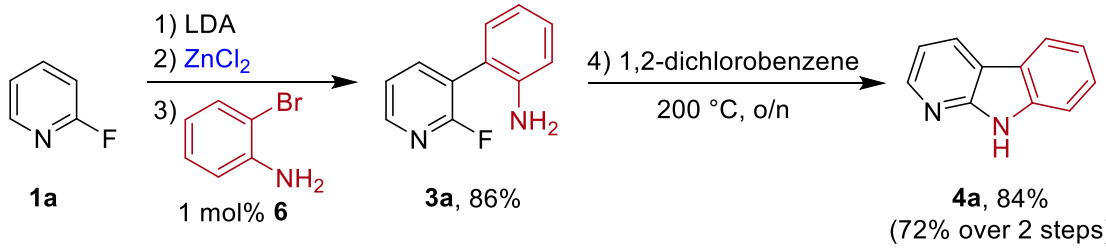


[a]1.0 mmol scale; yields of isolated products are given; reaction conditions: 1) fluoropyridine (1.1–1.2 equiv), LDA (1.3 equiv), THF (0.5 M), –25 ºC, 5 min; 2) $ZnCl_2$ (1.3 equiv), then –25 ºC → rt; 3) 2-bromoaniline (1.0 equiv) and precatalyst **6** (1.0 mol%) in THF (1.0 M), 60 ºC, 20 min. [b]2.0 mol% of precatalyst **6**.

Transmetallation of the organolithium intermediate with $ZnCl_2$ generated arylzinc species **2**, which were cross-coupled with a variety of 2-haloanilines. Biaryl **3a** was obtained from 2-bromo- or 2-iodoaniline in excellent yield after 20 min at 60 °C applying only 1.0 mol% of precatalyst **6** (Table 1). However, using 2-chloroaniline as coupling partner necessitated a higher catalyst loading of **6** (2.0 mol%) to give **3a** in 77% yield. Unfortunately, 2-aminophenyl triflates could not be applied as oxidative addition did not occur with these substrates under the reaction conditions. Protection of the free aniline was not required as no competing dimerisation of 2-haloaniles could be detected. As a variety of 2-bromoanilines is commercially available, these substrates were our preferred coupling partners for the following studies.

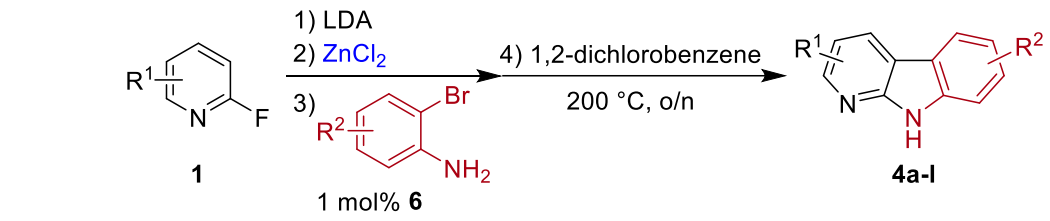
The substrate scope for a variety of fluoropyridine and 2-bromoaniline combinations was explored applying the optimised reaction conditions (Table 1). 2-Fluoropyridine could efficiently be coupled with a variety of substituted 2-bromoanilines carrying either electron withdrawing or donating substituents (**3b-f**). Substitution in all positions of the coupling partner was tolerated. Similar results were obtained starting from 2,6-difluoropyridine providing **3g-k** in good to excellent yields. Furthermore, metalation of 2,3-, 2,4- and 3,6-difluoropyridine provided regioisomerically pure products **3l-o** after cross-coupling. Only **3p**, derived from 3,5-difluoropyridine, was obtained in poor yield, which was attributed to thermal decomposition of arylzinc species **2p** during the cross-coupling step at elevated temperatures.

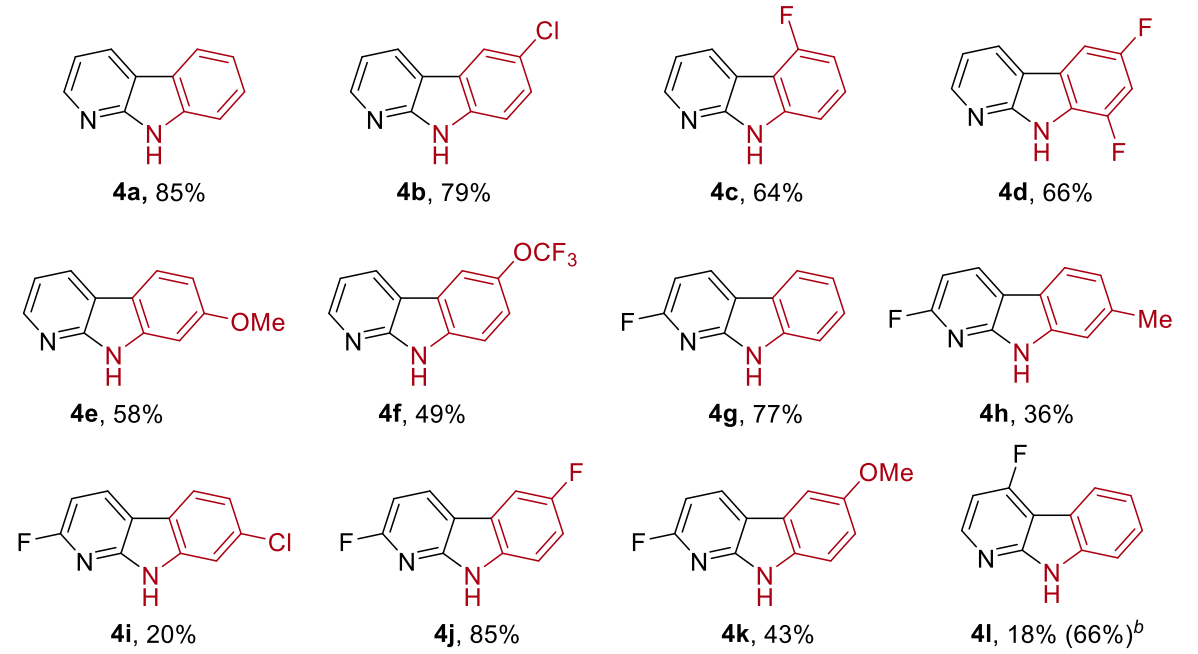
Next, we focused our efforts on the intramolecular S_NAr of **3a**. While Queguiner and co-workers reported acidic conditions using refluxing anhydrous pyridinium hydrochloride (bp 222–224 °C) to access all classes of carbolines,[13a] Achab and co-workers applied a variety of bases (NaH, K_2CO_3 or KH , catalytic 18-crown-6) at 100 °C in DMF to synthesise α-carbolines from 2-aminobiaryl substrates (Scheme 1a).[13b] Building upon these unlike procedures, we were curious if the intramolecular S_NAr could also be conducted under neutral conditions. For biaryl **3a**, we found that simple heating to 200 °C in a solution of 1,2-dichlorobenzene in a sealed tube was sufficient to facilitate the ring-closure. α-Carboline **4a** was afforded in 84% yield without the need for acidic or basic additives (Scheme 2).



Scheme 2. Two-step process for the synthesis of α-carboline **4a** via metallation and Negishi cross-coupling followed by thermal S_NAr.

Table 2. Scope of α-carbolines via telescoped metallation/cross-coupling/S_NAr reaction sequence.[a]





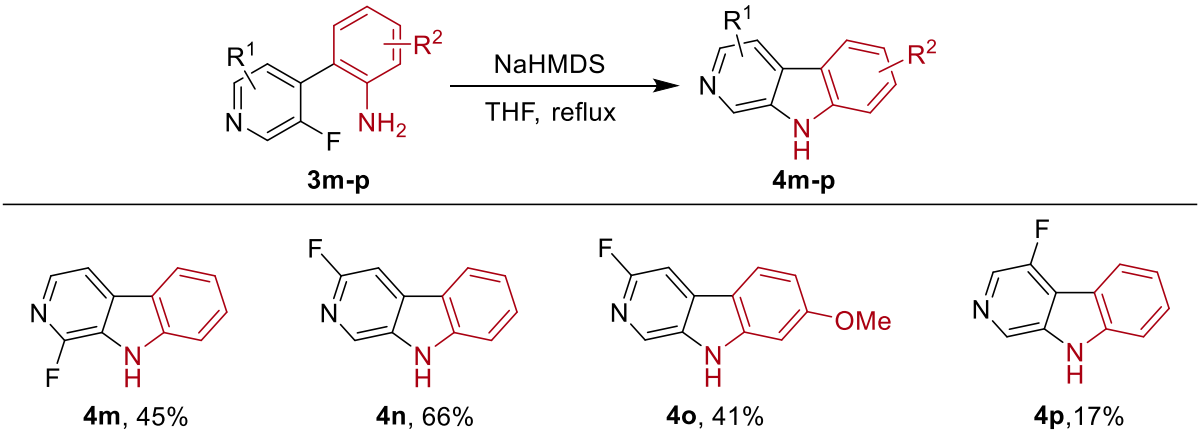
[a]1.0 mmol scale; yields of isolated products are given; reaction conditions: 1) fluoropyridine (1.2 equiv), LDA (1.3 equiv), THF (0.5 M), –25 °C, 5 min; 2) $ZnCl_2$ (1.3 equiv), then –25 °C → rt; 3) 2-bromoaniline (1.0 equiv) and precatalyst **6** (1.0 mol%) in THF (1.0 M), 60 °C, 20 min, followed by aqueous work-up; 4) 1,2-dichlorobenzene (0.3 M), 200 °C, 18 h, sealed tube. [b]Yield in parenthesis obtained by treatment with NaHMDS (1.9 equiv) in THF (0.1 M), reflux, 15 min; product isolated as 6:1 mixture of α- and γ-carboline determined by ^{19}F NMR.

With optimised reaction conditions for the S_NAr step, we were interested in streamlining the two-step process to access carbolines directly from commercially available fluoropyridines and 2-bromoanilines without isolation or purification of 2-aminobiaryl **3**. We found that all four synthetic operations could be conducted as a one-pot procedure, changing the reaction solvent from THF to 1,2-dichlorobenzene after the Negishi cross-coupling to give α-carboline **4a** in 60% yield. However, better results were obtained applying an aqueous work-up after biaryl formation, followed by thermal S_NAr. Under these conditions, α-carboline **4a** was obtained in 85% isolated yield from readily available reagents requiring just a single purification step (Table 2). Next, this streamlined procedure was applied to several 2-fluoropyrines **1** (2-fluoropyridine, 2,4- and 2,6-difluropuridine) in combination with a variety of 2-bromoanilines to provide α-carbolines **4b-l**. Most of these substrates were obtained in similar yield compared

to their 2-aminobiaryl precursor **3** (*cf.* Table 1), indicating that the intramolecular S_NAr occurred in nearly quantitative yield. However, carbolines **4h**, **4i**, **4k** and **4l** were isolated in significantly reduced yields due to the formation of undesired side products. Under thermal S_NAr conditions, carboline **4l** was obtained as a single regioisomer, albeit in poor yield. Applying basic conditions to promote the ring-closure increased the isolated yield to 66%. Yet, α-carboline **4l** was obtained as an inseparable 6:1 mixture along the regioisomeric γ-carboline.[20]

Next, the synthesis of β-carbolines was examined. Applying neutral reaction conditions to 2-aminobiaryls **3m-p** (1,2-dichlorobenzene, 200 ºC, 18 h), no conversion to the corresponding β-carbolines was observed. To overcome this, we applied basic conditions to facilitate the S_NAr reaction. Best results were obtained from purified 2-aminobiaryls after heating in THF in the presence of an excess of NaHMDS to give β-carbolines **4m-p** in moderate yields (Table 3).

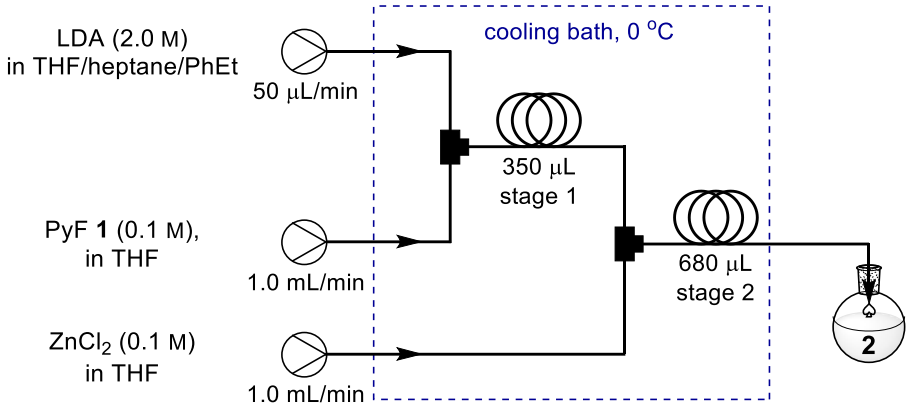
Table 3. β-Carbolines synthesised via base-mediated S_NAr.[a]



[a]0.5–1.0 mmol scale; yields of isolated products are given; reaction conditions: 1) 2-aminobiaryl (1.0 equiv), NaHMDS (1.9–2.0 equiv), THF (0.1 M), reflux, 15 min – 18 h. See the Supporting Information for details.

Finally, we envisioned to apply continuous flow conditions for the generation of arylzinc intermediates **2**. Based on our previous experience, high dilution and rapid flow rates were essential to avoid fouling and clogging of the reactor during the generation of these organometallic species.[14] The optimised flow process for the generation of **2** is depicted in Scheme 3.[20] Precise temperature and time control enabled by continuous flow technology allowed to conduct the *ortho*-lithiation of 2-fluoropyrine and 2,5-difluoropyridine with LDA at 0 ºC in just 20 s. This is significantly faster than our optimised batch procedure (–25 ºC, 5 min) and in strong contrast to previous conditions reported in the literature (–78 ºC for several hours).[19] After transmetallation of the organolithium intermediate with $ZnCl_2$, arylzinc species

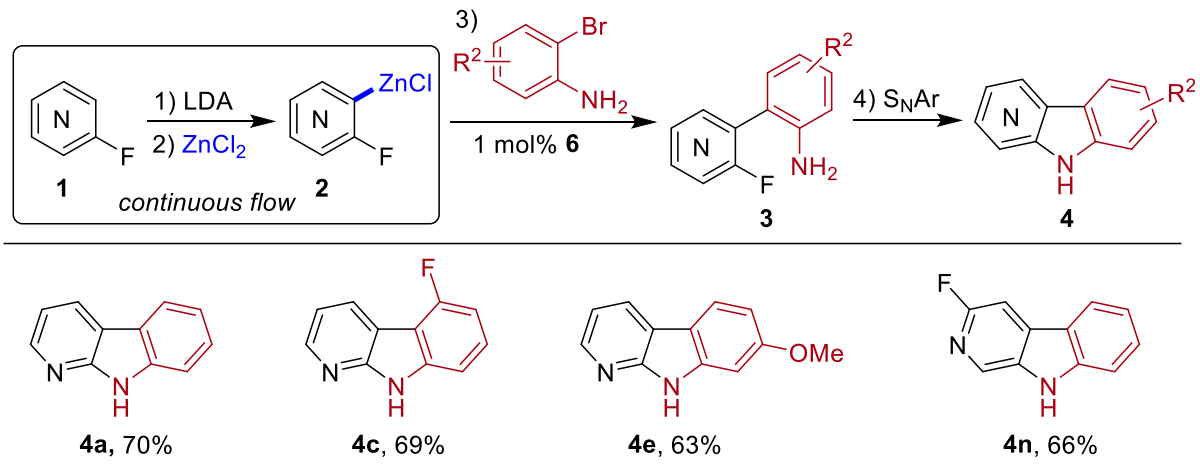
2 was collected in a flask under an inert atmosphere and subjected in batch to Negishi cross-coupling and intramolecular S_NAr as previously described (see Table 2 and 3).



Scheme 3. Experimental setup for the synthesis of arylzinc species **2** by directed *ortho*-lithiation and zincation.

Neither fouling nor clogging of the continuous flow reactor was observed under the optimised conditions. A representative set of carbolines (α-carbolines **4a**, **4c**, and **4e** and β-carboline **4n**) was prepared in similar yields compared to the ones obtained under batch conditions (Table 4). Here, the clear advantage of the continuous flow procedure is the potential to be reproducibly scaled up by simply extending the collection time of **2**.

Table 4. Scope of carbolines prepared in a semi-batch process.[a]



[a]0.5–1.0 mmol scale; yields of isolated products are given. See the Supporting Information for details.

In summary, we have developed a highly efficient route towards the synthesis of α- and β-carbolines. Fluoropyridines were subjected to a directed *ortho*-lithiation followed by zincation and Negishi cross-coupling with 2-haloanilines to afford 2-aminobiaryls. α-Carbolines were obtained after intramolecular S_NAr under neutral condition, while the formation of β-carbolines

required base. This reaction sequence was extended to a semi-batch process, employing continuous flow technology for the preparation of arylzinc intermediates. Our methodology takes advantage of readily available starting materials, mild reaction conditions, very low catalyst loading and excellent atom economy to provide a diverse range of carbolines. Currently, the expansion of this methodology to γ- and δ-carbolines is under investigation.

Conflicts of interest

There are no conflicts to declare.

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(20) See the Supporting Information for a detailed description.