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

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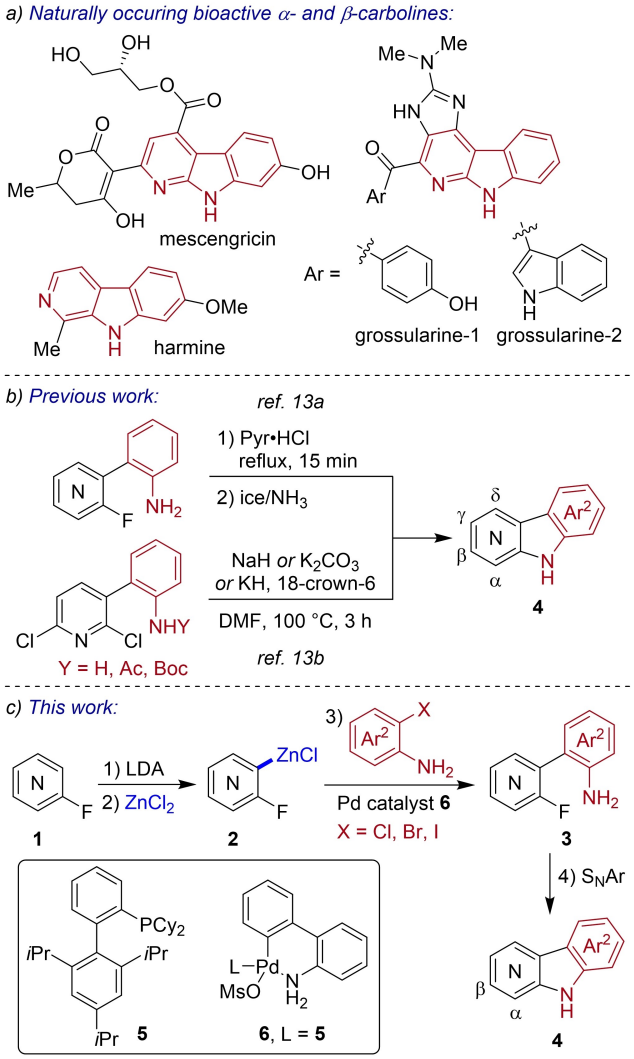
Abstract: A methodology for the synthesis of α- and β-carbolines from fluoropyridines and 2-haloanilines is reported. This procedure consists of a four-step directed *ortho*-lithiation, zincation, Negishi cross-coupling, and intramolecular nucleophilic aromatic substitution, providing access to a diverse set of functionalized carbolines. While the procedure is applicable to batch conditions, the generation of arylzinc intermediates in continuous flow has been demonstrated.

Keywords: palladium; cross-coupling; carbolines; directed metalation; flow chemistry

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 explored.[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 (Scheme 1a).[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.

Among common synthetic approaches towards the preparation of carbolines,[7] several cross-coupling procedures have been developed, including methods that utilize sequential palladium-catalyzed aryl amination followed by intramolecular arylation.[8] Alternative procedures have been reported that generate first the C–C bond followed by Buchwald-Hartwig amination,[9] condensation,[10] thermal[11] or metal-catalyzed[12] nitrene insertion, or nucleophilic aromatic substitution.[13] Typically, these reactions employ harsh reaction conditions and high catalyst loadings (3–10 mol%) 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. We 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 1b),[13] a reaction sequence comprising four synthetic operations was envisioned (Scheme 1c): 1) Directed *ortho*-lithiation of fluoropyridine **1**; 2) zincation of the organolithium 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 carboline **4**. We anticipated that XPhos-based palladium 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 intermediate **2** would be suitable to be conducted under continuous flow conditions, enabling rapid generation and safe handling



Scheme 1. a) Naturally occurring bioactive α- and β-carbolines and b/c) synthetic approaches towards carbolines.

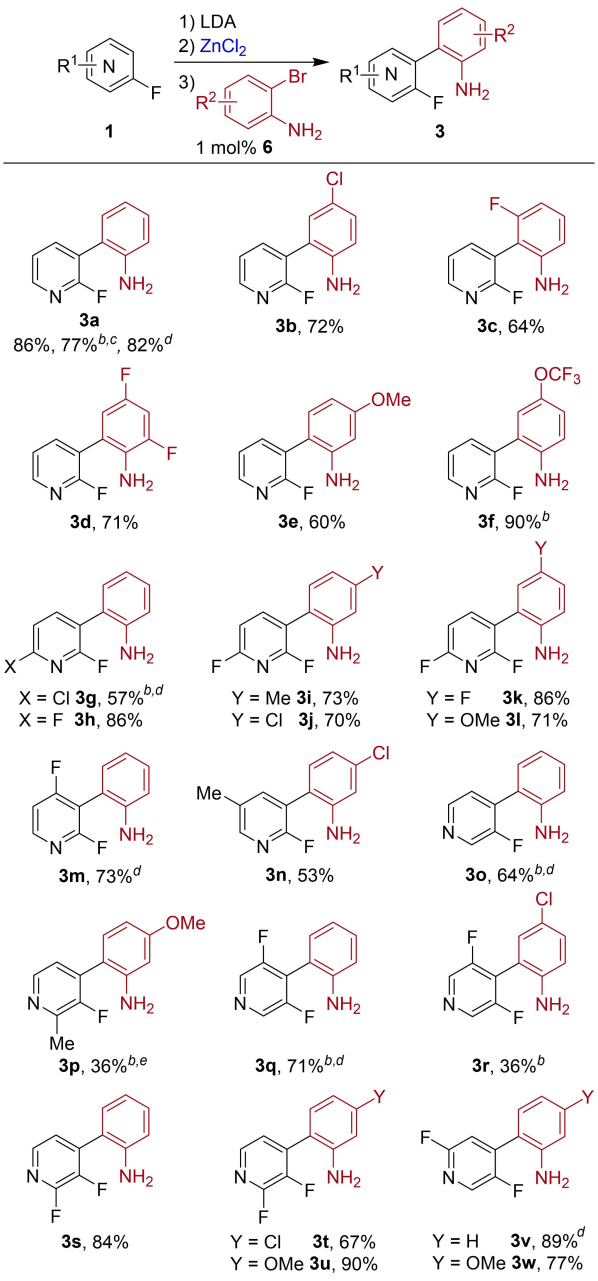
of thermally unstable organolithium intermediates.[16] A comparable procedure for the formation of (hetero)aryl zincates in flow followed by Negishi cross-coupling under batch conditions has been reported by Knochel and co-workers.[17] The synthesis of *ortho-ortho* substituted biaryl compounds **3** is interesting in its own right, as it has been reported that these structurally diverse species are currently underrepresented in medicinal chemistry.[18] Finally, the intramolecular S_NAr would 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.

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 reported 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 °C was an excellent compromise between reaction time and temperature. Increasing the lithiation temperature above −25 °C led to a dark brown discoloration of the reaction mixture, which indicated the decomposition of the aryllithium species. Instead of commercially available LDA solution, the amide base could also be generated *in situ* by addition of *n*-butyllithium to a mixture of **1** and diisopropylamine in THF to provide comparable results.[20]

Transmetalation of the organolithium intermediates 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). Though, using 2-chloroaniline as coupling partner necessitated a higher catalyst loading of **6** (2.0 mol%) to give **3a** in 77% yield. Protection of the free aniline was not required since no competing dimerisation of 2-haloanilines could be detected. As a range of functionalized 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 optimized reaction conditions (Table 1). 2-Fluoropyridine could efficiently be coupled with a diverse set of substituted 2-bromoanilines carrying either electron withdrawing or donating substituents (**3b–f**). Substitution in all positions of the coupling partner was tolerated. 2-Chloro-6-fluoropyridine was selectively metalated in the 5-position *ortho* to the fluorine substituent to afford **3g** in 57% yield after cross-coupling. Applying the reaction conditions to 2,6-difluoropyridine with differentially substituted 2-bromoanilines provided **3h–l** in 70–86% yield. 2,4-Difluoropyridine and 2-fluoro-5-methylpyridine were selectively functionalized in the 3-position to give **3m** and **3n**, respectively. 3-Fluoropyridine, 3-fluoro-2-methylpyridine, and 3,5-difluoropyridine required a higher catalyst loading of **6** (2.0 mol%) to give 2-aminobiaryls **3o–r**. Here, lower yields were attributed to thermal decomposition of the corresponding arylzinc species **2** during the cross-coupling step at elevated temperatures. Furthermore, for 3-fluoro-2-methylpyridine the lithiation procedure had to be adapted (30 min at −78 °C) as under standard conditions metalation predominately occurred in the benzylic position. Finally, metalation of 2,3- and 2,5-difluoropyridine occurred selectively in the 4-position providing regioisomerically pure 2-aminobiaryls **3s–w** after cross-coupling in 67–90% yield.

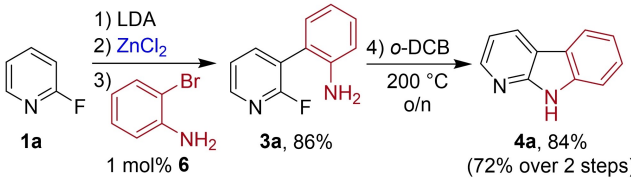
Table 1. Scope of 2-aminobiaryls **3**.[a]



[a] 1.0 mmol scale; reaction conditions: 1) fluoropyridine (1.1–1.2 equiv.), LDA (1.3 equiv.), THF (0.5 M), −25 °C, 5 min; 2) $ZnCl_2$ (1.3 equiv.), then −25 °C to rt; 3) 2-bromoaniline (1.0 equiv.) and **6** (1.0 mol%) in THF (1.0 M), 60 °C, 20 min.
[b] 2.0 mol% of **6**.
[c] 2-Chloroaniline applied as coupling partner.
[d] 2-Iodoaniline applied.
[e] Lithiation at −78 °C for 30 min.

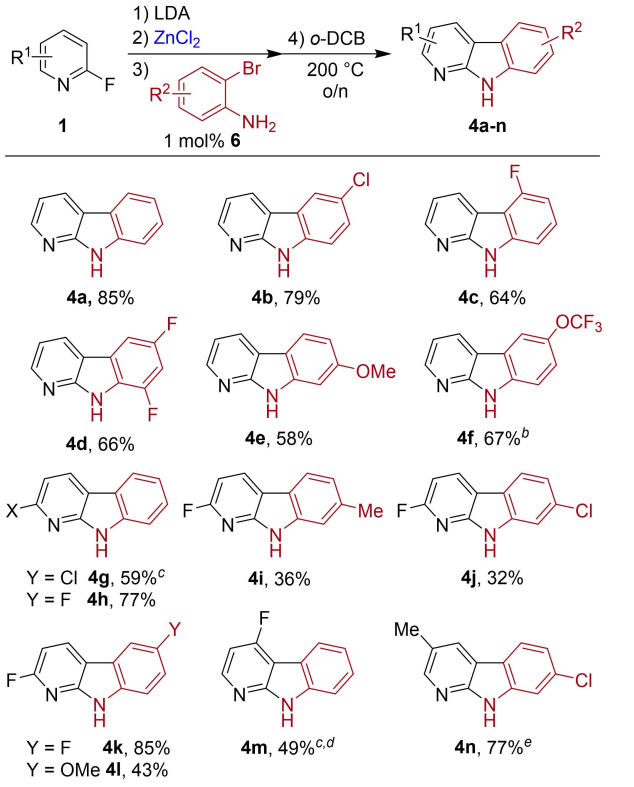
Next, we focused our efforts on the intramolecular S_NAr of **3a**. While Queguiner and co-workers reported acidic conditions using refluxing anhydrous pyridinium hydrochloride (bp 222–224 °C) to access all classes of carbolines,[13a] Achab and co-workers applied a variety of bases (NaH, K_2CO_3 or KH, catalytic 18-crown-6) at 100 °C in DMF to synthesize α-carbolines from 2-aminobiaryl substrates (Scheme 1b).[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 (*o*-DCB) in a sealed tube was sufficient to facilitate the ring-closure. Here, the fluorine substituent in α-position is sufficiently activated for intramolecular S_NAr that neither acidic nor basic additives are needed, affording α-carboline **4a** in 84% yield (Scheme 2).

With these optimized 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-haloanilines without isolation and purification of 2-aminobiaryls **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, higher yields were obtained by applying an aqueous work-up after biaryl formation, followed by intramolecular S_NAr. Under these conditions, **4a** was obtained in 85% isolated yield from readily available reagents requiring just a single purification step (Table 2). Next, the telescoped procedure was applied to a range of 2-fluoropyridines **1** in combination with a variety of 2-bromoanilines or 2-iodoaniline to provide α-carbolines **4b**–**m**. Most of these substrates were obtained in similar yields compared to their 2-aminobiaryl precursors **3** (*cf.* Table 1), indicating that the intramolecular S_NAr occurred in nearly quantitative yields. However, the formation of undesired side products led to reduced yields for carbolines **4i**, **4j** and **4l**. When we applied the reaction sequence to 2,4-difluoropyridine, an inseparable 5:1 mixture α-carboline **4m** along its regioisomeric γ-carboline was obtained.[20] Carrying an electron donating methyl group at the pyridine ring, thermal S_NAr under neutral conditions for the generation of **4n** was unsuccessful. In this case, base-mediated activation (NaHMDS) was employed to afford **4n** in 77% yield.



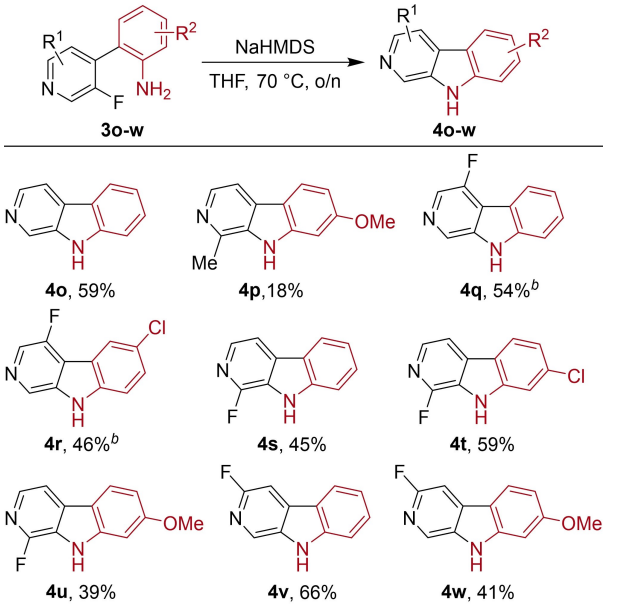
Scheme 2. Two-step process for the synthesis of α-carboline **4a**.

Table 2. Scope of α-carbolines.[a]



[a] 1.0 mmol scale; 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 to rt; 3) 2-bromoaniline (1.0 equiv.) and **6** (1.0 mol%) in THF (1.0 M), 60 °C, 20 min, then aq. work-up; 4) *o*-DCB (0.3 M), 200 °C, 18 h, sealed tube.
[b] 2.0 mol% of **6**.
[c] 2-Iodoaniline applied.
[d] Inseparable 5:1 mixture of α- and γ-carboline determined by ^{19}F NMR.
[e] NaHMDS (3.0 equiv.), THF (0.1 M), rt, 18 h.

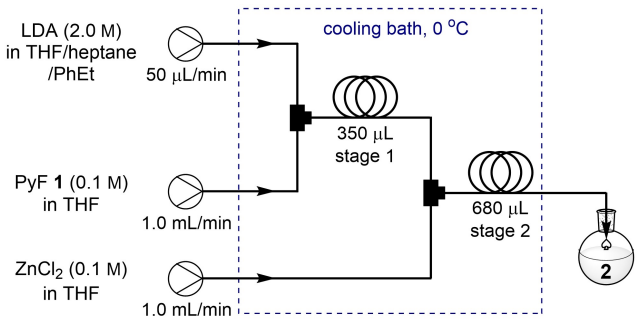
Table 3. β-Carbolines synthesized via base-mediated S_NAr.[a]



[a] Reaction conditions: 1) 2-aminobiaryl **3** (1.0 equiv.), NaHMDS (1.9–3.0 equiv.), THF (0.1 M), 70 °C, 15 min −18 h, sealed tube.
[b] Reaction conducted at rt.

Next, the synthesis of β-carbolines was examined. Applying neutral reaction conditions to 2-aminobiaryls **3o–w** (*o*-DCB, 200 °C, 18 h), no conversion to the corresponding β-carbolines was observed. To promote the intramolecular nucleophilic aromatic substitution, we applied basic conditions as previously shown for α-carboline **4n**. In these cases, deprotonation of the aniline was required to generate a more nucleophilic species to allow for efficient intramolecular displacement of the less activated fluorine substituent in β-position. Best results were obtained from purified 2-aminobiaryls in the presence of an excess of NaHMDS to provide β-carbolines **4o–w** in 18–66% yield (Table 3). This two-step reaction sequence starting from commercially available 3-fluoropyridines and 2-haloanilines represents to the best of our knowledge the shortest synthesis of the naturally occurring β-carbolines norharmane (**4o**) and harmine (**4p**).

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 optimized flow process for the generation of **2** is depicted in Scheme 3.[20] Precise temperature and time control, enabled by continuous flow technology, allowed us to conduct the *ortho*-lithiation of 2-fluoropyrine and 2,5-difluoropyridine with LDA at 0 °C in just 20 s.[21] This is significantly faster than our optimized batch procedure



Scheme 3. Continuous flow setup for the synthesis of arylzinc species **2**.

(−25 °C, 5 min) and in strong contrast to previously reported conditions in the literature (−78 °C for several hours).[19] After transmetalation 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).

Neither fouling nor clogging of the flow reactor was observed under the optimized conditions. Thus, a representative set of carbolines (α-carbolines **4a**, **4c**, and **4e** and β-carboline **4v**) 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.[22]

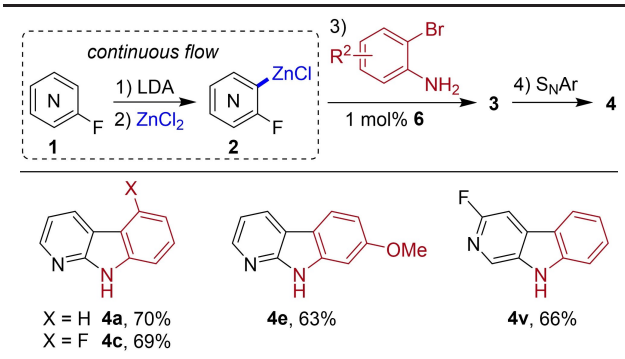
In summary, we have developed a highly efficient route towards the synthesis of α- and β-carbolines. Fluoropyridines were subjected to a directed *ortho*-lithiation followed by zincation and Negishi cross-coupling with 2-haloanilines to afford 2-aminobiaryls. α-Carbolines were obtained after intramolecular S_NAr under neutral conditions, 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.[23]

Experimental Section

Typical Procedure for the Synthesis of 2-Aminobiaryls 3

To a solution of fluoro-substituted pyridine **1** (1.2 mmol, 1.2 equiv.) in anhydrous THF (2.0 mL), was added a solution of LDA (1.3 mmol, 1.3 equiv.) dropwise at −25 °C. The reaction mixture was stirred at −25 °C for 5 min, followed by the addition of $ZnCl_2$ solution in THF (1.3 mmol, 1.3 equiv.). The cooling bath was removed, and the reaction mixture was allowed to warm to room temperature (ca. 3 min), after which a solution of 2-haloaniline (1.0 mmol, 1.0 equiv.) and precatalyst Pd XPhos G3 (**6**) (8.5 mg, 1.0 mol%) in THF (1.0 mL) was added. The reaction mixture was stirred at 60 °C for 20 min. Saturated NH_4Cl solution (20 mL) was added, and the mixture was extracted with EtOAc (3 × 20 mL). The combined organic layers were dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo*. The crude product was purified by column chromatography on silica gel to afford 2-aminobiaryls **3**.

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



[a] Reactions conducted on 1.0 mmol scale; see the Supporting Information for details.

Typical Procedure for the Telescoped Synthesis of α-Carbolines 4a–m

Following the typical procedure for the synthesis of 2-aminobiaryls, the crude product after aqueous work-up was dissolved in 1,2-dichlorobenzene (3.0 mL) and transferred into a sealed tube, followed by heating the reaction mixture to 200 °C for 18 h behind a blast shield. After cooling to room temperature, the mixture was transferred to a round-bottom flask and the solvent was removed *in vacuo* using a rotary evaporator. The residue was dissolved in a mixture of hot toluene/EtOAc and filtered through a short plug of Celite. The filtrate was concentrated *in vacuo* and the residue was recrystallized from hot toluene. The filtrate was decanted, the solid was washed with cold petroleum ether and dried under reduced pressure to give the pure α-carbolines **4**. The mother liquor was concentrated *in vacuo* and recrystallized from hot toluene until no further product could be isolated.

Typical Procedure for the Base-Mediated Synthesis of Carbolines 4n–w

To a solution of biaryl product **3** (1.0 mmol, 1.0 equiv.) in anhydrous THF (10 mL) was added NaHMDS solution in THF (2.0 mmol, 2.0 equiv.). The reaction mixture was heated to 70 °C for 16 h. After cooling to room temperature, the mixture was quenched with saturated NH_4Cl solution (20 mL). The reaction mixture was extracted with EtOAc (3 × 20 mL), and the combined organic layers were dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo*. The crude product was purified by column chromatography on silica gel to afford carbolines **4**.

Acknowledgements

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