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Synthesis of α-Carbolines Starting from 2,3-Dichloropyridines and Substituted Anilines

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This paper is dedicated to Professor A. Pozharskii on the occasion of his 70th birthday.

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Abstract: 9*H*-α-Carbolines have been prepared *via* consecutive intermolecular Buchwald–Hartwig reaction and Pd-catalyzed intramolecular direct arylation from commercially available 2,3-dichloropyridines and substituted anilines. The combination of a high reaction temperature (180 °C) and the use of DBU were found to be crucial for the intramolecular direct arylation reactions of the 3-chloro-*N*-phenylpyridin-2-amines as no reaction was observed at 120 °C and 180 °C using different inorganic and other organic bases. On the other hand, nitrogen-methylated pyridine analogues of these substrates {*N*-[3-chloro-1-methylpyridin-2(1*H*)-ylidene]anilines} do undergo ring closure at 120 °C, with K_3PO_4 as base, affording the respective 1-methyl-1*H*-α-carbolines in good yields.

Keywords: α-carbolines; C–H activation; direct arylation; malaria; microwave heating; palladium

Introduction

Currently, our group is involved in a project concerning the validation of the indoloquinoline alkaloid neocryptolepine[1] (**1**) (5-methyl-5*H*-indolo[2,3-*b*]quinoline) (Figure 1) as an antimalarial.[2,3] We reasoned that removal of the A ring might result in a compound, 1-methyl-1*H*-α-carboline (1-methyl-1*H*-pyrido[2,3-*b*]indole), with a decreased cytotoxicity since the natural product itself is rather cytotoxic because of DNA interactions. Similarly, Quéguiner and co-workers previously showed that the debenzo analogue (1-methyl-1*H*-δ-carboline) of the isomeric indoloquinoline cryptolepine (**2**) exhibits a much higher selectivity index (ratio of the IC_{50} values of cytotoxicity and antiplasmodial activity) against chloroquine-resistant strains of *Plasmodium falciparum*.[4]

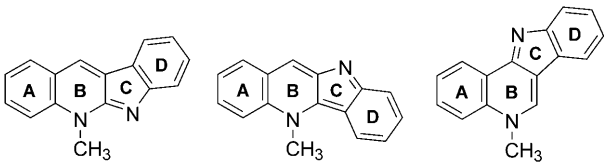
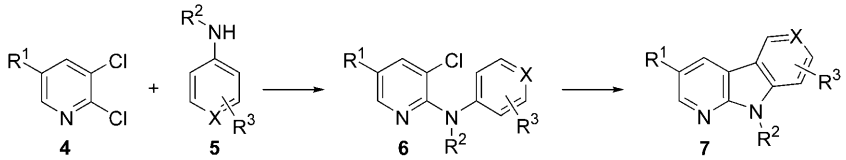
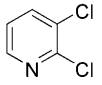
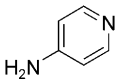
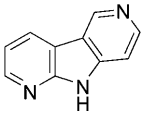
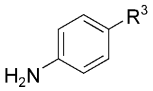
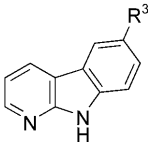
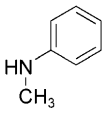
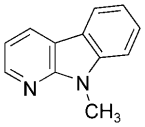
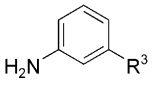
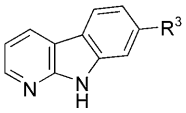
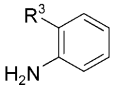
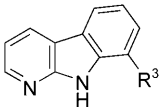
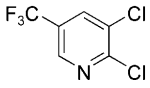
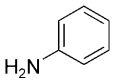
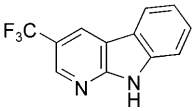
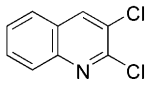
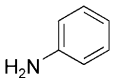
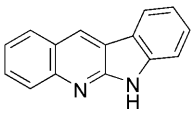


Figure 1. Neocryptolepine (**1**), cryptolepine (**2**) and isocryptolepine (**3**).

Over the past years, our laboratory has investigated the synthesis of azaheteroaromatic scaffolds *via* the combination of Buchwald–Hartwig reactions and Pd-catalyzed intramolecular direct arylation reactions.[5–9] In 2001 we described the regioselective Buchwald–Hartwig reaction of 2,3-dichloropyridine (**4a**) with a variety of substituted (azahetero)arylamines (**5**) (Table 1, entries 1, 3 and 4).[8] 3-Chloro-*N*-pyridin-4-ylpyridin-2-amine (**6a**), prepared *via* this methodology, was used as a model compound for the development of Pd-catalyzed intramolecular direct arylation reaction conditions. These conditions were subsequently applied for the synthesis of the indoloquinoline skeleton of the alkaloid isocryptolepine (**3**) (Figure 1) *via* ring closure of *N*-(2-chlorophenyl)quinolin-4-amine.[9] 9*H*-Pyrrolo[2,3-*b*:4,5-*c*′]dipyridine (6-aza-9*H*-α-carboline) (**7a**) could be obtained from **6a** in 52% yield using a 10 mol% $Pd_2(dba)_3$/40 mol% P(*t*-Bu)$_3$ catalytic system with K_3PO_4 as base in dioxane at 120 °C (sealed tube) for 36 h (standard conditions) (Table 1, entry 1). We wondered whether these earlier developed ring-closure conditions could also be used to construct 9*H*-α-carbolines[10] (**7**) from 3-chloro-*N*-phenylpyridin-2-amines (**6**).

Table 1. The synthesis of 9*H*-α-carbolines **7a**–**k** and 6*H*-indolo[2,3-*b*]quinoline **13**.



Entry	Starting materials		Amination Yield[a]		Arylation Product		Yield	
	Substrate	Arylamine					Oil bath[b]	μW[c]
1	 **4a**	 **5a**	80%[8]	**6a**		**7a**	52%[9]	90%
								
2		R^3 = H	**5b**	83%	**6b**		**7b**	traces	88%
3		R^3 = OMe	**5c**	93%[8]	**6c**		**7c**	traces	86%
4		R^3 = NO_2	**5d**	80%[8]	**6d**		**7d**	traces	21%[d]
5		R^3 = COOEt	**5e**	84%	**6e**		**7e**	–	76%
6			**5f**	74%[e]	**6f**		**7f**	37%[f]	77%[d,g]
								
7		R^3 = OMe	**5g**	82%	**6g**		**7g**	–	83%
8		R^3 = COOEt	**5h**	85%	**6h**		**7h**	–	62%[h]
								
9		R^3 = OMe	**5i**	91%	**6i**		**7i**	–	78%
10		R^3 = COOEt	**5j**	75%[i]	**6j**		**7j**	–	0%[26]
11	 **4b**	 **5b**	86%	**6k**		**7k**	–	90%
12	 **11**	 **5b**	90%	**12**		**13**	–	89%

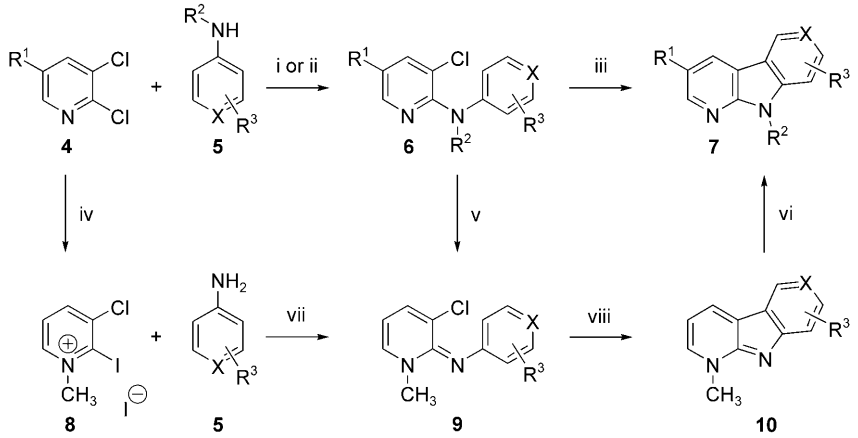
[a] *Reaction conditions:*[8] 2 mol% $Pd(OAc)_2$, 2 mol% (±)-BINAP, K_2CO_3, toluene, reflux, 18 h.
[b] *Reaction conditions:*[9] 10 mol% $Pd_2(dba)_3$, 40 mol% P(*t*-Bu)$_3$, K_3PO_4, dioxane, 120 °C, sealed tube, 36 h.
[c] *Reaction conditions:* 2.5 mol% $Pd_2(dba)_3$, 10 mol% P(*t*-Bu)$_3$, DBU, dioxane, μW, 180 °C, sealed tube, 10 min.
[d] 5 mol% $Pd_2(dba)_3$/20 mol% P(*t*-Bu)$_3$ were used.
[e] Alternative reaction conditions were used:[25] 1 mol% $Pd(OAc)_2$, 2 mol% 2-(dicyclohexylphosphino)biphenyl, NaO-*t*-Bu, toluene, μW, 150 °C, sealed tube, 10 min.
[f] 24% of starting material was recovered.
[g] A reaction time of 35 min was required.
[h] 3.75 mol% $Pd_2(dba)_3$/15 mol% P(*t*-Bu)$_3$ were used.
[i] A part of the desired reaction product undergoes lactamization.

Results and Discussion

9*H*-α-Carboline (**7b**) has been prepared *via* a Graebe–Ullmann reaction,[11a–c] a Borsche–Drechsel cyclization,[11d] a photocyclization reaction,[11e] an intramolecular S_NAr reaction,[11f] a nitrene insertion reaction[11g] and a reductive cyclization.[11h,i] Some of these methodologies have also been used for the synthesis of substituted derivatives.[12] A number of other methodologies have been published allowing the synthesis of specific classes of substituted 9*H*-α-carbolines.[13] All these methodologies suffer from low yields, long synthesis routes, harsh reaction conditions and/or lack of generality which make them rather unsuited for the synthesis of libraries of these compounds. The only literature report dealing with 9*H*-α-carboline skeleton construction involving Pd-catalyzed intramolecular direct arylation was published by Sakamoto.[14] 3-Bromo-*N*-phenylpyridin-2-amine could be transformed into 9*H*-α-carboline using $Pd(OAc)_2$ (10 mol%) and Na_2CO_3 in refluxing DMF. Besides the low yield (31%) a very long reaction time was required (67 h). Moreover, it is unclear whether this protocol is applicable for the synthesis of substituted derivatives. Our decision to attempt to develop a general protocol for the synthesis of 9*H*-α-carbolines from chlorinated substrates is inspired by the better availability of these substrates. Moreover, this poses an additional challenge due to the well known lower reactivity for oxidative addition of a C–Cl bond in comparison with a C–Br bond. Unfortunately, when applying our standard reaction conditions[9] on 3-chloro-*N*-phenylpyridin-2-amine (**6b**), only traces of 9*H*-pyrido[2,3-*b*]indole (9*H*-α-carboline) (**7b**) were formed (Table 1, entry 2). Instead, besides starting material a considerable amount of hydrodehalogenated starting material was detected. A similar outcome was observed with an electron-donating substitutent (4′-OMe) (**6c**) (Table 1, entry 3) as well as with an electron-withdrawing substituent (4′-NO_2) (**6d**) (Table 1, entry 4) on the phenyl ring. Interestingly, when using the *N*-methylated analogue of 3-chloro-*N*-phenylpyridin-2-amine (**6f**) (Scheme 1) as substrate, 9-methyl-9*H*-pyrido[2,3-*b*]indole[11e,13i] (9-methyl-9*H*-α-carboline) (**7f**) could be isolated in 37% yield with a 24% recovery of starting material (Table 1, entry 6). Clearly our earlier developed standard reaction conditions seem not to be suitable for the synthesis of *N*-9-unsubstituted 9*H*-α-carbolines.

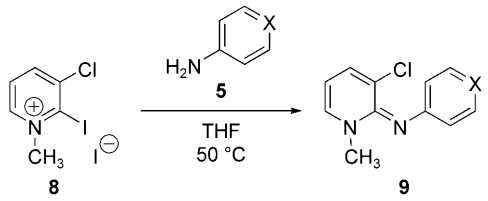
A similar beneficial effect of *N*-substitution was observed in 2002 by Bedford for the synthesis of 9-alkyl-9*H*-carbazoles.[15] Because our target compounds (1-methyl-1*H*-α-carbolines)[16] possess a methyl substituent at the pyridine nitrogen atom, 3-chloro-*N*-phenylpyridin-2-amine (**6b**) was methylated with an excess of iodomethane in DMF at 110 °C (Scheme 1) yielding *N*-[3-chloro-1-methylpyridin-2(1*H*)-ylidene]aniline (**9b**) in 96% yield. When subjecting compound **9b** to our standard intramolecular direct arylation reaction conditions[9] a clean conversion to 1-methyl-1*H*-α-carboline (**10b**) was observed in an overnight reaction. Interestingly, the palladium loading could be reduced as a gradual change to 10 and 2.5 mol% Pd in an overnight protocol resulted in isolated yields of 96% and 90%, respectively (Table 3, entries 1 and 2). Further reduction gave an incomplete conversion of starting material within 17 h.

In order to simplify our synthesis route by using a common intermediate, alternative reaction conditions for the synthesis of *N*-[3-chloro-1-methylpyridin-2(1*H*)-ylidene]anilines were developed. First, 3-chloro-2-iodo-1-methylpyridinium iodide (**8**) was prepared in 87% from **4a** using iodomethane in a sealed tube at 130 °C (Scheme 1).[17] Next, an S_NAr reaction



Scheme 1. General scheme for the synthesis of 9*H*-α-carbolines and 1-methyl-1*H*-α-carbolines. *Reaction conditions:* (i) 2 mol% $Pd(OAc)_2$, 4 mol% (±)-BINAP, K_2CO_3, toluene, reflux, 18 h; (ii) 1 mol% $Pd(OAc)_2$, 2 mol% 2-(dicyclohexylphosphino)biphenyl, NaO-*t*-Bu, toluene, μW, 150 °C, 10 min; (iii) see Table 1; (iv) CH_3I, 130 °C, 7 h; (v) CH_3I, DMF, 110 °C, 24 h, then NH_4OH; (vi) pyridine.HCl, NaI, μW, 220 °C, 15 min; (vii) see Table 2; (viii) see Table 3.

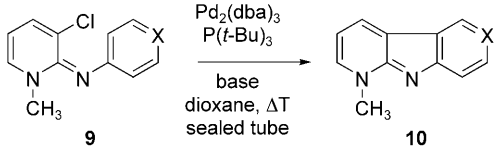
Table 2. Synthesis of *N*-[3-chloro-1-methylpyridin-2(1*H*)-ylidene]anilines (**9a–d**) *via* condensation of **8** with **5**.



Entry	Starting material	X	Additive	Product	Yield[a]
1	**5b**	C–H	–	**9b**	85%
2	**5c**	C–OMe	–	**9c**	92%
3	**5d**	C–NO_2	$POCl_3$ (1.5 equiv.)	**9d**	56%
4	**5d**	C–NO_2	LiCl (4.5 equiv.)	**9d**	60%
5	**5a**	N	–	**9a**	26%

[a] *Reaction conditions:* 1) **8**, 5 equiv. **5**, THF, 50 °C, Ar, 24 h (**9b**, **9c**) or 48 h (**9a**, **9d**) 2) 28–30% NH_4OH.

Table 3. Synthesis of 1-methyl-1*H*-α-carbolines (**10a–d**) *via* Pd-catalyzed intramolecular direct arylation of **9a–d**.



Entry	Starting material	X	Catalyst loading (mol% Pd)	Product	Yield Oil bath[a]	Yield μW[b]
1	**9b**	C–H	10	**10b**	96%	–
2	**9b**	C–H	2.5	**10b**	90%	89%
3	**9c**	C–OCH_3	2.5	**10c**	99%	99%
4	**9d**	C–NO_2	2.5	**10d**	86%	87%
5	**9a**	N	2.5	**10a**	76%	–

[a] *Reaction conditions:* 5 or 1.25 mol% $Pd_2(dba)_3$, 20 or 5 mol% P(*t*-Bu)$_3$, K_3PO_4, dioxane, 120 °C, sealed tube, 17 h.
[b] *Reaction conditions:* 1.25 mol% $Pd_2(dba)_3$, 5 mol% P(*t*-Bu)$_3$, DBU, dioxane, μW, 180 °C, sealed tube, 10 min.

was performed between **8** and anilines (**5b–d**) and pyridin-4-amine (**5a**) in THF at 50 °C. *N*-[3-Chloro-1-methylpyridin-2(1*H*)-ylidene]aniline (**9b**) and *N*-[3-chloro-1-methylpyridin-2(1*H*)-ylidene]-4-methoxyaniline (**9c**) could thus be obtained in excellent yield (Table 2, entries 1 and 2). On the other hand, when using **5d**, addition of a chloride source ($POCl_3$ or LiCl) to the reaction mixture was essential to obtain *N*-[3-chloro-1-methylpyridin-2(1*H*)-ylidene]-4-nitroaniline (**9d**) in an acceptable yield (Table 2, entries 3 and 4).[18] The reaction of **8** with **5a** gave *N*-[3-chloro-1-methylpyridin-2(1*H*)-ylidene]pyridin-4-amine (**9a**) in a low yield of only (26%) (Table 2, entry 5). With the optimal catalyst loading determined for **9b**, we subsequently managed to cyclize **9c**, **9d** and **9a** to the corresponding 6-substituted 1-methyl-1*H*-pyrido[2,3-*b*]indoles **10b–d** and **10a**, all in good to excellent yields (Table 3).

An attempt was made to further decrease the catalyst loading and speed up the reactions by using a higher reaction temperature.[7c,e] Because of its convenience to reach, maintain and monitor the high temperatures, a microwave unit was selected as heating source. A reaction temperature of 180 °C was chosen, leaving the other parameters unchanged. The solid inorganic base K_3PO_4 was not suitable for use in a 10-mL microwave vial as it frequently gave rise to explosions. Therefore, we searched for a soluble organic base to replace K_3PO_4. Nucleophilic amines such as triethylamine and *N,N*-dicyclohexylmethylamine proved not to be useful since partially demethylated substrate **9b** was observed in the reaction mixture.[19] DBU turned out to be the base of choice[20] and under these adapted standard reaction conditions [1.25 mol% $Pd_2(dba)_3$, P(*t*-Bu)$_3$, DBU, dioxane, 180 °C, μW], compounds **9b–d** were cyclized with similar yields in comparison to classical heating at 120 °C (Table 3). A reaction time of 10 min under microwave irradiation at 180 °C was sufficient. A loading of 1.25 mol% $Pd_2(dba)_3$ was required to obtain a complete conversion of substrate within 10 min.

As substituted 9*H*-α-carbolines have recently been reported as CDK1, CDK5 and GSK-3 inhibitors[21] an attempt was made to demethylate substrates **10b–d** using reaction conditions similar to those published by Quéguiner.[22] 9*H*-α-Carboline (**7b**) could thus be obtained in 97% yield (reaction conditions: pyridine hydrochloride, sodium iodide, μW, 220 °C, 15 min), but application of these reaction conditions on **10c** resulted in partially demethylated **7c** and in the case of **10d**, decomposition products were obtained. In parallel, we attempted the intramolecular direct arylation reactions of 3-chloro-*N*-phenylpyridin-2-amines (**6a–d**) using our high-temperature microwave conditions. After all, a beneficial effect of higher temperature for benzo-β- and δ-carboline synthesis and for unsubstituted 9*H*-carbazole synthesis *via* Pd-catalyzed intramolecular direct arylation reactions has already been reported by our and Bedfords team.[7c,e,23] When applying the above-mentioned, newly developed microwave conditions for 1-methyl-1*H*-α-carboline synthesis on **6a** and **6b–c**, 9*H*-pyrrolo[2,3-*b*:4,5-*c'*]dipyridine (**7a**) and the 9*H*-α-carbolines (**7b** and **c**), respectively, could be obtained in excellent yields in a 10 min reaction with a loading of 2.5 mol% $Pd_2(dba)_3$ (Table 1, entries 1–3). In the case of **6d** a catalyst loading of 5 mol% $Pd_2(dba)_3$ was required to obtain full conversion of starting material and an isolated yield of 21% was obtained (Table 1, entry 4). This low yield is due to the high acidity of **7d** (which is easily deprotonated by DBU) resulting in a troublesome work-up. The success of the microwave conditions applied on substrates **6b–d** seem to be due to the use of DBU in combination with the application of a high reaction temperature as the Pd-catalyzed intramolecular direct arylation of **6b** using several bases (DBU, K_3PO_4, K_2CO_3, KOAc) at 120 °C (oil bath) gave no or only traces of **7b** while at 180 °C (μW), only DBU of the base set proved effective. Other organic bases such as *N,N*-dicyclohexylmethylamine were also ineffective. The obtained results underline the crucial effect of reaction temperature and the crucial role of DBU in the Pd-catalyzed intramolecular direct arylation reactions of substrates **6b–d**. In contrast to **6b**, substrate **6f** required a loading of 5 mol% $Pd_2(dba)_3$ and an extended reaction time (35 min) to obtain full conversion under the microwave reaction conditions. Compound **7f** was isolated in 77% yield (Table 1, entry 6).

To show the generality of our methodology, other 3-chloro-*N*-phenylpyridin-2-amines bearing electron-donating (OMe) and electron-withdrawing (COOEt) substituents, also in other positions, were synthesized (**6e**, **6g–j**) (Table 1, entries 5 and 7–10). In the cases of **6e**, **6g** and **6i**, the corresponding 9*H*-α-carbolines could then be obtained in good yields (Table 1, entries 5, 7 and 9). When using *meta*-substituted anilines, a strong preference (≥25:1) for arylation at the *para* position relative to the substituent was observed, regardless of the electronic nature of the substituent (Table 1, entries 7 and 8). For substrate **6h** a slightly higher catalyst loading was required to obtain full conversion of starting material in 10 min (Table 1, entry 8). In the case of substrate **6j**, lactam formation occurred and no arylation product was formed.[26] Besides substitution in the aromatic ring, one example of pyridine ring substitution was also generated. Thus, 3-chloro-*N*-phenyl-5-trifluoromethylpyridin-2-amine (**6k**) was prepared in 86% *via* regioselective Pd-catalyzed amination of 2,3-dichloro-5-trifluoromethylpyridine (**4b**) with aniline (**5b**) (Table 1, entry 11). When applying our high temperature intramolecular direct arylation reaction conditions on **6k**, 3-trifluoromethyl-9*H*-pyrido[2,3-*b*]indole (**7k**) could be smoothly obtained in a high yield (Table 1, entry 11). The 9*H*-α-carboline synthesis protocol could also be applied in the synthesis of neocryptolepine (**1**) itself.[27] Therefore, 3-chloro-*N*-phenylquinolin-2-amine (**12**) was synthesized from 2,3-dichloroquinoline[28] (**11**) and **5b** using our amination protocol.[8] Subsequent Pd-catalyzed intramolecular direct arylation using our standard microwave conditions yielded 6*H*-indolo[2,3-*b*]quinoline (**13**) in 89% yield. When combining the published procedure of Ho et al. for the methylation of this indoloquinoline skeleton with our new synthesis of **13**, a new method for the synthesis of the natural product neocryptolepine is achieved.[27g]

In the past two years, the Bedford and the Ackermann groups reported the synthesis of *N*-substituted and *N*-unsubstituted 9*H*-carbazoles *via* tandem Pd-catalysis (intermolecular Buchwald–Hartwig reaction/Pd-catalyzed intramolecular direct arylation).[23,24] The Ackermann group showed one example on *N*-9-substituted 9*H*-α-carboline synthesis, namely 9-phenyl-3-trifluoromethyl-9*H*-pyrido[2,3-*b*]indole.[24] Similarly, our research group recently published reaction conditions for tandem Pd-catalyzed synthesis of substituted benzo-γ-carbolines (11*H*-indolo[3,2-*c*]quinolines).[7d] Therefore, an attempt was made to construct *N*-9-unsubstituted 9*H*-α-carbolines in a similar way. Because DBU as base was found to be crucial in the Pd-catalyzed intramolecular direct arylation step, our high-temperature direct arylation protocol was applied on **4a** and **5b**.[29] Unfortunately, no amination reaction occurred and therefore no **7b** was formed under these reaction conditions. The same outcome was observed when the solvent was changed to toluene.[29] Subsequently Ackermann's tandem protocol [reaction conditions: 5 mol% $Pd(OAc)_2$, 10 mol% PCy_3, K_3PO_4, NMP, 130 °C, 18 h] was tested for the synthesis of 3-trifluoromethyl-9*H*-pyrido[2,3-*b*]indole (**7k**) starting from **4b** and **5b** as it was already successfully used for the synthesis of one closely related *N*-9-substituted 9*H*-α-carboline, namely 9-phenyl-3-trifluoromethyl-9*H*-pyrido[2,3-*b*]indole.[24] Besides a lot of **6k** and an unidentified compound which is likely to be hydro-

lyzed 2,3-dichloro-5-trifluoromethylpyridine, only traces of the desired tricyclic product **7k** were detected. No further attempts were yet made to develop a tandem protocol for the synthesis of 9*H*-α-carbolines starting from 2,3-dichloropyridines and anilines.

Conclusions

In conclusion, we have established a new methodology for the synthesis of 1-methyl-1*H*-α-carbolines based on the combination of a condensation and a Pd-catalyzed intramolecular direct arylation reaction. In addition, we developed a new protocol for the synthesis of *N*-9-unsubstituted 9*H*-α-carbolines based on consecutive Pd-catalysis from commercially available 2,3-dichloropyridines and substituted anilines. The latter protocol gives superior results in terms of efficiency and generality over published procedures to prepare *N*-9-unsubstituted 9*H*-α-carbolines. A further extension of this methodology and mechanistic studies (Pd-catalyzed intramolecular direct arylations) are currently under investigation.

Experimental Section

General Procedure for the Synthesis of *N*-[3-Chloro-1-methylpyridin-2(1*H*)-ylidene]anilines (9b–d)

A 50-mL round-bottomed, flame-dried flask was charged with 3-chloro-2-iodo-1-methylpyridinium iodide (**8**) (0.7628 g, 2 mmol), aniline (**5b–d**) (10 mmol) and anhydrous THF (5 mL). The resulting suspension was stirred for 24 h at 50 °C under a nitrogen atmosphere. After cooling down, the solvent was removed under reduced pressure. In order to remove 3-chloropyridin-2(1*H*)-one, which is formed in small amounts as side product and is inseparable by column chromatography, dichloromethane (20 mL) was added to the dry residue. The yellow precipitate was collected on a glass filter and rinsed with dichloromethane (30 mL). Subsequently, the precipitate was transferred to a 250-mL flask and the glass filter was rinsed with methanol (50 mL). This organic phase was added to the precipitate and the solvent was subsequently removed under reduced pressure. Next, 28–30% NH_4OH (30 mL) was added followed by an extraction with dichloromethane (3×30 mL). The organic phase was dried using $MgSO_4$, filtered and evaporated to dryness. The crude product was purified *via* flash column chromatography on silica gel.

General Procedure for the Pd-Catalyzed Intramolecular Direct Arylation Reaction of 6a–k and 12 at High Temperature

First, stock solutions of catalyst were prepared depending on the required Pd concentration. For the preparation of a stock solution of 5 mol% Pd/1 mL a flask was charged with $Pd_2(dba)_3$ (0.1374 g, 0.15 mmol). Next, dry freshly distilled dioxane (9.4 mL) and P(*t*-Bu)$_3$ (1 M in toluene) (0.6 mL, 0.6 mmol) were added. The solution was subsequently stirred for 15 min under an argon atmosphere.

A 10-mL microwave vial was charged with **6a–k** or **12** (0.6 mmol), DBU (0.1370 g, 0.9 mmol) and 1 mL of stock solution of catalyst (2.5 mol% Pd/1 mL, 5 mol% Pd/1 mL or 10 mol% Pd/1 mL) and the mixture was stirred and flushed with argon for 1 min. Next, the vial was sealed with an Al crimp cap with a septum and heated at 180 °C in a CEM Discover microwave apparatus. The set power was 300 W and the total heating time was 10 min. After the reaction vial had cooled down to room temperature using a propelled air flow, it was opened and the reaction mixture transferred into a round-bottomed flask using dichloromethane (50 mL). The solvent was evaporated and the crude product purified *via* flash column chromatography on silica gel

Experimental details and the full characterization data for all compounds made are shown in the Supporting Information.

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References

[1] a) K. Cimanga, T. De Bruyne, L. Pieters, M. Claeys, A. Vlietinck, *Tetrahedron Lett.* **1996**, *37*, 1703–1706; b) M. H. M. Sharaf; P. L. Schiff Jr. , A. N. Tackie, C. H. Phoebe Jr. , G. E. Martin, *J. Heterocycl. Chem.* **1996**, *33*, 239–243.

[2] a) T. H. M. Jonckers, S. van Miert, K. Cimanga, C. Bailly, P. Colson, M. C. De Pauw-Gillet, H. van den Heuvel, M. Claeys, F. Lemière, E. L. Esmans, J. Rozenski, L. Quirijnen, L. Maes, R. Dommisse, G. L. F. Lemière, A. Vlietinck, L. Pieters, *J. Med. Chem.* **2002**, *45*, 3497–3508; b) S. Van Miert, T. Jonckers, K. Cimanga, L. Maes, B. Maes, G. Lemière, R. Dommisse, A. Vlietinck, L. Pieters, *Exp. Parasitol.* **2004**, *108*, 163–168; c) Z. Riedl, K. Monsieurs, G. Krajsovszky, P. Dunkel, B. U. W. Maes, P. Tapolcsányi, O. Egyed, S. Boros, P. Mátyus, L. Pieters, G. L. F. Lemière, G. Hajós, *Tetrahedron* **2006**, *62*, 121–129.

[3] S. Van Miert, S. Hostyn, B. U. W. Maes, K. Cimanga, R. Brun, M. Kaiser, P. Mátyus, R. Dommisse, G. Lemière, A. Vlietinck, L. Pieters, *J. Nat. Prod.* **2005**, *68*, 674–677.

[4] E. Arzel, P. Rocca, P. Grellier, M. Labaeïd, F. Frappier, F. Guéritte, C. Gaspard, F. Marsais, A. Godard, G. Quéguiner, *J. Med. Chem.* **2001**, *44*, 949–960.

[5] For recent reviews and accounts on the Buchwald–Hartwig reaction, see: a) A. R. Muci, S. L. Buchwald, *Top. Curr. Chem.* **2002**, *219*, 131–209; b) B. Schlummer, U. Scholz, *Adv. Synth. Catal.* **2004**, *346*, 1599–1626; c) J. F. Hartwig, *Synlett* **2006**, 1283–1294; d) D. S. Surry, S. L. Buchwald, *Angew. Chem. Int. Ed.* **2008**, *47*, 2–26.

[6] For recent reviews dealing with intramolecular direct arylation reactions, see: a) L. C. Campeau, K. Fagnou, *Chem. Commun.* **2006**, 1253–1264; b) D. Alberico, M. E. Scott, M. Lautens, *Chem. Rev.* **2007**, *107*, 174–238; c) I. V. Seregin, V. Gevorgyan, *Chem. Soc. Rev.* **2007**, *36*, 1173–1193.

[7] a) B. Dajka-Halász, K. Monsieurs, O. Éliás, L. Károlyházy, P. Tapolcsányi, B. U. W. Maes, S. Riedl, G. Hajós, R. A. Dommisse, G. L. F. Lemière, J. Košmrlj, P. Mátyus, *Tetrahedron* **2004**, *60*, 2283–2291; b) S. Hostyn, B. U. W. Maes, L. Pieters, G. L. F. Lemière, P. Mátyus, G. Hajós, R. Dommisse, *Tetrahedron* **2005**, *61*, 1571–1577; c) S. Hostyn, B. U. W. Maes, G. Van Baelen, A. Gulevskaya, C. Meyers, K. Smits, *Tetrahedron* **2006**, *62*, 4676–4684; d) C. Meyers, G. Rombouts, K. T. J. Loones, A. Coelho, B. U. W. Maes, *Adv. Synth. Catal.* **2008**, *350*, 465–470; e) P. Franck, S. Hostyn, B. Dajka-Halász, Á. Polonka-Bálint, K. Monsieurs, P. Mátyus, B. U. W. Maes, *Tetrahedron* **2008**, *64*, 6030–6037.

[8] T. H. M. Jonckers, B. U. W. Maes, G. L. F. Lemière, R. Dommisse, *Tetrahedron* **2001**, *57*, 7027–7034.

[9] T. H. M. Jonckers, B. U. W. Maes, G. L. F. Lemière, G. Rombouts, L. Pieters, A. Haemers, R. A. Dommisse, *Synlett* **2003**, 615–618.

[10] For general reviews dealing with α-carbolines, see: a) R. A. Abramovitch, I. D. Spenser, *Adv. Heterocycl. Chem.* **1964**, *3*, 79–207; b) A. A. Semenov, V. V. Tolstikhina, *Chemistry of Heterocyclic Compounds* **1984**, *20*, 345–356.

[11] a) R. H. Freak, R. Robinson, *J. Chem. Soc.* **1938**, 2013–2015; b) L. Stephenson, W. K. Warburton, *J. Chem. Soc. (C)* **1970**, 1355–1364; c) P. Vera-Luque, R. Alajarín, J. Alvarez-Builla, J. J. Vaquero, *Org. Lett.* **2006**, *8*, 415–418; d) S. Okuda, M. M. Robinson, *J. Am. Chem. Soc.* **1959**, *81*, 740–743; e) V. M. Clark, A. Cox, E. J. Herbert, *J. Chem. Soc. (C)* **1968**, 831–833; f) P. Rocca, F. Marsais, A. Godard, G. Quéguiner, *Tetrahedron* **1993**, *49*, 49–64; g) P. A. S. Smith, J. H. Boyer, *J. Am. Chem. Soc.* **1951**, *73*, 2626–2629; h) P. J. Bunyan, J. I. G. Cadogan, *J. Chem. Soc.* **1963**, 42–49; i) J. H. Smitrovich, I. W. Davies, *Org. Lett.* **2004**, *6*, 533–535.

[12] For some recent examples, see: a) S. Aubriot, E. Nicolle, M. Lattier, C. Morel, W. Cao, K. W. Daniel, S. Collins, G. Leclerc, P. Faure, *Bioorg. Med. Chem. Lett.* **2002**, *12*, 209–212; b) M. Pudlo, D. Csányi, F. Moreau, G. Hajós, Z. Riedl, J. Sapi, *Tetrahedron* **2007**, *63*, 10320–10329.

[13] For recent procedures, see: a) A. Abouabdellah, R. H. Dodd, *Tetrahedron Lett.* **1998**, *39*, 2119–2122; b) P. Molina, P. M. Fresneda, M. A. Sanz, C. Foces-Foces, M. C. Ramirez de Arellano, *Tetrahedron* **1998**, *54*, 9623–9638; c) A. Tahri, K. J. Buysens, E. V. Van der Eycken, D. M. Vandenberghe, G. J. Hoornaert, *Tetrahedron* **1998**, *54*, 13211–13226; d) O. Barun, P. K. Patra, H. Ila, H. Junjappa, *Tetrahedron Lett.* **1999**, *40*, 3797–3800; e) B. Joseph, H. Da Costa, J.-Y. Mérour, S. Léonce, *Tetrahedron* **2000**, *56*, 3189–3196; f) E. Erba, M. L. Gelmi, D. Pocar, *Tetrahedron* **2000**, *56*, 9991–9997; g) E. M. Beccalli, F. Clerici, A. Marchesini, *Tetrahedron* **2001**, *57*, 4787–4792; h) A. Ono, K. Narasaka, *Chem. Lett.* **2001**, 146–147; i) K. Tanaka, M. Kitamura, K. Narasaka, *Bull. Chem. Soc. Jpn.* **2005**, *78*, 1659–1664; j) C. Bonini, M. Funicello, P. Spagnolo, *Synlett* **2006**, 1574–1576; k) F. Liger, F. Popowycz, T. Besson, L. Picot, C. M. Galmarini, B. Joseph *Bioorg. Med. Chem.* **2007**, *15*, 5615–5619; l) V. O. Iaroshenko, U. Groth, N. V. Kryvokhyzha, S. Obeid, A. A. Tolmachev, T. Wesch, *Synlett* **2008**, 343–346.

[14] T. Iwaki, A. Yasuhara and T. Sakamoto, *J. Chem. Soc. Perkin Trans. 1* **1999**, 1505–1510.

[15] R. B. Bedford, C. S. J. Cazin, *Chem. Commun.* **2002**, 2310–2311.

[16] For procedures for the construction of 1-methyl-1*H*-α-carboline, see: a) see ref.[10b]; b) see ref.[11a]; c) see ref.[11b]; d) W. Peczyńska-Czoch, M. Mordarski, L. Kaczmarek, P. Nantka-Namirski, *Arch. Immunol. Ther. Exp.* **1986**, *34*, 327–331.

[17] a) these reaction conditions were developed for the synthesis of 2-iodo-1-methylpyridinium iodide starting from 2-chloropyridine, see: Y. Takahashi, S. Otsuka, H. Masuda, M. Hirota, Y. Ito, Y. Hamada, *Bull. Chem. Soc. Jpn.* **1976**, *49*, 2770–2774; b) the formation of 3-chloro-2-iodo-1-methylpyridinium iodide instead of 2,3-dichloro-1-methylpyridinium iodide can be explained by a nucleophilic substitution of the 2-Cl by the iodide anion in the initially formed 2,3-dichloro-1-methylpyridinium iodide; for a report on halogen exchanage reactions on 2-halopyridines, see: H. L. Bradlow, C. A. Vanderwerf, *J. Org. Chem.* **1951**, *16*, 1143–1152. The presence of small amounts of 3-chloro-2-iodopyridine in the reaction mixture suggests that 3-chloro-2-iodo-1-methylpyridinium chloride is demethylated in the course of the reaction. 3-Chloro-2-iodo-1-methylpyridinium iodide is then formed by methylation of 3-chloro-2-iodopyridine with iodomethane.

[18] It is very likely that a halogen exchange reaction between iodide and chloride anions occurs on substrate **8** whereby a more reactive pyridinium salt is formed. Initially, inspired by a literature report, we found that addition of $POCl_3$ to the reaction mixture of **8** and **5d** was crucial to obtain **9d**, see: C. T. Brain, S. A. Brunton, *Tetrahedron Lett.* **2002**, *43*, 1893–1895. Later we found that LiCl, which is readily soluble in THF, had a similar effect.

[19] a) For the use of triethylamine in Pd-catalyzed intramolecular direct arylations, see ref.[6b] and references cited therein. b) For the use of *N,N*-dicyclohexylmethylamine in Pd-catalyzed intramolecular direct arylations, see ref.[9].

[20] a) For examples of the use of DBU in Pd-catalyzed intramolecular direct arylation reactions, see ref.[6b] and references cited therein. b) Recently, Echavarren and co-workers found the use of DBU in the intramolecular direct arylation reaction on substituted 1-bromo-2-(2,2-diphenylethyl)benzenes to be ineffective; see: D. Garcia-Cuadrado, P. de Mendoza, A. A. C. Braga, F. Maseras, A. M. Echavarren, *J. Am. Chem. Soc.* **2007**, *129*, 6880–6886.

[21] a) N. Joseph, L. Meijer, F. Liger, French Patent, FR 28976377, **2006**; *Chem. Abstr.* **2006**, *144*, 390900; b) P. Sennhenn, A. Mantoulidis, M. Treu, U. Tontsch-Grunt, W. Spevak, D. McConnell, A. Schoop, R. Brückner, A. Jacobi, U. Guertler, G. Schnapp, C. Klein, F. Himmelsbach, A. Pautsch, B. Betzemeier, L. Herfurth, J. Mack, D. Wiedenmayer, G. Bader, U. Reiser, *Int. Appl.* WO 2006131552, **2006**; *Chem. Abstr.* **2006**, *146*, 62695.

[22] A. Ruiz, P. Rocca, F. Marsais, A. Godard, G. Quéguiner, *Tetrahedron Lett.* **1997**, *38*, 6205–6208.

[23] R. B. Bedford, M. Betham, *J. Org. Chem.* **2006**, *71*, 9403–9410.

[24] L. Ackermann, A. Althammer, *Angew. Chem. Int. Ed.* **2007**, *46*, 1627–1629.

[25] B. U. W. Maes, K. T. J. Loones, G. L. F. Lemière, R. A. Dommisse, *Synlett* **2003**, 1822–1825. In this paper the synthesis of the structurally related *N*-methyl-*N*-phenylpyridin-2-amine starting from 2-chloropyridine and *N*-methylaniline was described.

[26] A compound has been isolated in 31% with spectral data that is consistent with 11*H*-pyrido[2,1-*b*]quinazolin-11-one: ^{1}H NMR (400 MHz, DMSO-d_6): $\delta = 8.78$ (d, $J = 7.4$ Hz, 1H), 8.30 (dd, $J = 8.1$, 1.1 Hz, 1H), 7.90 (ddd, $J = 8.3$, 7.1, 1.5 Hz, 1H), 7.73 (d, $J = 8.6$ Hz, 1H), 7.71 (ddd, $J = 8.6$, 7.1, 1.5 Hz, 1H), 7.53–7.49 (m, 2H), 7.06 (ddd, $J = 7.4$, 6.3, 1.2 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): $\delta = 158.2$, 148.1, 147.3, 135.0, 134.9, 126.6, 126.6, 126.3, 125.7, 124.8, 115.6, 113.1; HR-MS (ESI): $m/z = 197.0719$, calcd. for $C_{12}H_9N_2O$ $[M+H]^+$: 197.0715.

[27] For recent procedures for the synthesis of neocryptolepine or its 6*H*-indolo[2,3-*b*]quinoline skeleton, see: a) M. Schmittel, J.-P. Steffen, B. Engels, C. Lennartz, M. Hanrath, *Angew. Chem. Int. Ed.* **1998**, *37*, 2371–2373; b) C. Shi, Q. Zhang, K. K. Wang *J. Org. Chem.* **1999**, *64*, 925–932; c) P. M. Fresneda, P. Molina, S. Delgado, *Tetrahedron Lett.* **1999**, *40*, 7275–7278; d) P. Molina, P. M. Fresneda, S. Delgado, *Synthesis* **1999**, 326–329; e) P. M. Fresneda, P. Molina, S. Delgado, *Tetrahedron* **2001**, *57*, 6197–6202; f) see ref.[2a]; g) T.-L. Ho, D.-G. Jou, *Helv. Chim. Acta* **2002**, *85*, 3823–3827; h) G. S. M. Sundaram, C. Venkatesh, U. K. Syam Kumar, H. Ila, H. Junjappa, *J. Org. Chem.* **2004**, *69*, 5760–5762; i) R. Engqvist, J. Bergman, *Org. Prep. Proc. Intern.* **2004**, *36*, 386–390; j) see ref.[11c]; k) T. Dhanabal, R. Sangeetha, P. S. Mohan, *Tetrahedron* **2006**, *62*, 6258–6263; l) P. T. Parvatkar, P. S. Parameswaran, S. G. Tilve, *Tetrahedron Lett.* **2007**, *48*, 7870–7872.

[28] M. R. Sabol, J. M. Owen, W. R. Erickson, *Synth. Commun.* **2000**, *30*, 427–432.

[29] DBU has been used previously in microwave-assisted Pd-catalyzed aminations involving nonaflates, see: R. E. Tundel, K. W. Anderson, S. L. Buchwald, *J. Org. Chem.* **2006**, *71*, 430–433.

