ORGANIC LETTERS

2013
Vol. 15, No. 5
1060–1063

"Base Effect" in the Auto-Tandem Palladium-Catalyzed Synthesis of Amino-Substituted 1-Methyl-1*H*-α-carbolines

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Received January 9, 2013

ABSTRACT

An auto-tandem Pd-catalyzed process consisting of an intramolecular direct arylation and an intermolecular Buchwald–Hartwig reaction for C-ring amino-substituted 1-methyl-1*H*-α-carboline synthesis has been developed. A mechanistic study of the direct arylation reaction revealed a rate effect of the inorganic base on the C–H activation step ("base effect"). The amines, reagents in the tandem protocol, appear to have a similar effect on the direct arylation.

Pyrido[2,3-*b*]indole (α-carboline) derivatives have attracted much attention because of their interesting biological activities.[1] In 2009, we reported the synthesis and antiplasmodial activity of amino-substituted derivatives of the natural product neocryptolepine (**1**) (Figure 1).[2] N^1,N^1-Diethyl-N^4-(5-methyl-5*H*-indolo[2,3-*b*]quinolin-8-yl)-pentane-1,4-diamine (**2**) is 2700 times more active than **1** and 1.6 times less cytotoxic. Interestingly, A-ring debenzoneocryptolepine (**3**), although 5 times less active, is 70 times less cytotoxic than **1**. Therefore, we concluded that the introduction of amino substituents on the C-ring of 1-methyl-1*H*-α-carboline (**3**) has the potential to deliver very potent antiplasmodial compounds with low cytotoxicity. To synthesize a broad set of C-ring-substituted amino-1-methyl-1*H*-α-carbolines, an efficient synthetic methodology is required, allowing regiospecific introduction and maximum variation in the amino substituent from a common intermediate. Auto-tandem palladium catalysis[3] on *N*-[3-chloro-1-methyl-pyridin-2(1*H*)-ylidene]-3, -4, and -2-chloroanilines (**7a–c**) consisting of an intramolecular direct arylation and an intermolecular Buchwald–Hartwig reaction with amines looks very attractive to achieve this goal.[4] However, auto-tandem protocols are not easy to develop as one needs to identify one catalyst suitable for all catalytic processes

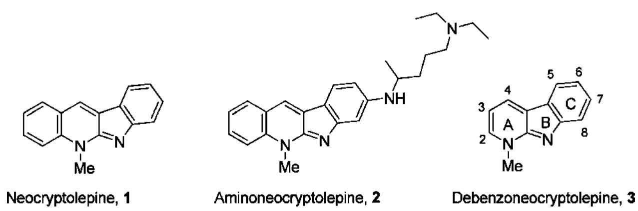

Figure 1. Neocryptolepine and analogues.

(1) For examples, see: (a) Helbecque, N.; Moquin, C.; Bernier, J. L.; Evelyne, M.; Henichart, J. P. *Cancer Biochem. Biophys.* **1987**, *9*, 271–279. (b) Sennhenn, P.; Mantoulidis, A.; Treu, M.; Tontsch-Grunt, U.; Spevak, W.; McConnell, D.; Schoop, A.; Brueckner, R.; Jacobi, A.; Guertler, U. Int. Appl. WO 2006131552, 2006; *Chem. Abstr.* 2006, *146*, 62695. (c) Kim, J.-S.; Shin-ya, K.; Furihata, K.; Hayakawa, Y.; Seto, H. *Tetrahedron Lett.* **1997**, *38*, 3431–3434.

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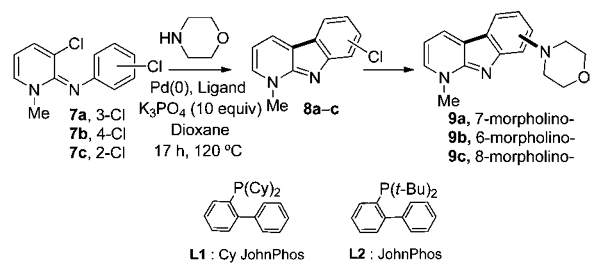
(3) For reviews dealing (partly) with auto-tandem catalysis, see: (a) Vlaar, T.; Ruijter, E.; Orru, R. V. A. *Adv. Synth. Catal.* **2011**, *353*, 809–841. (b) Shindoh, N.; Takemoto, Y.; Takasu, K. *Chem.—Eur. J.* **2009**, *15*, 12168–12179. (c) Fogg, D. E.; dos Santos, E. N. *Coord. Chem. Rev.* **2004**, *248*, 2365–2379. (d) Lautens, M.; Alberico, D.; Bressy, C.; Fang, Y.-Q.; Mariampillai, B.; Wilhelm, T. *Pure Appl. Chem.* **2006**, *78*, 351–361.

10.1021/ol400064r
Published on Web 02/14/2013

Table 1. Pd-Catalyzed Auto-Tandem Synthesis of 4-(1-Methyl-1*H*-pyrido[2,3-*b*]indol-7,6 and 8-yl)morpholines (**9a**–**c**)



entry	7	Pd source/ligand	yield (%) 3[a]	yield (%) 8a–c[a]	yield (%) 9a–c[a]
1	**7a**[b,c]	$Pd_2(dba)_3$/(t-Bu)$_3$P	trace		91
2	**7a**[b]	$Pd_2(dba)_3$/L1	29		53
3	**7a**[b]	$Pd_2(dba)_3$/L2		40	
4	**7a**[b]	$Pd(OAc)_2$/(t-Bu)$_3$P	trace		85
5	**7a**[b]	$Pd(OAc)_2$/L1			82
6	**7a**[b]	$Pd(OAc)_2$/L2		68	
7	**7b**[b]	$Pd_2(dba)_3$/(t-Bu)$_3$P	trace		83
8	**7b**[b]	$Pd(OAc)_2$/L1	6		73
9	**7c**[b]	$Pd_2(dba)_3$/(t-Bu)$_3$P	15	28	47
10	**7c**[d]	$Pd_2(dba)_3$/(t-Bu)$_3$P	20		62
11	**7c**[d]	$Pd(OAc)_2$/L1	23	40	20

[a] Isolated yield. [b] Pd/L: 5 mol %/10 mol %. [c] K_3PO_4 (5 equiv) gave **9a** (31%, NMR yield) in 24 h; a similar result was obtained with Cs_2CO_3 (5 equiv). [d] Pd/L: 10 mol %/20 mol %.

occurring in one pot. A variety of Pd-catalyzed auto-tandem reactions have been developed in recent years.[3] These are usually focused on functionalized scaffold synthesis in one step, and the final substitution diversity of the core is limited by the availability of the reagents used. Halogenated scaffold synthesis and subsequent in situ functionalization offers more possibility to create diversity. However, examples are still rare.[5] We herein report a new and efficient protocol for the synthesis of 6-, 7-, and 8-amino-1-methyl-1*H*-α-carbolines via auto-tandem Pd catalysis on **7a**–**c** using primary and secondary amines as the reagents.

The substrates **7a**–**c** were easily synthesized via methylation of commercially available 2,3-dichloropyridine (**4**), yielding 2,3-dichloro-1-methylpyridinium trifluoromethanesulfonate (**5**), followed by condensation with the correct chloroaniline.[6] In a similar way, *N*-[3-chloro-1-methylpyridin-2(1*H*)-ylidene]aniline (**6**) was synthesized. As a model substrate, we chose **7a** and as amine morpholine (Table 1).[7] A complete conversion to **9a** was obtained with (t-Bu)$_3$P as ligand using $Pd_2(dba)_3$ or $Pd(OAc)_2$ as Pd source and K_3PO_4 as the base (Table 1, entries 1 and 4). For the analogous tandem reactions involving Cy JohnPhos (L1) as a ligand, similar results were obtained, but with $Pd_2(dba)_3$, a significant amount of 1-methyl-1*H*-α-carboline (**3**) (dehalogenated **8a**) was isolated (Table 1, entry 2). In all cases, no 4-(1-methyl-1*H*-pyrido[2,3-*b*]indol-5-yl)morpholine was observed, pointing to a complete regioselective C(6) direct arylation on **7a**. The tandem process is completely chemoselective as direct arylation was not in competition with an amination reaction at C(3) of the pyridine ring. Remarkably, use of JohnPhos (L2) exclusively led to the ring-closed **8a** in moderate yield (Table 1, entries 3 and 6). Under the optimal reaction conditions for **7a** (Table 1, entries 1 and 5), regioisomeric **7b** yielded **9b** in 83 and 73% yield, respectively (Table 1, entries 7 and 8). When **7c** was used as the substrate, the $Pd_2(dba)_3$/(t-Bu)$_3$P catalytic system gave a mixture of 4-(1-methyl-1*H*-pyrido[2,3-*b*]indol-8-yl)morpholine (**9c**) and 8-chloro-1-methyl-1*H*-pyrido[2,3-*b*]indole (**8c**) (Table 1, entry 9). This points to a slow amination reaction which is not surprising taking into account that the C(8) chloro atom of **8c** is located in a *peri* position of the carboline scaffold. The presence of 20% dehalogenation product **3** further supports the hampering of the amination reaction of **8c** due to sterical hindrance.[8] For the tandem reaction of **7c** with morpholine, a double $Pd_2(dba)_3$/(t-Bu)$_3$P loading was therefore used (Table 1, entry 10). A similar loading of $Pd(OAc)_2$/L1 proved not to be sufficient (Table 1, entry 11). Next, we investigated if the protocol developed for morpholine could also be used for acyclic secondary amines.[7] Dibutylamine (Table 2) and *N*-methylaniline (Table 3) were selected. Similarly as for reactions involving morpholine, the $Pd_2(dba)_3$/(t-Bu)$_3$P catalytic system allowed synthesis of the *N*,*N*-dibutylamino-substituted carbolines **10a**–**c** (Table 2, entries 1, 3, and 4) and *N*,1-dimethyl-*N*-phenyl-1*H*-pyrido[2,3-*b*]indolamines (**11a**–**c**) (Table 3, entries 1, 3, and 4).

As observed for morpholine, the $Pd(OAc)_2$/L2 system on **7a** exclusively gave chlorocarboline **8a** (Tables 2 and 3, entries 2). The successful strategy was extended to primary amines, with hexylamine as a model (Table 4). In this case, a distinct reactivity was observed. The protocol proved to be successful provided that $Pd(OAc)_2$ was used as the Pd source. When using $Pd_2(dba)_3$ as catalyst precursor, for **7a**, only chlorocarboline **8a** was isolated (Table 4, entry 1), and

(4) For examples of an auto-tandem Pd-catalyzed amination/direct arylation reaction (reverse sequence), see: (a) Ackermann, L.; Althammer, A.; Mayer, P. *Synthesis* **2009**, 3494–3503. (b) Bryan, C. S.; Lautens, M. *Org. Lett.* **2008**, *10*, 4633–4636. (c) Bedford, R. B.; Betham, M. *J. Org. Chem.* **2006**, *71*, 9403–9410. (d) Bedford, R. B.; Cazin, C. S. J. *Chem. Commun.* **2002**, 2310–2311.

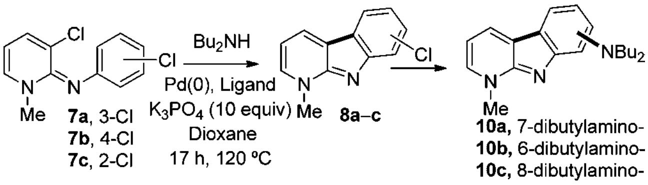
(5) *gem*-Dihalovinyl systems: (a) Chelucci, G. *Chem. Soc. Rev.* **2011**, *112*, 1344–1462. For selected examples, see: (b) Fang, Y.-Q.; Karisch, R.; Lautens, M. *J. Org. Chem.* **2007**, *72*, 1341–1346. (c) Fang, Y.-Q.; Yuen, J.; Lautens, M. *J. Org. Chem.* **2007**, *72*, 5152–5160. (d) Nagamochi, M.; Fang, Y.-Q.; Lautens, M. *Org. Lett.* **2007**, *9*, 2955–2958. (e) Fang, Y.-Q.; Lautens, M. *J. Org. Chem.* **2008**, *73*, 538–549. (f) Chai, D. I.; Lautens, M. *J. Org. Chem.* **2009**, *74*, 3054–3061. (g) Bryan, C. S.; Braunger, J. A.; Lautens, M. *Angew. Chem., Int. Ed.* **2009**, *48*, 7064–7068. (h) Bryan, C. S.; Lautens, M. *Org. Lett.* **2010**, *12*, 2754–2757. (i) Nicolaus, N.; Franke, P. T.; Lautens, M. *Org. Lett.* **2011**, *13*, 4236–4239. (j) Ye, S.; Liu, J.; Wu, J. *Chem. Commun.* **2012**, *48*, 5028–5030. (k) Liu, J.; Chen, W.; Ji, Y.; Wang, L. *Adv. Synth. Catal.* **2012**, *354*, 1585–1592. For examples dealing with other systems, see: (l) Leclerc, J. P.; André, M.; Fagnou, K. *J. Org. Chem.* **2006**, *71*, 1711–1714. (m) Turner, P. A.; Griffin, E. M.; Whatmore, J. L.; Shipman, M. *Org. Lett.* **2011**, *13*, 1056–1057.

(6) Hostyn, S.; Tehrani, A. K.; Lemière, F.; Smout, V.; Maes, B. U. W. *Tetrahedron* **2011**, *67*, 655–659.

(7) For recent reviews on the Buchwald–Hartwig reaction, see: (a) Surry, D. S.; Buchwald, S. L. *Chem. Sci.* **2011**, *2*, 27–50. (b) Maiti, D.; Fors, B. P.; Henderson, J. L.; Nakamura, Y.; Buchwald, S. L. *Chem. Sci.* **2011**, *2*, 57–68. (c) Surry, D. S.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2008**, *47*, 6338–6361.

(8) Beletskaya, I. P.; Bessertnykh, A. G.; Guilard, R. *Tetrahedron Lett.* **1999**, *40*, 6393–6397.

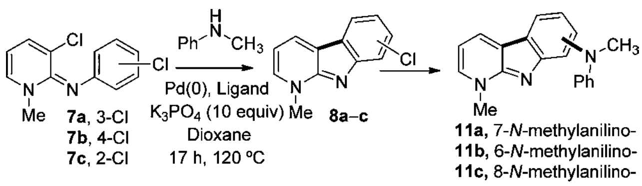
Table 2. Pd-Catalyzed Auto-Tandem Synthesis of *N*,*N*-Dibutyl-1-methyl-1*H*-pyrido[2,3-*b*]indol-7, 6, and 8-amines (**10a–c**)



entry	7	Pd source/ ligand	yield (%) **3**[a]	yield (%) **8a–c**[a]	yield (%) **10a–c**[a]
1	**7a**[b]	$Pd_2(dba)_3/(t\text{-}Bu)_3P$	6		77
2	**7a**[b]	$Pd(OAc)_2$/L2	6	72	
3	**7b**[b]	$Pd_2(dba)_3/(t\text{-}Bu)_3P$	19		70
4	**7c**[c]	$Pd_2(dba)_3/(t\text{-}Bu)_3P$	54		37

[a] Isolated yield. [b] Pd/L: 5 mol %/10 mol %. [c] Pd/L: 10 mol %/20 mol % .

Table 3. Pd-Catalyzed Auto-Tandem Synthesis of *N*,1-Dimethyl-*N*-phenyl-1*H*-pyrido[2,3-*b*]indol-7, 6, and 8-amines (**11a–c**)



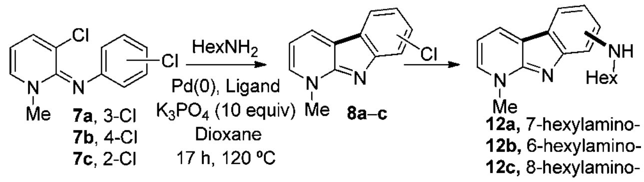
entry	7	Pd source/ligand	yield (%) **3**[a]	yield (%) **8a–c**[a]	yield (%) **11a–c**[a]
1	**7a**[b]	$Pd_2(dba)_3/(t\text{-}Bu)_3P$	6		66
2	**7a**[b]	$Pd(OAc)_2$/L2		87	
3	**7b**[b]	$Pd_2(dba)_3/(t\text{-}Bu)_3P$			70
4	**7c**[c]	$Pd_2(dba)_3/(t\text{-}Bu)_3P$	19	10	52

[a] Isolated yield. [b] Pd/L: 5 mol %/10 mol %. [c] Pd/L: 10 mol %/20 mol %.

for substrates **7b** and **7c**, a mixture of chlorocarboline **8** and end compound **12** was obtained (Table 4, entries 5 and 8). Substrate **7c** again required a higher catalyst loading for a complete conversion (Table 4, entry 9). Interestingly, the $Pd(OAc)_2$/L2 system almost exclusively gave chlorocarboline **8a** starting from **7a** (Table 4, entry 3) as seen with the other amine classes.

Inspired by the potent antiplasmodial activity of **2** and the presence of this amino side chain in the antimalarial drug chloroquine, we decided to test the more challenging N^1,N^1-diethylpentane-1,4-diamine. For each of the substrates **7a–c**, the catalyst systems identified to give the highest yield in the corresponding reactions with *n*-hexylamine were selected. Gratifyingly, the N^1,N^1-diethyl-N^4-(1-methyl-1*H*-pyrido[2,3-*b*]indol-7, 6, and 8-yl)pentane-1,4-diamines (**13a–c**) were obtained in moderate to good yields (Table 5, entries 1–3). Only in the auto-tandem reaction with **7c** was a substantial amount of dehalogenation product **3** observed, but even in this case, 47% of the target compound was obtained without further optimization.

Table 4. Pd-Catalyzed Auto-Tandem Synthesis of *N*-Hexyl-1-methyl-1*H*-pyrido[2,3-*b*]indol-7, 6 and 8-amines (**12a–c**)



entry	7	Pd source/ligand	yield (%) **3**[a]	yield (%) **8a–c**[a]	yield (%) **12a–c**[a]
1	**7a**[b]	$Pd_2(dba)_3/(t\text{-}Bu)_3P$		71	
2	**7a**[b]	$Pd(OAc)_2/(t\text{-}Bu)_3P$	12		59
3	**7a**[b]	$Pd(OAc)_2$/L2		79	8
4	**7a**[b]	$Pd(OAc)_2$/L1	4		87
5	**7b**[b]	$Pd_2(dba)_3/(t\text{-}Bu)_3P$		36	42
6	**7b**[b]	$Pd(OAc)_2$/L2	6		73
7	**7b**[b]	$Pd(OAc)_2$/L1	32		59
8	**7c**[c]	$Pd_2(dba)_3/(t\text{-}Bu)_3P$	5	58	24
9	**7c**[c]	$Pd(OAc)_2$/L1	26		60
10	**7c**[c]	$Pd(OAc)_2$/L2	25	5	43

[a] Isolated yield. [b] Pd/L: 5 mol %/10 mol %. [c] Pd/L: 10 mol %/20 mol %.

To get more insight into the tandem reactions on **7**, we decided to follow the reaction of **7a** with morpholine in function of time using the $Pd_2(dba)_3/(t\text{-}Bu)_3P$ catalytic system. This experiment confirmed that the direct arylation on **7a** is occurring first, followed by a Buchwald–Hartwig reaction on chlorocarboline **8a** (Supporting Information (SI) Figure 3). Interestingly, when lowering the excess of K_3PO_4 from 10 to 2.5 equiv, the disappearance rate of substrate **7a** was significantly retarded (SI Figures 3 and 4). This is remarkable as 2.5 equiv of K_3PO_4 already does not completely dissolve in dioxane. A "base effect" with inorganic bases in Buchwald–Hartwig reactions has been previously observed and rationalized by our group via a rate-determining interphase deprotonation of the Pd-amine complex.[9] A similar effect of insoluble excess of inorganic base on the rate of direct arylations is only reported once.[10] However, it is unclear at which stage of the catalytic cycle the base influences the direct $C(sp^2)$–H functionalization process.[11,12] To date, five main reaction mechanisms (oxidative addition, Heck-type, σ-bond metathesis, electrophilic substitution, base-assisted metalation) have been proposed for the $C(sp^2)$–H activation of (hetero)arenes.[13] We decided to

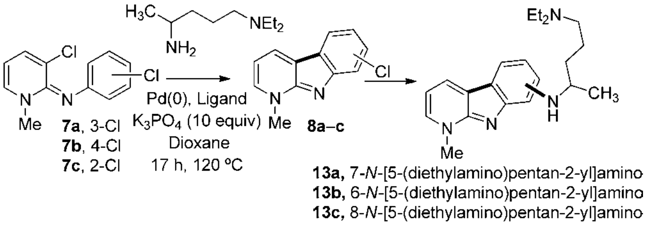
(9) For an example of a mechanistic study of the "base effect" in Pd-catalyzed amination reactions with aryl iodides, see: Meyers, C.; Maes, B. U. W.; Loones, K. T. J.; Bal, G.; Lemière, G. L. F.; Dommisse, R. A. *J. Org. Chem.* **2004**, *69*, 6010–6017. For a review discussing this effect, see ref 7b.

(10) Meyers, C.; Rombouts, G.; Loones, K. T. J.; Coelho, A.; Maes, B. U. W. *Adv. Synth. Catal.* **2008**, *350*, 465–470.

(11) The role of the type of base on the C–H activation step is well-documented, as exemplified by the importance of a "CO_2" structural entity. (a) Carboxylate: Ackermann, L. *Chem. Rev.* **2011**, *111*, 1315–1345. (b) Carbonate: Garcia-Quadrado, D.; de Mendoza, P.; Braga, A. A. C.; Maseras, F.; Echavarren, A. M. *J. Am. Chem. Soc.* **2007**, *129*, 6880–6886.

(12) For a study revealing the influence of the cation of the inorganic base on the C–H activation step, see: Theveau, L.; Verrier, C.; Lassalas, P.; Martin, T.; Dupas, G.; Querolle, O.; van Hijfte, L.; Marsais, F.; Hoarau, C. *Chem.—Eur. J.* **2011**, *17*, 14450–14463.

Table 5. Pd-Catalyzed Auto-Tandem Synthesis of N^1,N^1-Diethyl-N^4-(1-methyl-1*H*-pyrido[2,3-*b*]indol-7, 6, and 8-yl)-pentane-1,4-diamines (**13a−c**)



entry	**7**	Pd source/ ligand	yield (%) **3**[a]	yield (%) **8a−c**[a]	yield (%) **13a−c**[a]
1	**7a**[b]	$Pd(OAc)_2$/L1	7		62
2	**7b**[b]	$Pd(OAc)_2$/L2	6		65
3	**7c**[c]	$Pd(OAc)_2$/L1	52		47

[a] Isolated yield. [b] Pd/L: 5 mol %/10 mol %. [c] Pd/L: 10 mol %/20 mol %.

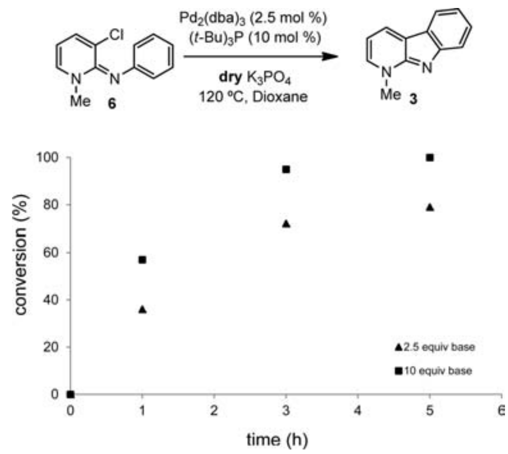


Figure 2. Effect of base loading (K_3PO_4) on the direct arylation reaction: 2.5 equiv versus 10 equiv of dry K_3PO_4.

study the base effect in the direct arylation on **6**, which lacks the chloro atom on the aniline, in more detail. The effect observed on **7a** was also present in this simplified substrate (Figure 2). To exclude an effect of water, flame-dried base was used. Both with dried and non-dried base, the effect was observed. When **6** and its pentadeuterated analogue were used, a significant KIE was observed (1.75), hereby revealing that the C−H bond cleavage is the rate-limiting step of the direct arylation process and justifying the sensitivity of the reaction for excess base (SI Figure 1).[14] This points to an interphase C−H activation step which (at least partly) can occur at the surface of the insoluble inorganic phosphate base, hereby generating a rate increase.

Next, the effect of amine on the direct arylation was also tested as in our tandem protocol amine is present as reagent. Interestingly, when comparing the cyclization reaction of **6** with $Pd_2(dba)_3$/(t-Bu)$_3$P and K_3PO_4 (10 equiv) (SI Figure 11) with a similar experiment in the presence of 2 equiv of different amine classes (Et_3N, $HexNH_2$, morpholine, Bu_2NH) (SI Figures 12−15), an additional acceleration of the cyclization was observed. No competitive Buchwald−Hartwig reaction occurred with primary and secondary amines. Reinvestigation of the primary kinetic isotope effect, using **6** and its pentadeuterated analogue, but this time in the presence of *n*-hexylamine (2 equiv), gave a value of 1.93 (SI Figure 2).[14] This shows that amine does not change the RDS (rate-determining step) of the catalysis and therefore must play, together with K_3PO_4, an active role in the C−H activation step. Amine presumably acts as a proton shuttle from the liquid to the solid phase of the reaction mixture, hereby increasing the rate further.[15] An experiment with **6** in the presence of *n*-hexylamine (2 equiv) but without addition of K_3PO_4 confirmed the proton shuttle hypothesis as no conversion to **3** was observed in this case. To exclude any assistance in the removal of remaining dba from the catalyst by K_3PO_4 or amine, hereby influencing the rate of the catalysis, both the loading of base and the effect of amines were also tested starting from $Pd(OAc)_2$ as the palladium source (SI Figures 7, 8, and 16−20).[16] The base effect of K_3PO_4 and amine was still observed, ruling out a dba removal by K_3PO_4 and amine.

In conclusion, we have developed an auto-tandem Pd-catalyzed process consisting of intramolecular direct arylation and a consecutive intermolecular Buchwald−Hartwig reaction starting from easily accessible *N*-[3-chloro-1-methylpyridin-2(1*H*)-ylidene]-3-, 4- and 2-chloroanilines (**7a−c**) and amines allowing the regioselective synthesis of respectively 7-, 6- and 8-amino-substituted 1-methyl-1*H*-α-carbolines, respectively. A variety of amine classes can be used, making the synthetic methodology suitable for library synthesis. Generally, (t-Bu)$_3$P is a good ligand for reactions involving secondary amines, while Cy JohnPhos (L1) has to be used for primary amines. A mechanistic study of the direct arylation reaction revealed a base effect of K_3PO_4 and amine on the RDS (C−H activation).

Acknowledgment. This work was financially supported by the University of Antwerp (BOF), the Fund for Scientific Research-Flanders (FWO-Flanders), and the Hercules Foundation.

Supporting Information Available. Experimental procedures and full spectroscopic data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.

(13) For reviews, see: (a) Seregin, I. V.; Gevorgyan, V. *Chem. Soc. Rev.* **2007**, *36*, 1173–1193. (b) Alberico, D.; Scott, M. E.; Lautens, M. *Chem. Rev.* **2007**, *107*, 174–238. (c) See ref 11a.

(14) (a) Simmons, E. M.; Hartwig, J. F. *Angew. Chem., Int. Ed.* **2012**, *51*, 3066–3072. (b) A noncompetive experiment was performed using product ratios to determine the KIE. The KIE value is therefore an underestimation of the actual value.

(15) Pivalate has been reported to act as a proton shuttle for carbonate bases in DMA as solvent: Lafrance, M.; Fagnou, K. *J. Am. Chem. Soc.* **2006**, *128*, 16496–16497.

(16) For the interaction of dba with Pd^0, see: Fairlamb, I. J. S. *Org. Biomol. Chem.* **2008**, *6*, 3645–3656.