Syntheses of New Quinoline-Containing Heterocyclic Scaffolds Using Inter- and Intramolecular Pd-Catalyzed Amination

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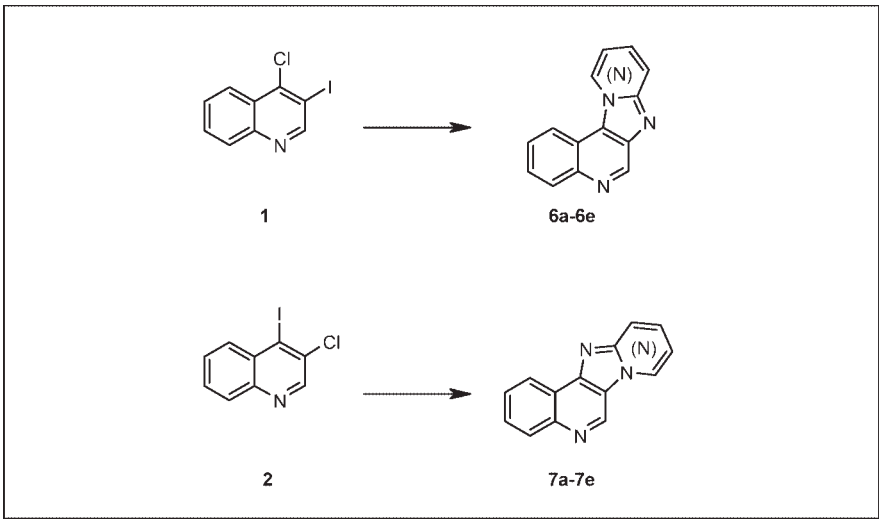

A tandem inter- and intramolecular Pd-catalyzed amination protocol was studied on 4-chloro-3-iodoquinoline and 3-chloro-4-iodoquinoline with different aminohetarenes. Applying this method, ten novel quinoline derivatives and eight new heterocyclic ring systems were synthesized.

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INTRODUCTION

The quinoline-containing polycyclic compounds are expected to have interesting biological activity. Pyrazoloquinoline derivatives are active agents for the treatment of cancer and herpes virus infections [1,2]. Substituted indoloquinolines display biological properties such as antimalarial, antimuscarinic, antibacterial, antiviral, and cytotoxic activities *in vivo*, and significant antitumor properties *in vitro* [3–6].

The aim of this work was to prepare new heterocyclic ring systems, containing the quinoline skeleton. 4-Chloro-3-iodoquinoline (**1**) and 3-chloro-4-iodoquinoline (**2**) were reacted with aminohetarenes **3a-3e** to get hitherto unknown heterocyclic scaffolds.

RESULTS AND DISCUSSION

In 2004, Loones *et al*. described the first auto-tandem inter- and intramolecular Pd-catalyzed amination protocol on 2-chloro-3-iodopyridine with different amino (benzo)(di)azines [7]. A few years later, they extended their amination procedure on the benzo-analogue of 2-chloro-3-iodopyridine; 2-chloro-3-iodoquinoline [8]. To the best of our knowledge, there are no reports on the above-mentioned Pd-catalyzed amination of either 4-chloro-3-iodoquinoline (**1**) or 3-chloro-4-iodoquinoline (**2**).

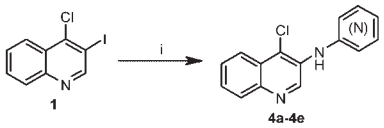
At the beginning of this work, we had some doubt whether this one-pot double amination reaction would work on our substrates **1-2**. To find the optimal conditions for the synthesis of **4-7,** some preliminary experiments were needed. The effects of solvent and ligand on the reaction rate were investigated for compound **1**.

In a first approach, we studied the effect of ligand on the auto-tandem Pd-catalyzed amination. *rac*-BINAP (2,2′-bis(diphenylphosphino)-1,1′-binaphthyl) [9] and XANTPHOS (4,5-bis(diphenylphosphino)-9,9-dimethylxanthene) [10] are commonly used ligands in the Buchwald-Hartwig aminations [11,12]. Concerning the amination of **1** with 2-aminopyridine (**3a**) under the same conditions ($Pd(OAc)_2$, Cs_2CO_3, toluene, reflux), XANTPHOS gave higher conversion for **6a** than *rac*-BINAP after the same reaction time (Scheme 1).

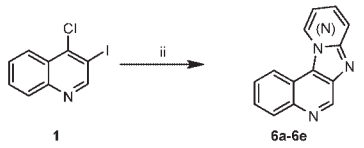
The effects of different solvents like toluene, DMF, and DME were studied keeping the other reaction conditions unchanged. The fastest reaction was observed in toluene.

On the basis of the small-scale experiments, different amino(benzo)(di)azines **3a-3e** were coupled with 4-

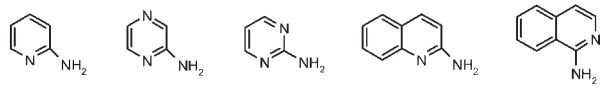
Scheme 1. Synthesis of **4a-4e** and **6a-6e**.



i, **1** (1.73 mmol), **3a-3e** (1.73 mmol), Cs_2CO_3 (6.92 mmol), $Pd(OAc)_2$ (0.04 mmol), XANTPHOS (0.04 mmol), toluene, reflux temperature



ii, **1** (1.73 mmol), **3a-3e** (1.73 mmol), Cs_2CO_3 (6.92 mmol), $Pd(OAc)_2$ (0.17 mmol), XANTPHOS (0.17 mmol), toluene, reflux temperature



chloro-3-iodoquinoline (**1**) in toluene in the presence of $Pd(OAc)_2$, XANTPHOS and Cs_2CO_3 at reflux temperature to get the unknown 3-amino-4-chloroquinoline derivatives **4a-4e** and the new polycyclic heterocycles **6a-6e**.

Table 1

Synthesis of **4a-4e.**

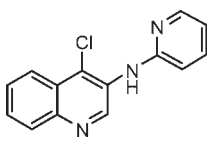
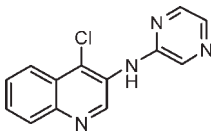
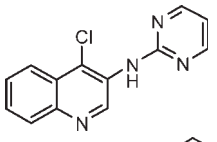
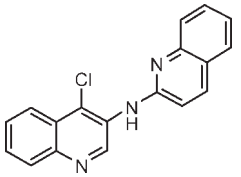
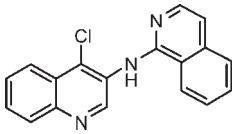
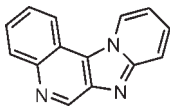
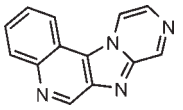
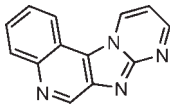
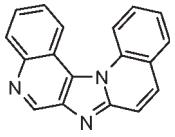
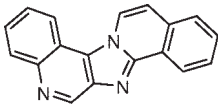
3	Time (h)	Yield (%)	4
3a	6	61	
3b	3	61	
3c	6 20	8 72	
3d	5	78	
3e	4	43	

Table 2

Synthesis of **6a-6e.**

3	Time (h)	Yield (%)	6
3a	21	32	
3b	20	84	
3c	21	Traces	
3d	29	30	
3e	22	51	

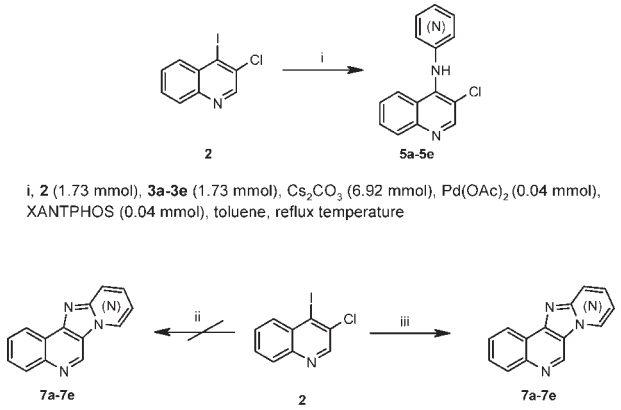
The desired intermediates **4a-4e** were obtained in moderate to good yields, 43–78%. The reaction time was different in every case but was comprised between 3 and 6 h. In the case of 4-chloro-3-(pyrimidin-2-yl)amino-quinoline (**4c**), only traces could be detected after 6 h; so the reaction was left longer (20 h) at reflux temperature resulting in a good yield of 72% being achieved. The results are reported in Table 1 and in the Experimental Section.

The new ring systems **6a, 6b, 6d, 6e** were obtained after 20–29 h, with varying yields (30–83%). 5,7,8,11a-Tetraazabenzo[*c*]fluorene (**6c**) was also formed, but only as a minor compound (Table 2).

We expanded our investigation to 3-chloro-4-iodoquinoline (**2**) as a substrate. The coupling reactions were carried out with the same aminohetarenes **3a-3e**. The monosubstituted intermediates **5a-5e** were prepared in the same way as when using 4-chloro-3-iodoquinoline (**1**) (Scheme 2).

A similar behavior was observed as in the case of **4a-4e**. The Pd-catalyzed intermolecular aminations afforded compounds **5a-5e** in moderate to good yields (50–78%). The reaction time was again the longest with 2-aminopyrimidine (**3c**), which resulted in 3-chloro-4-

Scheme 2. Synthesis of **5a-5e** and **7a-7e**.



(pyrimidin-2-yl)aminoquinoline (**5c**). The results are reported in Table 3 and in the Experimental Section.

In contrast, the reaction conditions optimized for **6a-6e** did not work for the synthesis of **7a-7e**: in all cases, the reactions stopped at the stage of **5a-5e**. No intramolecular amination was observed, so we had to change our strategy. We wondered if it would be possible to prepare **7a-7e** in one-pot *via* orthogonal tandem catalysis (with simultaneously operating palladium and copper catalysts). Fortunately, by adding CuI (0.2 eq) to the reaction mixture (**2**, **3a-3e**, $Pd(OAc)_2$, XANTPHOS, Cs_2CO_3 and DME as solvent), the desired heterocycles **7a-7e** could be synthesized [8] (Scheme 2).

The formation of **7a-7e** directly from 3-chloro-4-iodoquinoline (**2**) and **3a-3e** gave varying results. Only traces of 5,6b,10,11-tetraazabenzo[*a*]fluorene (**7c**) were formed. Low yields were obtained in the reaction with 2-aminopyridine (**3a**) and 2-aminoquinoline (**3d**). In the coupling with **3b** and **3e,** moderate yields were achieved (Table 4).

In conclusion, the tandem inter- and intramolecular Pd-catalyzed amination protocol was applied on 4-chloro-3-iodoquinoline (**1**) and 3-chloro-4-iodoquinoline (**2**) with five different amidines **3a-3e**, affording novel heterocyclic systems. The reactions that were performed with compound **1** gave higher yields compared to the experiments with the other isomer **2**. Unfortunately in two cases—**1** and **2** with 2-aminopyrimidine (**3c**)—the reactions only gave traces of the desired products **6c**, **7c**.

In summary, we succeeded in preparing ten monosubstituted intermediates **4a-4e** and **5a-5e** and eight new heterocyclic scaffolds **6a**, **6b**, **6d**, **6e**, **7a**, **7b**, **7d**, **7e** whose biological activity warrants further investigation.

EXPERIMENTAL

All melting points were measured on a Büchi-545 apparatus and are uncorrected. Magnetic resonance spectra (^{1}H NMR) were recorded on a Varian 400 MHz spectrometer. Chemical shift values are reported in δ (ppm) relative to an internal standard (tetramethylsilane). All coupling constants are given in Hertz. Multiplicity is indicated using the following abbreviations: br, broad; d, doublet; t, triplet; m, multiplet; s, singlet. The mass spectra were measured on a FISONS TRIO 1000. Elemental analyses were carried out on an Elementar VARIO EL. Reactions were monitored by TLC on silica gel-protected aluminium sheets (Type 60 F 254, Merck), and the spots were detected by exposure to a UV-Lamp at 254 nm for a few seconds. Column chromatography was performed on silica gel. 4-Chloro-3-iodoquinoline (**1**) and 3-chloro-4-iodoquinoline (**2**) were synthesized using a modification of a known procedure described in literature [13,14]. All reagents were purchased from Aldrich except 2-aminopyrazine and 2-aminoquinoline, which were ordered from Fluka and Apollo, respectively. All the solvents were of the highest analitical grade.

General procedure for the preparation of 4a-4e and 5a-5e. A round-bottomed flask was charged with $Pd(OAc)_2$ (9 mg, 0.04 mmol, 0.02 eq), Xantphos (4,5-bis(diphenylphosphino)-9,9-dimethylxanthene) (24 mg, 0.04 mmol, 0.02 eq) and toluene (8 mL). The solution thus obtained was flushed with argon for 1 h under magnetic stirring at room temperature. Meanwhile, a three-necked round-bottomed flask was charged with 4-chloro-3-iodoquinoline (**1**) (0.50 g, 1.73 mmol, 1.00 eq) or 3-chloro-4-iodoquinoline (**2**) (0.50 g, 1.73 mmol, 1.00 eq), the corresponding amidine **3a-3e** (1.73 mmol, 1.00 eq), Cs_2CO_3 (2.25 g, 6.92 mmol, 4.00 eq) and toluene (15 mL). To this suspension, the preformed Pd-catalyst was added. The resulting mixture was flushed with argon again and heated for 3–21 h at reflux temperature. After cooling to room temperature, toluene was removed by evaporation, the residue was mixed with silica gel, and it was brought on top of a silica gel column and purified by flash chromatography.

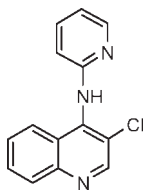
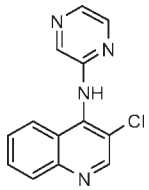
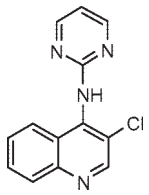
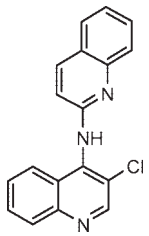
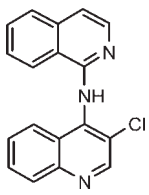
4-Chloro-3-(pyridin-2-yl)aminoquinoline (4a). Purification by flash chromatography using hexane:EtOAc = 7:3 resulted in a white solid. Yield: 0.27 g, 1.05 mmol, 61%; mp. 213.4–213.5°C; ^{1}H NMR ($CDCl_3$) δ 6.86–6.88 (m, 3H, ArH, NH), 7.57–7.64 (m, 3H, ArH), 8.05–8.11 (m, 2H, ArH), 8.25–8.27 (m, 1H, ArH), 9.62 (s, 1H, ArH); MS: m/z = 255 ($M^{+\cdot}$); *Anal.* Calcd. for $C_{14}H_{10}ClN_3$ (255.71) C, 65.76; H, 3.94; N, 16.43. Found: C, 65.94; H, 3.93; N 16.38.

4-Chloro-3-(pyrazin-2-yl)aminoquinoline (4b). Purification by flash chromatography using toluene:MeOH = 95:5 resulted in a brownish solid, which was recrystallized from toluene to give a beige solid. Yield: 0.27 g, 1.05 mmol, 61%; mp. 176.2–176.3°C; ^{1}H NMR ($CDCl_3$) δ 6.98 (br, 1H, NH), 7.61–7.68 (2H, m, Ar), 8.08–8.18 (m, 4H, ArH), 8.32 (d, 1H, ArH, J = 1.2 Hz), 9.70 (s, 1H, ArH); MS: m/z = 256 ($M^{+\cdot}$); *Anal.* Calcd. for $C_{13}H_9ClN_4$ (256.70) C, 60.83; H, 3.53; N, 21.83. Found: C, 60.62; H, 3.52; N 21.89.

4-Chloro-3-(pyrimidin-2-yl)aminoquinoline (4c). Purification by flash chromatography using hexane:EtOAc = 3:2 resulted in a white solid. Yield: 0.32 g, 1.25 mmol, 72%; mp. 156.5–157.2°C; ^{1}H NMR ($CDCl_3$) δ 6.81 (t, 1H, ArH, J = 4.8 Hz), 7.55–7.64 (m, 2H, ArH), 7.71 (br, 1H, NH), 8.05–8.10 (m, 2H, ArH), 8.44 (d, 2H, ArH, J = 4.8 Hz), 9.90 (s, 1H, ArH); MS:

Table 3

Synthesis of **5a-5e.**

3	Time (h)	Yield (%)	5
3a	3	57	
3b	3	50	
3c	21	74	
3d	3	66	
3e	6	78	

m/z = 256 (M^+); *Anal*. Calcd. for $C_{13}H_9ClN_4$ (256.70) C, 60.83; H, 3.53; N, 21.83. Found: C, 60.93; H, 3.52; N 21.88.

4-Chloro-3-(quinolin-2-yl)aminoquinoline (4d). Purification by flash chromatography using hexane:EtOAc = 7:3, 1:1 resulted in a light yellowish solid. Yield: 0.41 g, 1.34 mmol, 78%; mp. 171.0–172.1°C; ^{1}H NMR ($CDCl_3$) δ 7.00 (d, 1H, ArH, *J* = 8.8 Hz), 7.13 (br, 1H, NH), 7.33–7.37 (m, 1H, ArH), 7.59–7.69 (m, 4H, ArH), 7.83 (d, 1H, ArH, *J* = 8.4 Hz), 8.02 (d, 1H, ArH, *J* = 8.8 Hz), 8.03–8.13 (m, 2H, ArH), 10.23 (s, 1H, ArH); MS: m/z = 305 (M^+); *Anal*. Calcd. for $C_{18}H_{12}ClN_3$ (305.77) C, 70.71; H, 3.96; N, 13.74. Found: C, 70.84; H, 3.95; N 13.71.

4-Chloro-3-(isoquinolin-1-yl)aminoquinoline (4e). Purification by flash chromatography using hexane:EtOAc = 7:3 resulted in an orange solid which was recrystallized from EtOH to give a yellowish solid. Yield: 0.23 g, 0.75 mmol, 43%; mp. >250°C; ^{1}H NMR ($CDCl_3$) δ 7.26 (d, 1H, ArH, *J* = 6.0 Hz), 7.61–7.71 (m, 5H, ArH, NH), 7.81 (d, 1H, ArH, *J* = 8.0 Hz), 8.06–8.14 (m, 4H, ArH), 9.98 (s, 1H, ArH); MS: m/z = 305 ($M^{+\cdot}$); *Anal*. Calcd. for $C_{18}H_{12}ClN_3$ (305.77) C, 70.71; H, 3.96; N, 13.74. Found: C, 70.83; H, 3.95; N, 13.71.

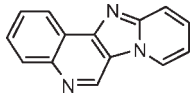
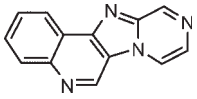
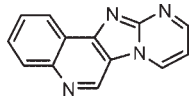
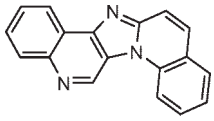
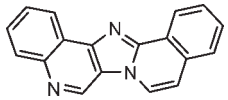
3-Chloro-4-(pyridin-2-yl)aminoquinoline (5a). Purification by flash chromatography using hexane:EtOAc = 3:2 resulted in a beige solid. Yield: 0.25 g, 0.98 mmol, 57%; mp. 177.6–178.5°C; ^{1}H NMR ($CDCl_3$) δ 6.41 (d, 1H, ArH, *J* = 8.0 Hz), 6.85–6.88 (m, 1H, ArH), 7.12 (br, 1H, NH), 7.46–7.50 (m, 2H, ArH), 7.69–7.72 (m, 1H, ArH), 7.81–7.83 (m, 1H, ArH), 8.11 (d, 1H, ArH, *J* = 8.4 Hz), 8.24–8.25 (m, 1H, ArH), 8.88 (s, 1H, ArH); MS: m/z = 255 ($M^{+\cdot}$); *Anal*. Calcd. for $C_{14}H_{10}ClN_3$ (255.71) C, 65.76; H, 3.94; N, 16.43. Found: C, 65.51; H, 3.95; N, 16.47.

3-Chloro-4-(pyrazin-2-yl)aminoquinoline (5b). Purification by flash chromatography using toluene:2-propanol = 9:1 resulted in a beige solid. Yield: 0.22 g, 0.86 mmol, 50%; mp. >250°C; ^{1}H NMR ($CDCl_3$) δ 7.08 (br, 1H, NH), 7.44–7.53 (m, 1H, ArH), 7.70–7.74 (m, 1H, ArH), 7.77–7.80 (m, 1H, ArH), 7.93 (d, 1H, ArH, *J* = 1.2 Hz), 8.10–8.14 (m, 3H, ArH), 8.89 (s, 1H, ArH); MS: m/z = 256 ($M^{+\cdot}$); *Anal*. Calcd. for $C_{13}H_9ClN_4$ (256.70) C, 60.83; H, 3.53; N, 21.83. Found: C, 60.62; H, 3.54; N, 21.87.

3-Chloro-4-(pyrimidin-2-yl)aminoquinoline (5c). Purification by flash chromatography using hexane:EtOAc = 3:2, 2:3, 1:9

Table 4

Synthesis of **7a-7e.**

3	Time (h)	Yield (%)	7
3a	19	5	
3b	28	66	
3c	28	Traces	
3d	28	4	
3e	21	43	

resulted in a white solid. Yield: 0.33 g, 1.28 mmol, 74%; mp. 232.8–232.9°C; ^{1}H NMR ($CDCl_3$) δ 6.80 (t, 1H, ArH, J = 4.8 Hz), 7.37 (br, 1H, NH), 7.49–7.53 (m, 1H, ArH), 7.68–7.72 (m, 1H, ArH), 7.87 (d, 1H, ArH, J = 8.4 Hz), 8.10 (d, 1H, ArH, J = 8.4 Hz), 8.37 (d, 2H, ArH, J = 4.8 Hz), 8.90 (m, 1H, ArH); MS: m/z = 256 ($M^{+\cdot}$); *Anal*. Calcd. for $C_{13}H_9ClN_4$ (256.70) (C, 60.83; H, 3.53; N, 21.83. Found: C, 60.71; H, 3.54; N 21.79.

3-Chloro-4-(quinolin-2-yl)aminoquinoline (5d). Purification by flash chromatography using hexane:EtOAc = 3:2 resulted in a white solid. Yield: 0.35 g, 1.14 mmol, 66%; mp. 118.3–119.2°C; ^{1}H NMR ($CDCl_3$) δ 6.61 (d, 1H, ArH, J = 8.8 Hz), 7.31–7.35 (m, 1H, ArH), 7.41–7.45 (m, 1H, ArH), 7.57–7.61 (m, 1H, ArH), 7.65–7.71 (m, 3H, ArH, NH), 7.85–7.89 (m, 2H, ArH), 8.10 (d, 1H, ArH, J = 8.0 Hz), 8.87 (s, 1H, ArH); MS: m/z = 305 ($M^{+\cdot}$); *Anal*. Calcd. for $C_{18}H_{12}ClN_3$ (305.77) C, 70.71; H, 3.96; N, 13.74. Found: C, 70.88; H, 3.95; N, 13.71.

3-Chloro-4-(isoquinolin-1-yl)aminoquinoline (5e). Purification by flash chromatography using hexane:EtOAc = 3:2, 1:1, 2:3 resulted in an orange solid. Yield: 0.41 g, 1.34 mmol, 78%; mp. >250°C; ^{1}H NMR ($CDCl_3$) (the mixture of two tautomers) δ 7.32–9.00 (m, 12 H, ArH, NH); MS: m/z = 305 ($M^{+\cdot}$); *Anal*. Calcd. for $C_{18}H_{12}ClN_3$ (305.77) C, 70.71; H, 3.96; N, 13.74. Found: C, 70.85; H, 3.95; N, 13.70.

General procedure for the preparation of 6a-6e. A round-bottomed flask was charged with $Pd(OAc)_2$ (39 mg, 0.17 mmol, 0.10 eq), Xantphos (4,5-bis(diphenylphosphino)-9,9-dimethyl-xanthene) (0.10 g, 0.17 mmol, 0.10 eq) and toluene (8 mL). The solution thus obtained was flushed with argon for 1 h under magnetic stirring at room temperature. Meanwhile, a three-necked round-bottomed flask was charged with 4-chloro-3-iodoquinoline (1) (0.50 g, 1.73 mmol, 1.00 eq), the corresponding amidine 3a-3e (1.73 mmol, 1.00 eq), Cs_2CO_3 (2.25 g, 6.92 mmol, 4.00 eq) and toluene (15 mL). To this suspension, the preformed Pd-catalyst was added. The resulting mixture was flushed with argon again and heated for 20–29 h at reflux temperature. After cooling to room temperature, toluene was removed by evaporation, the residue was mixed with silica gel and it was brought on top of a silica gel column and purified by flash chromatography.

5,7,11a-Triazabenzo[c]fluorene (6a). Purification by flash chromatography using toluene:2-propanol = 4:1, 3:2, 2:3 resulted in a brownish solid which was recrystallized from toluene to give a beige solid. Yield: 0.12 g, 0.55 mmol, 32%; mp. 192.5-193.3°C; ^{1}H NMR ($CDCl_3$) δ 7.05–7.08 (m, 1H, ArH), 7.47–7.51 (m, 1H, ArH), 7.66–7.71 (m, 2H, ArH), 7.85 (d, 1H, ArH, J = 6.4 Hz), 8.32–8.34 (m, 2H, ArH), 8.96 (d, 1H, ArH, J = 4.8 Hz), 9.51 (s, 1H, ArH); MS: m/z = 219 ($M^{+\cdot}$); *Anal*. Calcd. for $C_{14}H_9N_3$ (219.25) C, 76.70; H, 4.14. Found: C, 76.96; H, 4.13.

5,7,9,11a-Tetraazabenzo[c]fluorene (6b). Purification by flash chromatography using toluene:2-propanol = 9:1, 4:1, 3:2, 1:1 resulted in a light brownish solid. Yield: 0.32 g, 1.45 mmol, 84%; mp. >250°C; ^{1}H NMR (DMSO-d_6) δ 7.82–7.90 (m, 2H, ArH), 8.23 (d, 1H, ArH, J = 4.8 Hz), 8.30–8.32 (m, 1H, ArH), 8.88–8.91 (m, 1H, ArH), 9.52–9.57 (m, 3H, ArH); MS: m/z = 220 ($M^{+\cdot}$); *Anal*. Calcd. for $C_{13}H_8N_4$ (220.24) C, 70.90; H, 3.66. Found: C, 70.75; H, 3.96.

5,7,13b-Triazadibenzo[c,g]fluorene (6d). Purification by flash chromatography using DCM:MeOH = 100:1, 100:2, 95:5 resulted in a yellowish solid. Yield: 0.14 g, 0.52 mmol, 30%; mp. 179.6–181.0°C; ^{1}H NMR ($CDCl_3$) δ 7.55–7.78 (m, 6H, ArH), 7.89 (d, 1H, ArH, J = 7.6 Hz), 8.36 (d, 1H, ArH, J = 8.0 Hz), 8.62 (d, 1H, ArH, J = 8.4 Hz), 9.53 (s, 1H, ArH); MS: m/z = 269 ($M^{+\cdot}$); *Anal*. Calcd. for $C_{18}H_{11}N_3$ (269.31) C, 80.28; H, 4.12. Found: C, 80.55; H, 4.11.

6a,11,13-Triazadibenzo[a,g]fluorene (6e). Purification by flash chromatography using toluene:2-propanol = 4:1, 3:2, 2:3 resulted in a brownish solid which was recrystallized from EtOH to give a dark yellowish solid. Yield: 0.24 g, 0.89 mmol, 51%; mp. 229.7–229.8°C; ^{1}H NMR (DMSO-d_6) δ 7.57 (d, 1H, ArH, J = 7.6 Hz), 7.80–7.87 (m, 4H, ArH), 8.05–8.07 (m, 1H, ArH), 8.28–8.31 (m, 1H, ArH), 8.76–8.78 (m, 1H, ArH), 8.91–8.93 (m, 1H, ArH), 9.33 (d, 1H, ArH, J = 7.6 Hz), 9.52 (s, 1H, ArH); MS: m/z = 269 ($M^{+\cdot}$); *Anal*. Calcd. for $C_{18}H_{11}N_3$ (269.31) C, 80.28; H, 4.12. Found: C, 80.07; H, 4.13.

General procedure for the preparation of 7a-7e. A round-bottomed flask was charged with $Pd(OAc)_2$ (39 mg, 0.17 mmol, 0.10 eq), Xantphos (4,5-bis(diphenylphosphino)-9,9-dimethyl-xanthene) (0.10 g, 0.17 mmol, 0.10 eq) and 1,2-dimethoxy-ethane (8 mL). The suspension thus obtained was flushed with argon for 1 h under magnetic stirring at room temperature. Meanwhile, a three-necked round-bottomed flask was charged with 3-chloro-4-iodoquinoline (2) (0.50 g, 1.73 mmol, 1.00 eq), the corresponding amidine (1.73 mmol, 1.0 eq), Cs_2CO_3 (2.255 g, 6.92 mmol, 4.0 eq), CuI (66 mg, 0.35 mmol, 0.20 eq) and 1,2-dimethoxyethane (10 mL). To this mixture, the preformed Pd-catalyst was added. The resulting mixture was flushed with argon again and heated for 19–28 h at reflux temperature. After cooling to room temperature, 1,2-dimethoxyethane was removed by evaporation, the residue was mixed with silica gel and it was placed on top of a silica gel column and purified by flash chromatography.

5,6b,11-Triazabenzo[a]fluorene (7a). Purification by flash chromatography using toluene:MeOH = 95:5 resulted in a yellowish solid which was recrystallized from EtOH to give a beige solid. Yield: 0.02 g, 0.09 mmol, 5%; mp. 244.7–244.8°C; ^{1}H NMR ($CDCl_3$) δ 7.08–7.11 (m, 1H, ArH), 7.58–7.62 (m, 1H, ArH), 7.70–7.81 (m, 2H, ArH), 7.91–7.92 (m, 1H, ArH), 8.26–8.28 (m, 1H, ArH), 8.73–8.75 (m, 2H, ArH), 9.50 (s, 1H, ArH); MS: m/z = 219 ($M^{+\cdot}$) *Anal*. Calcd. for $C_{14}H_9N_3$ (219.25) C, 76.70; H, 4.14. Found: C, 76.81; H, 4.13.

5,6b,9,11-Tetraazabenzo[a]fluorene (7b). Purification by flash chromatography using toluene:MeOH = 9:1, 4:1, 1:1 resulted in a brownish solid which was recrystallized from EtOH to give a light brownish solid. Yield: 0.25 g, 1.14 mmol, 66%; mp. >250°C; ^{1}H NMR (DMSO-d_6) δ 7.75–7.85 (m, 2H, ArH), 8.19–8.22 (m, 1H, ArH), 8.27 (d, 1H, ArH, J = 4.8 Hz), 8.61–8.63 (m, 1H, ArH), 9.41–9.42 (m, 1H, ArH), 9.49–9.50 (m, 1H, ArH), 9.91 (s, 1H, ArH); MS: m/z = 220 ($M^{+\cdot}$); *Anal*. Calcd. for $C_{13}H_8N_4$ (220.24) C, 70.90; H, 3.66. Found: C, 70.79; H, 3.67.

5,6b,13-Triazadibenzo[a,g]fluorene (7d). Purification by flash chromatography using hexane:EtOAc = 3:2, 1:1, 2:3 resulted in a brownish solid which was recrystallized from EtOH to give a beige solid. Yield: 20 mg, 0.07 mmol, 4%; mp. >250°C; ^{1}H NMR ($CDCl_3$) δ 7.58–7.62 (m, 1H, ArH), 7.71–7.96 (m, 6H, ArH), 8.29 (d, 1H, ArH, J = 8 Hz), 8.67 (d, 1H, ArH, J = 8.4 Hz), 8.77–7.79 (m, 1H, ArH), 10.07 (s, 1H, ArH); MS: m/z = 269 ($M^{+\cdot}$); *Anal*. Calcd. for $C_{18}H_{11}N_3$ (269.31) C, 80.28; H, 4.12. Found: C, 80.05; H, 4.13.

5,6b,13-Triazadibenzo[a,i]fluorene (7e). Purification by flash chromatography using toluene:MeOH = 95:5, 1:1 resulted in a brownish solid which was recrystallized from EtOH to give a beige solid. Yield: 0.20 g, 0.74 mmol, 43%; mp. >250°C; ^{1}H NMR ($CDCl_3$) δ 7.28 (d, 1H, ArH, J = 7.2 Hz), 7.71–7.83 (m, 5H, ArH), 8.26–8.28 (m, 1H, ArH), 8.41 (d, 1H, ArH, J = 7.2 Hz), 8.81–8.83 (m, 1H, ArH), 8.95–8.98 (m, 1H, ArH), 9.46 (s, 1H, ArH); MS: m/z = 269 ($M^{+\cdot}$) *Anal.* Calcd. for $C_{18}H_{11}N_3$ (269.31) C, 80.28; H, 4.12. Found: C, 80.43; H, 4.11.

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