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Synthesis of pyrido[2′,1′:2,3]imidazo[4,5-*b*]quinoline and pyrido[1′,2′:1,2]imidazo[4,5-*b*]quinoline and their benzo and aza analogs via tandem catalysis

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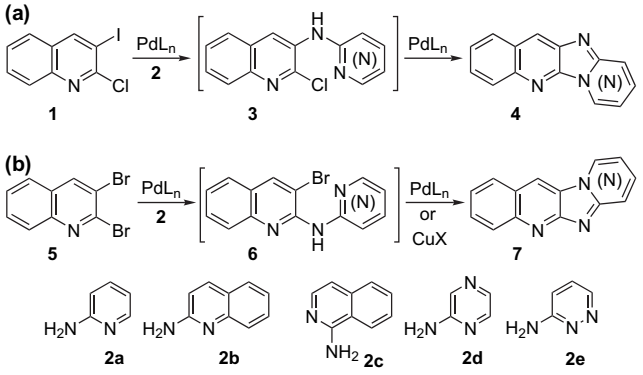
Abstract—In this paper we report regioselective tandem metal-catalyzed aminations on dihaloquinolines (2-chloro-3-iodoquinoline and 2,3-dibromoquinoline) with amino(benzo)(di)azines. Eight new heterocyclic scaffolds of the dipyridoimidazole type could be synthesized. By controlling the reaction temperature selective C-2 intermolecular Pd-catalyzed amination on 2,3-dibromoquinoline with amino(benzo)(di)-azines can be achieved.

1. Introduction

Arylamines are important entities with several important applications (pharmaceuticals, agrochemicals, polymers, and materials for the electronics and xerographic industry).[1,2] The most important method hitherto available to synthesize these arylamines is via metal-catalyzed C–N bond formation. One of the most popular and best explored representatives of this group is the Pd-catalyzed amination, autonomously developed by the groups of Buchwald[3] and Hartwig[4] in the mid 1990s. The Buchwald–Hartwig reaction has made tremendous progress, especially by the refinement of the ligands.[1,2,5–7] Since the beginning of this decade the Cu-catalyzed amination revives due to the introduction of Cu–ligand complexes through which the harsh conditions, necessary for the Ullmann-type C–N bond formation, can be substituted for milder coupling conditions.[8,9] One of the most daring challenges in this research field is the development of tandem metal-catalyzed amination protocols. Via these one-pot processes complex structures can be obtained starting from easily available building blocks. Until now, only a few examples of tandem metal-catalyzed aminations have been reported in the literature.[10] Most of them focused on the formation of the pyrrole ring of carbazoles, constructed via a double *N*-arylation of primary amines with 2,2′-di(pseudo)halobiaryls.[11–13] Also the pyrrole ring of substituted indoles can be synthesized via a tandem alkenyl C–N and aryl C–N bond formation with 2-(2-(pseudo)haloalkenyl)aryl halides.[14] In 2004 our group reported the first regioselective auto-tandem inter- and intramolecular Pd-catalyzed amination protocol.[15] 2-Chloro-3-iodopyridine was coupled with a set of amino(benzo)(di)azines upon which dipyrido[1,2-*a*:3′,2′-*d*]imidazole and its benzo and aza analogs were formed. More recently, we developed an orthogonal (Pd- and Cu-catalyst) and an auto-tandem (Pd-catalyst) regioselective inter- and intramolecular amination protocol on 2,3-dibromopyridine by which regioisomers of the dipyrido[1,2-*a*:3′,2′-*d*]imidazole analogs could be obtained.[16]

We wondered if our tandem amination procedures could be extended to the benzo-analogs of the substrates 2-chloro-3-iodopyridine and 2,3-dibromopyridine; 2-chloro-3-iodoquinoline (**1**) and 2,3-dibromoquinoline (**5**) (Scheme 1). This



Scheme 1. Orthogonal and auto-tandem inter- and intramolecular amination on dihaloquinolines (**1**, **5**) with amino(benzo)(di)azines (**2**).

Keywords: Tandem catalysis; Buchwald–Hartwig reaction; Dihaloquinolines.
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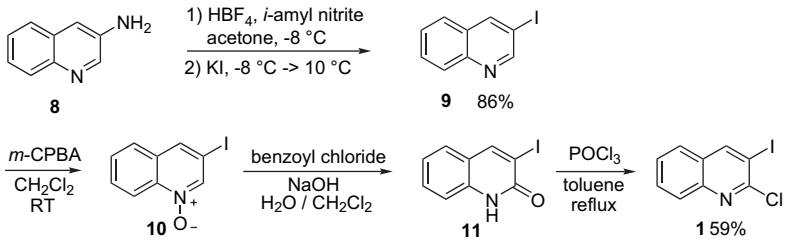
extension would show the generality of our optimized tandem inter- and intramolecular regioselective amination protocols in terms of substrate scope. To the best of our knowledge pyridoimidazoquinoline derivatives, except pyrido[2′,1′:2,3]imidazo[4,5-*b*]quinoline (**4a**)[17] and pyrido-[1′,2′:1,2]imidazo[4,5-*b*]quinoline (**7a**)[18] have not been described in the literature yet. So our concise tandem methodologies would allow to access eight hitherto unknown heterocyclic scaffolds of the dipyridoimidazole type.

2. Results and discussion

Starting material **1** is not commercially available and therefore it had to be synthesized first. The synthesis starts with the diazotization of readily available 3-aminoquinoline (**8**) followed by reaction with KI. 3-Iodoquinoline (**9**) is easily transformed into its *N*-oxide (**10**) with *m*-chloroperoxybenzoic acid (Scheme 2). Subsequently, a rearrangement of **10** to 3-iodoquinolin-2(1*H*)-one (**11**) could be obtained through the reaction of **10** with benzoyl chloride and hydroxide. The transformation of **9** to **11** is based on a method of Erickson for the synthesis of 2,3-dichloroquinoline starting from 3-bromoquinoline.[19] Finally, treatment of **11** with $POCl_3$ gave the desired compound **1** in an overall yield of 50% (Scheme 2).[20] It is important to mention that the developed procedure is very efficient as the transformation of 3-iodoquinoline (**9**) into **1** only requires one column chromatographic separation in the last step. Starting material **5** is commercially available.

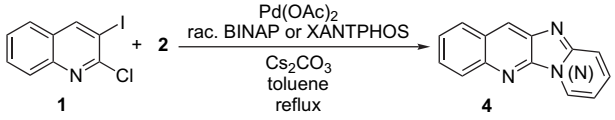
Subsequently, the applicability of **1** as substrate was examined. Using exactly the same reaction conditions as described for the auto-tandem Pd-catalyzed amination of 2-chloro-3-iodopyridine with 2-aminopyridine (**2a**) [$Pd(OAc)_2$, *rac*-BINAP (2,2′-bis(diphenylphosphino)-1,1′-binaphthyl), Cs_2CO_3, toluene, reflux][15] **1** was coupled with **2a**. After a reaction time of 17 h the desired pyrido-[2′,1′:2,3]imidazo[4,5-*b*]quinoline (**4a**) was formed but unfortunately only as minor compound. Mainly **1** and 2-chloro-*N*-(pyridin-2-yl)quinolin-3-amine (**3a**) were observed. The presence of **1** in the reaction mixture was an indication that *rac*-BINAP should be replaced by another ligand for the C–N coupling process. Because we earlier found that XANTPHOS (9,9-dimethyl-4,5-bis(diphenylphosphino)-9*H*-xanthene) is a more general ligand for tandem aminations, we decided to replace *rac*-BINAP by XANTPHOS, keeping the other reaction conditions unchanged.[15,16] Encouragingly, **1** could not be detected anymore in the reaction mixture. Unfortunately, 60% of the intermediate **3a** and only 15% of the desired tetracyclic compound **4a** were obtained. To increase the yield of **4a** the reaction temperature was elevated to 140 °C.[21] Using these modified reaction conditions [$Pd(OAc)_2$, XANTPHOS, Cs_2CO_3, toluene, 140 °C] 82% of **4a** could be isolated. There was no **3a** left in the reaction mixture, but surprisingly a substantial amount of *N*,*N*′-di(pyridin-2-yl)quinolin-2,3-diamine was formed. This competing reaction can be completely suppressed by decreasing the amount of **2a** from the standardly used 1.2 equiv to 1.0 equiv. In this way **4a** was obtained in an excellent yield (96%). The second auto-tandem Pd-catalyzed amination examined was the coupling of **1** with 2-aminoquinoline (**2b**). Gratifyingly, using the original reaction conditions for the coupling of 2-chloro-3-iodopyridine with **2b** [$Pd(OAc)_2$, *rac*-BINAP, Cs_2CO_3, toluene, reflux], 97% of diquino[1,2-*a*:3′,2′-*d*]-imidazole (**4b**) was isolated. The same reaction conditions were then used to perform the coupling with 1-aminoisoquinoline (**2c**) yielding isoquino[1′,2′:2,3]imidazo[4,5-*b*]quinoline (**4c**) in 98%. Reaction of **1** with aminopyrazine (**2d**) gave 81% of pyrazino[2′,1′:2,3]imidazo[4,5-*b*]quinoline (**4d**) and only traces of 2-chloro-*N*-(pyrazin-2-yl)quinolin-3-amine (**3d**) intermediate were left. Auto-tandem Pd-catalyzed amination of **1** with 3-aminopyridazine (**2e**) gave 93% of pyridazino[6′,1′:2,3]imidazo[4,5-*b*]quinoline (**4e**). In this case XANTPHOS was used as ligand as on substrate 2-chloro-3-iodopyridine as reported previously.[15] In conclusion, except for the reaction with 2-aminopyridine (**2a**), **1** can be coupled with all the amino(benzo)(di)azines (**2b**–**2e**) using the reaction conditions earlier developed for the auto-tandem Pd-catalyzed amination on 2-chloro-3-iodopyridine (see Table 1).[15] The desired compounds were isolated in high yields, proving the general applicability of our auto-tandem amination protocol.

Subsequently, 2,3-dibromoquinoline (**5**) was tackled as substrate. The optimized reaction conditions [$Pd_2(dba)_3$, XANTPHOS, CuI, Cs_2CO_3, DME at 140 °C[21]] for the orthogonal tandem amination of 2,3-dibromopyridine with **2** were tested on **5**.[16] For the coupling with **2a** 80% of pyrido[1′,2′:1,2]imidazo[4,5-*b*]quinoline (**7a**) was isolated, neither **5** nor 3-bromo-*N*-(pyridin-2-yl)quinolin-2-amine (**6a**) remained in the reaction mixture. A similar yield was obtained for the synthesis of diquino[1,2-*a*:2′,3′-*d*]imidazole (**7b**) (85%) using **2b** as amidine. The orthogonal tandem amination of **5** with **2c** yielded 90% of isoquino-[2′,1′:1,2]imidazo[4,5-*b*]quinoline (**7c**). Coupling of **5** with **2d** gave pyrazino[1′,2′:1,2]imidazo[4,5-*b*]quinoline (**7d**) in a rather low yield (14%). No remaining **5** or 3-bromo-*N*-(pyrazin-2-yl)quinolin-2-amine (**6d**) could be observed in the reaction mixture. This low yield is not entirely surprising knowing that the coupling of



Scheme 2. Synthesis of 2-chloro-3-iodoquinoline (**1**).

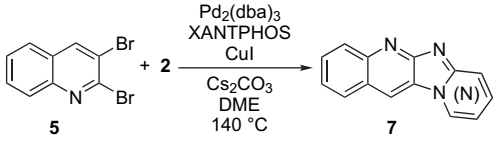
Table 1. Synthesis of pyrido[2′,1′:2,3]imidazo[4,5-*b*]quinoline and its benzo and aza analogs via auto-tandem amination on **1** with amino(benzo)-(di)azines[a]



2	Ligand	3 (%)	4 (%)	4
2a	XANTPHOS	0	96[b,c]	
2b	*rac*-BINAP	0	97	
2c	*rac*-BINAP	0	98	
2d	*rac*-BINAP	Traces	81	
2e	XANTPHOS	0	93	

[a] $Pd(OAc)_2$ (4 mol %), *rac*-BINAP (4 mol %) or XANTPHOS (4 mol %), **1** (1.5 mmol), **2** (1.8 mmol), Cs_2CO_3 (6.0 mmol), toluene (15 mL), reflux, 17 h.
[b] One equivalent of compound **2** was used instead of 1.2 equiv.
[c] Reaction temperature: 140 °C (80 mL pressure tube).[21]

Table 2. Synthesis of pyrido[1′,2′:1,2]imidazo[4,5-*b*]quinoline and its benzo and aza analogs via orthogonal tandem (Pd-catalyst and Cu-catalyst) amination on **5** with amino(benzo)(di)azines[a]



2	Ligand	6 (%)	7 (%)	7
2a	XANTPHOS	0	80	
2b	XANTPHOS	0	85	
2c	XANTPHOS	0	90	
2d	XANTPHOS	0	14	
2e	XANTPHOS	0	70	

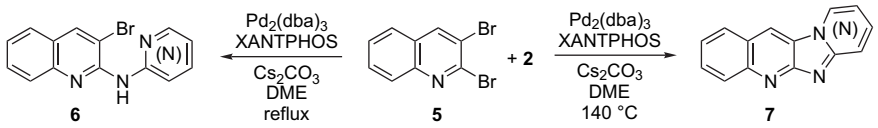
[a] $Pd_2(dba)_3$ (2 mol %), XANTPHOS (4.4 mol %), CuI, **1** (1.5 mmol), **2** (1.8 mmol), Cs_2CO_3 (6.0 mmol), DME (15 mL), reaction temperature: 140 °C (80 mL pressure tube),[21] 24 h.

2,3-dibromopyridine with **2d** yielded only 44% of the corresponding ring closed product pyrido[2′,3′:4,5]imidazo[1,2-*a*]pyrazine. We found that the reason for the low yield is the instability of the intermediate **6d** at 140 °C in the presence of CuI.[22] Finally, the orthogonal tandem amination of **5** with **2e** gave 70% of pyridazino[1′,6′:1,2]imidazo[4,5-*b*]quinoline (**7e**). Neither **5** nor 3-bromo-*N*-(pyridazin-3-yl)-quinolin-2-amine (**6e**) could be detected. In view of these results we can conclude that also the earlier developed orthogonal tandem amination protocol on 2,3-dibromopyridine shows generality and can be extended to 2,3-dibromoquinoline, preserving the good yields (see Table 2).

During the optimization of the tandem inter- and intramolecular amination of 2,3-dibromopyridine with amino(benzo)(di)azines we noticed that, for some amidines, the orthogonal tandem Pd- and Cu-catalyzed amination protocol could be simplified to an auto-tandem Pd-catalyzed protocol. Therefore we decided to investigate whether such an auto-tandem Pd-catalyzed amination would also be feasible when **5** was used as substrate instead of 2,3-dibromopyridine. When the auto-tandem amination conditions developed for the coupling of 2,3-dibromopyridine with **2** [$Pd_2(dba)_3$, XANTPHOS, Cs_2CO_3, DME at 140 °C][16] were used to couple **5** with **2a**, 66% of **6a** and 15% of the desired **7a** was isolated. No remaining **5** was detected. The coupling with **2b** gave no **5**, 10% of intermediate 3-bromo-*N*-(quinolin-2-yl)quinolin-2-amine (**6b**) and 66% of **7b**. We also detected a significant amount of *N*-(quinolin-2-yl)quinolin-2-amine, presumably formed by Pd-catalyzed hydrodebromination of **6b**. The auto-tandem Pd-catalyzed amination of **5** with **2c** yielded 3-bromo-*N*-(isoquinolin-1-yl)quinolin-2-amine (**6c**) in 13% and **7c** in 72%. Compound **7d** could not be synthesized via this auto-tandem Pd-catalyzed amination protocol. The coupling of **5** with **2e** gave 35% of **7e**. Neither **5** nor **6e** could be recovered, but 17% of hydrodebrominated **6e** could be isolated. All the results are summarized in Table 3. Looking at the results presented in Tables 2 and 3, one can easily conclude that the orthogonal tandem protocol on **5** is a generally more suitable methodology to prepare the desired pyrido[1′,2′:1,2]imidazo[4,5:*b*]quinoline and its benzo and aza analogs.

When the auto-tandem Pd-catalyzed inter- and intramolecular amination protocol (2 mol % $Pd_2(dba)_3$, 4.4 mol % XANTPHOS, Cs_2CO_3, DME, 140 °C, 24 h), described in the previous paragraph, was used at a lower temperature (85 °C) the corresponding *N*-(3-bromoquinolin-2-yl)azaheteroarylamines were obtained as the sole reaction products. For **2b**, **2c**, **2d**, and **2e** a loading of 4 mol % Pd-catalyst was sufficient, while for **2a** a double loading was required to get complete conversion of **5** in 7 h. The desired compounds **6** were in all cases obtained in a good yield. The results are presented in Table 3.

Table 3. Attempted auto-tandem Pd-catalyzed inter- and intramolecular amination and Pd-catalyzed intermolecular amination on **5** with amino(benzo)(di)-azines[a]



2	Pd loading (mol %)	Reaction time (h)	Reaction temperature (°C)	5 (%)	6 (%)	7 (%)
2a	4	24	Reflux[b]	9	82	0
2a	8	7	Reflux[b]	Traces	85	0
2a	4	24	140[c]	0	66	15
2b	4	7	Reflux[b]	Traces	87	0
2b	4	24	140[c]	0	10	66
2c	4	7	Reflux[b]	Traces	86	0
2c	4	24	140[c]	0	13	72
2d	4	7	Reflux[b]	Traces	79	0
2d	4	24	140[c]	0	78	0
2e	4	7	Reflux[b]	0	84	0
2e	4	24	140[c]	0	0	35

[a] $Pd_2(dba)_3$ (*x* mol %), XANTPHOS (2.2*x* mol %), **1** (1.5 mmol), **2** (1.8 mmol), Cs_2CO_3 (6.0 mmol), DME (15 mL).
[b] The experiments were carried out in a 100 mL flask.
[c] The experiments were carried out in an 80 mL pressure tube.[21]

3. Conclusion

In this paper we showed that the earlier developed tandem metal-catalyzed aminations on dihalopyridines with amino(benzo)(di)azines can be smoothly extended to dihaloquinolines, namely 2-chloro-3-iodoquinoline (**1**) and 2,3-dibromoquinoline (**5**). Selective C-2 intermolecular Pd-catalyzed amination on **5** can be achieved for all amidines (**2**) if the reaction temperature is controlled. Eight hitherto unknown heteroaromatic skeletons were synthesized.

4. Experimental

4.1. General information

All melting points were determined on a Büchi apparatus and are uncorrected. The ^1H NMR and ^{13}C NMR spectra were obtained on a Bruker Avance II 400 spectrometer with TMS as the internal standard. All coupling constants are given in hertz and the chemical shifts are given in parts per million. Multiplicity is indicated using the following abbreviations: br for broad, d for doublet, t for triplet, m for multiplet and s for singlet. For mass spectrometric analysis, samples were dissolved in CH_3OH containing 0.1% formic acid and diluted to a concentration of approximately 10^{-5} mol/L. Injections (1 μL) were directed to the mass spectrometer at a flow rate of 5 μL/min (CH_3OH and 0.1% formic acid), using a CapLC HPLC system (Waters-Micromass). Accurate mass data were acquired on a Qq-TOF 2 mass spectrometer (Waters-Micromass) equipped with a standard electrospray ionization (ESI) interface. Cone voltage (approx. 35 V) and capillary voltage (approx. 3.3 kV) were optimized on one compound and used for all others. For the determination of the accurate mass of the molecular ion $[M+H]^+$, a solution of polyethylene glycol 300 in CH_3OH/H_2O with 1 mmol ammonium acetate was added just before the mass spectrometer (at a rate of 1 μL/min) to the mobile phase. The calculated masses of PEG $[M+H]^+$ and $[M+NH_4]^+$ ions were used as internal calibrant (lock mass). XANTPHOS (9,9-dimethyl-4,5-bis(diphenylphosphanyl)-9*H*-xanthene) and Cs_2CO_3 (99%) were purchased from Aldrich, $Pd(OAc)_2$, $Pd_2(dba)_3$, and DME from Acros and *rac*-BINAP was obtained from Rhodia. 3-Aminopyridazine was prepared from 3-amino-6-chloropyridazine via hydrogenolysis.[23] All other reagents are obtained from commercial sources and used without extra purification. Flash column chromatography was performed on Kieselgel 60 (ROCC SI 1721, 40–60 μm).

4.1.1. Synthesis of 3-iodoquinoline (9). In a flask of 100 mL 3-aminoquinoline (4.85 mmol, 0.7 g) was dissolved in acetone (7.5 mL) and cooled to −8 °C. To this stirred solution a cold HBF_4 solution (1.2 mL HBF_4 in 1.0 mL acetone) was slowly added. Next a cold isoamyl nitrite solution (1.0 mL isoamyl nitrite in 1.0 mL acetone) was added in small portions to the reaction mixture. The reaction mixture was stirred for 1 h allowing the reaction mixture to reach 10 °C. Subsequently KI (12 mmol, 2.0 g) dissolved in H_2O (2.5 mL) was added to the reaction mixture in small portions and stirred for another 2 h. Next the solvent was evaporated. Water (40 mL) and 3 N NaOH (3 mL) was added to the residue. Then the basic solution was extracted with CH_2Cl_2 (8×40 mL). The organic fractions were combined and washed with saturated $Na_2S_2O_4$ solution (80 mL) and subsequently dried over $MgSO_4$ and evaporated to dryness. The residue was purified by column chromatography using CH_2Cl_2 as eluant.

Yield 1.064 g (86%); white solid; mp: 58 °C; ^1H NMR (400 MHz, $CDCl_3$): δ 9.03 (1H, d, J=1.9 Hz, H_2), 8.51 (1H, d, J=1.9 Hz, H_4), 8.06 (1H, d, J=8.5 Hz, H_8), 7.72 (1H, dd, J=8.5, 6.9 Hz, H_7), 7.69 (1H, d, J=8.2 Hz, H_5), 7.54 (1H, dd, J=8.2, 6.9 Hz, H_6); ^{13}C NMR (100 MHz, $CDCl_3$): δ 155.5, 146.3, 143.6, 129.9, 129.8, 129.4, 127.3, 126.7, 89.8; HRMS (ESI) for C_9H_7IN $[M+H]^+$ calcd 255.9623, found 255.9627.

4.1.2. Synthesis of 2-chloro-3-iodoquinoline (1). In a 100 mL flask *m*-chloroperoxybenzoic acid (4.8 mmol, 1.4 g) was added in portions to a stirred solution of 3-iodoquinoline (4.3 mmol, 1.1 g) in dichloromethane (10 mL) at room temperature. The mixture was stirred overnight

(17 h). Subsequently, saturated $NaHCO_3$ solution (10 mL) was added. After CO_2 evolvement ceases, 3 N NaOH (2 mL) was added. Next the mixture is extracted with dichloromethane (3×30 mL). The combined organic fractions were washed with water (100 mL) and brine (100 mL) and dried over $MgSO_4$. The solvent was removed under reduced pressure.

Benzoyl chloride (8.5 mmol, 1 mL) was added over 10 min to a vigorously stirred mixture of the crude 3-iodoquinoline *N*-oxide (**10**) and sodium hydroxide (11.0 mmol, 0.44 g) in water (12 mL) and dichloromethane (6 mL). When the addition was nearly complete, a vigorous reflux was observed. The flask was cooled in an ice-bath, and addition was resumed. After 1 h stirring the precipitate was filtered off, rinsed well with water (50 mL) and dichloromethane (50 mL) and dried in vacuo.

A mixture of the crude 3-iodoquinolin-2(1*H*)-one (**11**) and $POCl_3$ (3 mmol, 0.28 mL) in toluene (1.2 mL) was stirred for 10 min under a N_2 atmosphere. Subsequently the stirred suspension was heated at reflux for 2 h. Next the reaction mixture was poured onto ice and aq NH_4OH (70 mL) was added. The water phase was extracted with diethyl ether (3×50 mL) and the combined organic layers were washed with water (150 mL) and brine (150 mL). The organic phase was dried over $MgSO_4$. The solvent was evaporated and the crude product was purified by flash column chromatography on silica gel using dichloromethane/heptane (7:3) as the eluant.

To confirm that we prepared **10** and **11**, ^{1}H NMR spectra of the crude reaction products were recorded.

4.1.3. 3-Iodoquinoline *N*-oxide (10). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.75 (1H, s, H_2), 8.66 (1H, d, J=9.0 Hz, H_8), 8.09 (1H, s, H_4), 7.77−7.73 (2H, m, H_5, H_7), 7.64 (1H, dd, J=7.9, 7.1 Hz, H_6).

4.1.4. 3-Iodoquinolin-2(1*H*)-one (11). ^{1}H NMR (400 MHz, $CDCl_3$): δ 12.06 (1H, s, NH), 8.50 (1H, s, H_4), 7.62 (3H, m, H_5, H_6, H_8), 7.26−7.22 (1H, m, H_7).

4.1.5. 2-Chloro-3-iodoquinoline (1). Yield 0.734 g (59%); white solid; mp: 111 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.67 (1H, s, H_4), 7.99 (1H, br d, J=8.5 Hz, H_8), 7.75 (1H, br dd, J=8.5, 6.9 Hz, H_7), 7.72 (1H, br d, J=7.6 Hz, H_5), 7.58 (1H, br dd, J=7.6, 6.9 Hz, H_6); ^{13}C NMR (100 MHz, $CDCl_3$): δ 152.3, 148.6, 146.8, 131.0, 128.5, 128.1, 127.7, 126.4, 90.9; HRMS (ESI) for $C_9H_6Cl_1I_1N_1$ $[M+H]^+$ calcd 289.9233, found 289.9228.

4.2. General procedure for the preparation of pyrido[2′,1′:2,3]imidazo[4,5-*b*]quinoline and its benzo and aza analogs (4) via an auto-tandem inter- and intramolecular Pd-catalyzed amination

A round bottom flask of 50 mL was charged with $Pd(OAc)_2$ (0.06 mmol, 0.013 g, 4 mol %), *rac*-BINAP (0.06 mmol, 0.037 g, 4 mol %) or XANTPHOS (0.06 mmol, 0.035 g, 4 mol %) and toluene (5 mL). The obtained mixture was flushed with N_2 for 10 min under magnetic stirring. Meanwhile a round-bottomed flask of 100 mL was charged with 2-chloro-3-iodoquinoline (**1**) (1.5 mmol, 0.359 g), amidine (**2**) (1.8 mmol), and Cs_2CO_3 (6.0 mmol, 1.955 g). To this mixture, the preformed Pd-catalyst was added under an N_2 flow. The 50 mL flask was subsequently rinsed with 2×5 mL toluene. Then the resulting mixture was flushed with N_2 for 5 min and heated for 17 h at reflux (N_2 atmosphere). After cooling down to room temperature, toluene was removed by evaporation. Silica gel (1.5 g) was mixed with the crude product. This solid mixture was brought on top of a silica gel column and eluted with dichloromethane/methanol (99:1).

4.2.1. Pyrido[2′,1′:2,3]imidazo[4,5-*b*]quinoline (4a). The general procedure was followed using $Pd(OAc)_2$ (0.06 mmol, 0.013 g, 4 mol %), XANTPHOS (0.06 mmol, 0.035 g, 4 mol %), and 2-aminopyridine (**2a**) (1.5 mmol, 0.141 g). The oil bath temperature was 160 °C. Yield 0.316 g (96%); yellow solid; mp: 189 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.95 (1H, d, J=6.8 Hz, H_{11}), 8.65 (1H, s, H_6), 8.25 (1H, d, J=8.6 Hz, H_2), 8.10 (1H, d, J=8.3 Hz, H_5), 7.77−7.72 (2H, m, H_3, H_8), 7.63 (1H, dd, J=9.2, 6.6 Hz, H_9), 7.59 (1H, dd, J=8.3, 6.9 Hz, H_4), 6.95 (1H, dd, J=6.8, 6.6 Hz, H_{10}); ^{13}C NMR (100 MHz, $CDCl_3$): δ 151.3, 144.3 143.9, 135.0, 134.0, 128.4 (2Cs), 128.3, 128.2, 125.8, 125.2, 124.5, 117.8, 110.6; HRMS (ESI) for $C_{14}H_{10}N_3$ $[M+H]^+$ calcd 220.0875, found 220.0871.

4.2.2. Diquino[1,2-*a*:3′,2′-*d*]imidazole (4b). The general procedure was followed using $Pd(OAc)_2$ (0.06 mmol, 0.013 g, 4 mol %), *rac*-BINAP (0.06 mmol, 0.037 g, 4 mol %), and 2-aminoquinoline (**2b**) (1.8 mmol, 0.259 g). Yield 0.391 g (97%); yellow solid; mp: 188 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.23 (1H, d, J=8.1 Hz, H_{13}), 8.65 (1H, s, H_6), 8.37 (1H, d, J=8.6 Hz, H_2), 8.10 (1H, d, J=8.3 Hz, H_5), 7.87 (1H, ddd, J=8.1, 7.1, 1.4 Hz, H_{12}), 7.82 (2H, br d, J=9.2 Hz, not resolved, H_{10}, H_9 or H_8), 7.78 (1H, dd, J=8.6, 6.8 Hz, H_3), 7.60 (1H, dd, J=8.3, 6.8 Hz, H_4), 7.56 (1H, br d, J=9.6 Hz, H_8 or H_9), 7.52 (1H, br t, J=7.5 Hz, not resolved, H_{11}); ^{13}C NMR (100 MHz, $CDCl_3$): δ 151.7, 147.7, 144.6, 136.3, 135.6, 134.8, 130.7, 128.9, 128.6, 128.3, 128.0, 126.9, 124.8, 124.7 (2Cs), 122.6, 117.8, 117.4; HRMS (ESI) for $C_{18}H_{12}N_3$ $[M+H]^+$ calcd 270.1031, found 270.1037.

4.2.3. Isoquino[1′,2′:2,3]imidazo[4,5-*b*]quinoline (4c). The general procedure was followed using $Pd(OAc)_2$ (0.06 mmol, 0.013 g, 4 mol %), *rac*-BINAP (0.06 mmol, 0.037 g, 4 mol %), and 1-aminoisoquinoline (**2c**) (1.8 mmol, 0.259 g). Yield 0.395 g (98%); brown solid; mp: 277 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.85 (1H, d, J=7.9 Hz, H_1 or H_4), 8.67 (1H, s, H_{13}), 8.64 (1H, d, J=7.3 Hz, H_6), 8.26 (1H, d, J=8.5 Hz, H_9), 8.11 (1H, br d, J=8.2 Hz, H_{12}), 7.80−7.70 (4H, m, H_4 or H_1, H_2, H_3, H_{10}), 7.58 (1H, ddd, J=8.2, 6.8, 1.1 Hz, H_{11}), 7.11 (1H, d, J=7.3 Hz, H_5); ^{13}C NMR (100 MHz, $CDCl_3$): δ 151.4, 145.4, 144.5, 135.8, 133.5, 131.6, 128.6, 128.4, 128.2, 128.1, 127.7, 127.4, 125.5, 124.8, 124.7, 123.3, 121.1, 111.3; HRMS (ESI) for $C_{18}H_{12}N_3$ $[M+H]^+$ calcd 270.1031, found 270.1038.

4.2.4. Pyrazino[2′,1′:2,3]imidazo[4,5-*b*]quinoline (4d). The general procedure was followed using $Pd(OAc)_2$ (0.06 mmol, 0.013 g, 4 mol %), *rac*-BINAP (0.06 mmol,

0.037 g, 4 mol %), and aminopyrazine (**2d**) (1.8 mmol, 0.171 g). Yield 0.267 g (81%); yellow solid; mp: 246 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.33 (1H, d, J=1.6 Hz, H_1), 8.84 (1H, s, H_{11}), 8.77 (1H, dd, J=4.6, 1.6 Hz, H_3), 8.28 (1H, br d, J=8.6 Hz, H_7), 8.14 (1H, dd, J=8.4, 1.2 Hz, H_{10}), 8.04 (1H, d, J=4.6 Hz, H_4), 7.82 (1H, ddd, J=8.6, 6.7, 1.2 Hz, H_8), 7.63 (1H, br dd, J=8.4, 6.7 Hz, H_9); ^{13}C NMR (100 MHz, $CDCl_3$): δ 146.6, 145.4, 144.7, 142.8, 135.5, 129.3, 128.7, 128.6, 128.5, 127.7, 126.9, 125.6, 117.6; HRMS (ESI) for $C_{13}H_9N_4$ $[M+H]^+$ calcd 221.0827, found 221.0832.

4.2.5. Pyridazino[6′,1′:2,3]imidazo[4,5-*b*]quinoline (4e). The general procedure was followed using $Pd(OAc)_2$ (0.06 mmol, 0.013 g, 4 mol %), XANTPHOS (0.06 mmol, 0.035 g, 4 mol %), and 3-aminopyridazine (**2e**) (1.8 mmol, 0.171 g). Yield 0.307 g (93%); brown solid; mp: 199 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.76 (1H, s, H_{11}), 8.52 (1H, dd, J=4.0, 1.4 Hz, H_3), 8.42 (1H, d, J=8.6 Hz, H_7), 8.12 (1H, d, J=8.3 Hz, H_{10}), 8.06 (1H, dd, J=9.6, 1.4 Hz, H_1), 7.80 (1H, dd, J=8.6, 6.8 Hz, H_8), 7.61 (1H, dd, J=8.3, 6.8 Hz, H_9), 7.40 (1H, dd, J=9.6, 4.0 Hz, H_2); ^{13}C NMR (100 MHz, $CDCl_3$): δ 146.7, 145.5, 144.2, 141.7, 134.6, 129.1, 128.9, 128.4, 128.2, 127.0, 126.6, 125.3, 124.6; HRMS (ESI) for $C_{13}H_9N_4$ $[M+H]^+$ calcd 221.0827, found 221.0832.

4.3. General procedure for the synthesis of pyrido-[1′,2′:1,2]imidazo[4,5-*b*]quinoline and its benzo and aza analogs via an orthogonal tandem intermolecular Pd- and intramolecular Cu-catalyzed amination

A round-bottomed flask of 50 mL was charged with $Pd_2(dba)_3$ (0.030 mmol, 0.028 g, 2.0 mol %), XANTPHOS (0.066 mmol, 0.038 g, 4.4 mol %), and DME (5 mL). The obtained mixture was flushed with N_2 for 10 min under magnetic stirring. Meanwhile a pressure tube of 80 mL was charged with CuI (0.15 mmol, 0.028 g, 10 mol %), 2,3-dibromoquinoline (**5**) (1.5 mmol, 0.355 g), amidine (**2**) (1.8 mmol), and cesium carbonate (6.0 mmol, 1.955 g). To this mixture, the preformed Pd-catalyst was added under an N_2 flow. The 50 mL flask was subsequently rinsed with 2×5 mL DME. Then the resulting mixture was flushed with N_2 for 5 min, sealed, and heated (oil bath temperature: 160 °C) under vigorous magnetic stirring for 24 h. After cooling down to room temperature, DME was removed by evaporation. Silica gel (1.5 g) was mixed with the crude product. This solid mixture was brought on top of a silica gel column and eluted with dichloromethane/methanol (97:3).

4.3.1. Pyrido[1′,2′:1,2]imidazo[4,5-*b*]quinoline (7a). The general procedure was followed using 2-aminopyridine (**2a**) (1.8 mmol, 0.169 g). Yield 0.263 g (80%); yellow solid; mp: 294 °C (decomp.), ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.62 (1H, s, H_6), 8.56 (1H, d, J=6.8 Hz, H_8), 8.33 (1H, d, J=8.7 Hz, H_2), 8.03 (1H, d, J=8.2 Hz, H_5), 7.79 (1H, d, J=9.3 Hz, H_{11}), 7.77 (1H, dd, J=8.7, 6.8 Hz, H_3), 7.60 (1H, dd, J=9.3, 6.8 Hz, H_{10}), 7.53 (1H, dd, J=8.2, 6.8 Hz, H_4), 6.92 (1H, t, J=6.8 Hz, H_9); ^{13}C NMR (100 MHz, $CDCl_3$): δ 157.2, 153.7, 148.5, 133.1, 129.4, 128.9, 127.9, 126.7, 124.3, 123.7, 122.2, 118.4, 116.5, 110.6; HRMS (ESI) for $C_{14}H_{10}N_3$ $[M+H]^+$ calcd 220.0875, found 220.0864.

4.3.2. Diquino[1,2-a;2′,3′-*d*]imidazole (7b). The general procedure was followed using 2-aminoquinoline (**2b**) (1.8 mmol, 0.259 g). Yield 0.343 g (85%); brown solid; mp: 237 °C, ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.95 (1H, s, H_6), 8.51 (1H, d, J=8.3 Hz, H_8), 8.30 (1H, d, J=8.5 Hz, H_2), 8.05 (1H, d, J=8.2 Hz, H_5), 7.83 (2H, m, H_9, H_{11}), 7.82 (1H, d, J=9.5 Hz, H_{12}), 7.73 (1H, dd, J=8.5, 6.7 Hz, H_3), 7.68 (1H, d, J=9.5 Hz, H_{13}), 7.54 (1H, dd, J=8.2, 6.7 Hz, H_4), 7.51 (1H, dd, J=7.8, 7.5 Hz, H_{10}); ^{13}C NMR (100 MHz, $CDCl_3$): 157.2, 153.8, 146.8, 135.8, 134.6, 130.8, 130.1, 129.1, 128.7, 128.0, 124.7, 124.6 (2Cs), 123.8, 123.0, 119.7, 117.7, 114.8; HRMS (ESI) for $C_{18}H_{12}N_3$ $[M+H]^+$ calcd 270.1031, found 270.1038.

4.3.3. Isoquino[2′,1′:1,2]imidazo[4,5-*b*]quinoline (7c). The general procedure was followed using 1-aminoisoquinoline (**2c**) (1.8 mmol, 0.259 g). Yield 0.363 g (90%); brown solid; mp: 304 °C (decomp.); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.97 (1H, d, J=6.9 Hz, H_1 or H_4), 8.51 (1H, s, H_8), 8.34 (1H, d, J=8.6 Hz, H_{12}), 8.22 (1H, d, J=7.3 Hz, H_6), 8.03 (1H, d, J=8.3 Hz, H_9), 7.78−7.72 (4H, m, H_4 or H_1, H_2, H_3, H_{11}), 7.54 (1H, br dd, J=8.3, 6.7 Hz, H_{10}), 7.12 (1H, d, J=7.3 Hz, H_5); ^{13}C NMR (100 MHz, $CDCl_3$): δ 157.1, 153.4, 147.6, 132.7, 131.8, 129.5, 128.7, 128.4, 127.7, 127.1, 126.8, 124.5, 124.4, 123.3, 123.0, 121.6, 115.4, 111.5; HRMS (ESI) for $C_{18}H_{12}N_3$ $[M+H]^+$ calcd 270.01031, found 270.1029.

4.3.4. Pyrazino[1′,2′:1,2]imidazo[4,5-*b*]quinoline (7d). The general procedure was followed using aminopyrazine (**2d**) (1.8 mmol, 0.171 g). Yield 0.046 g (14%); yellow solid; mp: 338 °C (decomp.); ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.46 (1H, d, J=1.5 Hz, H_4), 8.81 (1H, s, H_{11}), 8.46 (1H, dd, J=4.6, 1.5 Hz, H_2), 8.39 (1H, d, J=8.8 Hz, H_7), 8.11 (1H, d, J=8.2 Hz, H_{10}), 8.10 (1H, d, J=4.6 Hz, H_1), 7.85 (1H, br dd, J=8.8, 6.7 Hz, H_8), 7.62 (1H, br dd, J=8.2, 6.7, H_9); ^{13}C NMR (100 MHz, $CDCl_3$): δ 155.9, 149.6, 146.4, 146.1, 129.8, 129.7, 128.0, 127.4, 125.4, 124.6, 120.9, 118.8, 118.2; HRMS (ESI) for $C_{13}H_9N_4$ $[M+H]^+$ calcd 221.0827, found 221.0832.

4.3.5. Pyridazino[1′,6′:1,2]imidazo[4,5-*b*]quinoline (7e). The general procedure was followed using 3-aminopyridazine (**2e**) (1.8 mmol, 0.171 g). Yield 0.231 g (70%); brown solid; mp: 217 °C (decomp.); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.94 (1H, s, H_{11}), 8.45 (1H, dd, J=4.1, 1.3 Hz, H_2), 8.36 (1H, d, J=8.7 Hz, H_7), 8.16 (1H, dd, J=9.5, 1.3 Hz, H_4), 8.11 (1H, br d, J=8.2 Hz, H_{10}), 7.81 (1H, dd, J=8.7, 6.7 Hz, H_8), 7.58 (1H, dd, J=8.2, 6.7 Hz, H_9), 7.43 (1H, dd, J=9.5, 4.1 Hz, H_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ 154.9, 148.9, 148.3, 141.1, 129.5, 129.2, 128.3, 126.5, 124.9, 124.8, 124.4, 123.3, 118.4; HRMS (ESI) for $C_{13}H_9N_4$ $[M+H]^+$ calcd 221.0827, found 221.0817.

4.4. General procedure for the synthesis of pyrido-[1′,2′:1,2]imidazo[4,5-*b*]quinoline and its benzo and aza analogs via an auto-tandem inter- and intramolecular Pd-catalyzed amination

A round-bottomed flask of 50 mL was charged with $Pd_2(dba)_3$ (0.030 mmol, 0.028 g, 2.0 mol %), XANTPHOS (9,9-dimethyl-4,5-bis(diphenylphosphanyl)-9*H*-xanthene) (0.066 mmol, 0.038 g, 4.4 mol %), and DME (5 mL). The

obtained mixture was flushed with N_2 for 10 min under magnetic stirring. Meanwhile a pressure tube of 80 mL was charged with 2,3-dibromoquinoline (**5**) (1.5 mmol, 0.355 g), amidine (**2**) (1.8 mmol), and cesium carbonate (6.0 mmol, 1.955 g). To this mixture, the preformed Pd-catalyst was added under an N_2 flow. The 50 mL flask was subsequently rinsed with 2×5 mL DME. Then the resulting mixture was flushed with N_2 for 5 min, sealed, and heated (oil bath temperature: 160 °C) under vigorous magnetic stirring for 24 h. After cooling down to room temperature, DME was removed by evaporation. Silica gel (1.5 g) was mixed with the crude product. This solid mixture was brought on top of a silica gel column and eluted with dichloromethane/methanol (97:3).

4.4.1. Pyrido[1′,2′:1,2]imidazo[4,5-*b*]quinoline (7a). The general procedure was followed using 2-aminopyridine (**2a**) (1.8 mmol, 0.169 g). Yield 0.051 g (15%).

4.4.2. Diquino[1,2:*a*;2′,3′:*d*]imidazole (7b). The general procedure was followed using 2-aminoquinoline (**2b**) (1.8 mmol, 0.259 g). Yield 0.266 g (66%).

4.4.3. Isoquino[2′,1′:1,2]imidazo[4,5-*b*]quinoline (7c). The general procedure was followed using 1-aminoisoquinoline (**2c**) (1.8 mmol, 0.259 g). Yield 0.291 g (72%).

4.4.4. Pyrazino[1′,2′:1,2]imidazo[4,5-*b*]quinoline (7d). The general procedure was followed using aminopyrazine (**2d**) (1.8 mmol, 0.171 g). Yield 0.0 g (0%).

4.4.5. Pyridazino[1′,6′:1,2]imidazo[4,5-*b*]quinoline (7e). The general procedure was followed using 3-aminopyridazine (**2e**) (1.8 mmol, 0.171 g). Yield 0.116 g (35%).

4.5. General procedure for the synthesis of 3-bromo-*N*-(azaheteroaryl)quinolin-2-amines

A round-bottomed flask of 50 mL was charged with $Pd_2(dba)_3$ (0.030 mmol, 0.028 g, 2.0 mol %), XANTPHOS (9,9-dimethyl-4,5-bis(diphenylphosphanyl)-9*H*-xanthene) (0.066 mmol, 0.038 g, 4.4 mol %), and DME (5 mL). The obtained mixture was flushed with N_2 for 10 min under magnetic stirring. Meanwhile a round-bottomed flask of 100 mL was charged with 2,3-dibromoquinoline (**5**) (1.5 mmol, 0.355 g), amidine (**2**) (1.8 mmol), and cesium carbonate (6.0 mmol, 1.955 g). To this mixture, the preformed Pd-catalyst was added under an N_2 flow. The 50 mL flask was subsequently rinsed with 2×5 mL DME. Then the resulting mixture was flushed with N_2 for 5 min and heated at reflux (oil bath temperature: 95 °C) (N_2 atmosphere) under vigorous magnetic stirring for 7 h. After cooling down to room temperature, DME was removed by evaporation. Silica gel (1.5 g) was mixed with the crude product. This solid mixture was brought on top of a silica gel column and eluted with dichloromethane/methanol (99:1).

4.5.1. 3-Bromo-*N*-(pyridin-2-yl)quinolin-2-amine (6a). The general procedure was followed using $Pd_2(dba)_3$ (0.060 mmol, 0.056 g, 4.0 mol %), XANTPHOS (0.132 mmol, 0.076 g, 8.8 mol %), and 2-aminopyridine (**2a**) (1.8 mmol, 0.169 g). Yield 0.384 g (85%); yellow solid; mp: 119 °C; ^{1}H NMR (400 MHz, $CDCl_3$): 8.89 (1H, d, J=8.3 Hz, $H_{3'}$), 8.32 (1H, dd, J=4.9, 1.9 Hz, $H_{6'}$), 8.26 (1H, s, H_4), 8.19 (1H, s, NH), 7.87 (1H, d, J=8.5 Hz, H_8), 7.78 (1H, ddd, J=8.3, 7.3, 1.9 Hz, $H_{4'}$), 7.65 (1H, dd, J=8.5, 6.9 Hz, H_7), 7.62 (1H, d, J=7.9 Hz, H_5), 7.36 (1H, dd, J=7.9, 6.9 Hz, H_6), 6.99 (1H, dd, J=7.3, 4.9 Hz, $H_{5'}$); ^{13}C NMR (100 MHz, $CDCl_3$): 152.8, 148.2, 147.8, 145.7, 139.6, 138.0, 130.1, 127.0, 126.5, 125.2, 124.4, 118.1, 112.9, 108.2; HRMS (ESI) for $C_{14}H_{11}N_3Br$ $[M+H]^+$ calcd 300.0136, found 300.0144.

4.5.2. 3-Bromo-*N*-(quinolin-2-yl)quinolin-2-amine (6b). The general procedure was followed using 2-aminoquinoline (**2b**) (1.8 mmol, 0.259 g). Yield: 0.458 g (87%); yellow solid; mp: 146 °C; ^{1}H NMR (400 MHz, $CDCl_3$): 9.06 (1H, d, J=8.7 Hz, $H_{4'}$), 8.43 (1H, s, NH), 8.32 (1H, s, H_4), 8.24 (1H, d, J=8.7 Hz, $H_{3'}$), 7.93−7.88 (2H, m, H_8, $H_{8'}$), 7.81 (1H, d, J=7.9 Hz, $H_{5'}$), 7.71−7.60 (3H, m, H_7, $H_{7'}$, H_5), 7.45−7.39 (2H, m, $H_{6'}$, H_6); ^{13}C NMR (100 MHz, $CDCl_3$): 152.4, 148.4, 147.2, 145.7, 139.9, 137.9, 130.2, 129.8, 127.5, 127.2, 126.6 (2Cs), 125.8, 125.4, 124.6, 124.3, 114.1, 108.3; HRMS (ESI) for $C_{18}H_{13}N_3Br$ $[M+H]^+$ calcd 350.0293, found 350.0280.

4.5.3. 3-Bromo-*N*-(isoquinolin-1-yl)quinolin-2-amine (6c). The general procedure was followed using 1-aminoisoquinoline (**2c**) (1.8 mmol, 0.259 g). Yield 0.453 g (86%); orange solid; mp: 139 °C; ^{1}H NMR (400 MHz, $CDCl_3$): 15.93 (1H, s, NH), 9.01 (1H, m, H_8), 8.32 (1H, s, H_4), 7.76 (1H, d, J=8.7 Hz, $H_{5'}$ or $H_{8'}$), 7.67 (1H, dd, J=7.2, 6.8 Hz, H_7), 7.61−7.57 (4H, m, H_5, $H_{5'}$ or $H_{8'}$, $H_{6'}$, $H_{7'}$), 7.45 (1H, m, $H_{3'}$ or $H_{4'}$), 7.33 (1H, dd, J=7.8, 7.2 Hz, H_6), 6.82 (1H, br d, J=6.7 Hz, $H_{4'}$ of $H_{3'}$); ^{13}C NMR (100 MHz, $CDCl_3$): 156.9, 154.3, 144.0, 139.2, 137.3, 137.0, 136.4, 131.7, 129.4, 127.7, 127.5, 127.3, 126.5, 125.9, 125.0, 124.1, 119.2, 110.1; HRMS (ESI) for $C_{18}H_{13}N_3Br$ $[M+H]^+$ calcd 350.0293, found 350.0299.

4.5.4. 3-Bromo-*N*-(pyrazin-2-yl)quinolin-2-amine (6d). The general procedure was followed using aminopyrazine (**2d**) (1.8 mmol, 0.171 g). Yield: 0.357 g (79%); yellow solid; mp: 134 °C; ^{1}H NMR (400 MHz, $CDCl_3$): 10.24 (1H, d, J=1.3 Hz, $H_{3'}$), 8.30 (3H, m, H_4, $H_{5'}$, $H_{6'}$), 8.11 (1H, br s, NH), 7.91 (1H, d, J=8.4 Hz, H_8), 7.68 (1H, dd, J=8.4, 7.1 Hz, H_7), 7.65 (1H, d, J=7.9 Hz, H_5), 7.40 (1H, dd, J=7.9, 7.1 Hz, H_6); ^{13}C NMR (100 MHz, $CDCl_3$): 149.5, 147.4, 145.6, 142.0, 140.0, 138.5, 136.3, 130.5, 127.3, 126.5, 125.5, 124.9, 107.5; HRMS (ESI) for $C_{13}H_{10}N_4Br$ $[M+H]^+$ calcd 301.0089, found 301.0089.

4.5.5. 3-Bromo-*N*-(pyridazin-3-yl)quinolin-2-amine (6e). The general procedure was followed using aminopyridazine (**2e**) (1.8 mmol, 0.171 g). Yield: 0.379 g (84%); yellow solid; mp: 158 °C; ^{1}H NMR (400 MHz, $CDCl_3$): 9.10 (1H, br d, J=9.1 Hz, $H_{4'}$), 8.88 (1H, br d, J=4.6 Hz, $H_{6'}$), 8.65 (1H, br s, NH), 8.29 (1H, s, H_4), 7.84 (1H, d, J=8.4 Hz, H_8), 7.65 (1H, br dd, J=8.4, 6.9 Hz, H_7), 7.63 (1H, d, J=8.2 Hz, H_5), 7.51 (1H, dd, J=9.1, 4.6 Hz, $H_{5'}$), 7.39 (1H, br dd, J=8.2, 6.9 Hz, H_6); ^{13}C NMR (100 MHz, $CDCl_3$): 156.5, 148.0, 147.1, 145.4, 140.1, 120.4, 127.7, 127.0, 126.6, 125.5, 124.9, 117.5, 108.0; HRMS (ESI) for $C_{13}H_{10}N_4Br$ $[M+H]^+$ calcd 301.0089, found 301.0089.

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References and notes

1. Muci, A. R.; Buchwald, S. L. *Top. Curr. Chem.* **2002**, *219*, 131.
2. Schlummer, B.; Scholz, U. *Adv. Synth. Catal.* **2004**, *346*, 1599.
3. Guram, A. S.; Rennels, R. A.; Buchwald, S. L. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 1348.
4. Louie, J.; Hartwig, J. F. *Tetrahedron Lett.* **1995**, *36*, 3609.
5. Hartwig, J. F. *Synlett* **2006**, 1283.
6. Littke, A. F.; Fu, G. C. *Angew. Chem., Int. Ed.* **2002**, *41*, 4176.
7. Buchwald, S. L.; Mauger, C.; Mignani, G.; Scholz, U. *Adv. Synth. Catal.* **2006**, *348*, 23.
8. Beletskaya, I. P.; Cheprakov, A. V. *Coord. Chem. Rev.* **2004**, *248*, 2337.
9. Ley, S. V.; Thomas, A. W. *Angew. Chem., Int. Ed.* **2003**, *42*, 5400.
10. For taxonomy of tandem catalysis see: Fogg, D. E.; dos Santos, E. N. *Coord. Chem. Rev.* **2004**, *248*, 2365.
11. (a) Nozaki, K.; Takahashi, K.; Nakano, K.; Hiyama, T.; Tang, H. Z.; Fujiki, M.; Yamaguchi, S.; Tamao, K. *Angew. Chem., Int. Ed.* **2003**, *42*, 2051; (b) Nakano, K.; Hidehira, Y.; Takahashi, K.; Hiyama, T.; Nozaki, K. *Angew. Chem., Int. Ed.* **2005**, *44*, 7136; (c) Kuwahara, A.; Nakano, K.; Nozaki, K. *J. Org. Chem.* **2005**, *70*, 413.
12. (a) Kitawaki, T.; Hayashi, Y.; Chida, N. *Heterocycles* **2005**, *65*, 1561; (b) Kitawaki, T.; Hayashi, Y.; Ueno, A.; Chida, N. *Tetrahedron* **2006**, *62*, 6792.
13. Koeckelberghs, G.; De Cremer, L.; Vanormelingen, W.; Dehaen, W.; Verbiest, T.; Persoons, A.; Samyn, C. *Tetrahedron* **2005**, *61*, 687.
14. (a) Willis, M. C.; Brace, G. N.; Holmes, I. P. *Angew. Chem., Int. Ed.* **2005**, *44*, 403; (b) Willis, M. C.; Brace, G. N.; Findlay, T. J. K.; Holmes, I. P. *Adv. Synth. Catal.* **2006**, *348*, 851.
15. Loones, K. T. J.; Maes, B. U. W.; Dommisse, R. A.; Lemière, G. L. F. *Chem. Commun.* **2004**, 2466.
16. Loones, K. T. J.; Maes, B. U. W.; Meyers, C.; Deruytter, J. *J. Org. Chem.* **2006**, *71*, 260.
17. Abramovitch, R. A.; Hey, D. H. *J. Chem. Soc. C* **1966**, *12*, 1095.
18. Desbois, N.; Chezal, J. M.; Fauvelle, F.; Debouzy, J. C.; Lartigue, C.; Gueiffier, A.; Blache, Y.; Moreau, E.; Madelmont, J. C.; Chavignon, O.; Teulade, J. C. *Heterocycles* **2005**, *65*, 1121.
19. Sabol, M. R.; Owen, J. M.; Erickson, W. R. *Synth. Commun.* **2000**, *30*, 427.
20. (a) For other methods published to prepare **1** see: Marsais, F.; Godard, A.; Quéguiner, G. *J. Heterocycl. Chem.* **1989**, *26*, 1589; (b) Hong, C. S.; Seo, J. Y.; Yum, E. K.; Sung, N. *Heterocycles* **2004**, *63*, 631; (c) Arrington, K.; Fraley, M.; Hartman, G. Patent no: WO2003037252, 2003.
21. Temperature measured inside the vessel (fiber optic probe). Oil bath temperature: 160 °C. For more information see: Ref. 16.
22. A test reaction was carried out in which intermediate **6d** was heated for 24 h at 140 °C in the presence of CuI and cesium carbonate. After analysis of the reaction mixture only traces of **6d** and **7d** could be detected. The reaction mixture had a black color so we assume that **6d** decomposed at this high temperature.
23. Turck, A.; Plé, N.; Ndzi, B.; Quéguiner, G.; Haider, N.; Schuller, H.; Heinisch, G. *Tetrahedron Lett.* **1993**, *34*, 161.