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Synthesis of new tetracyclic azaheteroaromatic cores via auto-tandem Pd-catalyzed and one-pot Pd- and Cu-catalyzed double C–N bond formation

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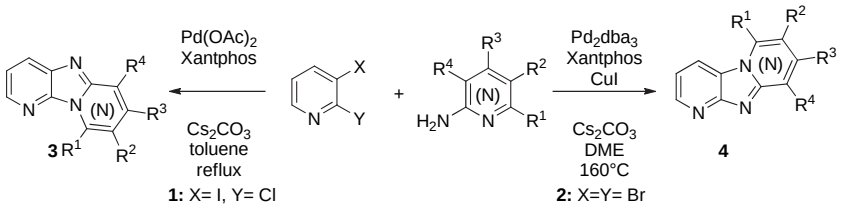
ABSTRACT

Inter- and intramolecular transition metal-catalyzed amination of 2-chloro-3-iodopyridine and 2,3-dibromopyridine, respectively, with benzodiazinamines yielded six hitherto unknown tetracyclic azaheteroaromatic cores. C–N bond formation was achieved via auto-tandem (Pd-catalyst) as well as one-pot (sequential use of a Pd- and Cu-catalyst) catalysis.

1. Introduction

Aryl amines are important entities with several important applications (pharmaceuticals, agrochemicals, polymers and materials for the electronics and xerographic industry).[1–6] The most important method available to synthesize these aryl amines is the Pd-catalyzed amination, autonomously discovered by the groups of Buchwald and Hartwig in the mid 1990s.[7,8] Over the years the Buchwald–Hartwig reaction has made tremendous progress, especially by the refinement of the ligands.[9–16] More recently a revival of the Cu-catalyzed amination has occurred via the introduction of ligands through which the harsh reaction conditions, required for the Ullmann-type C–N bond formation, could be avoided.[6,17–21] Meanwhile, Pd- and Cu-catalyzed aminations have been used to construct nitrogen-containing heterocyclic skeletons.[22–27] One of the challenges in this research field is the development of tandem or one-pot metal-catalyzed protocols for scaffold design in which several bonds can be formed in one reaction step.[28,29] Using such processes relatively complex heterocyclic structures can be obtained starting from easily available building blocks. In 2004 our group reported the first regioselective auto-tandem inter- and intramolecular Pd-catalyzed double amination of 2-chloro-3-iodopyridine (**1**) with a set of benzoazinamines and (di)azinamines (Scheme 1).[30–32] More recently, regioisomers (**4**) of dipyrido[1,2-*a*:3′,2′-*d*]imidazole and its benzo and aza analogues (**3**) were obtained via an orthogonal (Pd- and Cu-catalyst) regioselective inter- and intramolecular double amination on 2,3-dibromopyridine (**2**) (Scheme 1).[31,33]



Scheme 1. Schematic overview of previously reported auto-(left) and orthogonal (right) tandem double aminations.

In this article we report a further exploration of the scope of the transition metal-catalyzed double amination of dihalopyridines

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using hitherto unexplored benzodiazinamines (phtalazin-1-amine (**5a**), quinazolin-4-amine (**5b**) and quinoxalin-2-amine (**5c**)) as coupling partners.

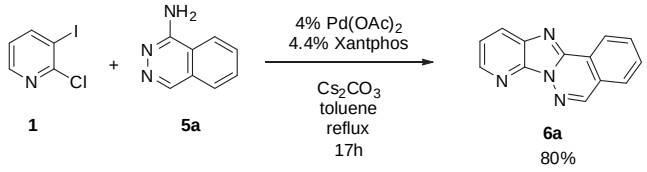
2. Results and discussion

2.1. Synthesis of the benzodiazinamines (5)

The required benzodiazinamines phtalazin-1-amine (**5a**), quinazolin-4-amine (**5b**) and quinoxalin-2-amine (**5c**) were not commercially available and thus had to be synthesized. Compound **5a** was obtained by dehalogenation of 4-chlorophtalazin-1-amine, **5b** via ONSH (oxidative nucleophilic substitution of hydrogen) on quinazoline with liquid ammonia in the presence of $KMnO_4$ as oxidant[34] and **5c** via aminolysis of 2-chloroquinoxaline.

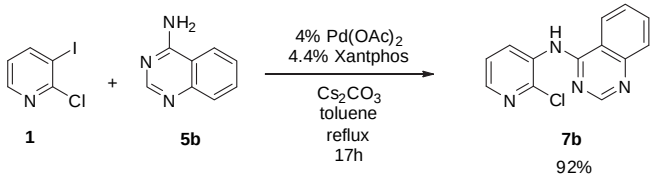
2.2. Transition metal-catalyzed double amination of 2-chloro-3-iodopyridine (1) with benzodiazinamines (5)

The previously developed reaction conditions for the auto-tandem Pd-catalyzed double amination of 2-chloro-3-iodopyridine (**1**) with (di)azinamines and benzoazinamines (4% $Pd(OAc)_2$, 4.4% Xantphos, 4 equiv Cs_2CO_3, toluene, reflux)[30] were applied for benzodiazinamine **5a**. The desired pyrido[3′,2′:4,5]imidazo[2,1-*a*]phthalazine (**6a**) scaffold could be obtained in 80% yield (Scheme 2). Based on the reaction of **1** with isoquinolin-1-amine previously reported by us, a ring closure mechanism involving a S_NAr rather than a transition metal-catalyzed C–N bond formation for the intramolecular amination cannot be excluded.[35]



Scheme 2. Auto-tandem Pd-catalyzed double amination on 2-chloro-3-iodopyridine (**1**) using phtalazin-1-amine (**5a**).

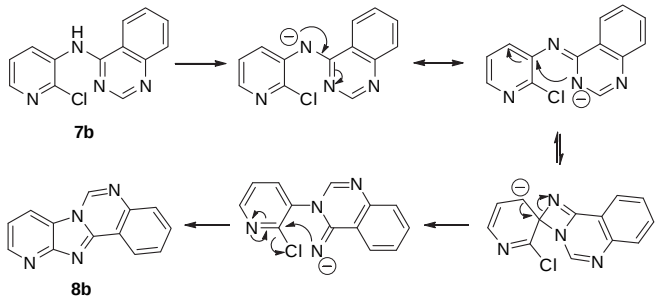
However, applying the same reaction conditions for the coupling of **1** with **5b**, no pyrido[3′,2′:4,5]imidazo[1,2-*c*]quinazoline (**6b**) was formed. Instead, 92% of *N*-(2-chloropyridin-3-yl)quinazolin-4-amine (**7b**) was isolated (Scheme 3). Neither an increase of the loading of Pd from 4 to 6% nor the changing of the Pd/ligand ratio to 1:2 did affect the outcome.



Scheme 3. Attempted auto-tandem Pd-catalyzed double amination on 2-chloro-3-iodopyridine (**1**) using quinazolin-4-amine (**5b**).

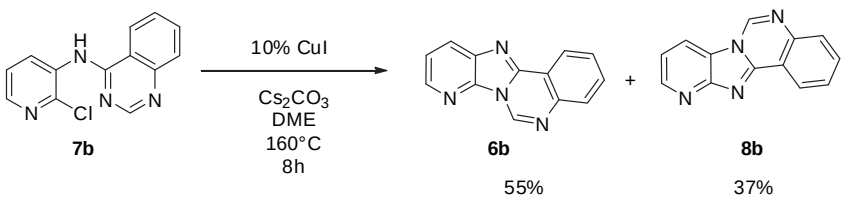
In accordance with our previous work we then tried to use CuI in combination with a higher reaction temperature to induce the ring closure reaction of **7b**.[33] When successful an orthogonal tandem process towards **6b** could be attempted. Treating **7b** with CuI and base at high temperature gave indeed the expected pyrido[3′,2′:4,5]imidazo[1,2-*c*]quinazoline (**6b**) in 55% yield. Surprisingly, we also isolated 37% of regioisomeric pyrido[2′,3′:4,5]imidazo[2,1-*a*]quinazoline (**8b**) (Scheme 4), which we actually envisioned (Section 2.3) to make by double aminating of **2** with **5b**.

A control experiment without the addition of CuI showed also transformation to **6b** and its regioisomer **8b**, this time in 44% and 42%, respectively. This shows that no copper is necessary to obtain **8b**. The formation of **8b** can be rationalized by a Smiles type rearrangement where the negative charge of the *N*-(2-chloropyridin-3-yl)quinazolin-4-amide is delocalized onto the pyrimidine *N*-3, which subsequently performs an *ipso*-substitution on C-3 of the pyridine ring.[36,37] The hereby generated anion gives access to **8b** via a classical addition elimination mechanism on C-2 of the pyridine ring (Scheme 5).



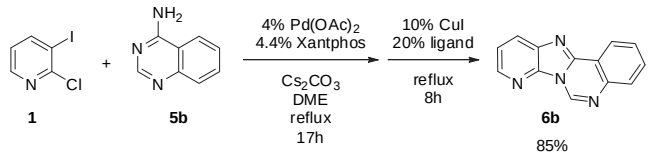
Scheme 5. Smiles rearrangement of *N*-(2-chloropyridin-3-yl)quinazolin-4-amine (**7b**) followed by S_NAr.

Since the intramolecular amination reaction at high temperature gave an undesired Smiles rearrangement we turned our attention to the use of ligands for the copper catalyst in order to achieve ring closure of **7b** at a lower temperature. Unfortunately, previous results of our laboratory indicated that a CuI/ligand catalyst system at lower temperature hampered an orthogonal tandem approach starting from **2** since the copper species partly inhibits the Pd-catalyzed intermolecular amination reaction.[33] In order to circumvent this inhibitory action of copper catalyst on the palladium catalyzed amination we attempted to develop a one-pot approach consisting of a Pd-catalyzed intermolecular amination step followed by the addition of the copper catalyst, upon completion of the first amination, in order to allow the intramolecular amination reaction. Interestingly, repeating the Cu-catalyzed ring closure reaction on **7b** with *rac*, *trans*-cyclohexane-1,2-diamine as ligand, in a Cu/L ratio of 1:2, indeed allowed a ring closure at lower temperature without rearrangement as a full conversion to pyrido[3′,2′:4,5]imidazo[1,2-*c*]quinazoline (**6b**) was achieved within 8 h at reflux. Gratifyingly, upon combining the Pd-catalyzed intermolecular amination presented in Scheme 3, with DME instead of toluene as solvent, with this



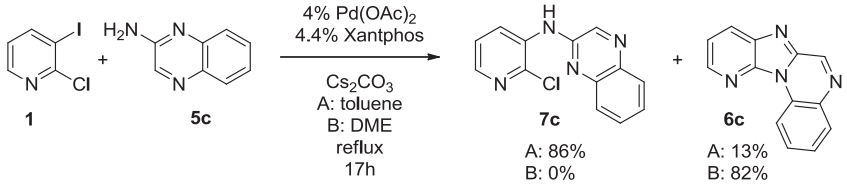
Scheme 4. Ring closure reaction of *N*-(2-chloropyridin-3-yl)quinazolin-4-amine (**7b**) using CuI at high temperature.

Cu-catalyzed intramolecular amination reaction pyrido[3′,2′:4,5]imidazo[1,2-*c*]quinazoline (**6b**) was obtained as the sole reaction product in 85% yield (Scheme 6).



Scheme 6. One-pot Pd-catalyzed intermolecular and Cu-catalyzed intramolecular amination reaction of 2-chloro-3-iodopyridine (**1**) with quinazolin-4-amine (**5b**).

For the reaction of **1** with quinoxalin-2-amine (**5c**) we initially tested the auto-tandem double amination protocol, which allowed to access **6a** via coupling of **1** with **5a** (Scheme 2). Only a partial conversion to the desired pyrido[3′,2′:4,5]imidazo[1,2-*a*]quinoxaline **6c** (13% isolated yield) along with 86% of the intermediate intermolecular amination reaction product **7c** was obtained (Scheme 7). Switching toluene to DME as solvent gave a full conversion to pyrido[3′,2′:4,5]imidazo[1,2-*a*]quinoxaline (**6c**) in 17 h and an isolated yield of 82% (Scheme 7). As S_NAr reactions are promoted in more polar solvents the ring closure reaction of **7c** is therefore most probably not Pd-catalyzed and a tandem reaction involving a Pd-catalyzed amination—S_NAr reaction sequence rather than an auto-tandem Pd-catalyzed double amination mechanistically occurs.[35]



Scheme 7. Auto-tandem Pd-catalyzed double amination on 2-chloro-3-iodopyridine (**1**) using quinoxalin-2-amine (**5c**).

2.3. Transition metal-catalyzed double amination of 2,3-dibromopyridine (2) with benzodiazinamines (5)

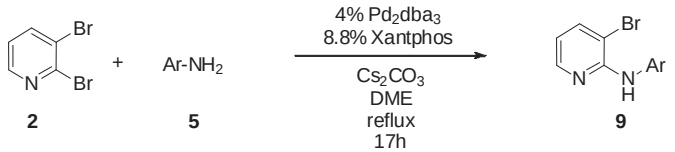
For the coupling of 2,3-dibromopyridine (**2**) with (di)azinamines and benzoazinamines we previously developed an orthogonal Pd-catalyzed inter- and Cu-catalyzed intramolecular amination protocol (2% $Pd_2(dba)_3$, 4.4% Xantphos, 10% CuI, DME) requiring a high reaction temperature (oil bath temperature: 160 °C).[33] Taking into account the result obtained for substrate **1**, we decided to immediately investigate the possibility of the use of the lower temperature one-pot protocol involving a Pd and Cu-catalyst in a sequential manner (Section 2.2).

Pd-catalyzed amination conditions previously used to regioselectively functionalize **2** in C-2 yielded *N*-(3-bromopyridin-2-yl) phthalazin-1-amine (**9a**) in good yield (Table 1). In order to check that the amination reaction had indeed taken place at C-2 of the pyridine ring, **9a** was dehalogenated using Pd/C and H_2. The ^1H NMR coupling pattern of this compound confirmed the C-2 regioselectivity (Table 2).

Subsequently, we attempted to use this catalyst system in a one-pot protocol. Therefore, after 17 h intermolecular amination CuI/*rac*, *trans*-cyclohexane-1,2-diamine was added to the reaction mixture in order to induce the intramolecular amination step. In this way pyrido[2′,3′-4,5]imidazo[2,1-*a*]phthalazine was obtained in 65% (Scheme 8).

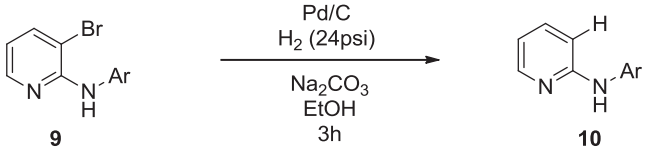
For the coupling of **2** with **5b** we again first verified if the Pd-catalyst allowed full conversion to *N*-(3-bromopyridin-2-yl)quinazolin-4-amine (**9b**) within 17 h. Unfortunately, this was not the case and an increase of the reaction time to 24 h did not solve this problem as a work-up gave only 49% **9b** and a recovery of 30% of substrate **2**. (Table 1) Again, C-2 substitution could be confirmed via dehalogenation of **9b**. (Table 2) Fortunately, increasing the loading to 6% Pd allowed a full conversion of **2** into **9b** in 17 h and a subsequent addition of copper catalyst gave pyrido[2′,3′-4,5]imidazo[1,2-*c*]quinazoline (**8b**) in an excellent isolated yield (Scheme 9).

Table 1
Intermolecular Pd-catalyzed amination on **2** with benzodiazinamines **5**

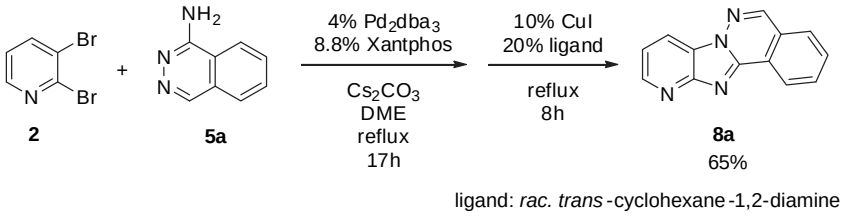


Benzodiazinamine **5**	Product **9**	Yield
5a	**9a**	76%
5b	**9b**	49% (24 h) (30% **2**)
5c	**9c**	86%

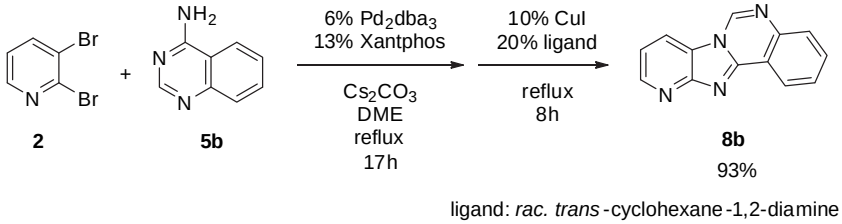
Table 2
Dehalogenation of *N*-(3-bromopyridin-2-yl)benzodiazinamines **9**



N-(3-bromopyridin-2-yl) benzodiazinamine	Product **10**	Yield
9a	**10a**	99%
9b	**10b**	50%
9c	**10c**	50%



Scheme 8. One-pot Pd-catalyzed intermolecular and Cu-catalyzed intramolecular amination reaction of 2,3-dibromopyridine (**2**) with phthalazin-1-amine (**5a**).



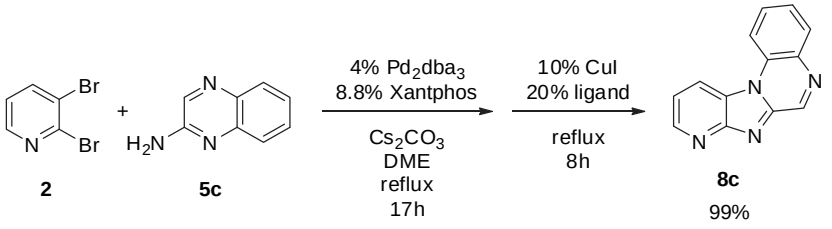
Scheme 9. One-pot Pd-catalyzed intermolecular and Cu-catalyzed intramolecular amination reaction of 2,3-dibromopyridine (**2**) with quinazolin-4-amine (**5b**).

For the coupling of **2** with **5c**, the same procedure was followed as for **5a** and **5b**. In this case there was no need to increase the palladium loading for the intermolecular amination and *N*-(3-bromopyridin-2-yl)quinoxalin-2-amine (**9c**) could be isolated in 86%. (Table 1) Dehalogenation of **9c** confirmed C-2 functionalization through analysis via ^{1}H NMR. (Table 2) Finally, one-pot Pd-catalyzed intermolecular and Cu-catalyzed intramolecular amination reaction of **2** with **5c** yielded pyrido[3′,2′-4,5]imidazo[1,2-*a*]quinoxaline (**8c**) in 99% yield (Scheme 10).

4. Experimental section

4.1. General information

All melting points were determined on a Büchi apparatus and are uncorrected. The ^{1}H NMR and ^{13}C NMR spectra were recorded 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



Scheme 10. One-pot Pd-catalyzed intermolecular and Cu-catalyzed intramolecular amination reaction of 2,3-dibromopyridine (**2**) with quinazolin-2-amine (**5c**).

3. Conclusions

It appears that the previously developed auto-tandem double amination protocol for the coupling of **1** with benzoazinamines and (di)azinamines cannot be generally applied for benzodiazinamines. Attempts to use an orthogonal (Pd and Cu-catalyst) tandem double amination protocol, as developed for the coupling of **2** with benzoazinamines and (di)azinamines, revealed unexpected rearrangement problems due to the high temperature applied. The use of rac, *trans*-cyclohexane-1,2-diamine as ligand for the copper catalyst allowed to work at a lower reaction temperature, but required the performance of the intermolecular and intramolecular reaction in a sequential manner. Application of the two catalysts in a one-pot fashion was tested on **1** and **2** with the benzodiazinamines phtalazin-1-amine, quinazolin-4-amine and quinoxalin-2-amine (**5**) and allowed the synthesis of six new nitrogen-containing heterocyclic scaffolds of significant complexity in a short, practical and efficient way.

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 Q-TOF 2 mass spectrometer (Waters-Micromass) equipped with a standard electrospray ionisation (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. 4-Chlorophthalazin-1-amine was prepared following a literature procedure.[38] 2-Chloro-3-iodopyridine is commercially available from Lancaster. It can also be synthesized starting from 2-chloropyridin-3-amine (Acros) via diazotization and subsequent reaction with KI.[39] All commercial reagents were used without extra purification. Column chromatography was performed on Kieselgel 60 (ROCC SI 1721, 40–60 μm).

*4.1.1. Phthalazin-1-amine (**5a**).* In a Parr-apparatus flask 4-chlorophthalazin-1-amine (1 mmol, 0.179 g), NaOH (2 mmol, 0.080 g) and Pd/C 10% w/w (0.020 g) were weighed off. MeOH (30 mL) was added and the resulting mixture was shaken in the Parr hydrogenation apparatus for 3 h under a H_2 pressure of 23 psi. The mixture was subsequently purified by filtration over a filter paper, evaporated to dryness and purified via column chromatography on silicagel using CH_2Cl_2/MeOH (85/15) as the eluent. Yield: 80%; 0.116 g as a white fluffy solid.

^{1}H NMR (400 MHz, $CDCl_3$): 8.89 (s, 1H, H_4), 8.25 (br d, J=6.4 Hz, 1H, H_5 or H_8), 7.88 (m, 3H, H_5 or H_8, H_6, H_7), 6.98 (br s, 2H, NH_2).

*4.1.2. Quinazolin-4-amine (**5b**)[34].* To a four-necked flame-dried 250 mL flask 2 glass tubes, each connected by a piece of rubber tubing, and an oil bubbler were connected. In the two glass tubes quinazoline (2 mmol, 0.2602 g) and $KMnO_4$ (7 mmol, 1.1062 g) were weighed off. Ammonia was condensed in the 250 mL flask by cooling the flask in an acetone/dry ice bath under magnetic stirring while passing a stream of ammonia (generated by gently adding aqueous ammonia on NaOH) through the apparatus built. When approximately 30 mL of NH_3 was condensed, quinazoline was added in one portion and stirring was continued for 5 min, then the $KMnO_4$ was added in small portions over a 10 min period. Subsequently, the cooling bath was taken away, the flask wrapped in aluminium foil and stirring was continued until all of the NH_3 had evaporated. Then silicagel (1 g) was added along with 30 mL of MeOH. The resulting slurry is evaporated in vacuo and brought on a silicagel column for chromatography using CH_2Cl_2/MeOH (95/5) until all the undesired quinazolin-4(3*H*)-one had come off and then the eluent composition was changed to CH_2Cl_2/MeOH (85/15). Yield: 76%; 0.220 g as a white solid.

^{1}H NMR (400 MHz, DMSO-d_6): 8.38 (s, 1H, H_2), 8.20 (d, J=8.3 Hz, 1H, H_5 or H_8), 7.75 (ddd, J=8.3, 6.9, 1.3 Hz, 1H, H_6 or H_7), 7.71 (br s, 2H, NH_2), 7.65 (d, J=7.6 Hz, 1H, H_5 or H_8), 7.48 (ddd, J=8.2, 6.9, 1.2 Hz, 1H, H_6 or H_7).

*4.1.3. Quinoxalin-2-amine (**5c**)[34].* 2-Chloroquinoxaline (9 mmol, 1.481 g) was brought in a pressure tube. NH_3 (aq 25%, 25 mL) was added and the mixture was heated at 120 °C for 4 h under magnetic stirring. After the mixture was cooled to room temperature the quinoxalin-2-amine was filtered off, rinsed well with 25 mL of water and dried in vacuo. Yield: 54%; 0.705 g as an off-white solid.

^{1}H NMR (400 MHz, DMSO-d_6): 8.28 (s, 1H, H_3), 7.75 (br d, J=8.0 Hz, 1H, H_5 or H_8), 7.52 (ddd, J=8.3, 6.8, 1.4 Hz, 1H, H_6 or H_7), 7.51 (dd, J=8.2, 1.6 Hz, 1H, H_5 or H_8), 7.32 (ddd, J=8.5, 6.6, 1.6 Hz, 1H, H_6 or H_7), 6.95 (br s, 2H, NH_2).

4.2. General procedure A for the synthesis of *N*-(3-bromopyridin-2-yl)benzodiazinamines (9)

A round-bottomed flask of 50 mL was charged with Pd_2dba_3 (0.06 mmol, 0.0549 g, 4 mol %), Xantphos (0.132 mmol, 0.0763 g, 8.8 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-dibromopyridine (**2**) (1.5 mmol, 0.355 g), benzodiazinamine (**5**) (1.8 mmol) and caesium carbonate (6.0 mmol, 1.955 g). To this mixture, the preformed Pd-catalyst was added under a 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 under vigorous magnetic stirring for 17 h. After cooling down to room temperature, the mixture was filtered, rinsed well with 150 mL CH_2Cl_2 and evaporated to dryness. The crude product was purified by column chromatography on silicagel.

4.3. General procedure B for the synthesis of *N*-(pyridin-2-yl) benzodiazinamines (10)

In a Parr-apparatus flask *N*-(3-bromopyridin-2-yl)benzodiazinamine (**9**) (0.5 mmol), Pd/C 10% (0.050 g) and Na_2CO_3 (1.1 mmol) were brought. Ethanol (15 mL) was added and the mixture was flushed with argon. Then the mixture was hydrogenated under a H_2 pressure of 24 psi in a Parr apparatus for 3 h. The mixture was subsequently filtered and rinsed with 20 mL of CH_2Cl_2, evaporated to dryness and purified by column chromatography on silicagel using CH_2Cl_2 as eluent.

*4.3.1. N-(3-Bromopyridin-2-yl)phthalazin-1-amine (**9a**).* The general procedure A was followed using phthalazin-1-amine (**5a**) (1.8 mmol, 0.264 g). Eluent: CH_2Cl_2 to CH_2Cl_2/MeOH (98/2). Yield: 76%, 0.343 g as a beige solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ 15.11 (br s, 1H, NH), 8.87 (br d, J=7.2 Hz, 1H, H_8), 8.29 (dd, J=4.9, 1.6 Hz, 1H, $H_{6'}$), 8.21 (s, 1H, H_4), 7.95 (dd, J=7.7, 1.7 Hz, 1H, $H_{4'}$), 7.79 (m, 2H, H_6 and H_7), 7.64 (br d, J=6.9 Hz, 1H, H_5), 6.78 (dd, J=7.7, 4.9 Hz, 1H, $H_{5'}$); ^{13}C NMR (100 MHz, $CDCl_3$): δ 158.3, 149.5, 144.6, 141.1, 140.2, 132.6, 132.2, 129.4, 127.9, 126.3, 126.0, 118.2, 117.5. $[M+H]^+$ calcd: 301.0089, found: 301.0098. Mp: 167–169.7 °C.

*4.3.2. N-(Pyridin-2-yl)phthalazin-1-amine (**10a**).* The general procedure B was followed using *N*-(3-bromopyridin-2-yl)phthalazin-1-amine (**9a**). Yield: 99%, 0.110 g as white plates.

^{1}H NMR (400 MHz, $CDCl_3$): δ 15.45 (br s, 1H, NH), 8.72 (d, J=6.1 Hz, 1H, H_5 or H_8), 8.36 (d, J=5.0 Hz, 1H, $H_{6'}$), 8.15 (s, 1H, H_4), 7.70 (m, 4H, $H_{4'}$, H_5 or H_8, H_6 and H_7), 7.32 (d, J=8.0 Hz, 1H, $H_{3'}$), 6.92 (t, J=5.8 Hz, 1H, $H_{5'}$); ^{13}C NMR (100 MHz, $CDCl_3$): δ 162.0, 149.2, 145.6, 139.5, 137.5, 132.2, 131.9, 129.1, 127.8, 126.0, 125.6, 122.2, 117.1. Mp: >300 °C. $[M+H]^+$ calcd: 223.0984, found: 223.0984.

*4.3.3. N-(3-Bromopyridin-2-yl)quinazolin-4-amine (**9b**).* The general procedure A was followed using 4-aminoquinazoline (**5b**) (1.8 mmol, 0.2636 g). Catalyst loading was increased to Pd_2dba_3 (0.06 mmol, 0.0550 g, 6 mol %) and Xantphos (0.132 mmol, 0.0762 g, 13.2 mol %). Reaction time was 24 h. Eluent: CH_2Cl_2/MeOH (98/2). Yield: 49%, 0.221 as white needles.

^{1}H NMR (400 MHz, $CDCl_3$): δ 14.80 (br s, 1H, NH), 8.72 (dd, J=8.0, 1.1 Hz, 1H, H_5 or H_8), 8.28 (dd, J=4.9, 1.7 Hz, 1H, $H_{6'}$), 8.09 (s, 1H, H_2), 8.00 (dd, J=7.8, 1.7 Hz, 1H, $H_{4'}$), 7.73 (m, 1H, H_6 or H_7), 7.67 (dd, J=8.1, 1.1 Hz, 1H, H_5 or H_8), 7.54 (m, 1H, H_6 or H_7), 6.85 (dd, J=7.8, 4.9 Hz, 1H, $H_{5'}$); ^{13}C NMR (100 MHz, $CDCl_3$): δ 158.4, 150.2, 146.9, 144.3, 142.0, 141.7, 133.5, 127.6, 127.4, 126.2, 123.5, 119.0, 118.5. Mp: 154.1–156.4 °C. $[M+H]^+$ calcd: 301.0089, found: 301.0089.

*4.3.4. N-(Pyridin-2-yl)quinazolin-4-amine (**10b**).* The general procedure B was followed using *N*-(3-bromopyridin-2-yl)quinazolin-4-amine (**9b**). Yield: 50%, 0.056 g as a yellow solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.87 (s, 1H, NH), 8.76 (br d, J=7.0 Hz, 1H, H_5 or H_8), 8.53 (br s, 1H, H_2), 8.33 (dd, J=4.7, 1.5 Hz, 1H, $H_{6'}$), 8.03 (d, J=6.4 Hz, 1H, $H_{3'}$), 7.95 (br d, J=7.0 Hz, 1H, H_5 or H_8), 7.80 (m, 2H, H_6 or H_7 and $H_{4'}$), 7.56 (m, J=6.9 Hz, 1H, H_6 or H_7), 7.04 (dd, J=7.4, 4.9 Hz, 1H, $H_{5'}$); ^{13}C NMR (100 MHz, $CDCl_3$): δ 156.6, 154.4, 152.0, 150.1, 147.9, 138.2, 133.1, 129.0, 127.0, 120.6, 119.2, 115.2, 115.0 Mp: 104.9–105.4 °C. $[M+H]^+$ calcd: 223.0978, found: 223.0984.

*4.3.5. N-(3-Bromopyridin-2-yl)quinoxalin-2-amine (**9c**).* The general procedure A was followed using 2-aminoquinoxaline

(1.8 mmol, 0.2613 g). Eluent: CH_2Cl_2/MeOH (98/2). Yield: 86%, 0.388 g as a brown solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ 9.99 (s, 1H, H_3), 8.26 (dd, J=4.8, 1.5 Hz, 1H, $H_{5'}$), 8.04 (dd, J=8.2, 1.0 Hz, 1H, H_5 or H_8), 7.97 (br s, 1H, NH), 7.85 (dd, J=7.8, 1.5 Hz, 1H, $H_{4'}$), 7.83 (dd, J=8.2, 0.9 Hz, 1H, H_5 or H_8) 7.67 (ddd, J=8.4, 7.0, 1.4 Hz, 1H, H_6 or H_7), 7.58 (ddd, J=8.4, 7.0, 1.3 Hz, 1H, H_6 or H_7), 6.83 (dd, J=7.8, 4.8 Hz, 1H, $H_{6'}$); ^{13}C NMR (100 MHz, $CDCl_3$): δ 150.1, 148.0, 146.5, 141.2, 141.1, 139.7, 139.5, 130.2, 129.0, 1127.0, 127.0, 118.2, 107.0. Mp: 166.7–166.9 °C. $[M+H]^+$ calcd: 301.0098, found: 301.0091.

*4.3.6. N-(Pyridin-2-yl)quinoxalin-2-amine (**10c**).* The general procedure B was followed using *N*-(3-bromopyridin-2-yl)quinoxalin-2-amine (**9c**). Yield: 50%, 0.056 g as a grey solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.80 (br s, 1H, NH), 8.72 (s, 1H, H_3), 8,49 (d, J=8.6 Hz, 1H, $H_{3'}$), 8.33 (dd, J=5.0, 0.6 Hz, 1H, $H_{6'}$), 7.94 (dd, J=8.2, 1.1 Hz, 1H, H_5 or H_8), 7.82 (dd, J=8.3, 0.9 Hz, 1H, H_5 or H_8), 7.74 (ddd, J=8.7, 7.2, 1.8 Hz, 1H, $H_{4'}$), 7.63 (ddd, J=8.3, 7.0, 1.3 Hz, 1H, H_6 or H_7), 7.49 (ddd, J=8.2, 7.3, 1.3 Hz, 1H, H_6 or H_7), 6.99 (ddd, J=7.2, 5.0, 0.7 Hz, 1H, $H_{5'}$); ^{13}C NMR (100 MHz, $CDCl_3$): δ 153.0, 148.2, 140.7, 139.7, 138.9, 138.5, 130.5, 129.2, 129.2, 127.1, 126.5, 118.3, 113.4. Mp: 151.4–152.1 °C. $[M+H]^+$ calcd: 223.0984, found: 223.0979.

4.4. General procedure C for the synthesis of pyrido[3′,2′:4,5] imidazobenzodiazines (6)

A round bottomed flask of 50 mL was charged with $Pd(OAc)_2$ (0.06 mmol, 0.013 g, 4 mol %), Xantphos (0.066 mmol, 0.0385 g, 4.4 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-iodopyridine (**1**) (1.5 mmol, 0.359 g), benzodiazinamine **5** (1.8 mmol) and Cs_2CO_3 (6.0 mmol, 1.955 g). To this mixture, the preformed Pd-catalyst was added under a 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. After cooling down to room temperature, the reaction mixture was filtered and rinsed well with CH_2Cl_2 (150 mL). The filtrate was evaporated and the crude product was purified by column chromatography on silicagel.

4.5. General procedure D for the synthesis of pyrido[2′,3′:4,5] imidazobenzodiazines (8)

A round bottomed flask of 50 mL was charged with Pd_2dba_3 (0.04 mmol, 0.0366 g, 4 mol %), Xantphos (0.088 mmol, 0.0501 g, 8.8 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-dibromopyridine (**2**) (1 mmol, 0.237 g), benzodiazinamine **5** (1.2 mmol) and Cs_2CO_3 (4.0 mmol, 1.303 g). To this mixture, the preformed Pd-catalyst was added under a N_2-flow. The 50 mL flask was subsequently rinsed with 2×2.5 mL DME. Then the resulting mixture was flushed with N_2 for 5 min and heated at reflux. After 17 h, CuI (0.10 mmol, 0.0190 g, 10 mol %) and *rac*, *trans*-cyclohexane-1,2-diamine (0.20 mmol, 1 mL of a 0.2 M stock solution in DME, 20 mol %) were added and the mixture was refluxed for an additional 8 h. After cooling down to room temperature, the reaction mixture was filtered and rinsed well with CH_2Cl_2 (150 mL) and 3 times 10 mL of a mixture of CH_2Cl_2/NH_3 in MeOH (ca. 7 N) (1/1). The filtrate was evaporated to dryness and the crude product was purified by column chromatography on silicagel.

*4.5.1. Pyrido[3′,2′:4,5]imidazo[2,1-a]phthalazine (**6a**).* The general procedure C was followed using 1-aminophthalazine (1.8 mmol, 0.2613 g). Eluent: EtOAc/MeOH (98/2). Yield: 80%, 0.264 g of a white solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.84 (d, J=8.9 Hz, 1H, H_1 or H_4), 8.83 (s, 1H, H_5), 8.67 (d, J=4.6 Hz, 1H, H_9), 8.33 (d, J=8.1 Hz, 1H, H_{11}), 8.00 (m, 2H, H_1 and H_3 or H_2 and H_4), 7.90 (br t, J=7.3 Hz, 1H, H_2 or H_3); 7.54 (dd, J=8.1, 4.6 Hz, 1H, H_{10}); ^{13}C NMR (100 MHz, $CDCl_3$): δ 144.6, 144.6, 143.4, 142.1, 134.6, 133.1, 131.2, 127.8, 127.8, 125.1, 124.9, 123.7, 120.9. Mp: 181.3–182 °C. $[M+H]^+$ calcd: 221.0827, found: 221.0828.

*4.5.2. Pyrido[2′,3′:4,5]imidazo[2,1-a]phthalazine (**8a**).* The general procedure D was followed using phthalazin-1-amine (1.2 mmol, 0. 1742 g).

The residue on the filter was rinsed with an extra portion of CH_2Cl_2 and NH_3 (ca. 7 N in MeOH) (3×50 mL each). Eluent: gradient CH_2Cl_2/MeOH (98/2 to 96/4). Yield: 65%, 0.143 g as an off-white solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.85 (d, J=7.8, 1H, H_1 or H_4), 8.81 (dd, J=4.6, 1.2 Hz, 1H, H_{10}), 8.71 (s, 1H, H_5), 8.39 (dd, J=8.1, 1.2 Hz, 1H, H_8), 7.97 (dd, J=8.0, 7.4 Hz, 1H, H_2 or H_3), 7.95 (d, J=8.0 Hz, 1H, H_1 or H_4), 7.86 (dd, J=7.8, 7.4 Hz, 1H, H_2 or H_3), 7.41 (dd, J=8.1, 4.6 Hz, 1H, H_9); ^{13}C NMR (100 MHz, $CDCl_3$): δ 154.1, 147.8, 144.3, 142.9, 133.2, 131.3, 127.7, 125.1, 124.8, 124.6, 123.9, 119.2, 118.0. Mp: 183.9–184.5 °C. $[M+H]^+$ calcd: 221.0827, found: 221.0836.

*4.5.3. N-(2-Chloropyridin-3-yl)quinazolin-4-amine (**7b**).* The general procedure C was followed using quinazolin-4-amine (**5b**) (1.8 mmol, 0.2613 g). Eluent: CH_2Cl_2/MeOH (98/2). Yield: 92%, 0.352 g as a pale yellow solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ 9.25 (d, J=8.0 Hz, 1H, $H_{4'}$), 8.85 (s, 1H, H_2), 8.21 (br s, 1H, NH), 8.14 (br d, J=4.6 Hz, 1H, $H_{6'}$), 7.97 (m, 2H, H_6 and H_7), 7.88 (br t, J=7.5 Hz, 1H, H_5 or H_8), 7.66 (br t, J=7.5 Hz, 1H, H_5 or H_8), 7.37 (dd, J=8.0, 4.6 Hz, 1H, $H_{5'}$); ^{13}C NMR (100 MHz, $CDCl_3$): 156.7, 154.2, 150.1, 143.1, 140.6, 133.4, 132.6, 129.5, 129.3, 127.4, 123.3, 120.0, 115.4. Mp: 149.6–151 °C. $[M+H]^+$ calcd: 257.0594, found: 257.0582.

*4.5.4. Pyrido[3′,2′:4,5]imidazo[1,2-c]quinazoline (**6b**).* The general procedure C was followed using quinazolin-4-amine (1.8 mmol, 0.2613 g). Toluene was substituted for DME. After 17 h reflux, CuI (0.15 mmol, 0.0285 g, 10 mol %) and *rac*, *trans*-cyclohexane-1,2-diamine (0.30 mmol, as a solution in 1 mL of DME, 20 mol %) were added and heating was continued for an additional 8 h. Eluent: gradient CH_2Cl_2/MeOH (98/2 to 96/4). Yield: 85%, 0.281 g as a pale yellow solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ 9.46 (s, 1H, H_6), 8.68 (dd, J=7.9, 1.4 Hz, 1H, H_1 or H_4), 8.56 (dd, J=4.7, 1.4 Hz, 1H, H_9), 8.29 (dd, J=8.1, 1.4 Hz, 1H, H_{11}), 8.03 (br d, J=8.1 Hz, 1H, H_1 or H_4), 7.85 (ddd, J=8.1, 7.3, 1.4 Hz, 1H, H_2 or H_3), 7.74 (br t, J=7.3 Hz, 1H, H_2 or H_3), 7.56 (dd, J=8.1, 4.7 Hz, 1H, H_{10}); ^{13}C NMR (100 MHz, $CDCl_3$): δ 146.7, 144.0, 143.3, 142.2, 136.3, 135.5, 132.5, 128.9, 128.9, 127.9, 124.1, 122.0, 119.1. Mp: 214.5 °C. $[M+H]^+$ calcd: 221.0827, found: 221.0825.

*4.5.5. Pyrido[2′,3′:4,5]imidazo[1,2-c]quinazoline (**8b**).* The general procedure D was followed using Pd_2dba_3 (0.06 mmol, 0.0550 g, 6 mol %) Xantphos (0.132 mmol, 0.0762 g, 13.2 mol %) and quinazolin-1-amine (**5b**) (1.2 mmol, 0. 174 g). Eluent: gradient CH_2Cl_2/MeOH (98/2 to 96/4). Yield: 93%, 0.205 g as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ 9.15 (s, 1H, H_6), 8.85 (dd, J=4.8, 1.5 Hz, 1H, H_{10}), 8.81 (ddd, J=8.0, 1.5, 0.5 Hz, 1H, H_1 or H_4), 8.30 (dd, J=8.1, 1.5 Hz, 1H, H_8), 8.02 (dd, J=8.1 Hz, 1H, H_1 or H_4), 7.85 (m, 1H, H_2 or H_3), 7.75 (br t, J=7.3 Hz, 1H, H_2 or H_3), 7.56 (dd, J=8.1, 4.7 Hz, 1H, H_9); ^{13}C NMR (100 MHz, $CDCl_3$): δ 146.7, 144.03, 143.3, 142.2, 136.3, 135.5, 132.5, 128.9 (2), 127.9, 124.1, 122.0, 119.1. Mp: >300 °C. $[M+H]^+$ calcd: 221.0827, found: 221.0832.

*4.5.6. N-(2-Chloropyridin-3-yl)quinoxalin-2-amine (**7c**).* The general procedure C was followed using quinoxalin-2-amine (**5c**) (1.8 mmol, 0.2613 g). No copper catalyst was added after 17 h but the mixture was directly worked up. Eluent: CH_2Cl_2/MeOH (98/2). Yield: 86%, 0.331 g as a yellow solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ 9.33 (dd, J=8.2, 1.6 Hz, 1H, $H_{4'}$), 8.50 (s, 1H, H_3), 8.09 (d, J=4.6, 1.6 Hz, 1H, $H_{6'}$), 7.98 (d, J=8.2 Hz, 1H, H_5 or H_8), 7.85 (d, J=8.4 Hz, 1H, H_5 or H_8), 7.68 (m, 1H, H_6 or H_7), 7.55 (m, 1H, H_6 or H_7), 7.39 (s, 1H, NH), 7.34 (dd, J=8.2, 4.6 Hz, 1H, $H_{5'}$); ^{13}C NMR (100 MHz, $CDCl_3$): δ 148.0, 142.1, 140.3, 139.5, 139.0, 138.3, 133.4, 130.6, 129.1, 127.2, 127.1, 126.6, 123.3. Mp: 149.6–151 °C. $[M+H]^+$ calcd: 257.0589, found: 257.0594.

*4.5.7. Pyrido[3′,2′:4,5]imidazo[1,2-a]quinoxaline (**6c**).* The general procedure C was followed using quinoxalin-2-amine (1.8 mmol, 0.2613 g). Toluene was substituted for DME. Eluent: CH_2Cl_2/MeOH (98/2). Yield: 86%, 0.284 g as a beige solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ 9.61 (dd, J=8.3, 1.1 Hz, 1H, H_1 or H_4), 9.23 (s, 1H, H_6), 8.73 (dd, J=4.6, 1.5 Hz, 1H, H_{10}), 8.38 (dd, J=8.3, 1.5 Hz, 1H, H_8), 8.14 (dd, J=8.1, 1.3 Hz, 1H, H_1 or H_4), 7.78 (m, 1H, H_9), 7.61 (m, 1H, H_2 or H_3), 7.59 (m, 1H, H_2 or H_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ 145.9, 145.7, 144.3, 136.6, 135.4, 130.4, 130.3, 129.5, 128.6, 126.2, 121.3, 117.3. Mp: 281.2 °C. $[M+H]^+$ calcd: 221.0827, found: 221.0824.

*4.5.8. Pyrido[2′,3′:4,5]imidazo[1,2-a]quinoxaline (**8c**).* The general procedure D was followed using quinoxalin-2-amine (**5c**) (1.2 mmol, 0.1742 g). Eluent: CH_2Cl_2/MeOH 95/5. Yield: 99%, 0.218 g as a brown solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ 9.37 (s, 1H, H_6), 8.95 (dd, J=4.6, 1.4 Hz, 1H, H_9), 8.71 (dd, J=8.4, 1.4 Hz, 1H, H_{11}), 8.37 (dd, J=8.4, 0.9 Hz, 1H, H_1 or H_4), 8.22 (dd, J=8.0, 1.4 Hz, 1H, H_1 or H_4), 7.81 (ddd, J=8.1, 7.3, 1.4 Hz, 1H, H_2 or H_3), 7.66 (ddd, J=7.9, 7.5, 1.3 Hz, 1H, H_2 or H_3), 7.55 (dd, J=8.4, 4.6 Hz, 1H, H_{10}); ^{13}C NMR (100 MHz, $CDCl_3$): δ 155.6, 149.0, 146.1, 141.9, 135.8, 131.8, 130.4, 129.2, 126.3, 122.6, 122.5, 119.3, 114.6. Mp: 193–195.1 °C. $[M+H]^+$ calcd: 221.0827, found: 221.0828.

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Supplementary data

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