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Examination of the mechanism of the intramolecular amination of *N*-(3-bromopyridin-2-yl)azaheteroarylamines and *N*-(2-chloropyridin-3-yl)azaheteroarylamines: a Pd-catalyzed amination and/or a base-assisted nucleophilic aromatic substitution?

Kristof T. J. Loones, Bert U. W. Maes,* Wouter A. Herrebout, Roger A. Dommisse, Guy L. F. Lemière and Benjamin J. Van der Veken

Department of Chemistry, University of Antwerp, Groenenborgerlaan 171, B-2020 Antwerp, Belgium

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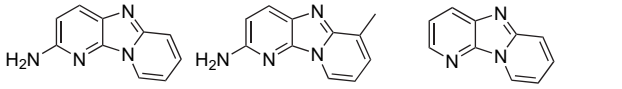
This paper is dedicated to Professor G. Quéguiner on the occasion of his 70th birthday

Abstract—The intramolecular amination of *N*-(3-bromopyridin-2-yl)azaheteroarylamines and *N*-(2-chloropyridin-3-yl)azaheteroarylamines was investigated. In this way we unraveled the mechanism of the ring closure reaction in the auto-tandem amination (inter- and intramolecular Pd-catalyzed amination) of 2,3-dibromopyridine with amino(benzo)(di)azines and 2-chloro-3-iodopyridine with amino(benzo)(di)azines, respectively. Depending on the substrate a Pd-catalyzed amination, a base-assisted nucleophilic aromatic substitution or a combination of both is occurring. An explanation based on the aromaticity of the amidine, supported by theoretical calculations, is provided. In addition we gained evidence that the intramolecular metal-catalyzed amination of *N*-(3-bromopyridin-2-yl)azaheteroarylamines and *N*-(2-chloropyridin-3-yl)azaheteroarylamines indeed involves a nitrogen atom that is not substituted with a hydrogen atom.

1. Introduction

During the heating of protein rich food mutagenic heterocyclic amines (HCA's) are formed. They are so called 'food borne carcinogens' and hitherto more than 20 have already been isolated.[1] These HCA's can be subdivided in two main families, the first one consisting of IQ-type HCA's, also called thermic HCA's. They are generated through the reaction of free amino acids, creati(ni)ne and sugars at temperatures below 300 °C. The HCA's of the second family, called non-IQ type or pyrolytic HCA's are formed through the pyrolytic reaction of amino acids and proteins at temperatures above 300 °C.[2–4] Representatives of the latter group are Glu-P-1 and Glu-P-2, which are pyrolysis products of L-glutamic acid (Scheme 1).[5] The Glu-P's are transformed into carcinogenic species by N-hydroxylation, catalyzed by cytochrome P-450, followed by an enzymatic esterification of the hydroxylamino group with acetyltransferases.[2,4,6–8] The formation of a DNA adduct in position 8 of a guanine is preceded by the intercalation of the activated Glu-P's in DNA via their tricyclic dipyrido[1,2-*a*:3′,2′-*d*]-imidazole core (Scheme 1).[9]



Scheme 1. Structures of Glu-P's and the dipyrido[1,2-*a*:3′,2′-*d*]imidazole core skeleton.

An attractive new synthetic method to prepare heterocyclic amines is the Pd-catalyzed amination reaction (Buchwald–Hartwig reaction). Due to the pioneering diligence of the research groups of Buchwald[10] and Hartwig,[11] tin-free Pd-catalyzed amination has since the mid nineties emerged as an extremely powerful tool for C(sp^2)–N bond formation.[12–15] In 2004 our group reported that the Buchwald–Hartwig methodology can be used to synthesize dipyrido[1,2-*a*:3′,2′-*d*]imidazole, the core skeleton of Glu-P's, via auto-tandem Pd-catalyzed amination of 2-chloro-3-iodopyridine with 2-aminopyridine.[16] Aza and benzo analogues could also be obtained in a similar way using the corresponding amino(benzo)(di)azines (Scheme 2b). Recently, we also synthesized regioisomers of these

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* Corresponding author. Tel.: +3232653205; fax: +3232653233; e-mail: bert.maes@ua.ac.be

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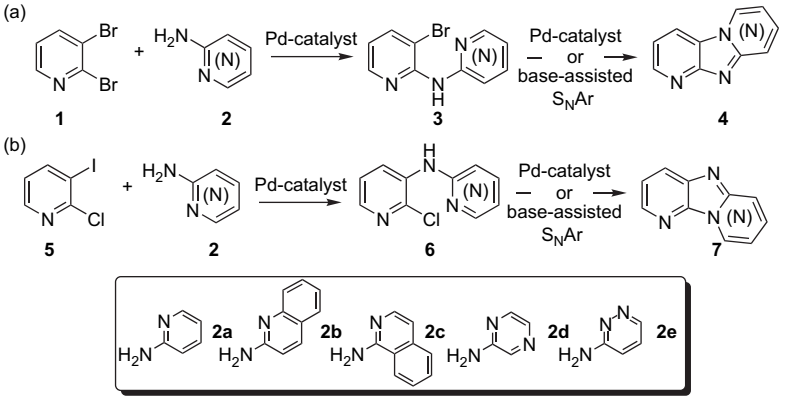


Scheme 2. Possible mechanistic pathways for the synthesis of dipyrido[1,2-*a*:2′,3′-*d*]imidazole, dipyrido[1,2-*a*:3′,2′]imidazole, and their benzo and aza analogues.

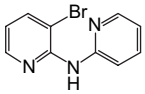
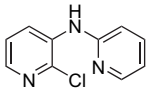
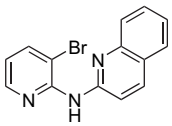
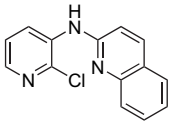
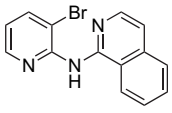
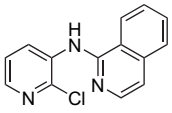
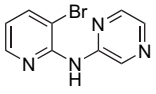
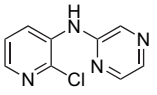
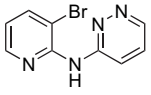
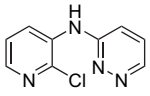
Glu-P analogues via an auto-tandem Pd-catalyzed or an orthogonal-tandem Pd-catalyzed inter and Cu-catalyzed intramolecular amination on 2,3-dibromopyridine with amino(benzo)(di)azines (Scheme 2a).[17] When only a Pd-catalyst is required for the amination reactions the mechanism of the intramolecular amination remains undefined since it can in principle proceed via a Pd-catalyzed mechanism as well as via a nucleophilic aromatic substitution reaction. In the former case the reaction is auto-tandem catalyzed, while in the latter case no tandem catalysis but a tandem reaction (involving an intermolecular Pd-catalyzed amination and an intramolecular S_NAr) is occurring. Full comprehension of the mechanism of the cyclization step is interesting from a fundamental point of view and is moreover highly valuable in order to be able to perform a further rational optimization of the tandem reaction conditions. In this paper information on the mechanism of the intramolecular amination is gained by studying the cyclization of the intermediates of the double amination on 2,3-dibromopyridine (**1**) (*N*-(3-bromopyridin-2-yl)azaheteroarylamines **3**) and 2-chloro-3-iodopyridine (**5**) (*N*-(2-chloropyridin-3-yl)azaheteroarylamines **6**).

2. Results and discussion

We previously found that for the intramolecular amination of *N*-(3-bromopyridin-2-yl)pyridin-2-amine (**3a**) and *N*-(3-bromopyridin-2-yl)pyrazin-2-amine (**3d**), the use of CuI catalyst was essential.[17] Only the simultaneous use of $Pd_2(dba)_3$/XANTPHOS and CuI gave access to dipyrido-[1,2-*a*:2′,3′-*d*]imidazole (**4a**) and pyrido[2′,3′:4,5]imidazo-[1,2-*a*]pyrazine (**4d**) starting from 2,3-dibromopyridine, 2-aminopyridine, and aminopyrazine, respectively. For the double amination of 2,3-dibromopyridine (**1**) with 2-aminoquinoline (**2b**), 1-aminoisoquinoline (**2c**), and 3-aminopyridazine (**2e**) the use of $Pd_2(dba)_3$/XANTPHOS was sufficient to get double amination. To exclude a base-assisted addition–elimination ring closure mechanism, *N*-(3-bromopyridin-2-yl)quinolin-2-amine (**3b**), *N*-(3-bromopyridin-2-yl)isoquinolin-1-amine (**3c**), and *N*-(3-bromopyridin-2-yl)-pyridazin-3-amine (**3e**) were therefore subjected to the same reaction conditions and heated for the same reaction time as used for the presumed auto-tandem protocol, only the Pd-catalyst was omitted (Cs_2CO_3 and DME at 140 °C for 24 h). Interestingly, **3b** and **3e** were partly converted to pyrido[2′,3′:4,5]imidazo[1,2-*a*]quinoline (**4b**) (53%) and pyrido[2′,3′:4,5]imidazo[1,2-*b*]pyridazine (**4e**) (87%), respectively (Table 1).[18] These results imply that during the tandem process on **1** the ring closure not only proceeds via a Buchwald–Hartwig intramolecular amination but also partly through a base-assisted addition–elimination pathway. Interestingly, the ring closure of **3c** gave an isolated yield of 97% of pyrido[2′,3′:4,5]imidazo[2,3-*a*]isoquinoline (**4c**) (Table 1). Of course, this ring closure experiment on **3c** does not exclude that metal catalyst is additionally involved in the second step of the tandem process on **1** with 1-aminoisoquinoline (**2c**).

These remarkable results inspired us to investigate whether these base-assisted addition–elimination cyclization reactions also occur in the presumed auto-tandem Pd-catalyzed inter- and intramolecular amination of 2-chloro-3-iodopyridine (**5**) with amino(benzo)(di)azines (**2**) (Scheme 2b).[16] Therefore the *N*-(2-chloropyridin-3-yl)azaheteroarylamines (**6**)[19] were heated under the same reaction conditions and for the same reaction time as used for the presumed auto-tandem protocol only the Pd-catalyst was omitted (Cs_2CO_3 and toluene at reflux for 17 h). The reaction with *N*-(2-chloropyridin-3-yl)isoquinolin-1-amine (**6c**) gave full conversion and pyrido[3′,2′:4,5]imidazo[2,3-*a*]isoquinoline (**7c**) was isolated in 99% yield. Of course, this experiment does not exclude that metal catalyst is additionally involved in the second step of the tandem process on **5** with 1-aminoisoquinoline (**2c**). On the contrary, the intramolecular amination with the other analogues of **6** only gave traces of ring-closed product and for these amidines the corresponding tandem processes surely involve only Pd-catalysis in the ring closure reaction. At this stage of the project the question raised whether the reactivity of the base-assisted ring closure was either influenced by the halopyridine or by the amidine moiety. General conclusions can of course only be made, provided that the ring closure of **3** and **6** are performed under exactly the same reaction conditions. Therefore the cyclizations of **3** were first performed under the same reaction conditions as used for **6** (Cs_2CO_3 and toluene at reflux for 17 h). Only the intramolecular amination of **3c** gave some conversion into **4c** (11%) but the remaining analogues of **3** were completely recovered after 17 h. Secondly, the cyclizations of **6** were also investigated under the same reaction conditions of **3** (Cs_2CO_3 and DME at 140 °C for 24 h). *N*-(2-Chloropyridin-3-yl)pyridin-2-amine

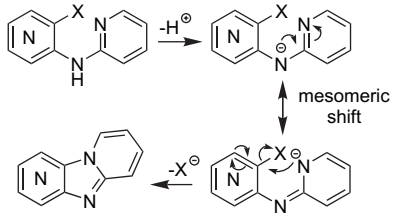
Table 1. Attempted ring closure of *N*-(3-bromopyridin-2-yl)azaheteroarylamines **3**, and *N*-(2-chloropyridin-3-yl)azaheteroarylamines **6** via S_NAr

Compound **3**	DME 140 °C[a] (%)		Toluene reflux[b] (%)		Compound **6**	DME 140 °C[a] (%)		Toluene reflux[b] (%)	
	3	**4**	**3**	**4**		**6**	**7**	**6**	**7**
 **3a**	100[c]	0[c]	99	0	 **6a**	94	3	95	5
 **3b**	39	53	98	0	 **6b**	52	42	88	2
 **3c**	0	93	83	11	 **6c**	0	96	0	99
 **3d**	100[c]	0[c]	96	0	 **6d**	59	31	98	0
 **3e**	12	87	98	0	 **6e**	0	72	94	3

[a] Compound **3** or **6** (0.5 mmol), Cs_2CO_3 (2.0 mmol), DME (5 mL), 160 °C (oil bath). Experiments were performed in a 10 mL microwave vial.
[b] Compound **3** or **6** (0.5 mmol), Cs_2CO_3 (2.0 mmol), toluene (5 mL), 120 °C (oil bath). Experiments were performed in a 25 mL flask.
[c] Via an auto-tandem Pd-catalyzed amination protocol **4a** and **4d** could not be formed. These results imply that also via a nucleophilic aromatic substitution reaction using the same base at the same reaction temperature **4a** and **4d** cannot be synthesized.

(**6a**) could almost fully be recovered. Merely 3% of dipyrido[1,2-*a*:3′,2′-*d*]imidazole (**7a**) was formed. *N*-(2-Chloropyridin-3-yl)quinolin-2-amine (**6b**) and *N*-(2-chloropyridin-3-yl)pyrazin-2-amine (**6d**) gave partial conversion since pyrido[3′,2′:4,5]imidazo[1,2-*a*]quinoline (**7b**) and pyrido[3′,2′:4,5]imidazo[1,2-*a*]pyrazine (**7d**) were isolated in, respectively, 42% and 31%. *N*-(2-Chloropyridin-3-yl)pyridazin-3-amine (**6e**) and *N*-(2-chloropyridin-3-yl)isoquinolin-1-amine (**6c**) gave full conversion. All the obtained results are summarized in Table 1.

When one looks at the cyclization data of **6a–e** (DME, 140 °C) in Table 1 the following amidine sequence (going from a low to a high conversion in 24 h) can be deduced: 2-aminopyridine<aminopyrazine<2-aminoquinoline<3-aminopyridazine<1-aminoisoquinoline. Interestingly, the reactivity of the substrates **3a–e** under the same reaction conditions seems to follow the same sequence. The only difference is that **6d** still undergoes base-assisted nucleophilic aromatic substitution and **3d** does not give any conversion. Also in toluene a trend can be seen but in this case only the most reactive amidine (of the sequence observed in DME at 140 °C) namely the isoquinoline derivatives **3c** and **6c** give conversion. Since the reaction conditions in toluene are less harsh it is not surprising that only the most reactive amidine gives cyclization. These observations can be rationalized in view of the reaction mechanism. After deprotonation the aromaticity of the ring that contains the amidine must be broken in order to enable the mesomeric electron pair shift of the negative charge toward the endocyclic nitrogen (Scheme 3). Therefore one can expect that the ring with the lowest aromaticity is the most reactive for S_NAr. The fact that in DME at 140 °C **6d** can undergo S_NAr and **3d** cannot, can be explained on the basis of the reactivity of the halopyridine part. After all, a bromine atom in the β-position of a pyridine nucleus is less reactive for nucleophilic substitution than a chlorine atom in the α-position.



Scheme 3. Reaction mechanism of the cyclization via S_NAr.

To support the aromaticity theory, for the different ring structures containing the amidine moiety, theoretical information on the resonance energy was obtained by applying the model described by Bird.[20] For all species under study, the equilibrium geometry was calculated at the B3LYP/6-31G(d,p) level. Subsequently, the calculated values for the carbon–carbon, the carbon–nitrogen, and the nitrogen–nitrogen bond lengths were used to estimate the resonance energy. The resulting values for the resonance energies, obtained by weighting the values derived from the different resonance

Table 2. Resonance energies, in kJ mol^{-1}, for the amidine fragments in the *N*-(3-bromopyridin-2-yl)azaheteroarylamines **3** and *N*-(2-chloropyridin-3-yl)azaheteroarylamines **6**

3	RE (kJ mol^{-1})[a]	**6**	RE (kJ mol^{-1})[a]
3a	42.1	**6a**	42.9
3b	23.2 (69.2)[b]	**6b**	24.4 (70.4)[b]
3c	23.0 (69.0)[b]	**6c**	24.1 (70.1)[b]
3d	38.2	**6d**	39.2
3e	32.6	**6e**	34.3

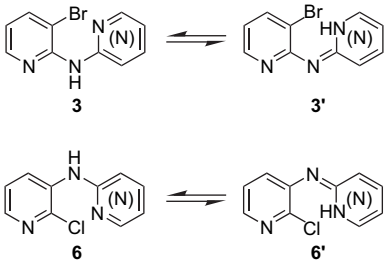
[a] The resonance energies were obtained using a procedure similar to that reported by Bird.[20] The carbon–carbon, carbon–nitrogen and nitrogen–nitrogen bond lengths used were derived from DFT geometry optimizations, at the B3LYP/6-31G(d,p) level.

[b] The values for **3b**, **6b**, **3c**, and **6c**, given in brackets, refer to the resonance energy of the complete bicyclic system; the other values refer to the resonance energy of the ring structure involved in the reaction.

structures involved, are summarized in Table 2. For the 2-aminoquinoline (**3b** and **6b**) and 1-aminoisoquinoline (**3c** and **6c**) derivatives, two different values are reported, which correspond to the resonance energy of the whole system and that of the ring structure (pyridine moiety) directly involved in the reaction. The latter is calculated by subtracting the value for benzene (46.0 kJ mol^{-1}), obtained using the same procedure, from the resonance energy of the complete bicyclic system.

For our series of (di)azines the theoretical resonance energy sequence matches perfectly with the experimental observations. The resonance energy of the aminobenzazines should, however, be interpreted with care when one wants to incorporate them in the amino(di)azine list as the aromaticity of the entire bicyclic system is calculated. Therefore the value obtained by subtracting the resonance energy of benzene should be used for the aminobenzazines. However, this still yields a general sequence for the (di)azines and aminobenzazines, which is not fully, but almost, in agreement with the observed S_NAr reactivity (sequence based on calculated resonance energies: 1-aminoisoquinoline>2-aminoquinoline>3-aminopyridazine>aminopyrazine>2-aminopyridine; sequence based on the experimentally observed reactivity: 1-aminoisoquinoline>3-aminopyridazine>2-aminoquinoline>aminopyrazine>2-aminopyridine). In contrast with the small difference in the calculated values obtained between the 1-aminoisoquinoline and 2-aminoquinoline derivatives (Table 2) their difference in reactivity is significant. The variation of the reactivity can easily be explained by taking into account the geometric difference between these two amidines, which is of course not incorporated in our calculated resonance energy values. The *peri*-hydrogen of the benzene moiety of **3b** and **6b** hampers the nucleophilic attack of the endocyclic nitrogen of the amidine onto the halopyridine part sterically, in comparison with **3c** and **6c**. Therefore the reactivity of **3b** and **6b** is less than that expected on the basis of the resonance energy and drops from the second to the third place (taking the calculated resonance energies as reference list) yielding the experimentally observed sequence 1-aminoisoquinoline>3-aminopyridazine>2-aminoquinoline>aminopyrazine>2-aminopyridine.

Since the intramolecular amination reaction of our auto- and orthogonal-tandem catalysis seems to involve a nitrogen atom that is not substituted with a hydrogen atom, we wondered whether the proton indeed is removed from the exocyclic nitrogen atom during the catalytic cycle or a tautomeric equilibrium has to be taken into account for the amidines. Therefore the equilibrium constants between the tautomers **3** and **3′** and **6** and **6′** were calculated (Scheme 4). Theoretical information on the differences in free energy ΔG and the equilibrium constants for the tautomeric equilibria **3/3′** and **6/6′** were obtained from density functional calculations, at the B3LYP/6-31G(d,p) level. To this end, for all species under interest, geometry optimizations and frequency calculations were performed. For the chlorine containing species, the effect of the solvent was modeled by using the polarizable continuum (SCRF) model developed by Barone and co-workers,[21,22] and by using the internally stored parameters for toluene. For the bromine containing molecules, the SCRF model was used in combination with the parameters for THF, which has solvent properties similar to those of the DME used in the experimental study. The differences in free energy ΔG and the equilibrium constants, obtained by applying standard statistical thermodynamics, are summarized in Table 3.[23] The values clearly show that the presence of the tautomers with the hydrogen atom on the endocyclic nitrogen (**3′** and **6′**) can be neglected. These data therefore clearly support our previous hypothesis that the endocyclic nitrogen atom of the amidine, that is not substituted with a hydrogen atom, can indeed be involved in an intramolecular Pd- or Cu-catalyzed amination reaction and deprotonation (of the exocyclic nitrogen atom) occurs after metal coordination of the endocyclic nitrogen of the amidine (Schemes 5 and 6).[16,17]



Scheme 4. Possible tautomers of **3** and **6**.

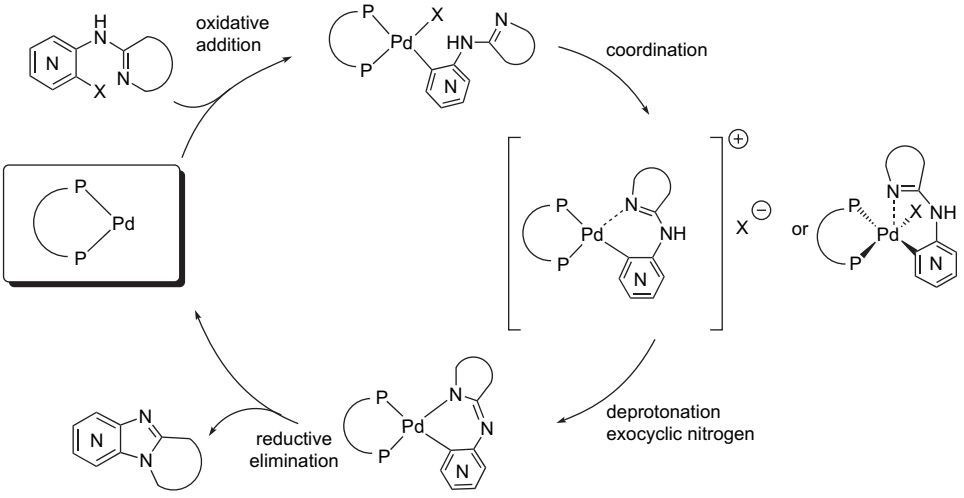
Table 3. B3LYP/6-31G(d,p) free energy differences ΔG, in kJ mol^{-1}, and equilibrium constants for the tautomeric equilibria **3/3′** and **6/6′**

Compound **3**	ΔG/kJ mol^{-1}	K_{eq}	Compound **6**	ΔG/kJ mol^{-1}	K_{eq}
3a	39.2	8.1×10^{-7}	**6a**	47.5	5.4×10^{-9}
3b	17.8	7.9×10^{-4}	**6b**	31.2	3.7×10^{-6}
3c	17.6	8.6×10^{-4}	**6c**	21.9	1.5×10^{-4}
3d	46.9	6.8×10^{-9}	**6d**	52.0	8.8×10^{-10}
3e	25.8	3.2×10^{-5}	**6e**	22.2	1.4×10^{-4}

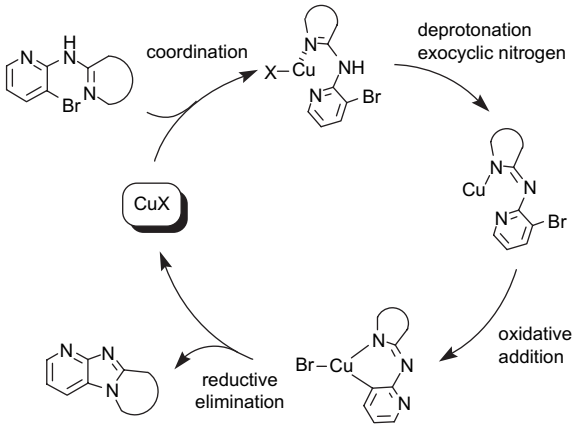
The values for **3/3′** were obtained for a solution in THF; while those for **6/6′** were obtained for a solution in toluene.

3. Conclusion

In conclusion we examined the intramolecular amination of *N*-(3-bromopyridin-2-yl)azaheteroarylamines **3** and *N*-(2-chloropyridin-3-yl)azaheteroarylamines **6**. Two possible cyclization pathways are observed: Pd-catalyzed amination and base-assisted nucleophilic aromatic substitution. We found that the occurrence of the base-assisted nucleophilic



Scheme 5. Mechanistic proposal for the intramolecular Pd-catalyzed amination of **3** and **6**.



Scheme 6. Mechanistic proposal for the intramolecular Cu-catalyzed amination of **3**.

aromatic substitution depends on the aromaticity of the ring that contains the amidine moiety. The experimental reactivity sequence (2-aminopyridine<aminopyrazine<2-aminoquinoline<3-aminopyridazine<1-aminoisoquinoline) is in agreement with the calculated resonance energy of the ring that contains the amidine in **3** and **6** (the lower its aromaticity the higher the S_NAr reactivity), taking into account the steric effect when a quinoline moiety is involved. For intramolecular aminations that occur via the involvement of a metal catalyst we gained evidence that nitrogen atoms that are not substituted with a hydrogen atom can indeed be involved in the catalytic cycle.

4. Experimental section

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. Accurate mass data were acquired on a Q-TOF 2 (Micromass) mass spectrometer 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 lock mass. For the product ion experiments (MS) the mass of the $[M+H]^+$was used as lock mass for the fragments. Fragmentation was induced by low energy collisional activation using different collision energies of 20 eV. All signals with a signal-to-noise ratio ≥5/1 were reported. Density Functional theory (DFT) calculations were performed with the use of Gaussian03/TCP Linda as implemented in the CalcUA supercomputing cluster.[24] For all calculations the B3LYP methodology was used, while the effects of the solvent were modeled using the polarizable continuum model developed by Barone and co-workers.[21,22] All reagents (except 3-aminopyridazine) are obtained form commercial sources and used without extra purification. 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 (ethylene glycol dimethyl ether) from Acros and (±)-BINAP (2,2′-bis(diphenylphosphino)-1,1′-binaphthyl) from Rhodia. 3-Aminopyridazine was prepared from 3-amino-6-chloropyridazine via hydrogenolysis.[25] Flash column chromatography was performed on Kieselgel 60 (ROCC SI 1721, 40–60 μm).

4.1.1. General procedure for the preparation of *N*-(2-chloropyridin-3-yl)azaheteroarylamines (6).[26] A round-bottomed flask of 50 mL was charged with $Pd(OAc)_2$ (0.12 mmol, 0.027 g), (±)-BINAP (0.12 mmol, 0.0747 g) or XANTPHOS (0.12 mmol, 0.069 g), and toluene

(10 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 (3.0 mmol, 0.722 g), amidine (**2**) (3.6 mmol), and cesium carbonate (12 mmol, 3.910 g). To this mixture, the preformed Pd(II) precatalyst was added under a N_2 flow. The flask of 50 mL was subsequently rinsed with toluene (2×10 mL). Then the resulting mixture was flushed with N_2 for 5 min and heated at reflux (oil bath temperature: 120 °C) (N_2 atmosphere) under vigorous magnetic stirring. After cooling down the reaction mixture to room temperature, dichloromethane (20 mL) was added and the suspension was filtered over a glass filter. The filter was rinsed well with dichloromethane (130 mL) and the filtrate evaporated under reduced pressure. The residue was purified by flash column chromatography on silica gel using dichloromethane/methanol (99/1) as the eluent.

4.1.1.1. *N*-(2-Chloropyridin-3-yl)pyridin-2-amine (6a). The general procedure was followed using 2-aminopyridine **2a** (3.6 mmol, 0.338 g) as amine and *rac*-BINAP as ligand. Reaction time: 8 h; white solid; mp: 117 °C; ^{1}H NMR (400 MHz, $CDCl_3$): 8.76 (1H, dd, *J*=8.0, 1.7 Hz), 8.26 (1H, dd, *J*=5.0, 1.9 Hz), 7.97 (1H, dd, *J*=4.6, 1.7 Hz), 7.58 (1H, ddd, *J*=8.8, 6.7, and 1.9 Hz), 7.21 (1H, dd, *J*=8.0, 4.6 Hz), 6.92 (1H, s, NH), 6.87 (1H, dd, *J*=6.7, 5.0 Hz), 6.82 (1H, d, *J*=8.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): 154.4, 148.1, 141.0, 139.6, 138.0, 134.8, 126.3, 123.2, 116.9, 111.5; MS (ESI): 206, 170, 143; HRMS (ESI) for $C_{10}H_9N_3{}^{35}Cl$ $[M+H]^+$: calcd: 206.0485, found: 206.0860.

4.1.1.2. *N*-(2-Chloropyridin-3-yl)quinolin-2-amine (6b). The general procedure was followed using 2-aminoquinoline **2b** (3.6 mmol, 0.520 g) as amine and *rac*-BINAP as ligand. Reaction time: 4 h; white solid; mp: 136 °C; ^{1}H NMR (400 MHz, $CDCl_3$): 9.36 (1H, dd, *J*=8.2, 1.7 Hz), 8.02 (1H, dd, *J*=4.7, 1.7 Hz), 8.01 (1H, d, *J*=8.7 Hz), 7.86 (1H, d, *J*=8.3 Hz), 7.69 (1H, d, *J*=8.0 Hz), 7.64 (1H, dd, *J*=8.3, 7.0 Hz), 7.38 (1H, dd, *J*=8.0, 7.0 Hz), 7.31 (1H, dd, *J*=8.2, 4.7 Hz), 7.18 (1H, s, NH), 6.95 (1H, d, *J*=8.7 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): 152.5, 146.8, 141.2, 139.3, 138.1, 134.3, 130.1, 127.5, 127.2, 127.0, 124.4, 124.2, 123.2, 113.5; MS (ESI): 256, 220; HRMS (ESI) for $C_{14}H_{11}N_3{}^{35}Cl$ $[M+H]^+$: calcd: 256.0642, found: 256.0363.

4.1.1.3. *N*-(2-Chloropyridin-3-yl)isoquinolin-1-amine (6c). The general procedure was followed using 1-aminoisoquinoline **2c** (3.6 mmol, 0.520 g) as amine and *rac*-BINAP as ligand. Reaction time: 4 h; white solid; mp: 108 °C; ^{1}H NMR (400 MHz, $CDCl_3$): 9.12 (1H, br d, *J*=8.1 Hz), 8.11 (1H, d, *J*=5.7 Hz), 8.05 (1H, dd, *J*=4.7, 1.6 Hz), 8.02 (1H, d, *J*=8.4 Hz), 7.81 (1H, d, *J*=8.0 Hz), 7.72 (1H, dd, *J*=8.0, 7.0 Hz), 7.64 (1H, dd, *J*=8.4, 7.0 Hz), 7.29 (1H, dd, *J*=8.1, 4.7 Hz), 7.25 (1H, br d, *J*=6.3 Hz, not resolved); ^{13}C NMR (100 MHz, $CDCl_3$): 151.0, 141.2, 140.2, 139.6, 137.4, 134.3, 120.3, 127.7, 127.3 (2*C), 123.2, 121.1, 119.2, 114.9; MS (ESI): 256, 220, 128; HRMS (ESI) for $C_{14}H_{11}N_3{}^{35}Cl$ $[M+H]^+$: calcd: 256.0642, found: 256.0639.

4.1.1.4. *N*-(2-Chloropyridin-3-yl)pyrazin-2-amine (6d). The general procedure was followed using aminopyrazine **2d** (3.6 mmol, 0.342 g) as amine and *rac*-BINAP as ligand. Reaction time: 8 h; white solid; mp: 108 °C; ^{1}H NMR (400 MHz, $CDCl_3$): 8.81 (1H, dd, *J*=8.1, 1.8 Hz), 8.29 (1H, d, *J*=1.5 Hz), 8.18 (1H, dd, *J*=2.6, 1.5 Hz), 8.12 (1H, d, *J*=2.6 Hz), 8.04 (1H, dd, *J*=4.6, 1.8 Hz), 7.26 (1H, dd, *J*=8.1, 4.6 Hz), 7.1 (1H, s, NH); ^{13}C NMR (100 MHz, $CDCl_3$): 150.9, 141.9, 141.3, 139.7, 136.3, 135.0, 133.5, 126.7, 123.2; MS (ESI): 207, 189, 171; HRMS (ESI) for $C_9H_8N_4{}^{35}Cl$ $[M+H]^+$: calcd: 207.0954, found: 207.0430.

4.1.1.5. *N*-(2-Chloropyridin-3-yl)pyridazin-3-amine (6e). The general procedure was followed using 3-aminopyridazine **2e** (3.6 mmol, 0.342 g) as amine and XANTPHOS as ligand. Reaction time: 8 h; white solid; mp: 153 °C; ^{1}H NMR (400 MHz, $CDCl_3$): 8.88 (1H, dd, *J*=8.2, 1.5 Hz), 8.81 (1H, br d, *J*=4.6 Hz), 8.08 (1H, dd, *J*=4.6, 1.5 Hz), 7.40 (1H, dd, *J*=9.0, 4.6 Hz), 7.29 (1H, dd, *J*=8.2, 4.6 Hz), 7.07 (1H, dd, *J*=9.0, 1.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): 156.2, 145.8, 142.8, 140.7, 133.0, 128.7, 128.5, 123.4, 117.1; MS (ESI): 207, 171, 144; HRMS (ESI) for $C_9H_8N_4{}^{35}Cl$ $[M+H]^+$: calcd: 207.0954, found: 207.0430.

4.1.2. General procedure I for the attempted ring closure of *N*-(3-bromopyridin-2-yl)azaheteroarylamines (3) or *N*-(2-chloropyridin-3-yl)azaheteroarylamines (6) via S_NAr. In a 10 mL microwave vial (Discover system) **3** (0.5 mmol) or **6** (0.5 mmol) and cesium carbonate (2.0 mmol, 0.652 g) (Aldrich, 99%) were weighed. DME (5 mL) was added and the resulting mixture was heated (oil bath temperature: 160 °C) with vigorous stirring for 24 h. After cooling down to room temperature the reaction mixture was filtered over a glass filter and (a) rinsed with dichloromethane (150 mL) for compounds **4b**, **4c**, **7a**, **7b**, and **7c** or (b) rinsed with 7 N NH_3 in MeOH (75 mL) and dichloromethane (50 mL) for compounds **4e**, **7d**, and **7e**. The solvent was removed under reduced pressure and the residue was purified by column chromatography on silica gel using dichloromethane/methanol (99:1) as the eluent to recover **3** and **6** and dichloromethane/methanol (97:3) to isolate **4** and **7**.

4.1.2.1. Pyrido[2′,3′:4,5]imidazo[1,2-*a*]quinoline (4b). General procedure I was followed using **3b** (0.50 mmol, 0.150 g). Yield: 0.058 g (53%); the characterization data obtained for **4b** are identical to those previously reported.[17]

4.1.2.2. Pyrido[2′,3′:4,5]imidazo[2,3-*a*]isoquinoline (4c). General procedure I was followed using **3c** (0.50 mmol, 0.150 g). Yield: 0.101 g (92%); the characterization data obtained for **4c** are identical to those previously reported.[17]

4.1.2.3. Pyrido[2′,3′:4,5]imidazo[1,2-*b*]pyridazine (4e). General procedure I was followed using **3e** (0.50 mmol, 0.125 g). Yield: 0.109 g (87%); the characterization data obtained for **4e** are identical to those previously reported.[17]

4.1.2.4. Pyrido[3′,2′:4,5]imidazo[1,2-*a*]pyridine (7a). General procedure I was followed using **6a** (0.50 mmol, 0.103 g). Yield: 0.003 g (3%); the characterization data obtained for **7a** are identical to those previously reported.[16]

4.1.2.5. Pyrido[3′,2′:4,5]imidazo[1,2-*a*]quinoline (7b). General procedure I was followed using **6b** (0.50 mmol,

0.128 g). Yield: 0.046 g (42%); the characterization data obtained for **7b** are identical to those previously reported.[16]

4.1.2.6. Pyrido[3′,2′:4,5]imidazo[2,1-*a*]isoquinoline (7c). General procedure I was followed using **6c** (0.50 mmol, 0.128 g). Yield: 0.106 g (96%); the characterization data obtained for **7c** are identical to those previously reported.[16]

4.1.2.7. Pyrido[3′,2′:4,5]imidazo[1,2-*a*]pyrazine (7d). General procedure I was followed using **6d** (0.50 mmol, 0.103 g). Yield: 0.026 g (31%); the characterization data obtained for **7d** are identical to those previously reported.[16]

4.1.2.8. Pyrido[3′,2′:4,5]imidazo[1,2-*b*]pyridazine (7e). General procedure I was followed using **6a** (0.50 mmol, 0.103 g). Yield: 0.061 g (72%); the characterization data obtained for **7e** are identical to those previously reported.[16]

4.1.3. General procedure II for the attempted ring closure of *N*-(2-chloropyridin-3-yl)azaheteroarylamines (6) or *N*-(3-bromopyridin-2-yl)azaheteroarylamines (3) via S_NAr. In a 25 mL flask **6** (0.5 mmol) or **3** (0.5 mmol) and cesium carbonate (2.0 mmol, 0.652 g) (Aldrich, 99%) were weighed. Toluene (5 mL) was added and the resulting mixture was heated (oil bath temperature: 120 °C) with vigorous stirring for 17 h. After cooling down to room temperature the reaction mixture was filtered over a glass filter and (a) rinsed with dichloromethane (150 mL) for compounds **4b**, **4c**, **7a**, **7b**, and **7c** or (b) rinsed with 7 N NH_3 in MeOH (75 mL) and dichloromethane (50 mL) for compounds **4e**, **7d**, and **7e**. The solvent was removed under reduced pressure and the residue was purified by column chromatography on silica gel using dichloromethane/methanol (99:1) as the eluent to recover **3** and **6** and dichloromethane/methanol (97:3) to isolate **4** and **7**.

4.1.3.1. Pyrido[3′,2′:4,5]imidazo[1,2-*a*]pyridine (7a). General procedure II was followed using **6a** (0.50 mmol, 0.103 g). Yield: 0.004 g (5%).

4.1.3.2. Pyrido[3′,2′:4,5]imidazo[1,2-*a*]quinoline (7b). General procedure II was followed using **6b** (0.50 mmol, 0.128 g). Yield: 0.002 g (2%).

4.1.3.3. Pyrido[3′,2′:4,5]imidazo[2,1-*a*]isoquinoline (7c). General procedure II was followed using **6c** (0.50 mmol, 0.128 g). Yield: 0.109 g (99%).

4.1.3.4. Pyrido[3′,2′:4,5]imidazo[1,2-*a*]pyrazine (7d). General procedure II was followed using **6d** (0.50 mmol, 0.103 g). Yield: 0 g (0%).

4.1.3.5. Pyrido[3′,2′:4,5]imidazo[1,2-*b*]pyridazine (7e). General procedure II was followed using **6e** (0.50 mmol, 0.103 g). Yield: 0.003 g (3%).

4.1.3.6. Pyrido[2′,3′:4,5]imidazo[1,2-*b*]pyridine (4a). General procedure II was followed using **3a** (0.50 mmol, 0.125 g). Yield: 0 g (0%).

4.1.3.7. Pyrido[2′,3′:4,5]imidazo[1,2-*a*]quinoline (4b). General procedure II was followed using **3b** (0.50 mmol, 0.150 g). Yield: 0 g (0%).

4.1.3.8. Pyrido[2′,3′:4,5]imidazo[2,3-*a*]isoquinoline (4c). General procedure II was followed using **3c** (0.50 mmol, 0.150 g). Yield: 0.012 g (11%).

4.1.3.9. Pyrido[2′,3′:4,5]imidazo[1,2-*b*]pyrazine (4d). General procedure II was followed using **3d** (0.50 mmol, 0.125 g). Yield: 0 g (0%).

4.1.3.10. Pyrido[2′,3′:4,5]imidazo[1,2-*b*]pyridazine (4e). General procedure II was followed using **3e** (0.50 mmol, 0.125 g). Yield: 0 g (0%).

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References and notes

1. Sugimura, T. *Mutat. Res.* **1997**, *376*, 211–219.
2. Kataoka, H. *J. Chromatogr., A* **1997**, *774*, 121–142.
3. Toribio, F.; Moyano, E.; Puignou, L.; Galceran, M. T. *J. Chromatogr., A* **2002**, *948*, 267–281.
4. Wakabayashi, K.; Sugimura, T. *J. Nutr. Biochem.* **1998**, *9*, 604–612.
5. Takeda, K.; Shudo, K.; Okamoto, T.; Kosuge, T. *Chem. Pharm. Bull.* **1978**, *26*, 2924–2925.
6. Novak, M.; Toth, K.; Rajagopal, S.; Brooks, M.; Hott, L. L.; Moslener, M. *J. Am. Chem. Soc.* **2002**, *124*, 7972–7981.
7. Hashimoto, Y.; Shudo, K.; Okamoto, T. *J. Am. Chem. Soc.* **1982**, *104*, 7636–7640.
8. Weisburger, J. H. *Nutrition* **2000**, *16*, 767–773.
9. Imamura, M.; Takeda, K.; Shudo, K.; Okamoto, T.; Nagata, C.; Kodama, M. *Biochem. Biophys. Res. Commun.* **1980**, *96*, 611–617.
10. Guram, A. S.; Rennels, R. A.; Buchwald, S. L. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 1348–1350.
11. Louie, J.; Hartwig, J. F. *Tetrahedron Lett.* **1995**, *36*, 3609–3612.
12. Hartwig, J. F. *Synlett* **2006**, 1283–1294.
13. Littke, A. F.; Fu, G. C. *Angew. Chem., Int. Ed.* **2002**, *41*, 4176–4211.
14. Schlummer, B.; Scholz, U. *Adv. Synth. Catal.* **2004**, *346*, 1599–1626.
15. Yang, B. H.; Buchwald, S. L. *J. Organomet. Chem.* **1999**, *576*, 125–146.
16. Loones, K. T. J.; Maes, B. U. W.; Dommisse, R. A.; Lemière, G. L. F. *Chem. Commun.* **2004**, 2466–2467.
17. Loones, K. T. J.; Maes, B. U. W.; Meyers, C.; Deruytter, J. *J. Org. Chem.* **2006**, *71*, 260–264.
18. In our previous publication (Ref. 17) an incorrect yield for the attempted ring closure of **3e** via S_NAr was published. The correct yield is 87%.

19. The *N*-(2-chloropyridin-3-yl)azaheteroarylamines are synthesized using the conditions for the synthesis of dipyrido[1,2-*a*:3′,2′-*d*]imidazole and its benzo and aza analogues (see Ref. 16), only the reaction time was shortened.
20. Bird, C. W. *Tetrahedron* **1997**, *53*, 13111–13118.
21. Cossi, M.; Rega, N.; Scalmani, G.; Barone, V. *J. Chem. Phys.* **2001**, *114*, 5691–5701.
22. Cossi, M.; Scalmani, G.; Rega, N.; Barone, V. *J. Chem. Phys.* **2002**, *117*, 43–54.
23. McQuarrie, D. A.; Simon, J. D. *Physical Chemistry: A Molecular Approach*, 2nd ed.; University Science Books: Sausalito, 1997.
24. Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Montgomery, J. A., Jr.; Vreven, T.; Kudin, K. N.; Burant, J. C.; Millam, J. M.; Iyengar, S. S.; Tomasi, J.; Barone, V.; Mennucci, B.; Cossi, M.; Scalmani, G.; Rega, N.; Petersson, G. A.; Nakatsuji, H.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Klene, M.; Li, X.; Knox, J. E.; Hratchian, H. P.; Cross, J. B.; Bakken, V.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Ayala, P. Y.; Morokuma, K.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Zakrzewski, V. G.; Dapprich, S.; Daniels, A. D.; Strain, M. C.; Farkas, O.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Ortiz, J. V.; Cui, Q.; Baboul, A. G.; Clifford, S.; Cioslowski, J.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Challacombe, M.; Gill, P. M. W.; Johnson, B.; Chen, W.; Wong, M. W.; Gonzalez, C.; Pople, J. A. *Gaussian 03, Revision C.02*; Gaussian: Wallingford, CT, 2004.
25. Turck, A.; Plé, N.; Ndzi, B.; Quéguiner, G.; Haider, N.; Schuller, H.; Heinisch, G. *Tetrahedron* **1993**, *49*, 599–606.
26. The reaction conditions are not optimized.