Synthesis of Nitro *N*,*N*′-Dipyridinylamines via Oxidative Nucleophilic Substitution of Hydrogen

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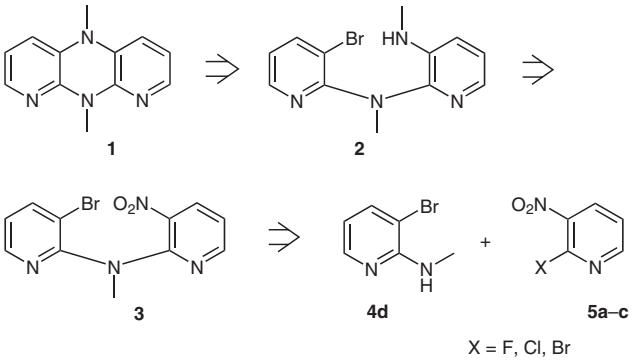
Abstract: The amination of 3-nitropyridines with aromatic amides generated from various aminopyridine derivatives proceeded unexpectedly in the position *para* to the nitro group, giving the oxidative nucleophilic substitution of hydrogen (ONSH) derived compounds. After optimization, this reaction allowed easy access to interesting 3-nitro-substituted *N*,*N*′-dipyridinylamines.

Key words: heterocycles, pyridines, amination, nucleophilic aromatic substitution, palladium

Synthetic approaches to aminopyridine derivatives continue to receive considerable attention both due to their presence in numerous natural products[1] and due to their potential application in the synthesis of a wide variety of compounds with pharmacological activity.[2] Strategies for the selective synthesis of aminopyridine derivatives include modification of commercially available aminopyidines,[3] selective nitration and reduction of pyridines,[4] and *de novo* construction of the pyridine nucleus incorporating properly disposed amino groups,[5] as well as nucleophilic substitution of halopyridines with appropriate amines.[6]

Nucleophilic aromatic substitution (S_NAr) is one of the most widely used approaches for the functionalization of aromatics and forms the backbone of various important syntheses of pharmaceuticals and potential drugs.[7]

In connection with our previous studies to develop the univocal synthesis of dihydrodipyridopyrazines[8] (DHDPP) **1** (Scheme 1), which are potential antitumor compounds,[9] we considered that the nucleophilic aromatic substitution could be exploited in the construction of the key intermediate **3**.

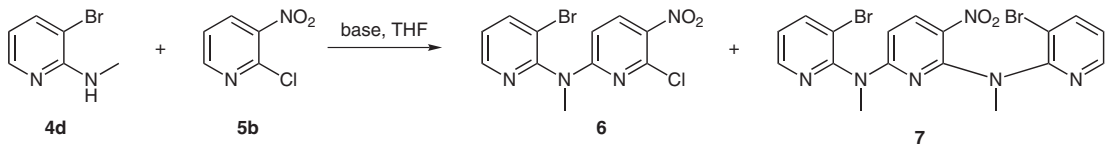


Scheme 1

As a consequence, we decided to generate the C–N bond by nucleophilic substitution of a leaving group in the 2-position of the 3-nitropyridine ring and the results of our studies are presented herein.

Treatment of 3-bromo-2-(methylamino)pyridine (**4d**) with lithium hexamethyldisilazide (LiHMDS), in tetrahydrofuran (THF) at 60 °C, to form the anion, and the addition of 2-chloro-3-nitropyridine (**5b**) did not lead to the expected product **3**. Surprisingly, this reaction gave access to a mixture of two different compounds, **6** and **7**, in 27% and 12% yield, respectively. The starting aminopyridine **4d** was also partially recovered (41%) (Scheme 2).

Preliminary NMR and MS analysis of compound **6** revealed the presence of five aromatic hydrogens over two pyridine rings (with the next protons sequences: *para*/*meta*/*ortho* and *para*/*meta*) and all substituents (bromine, chlorine and nitro groups) still present. This indicated that the major product **6** formed through nucleophilic aromatic substitution of hydrogen (S_NH) in the position *para* to the



Scheme 2

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nitro group; compound **7** presumably resulted from a nucleophilic attack of **4d** on **6**.

Nucleophilic substitution in nitroarenes has been extensively studied by Makosza and co-workers, who showed that the S_NAr of a leaving group often competes with other processes such as oxidative nucleophilic substitution of hydrogen (ONSH) or vicarious nucleophilic substitution (VNS) and the factors responsible for the reactions course are various and difficult to control.[10] In nitroaromatic rings there is usually more than one position (*ortho* and *para*) in which the ONSH or VNS can take place, thus the orientation of the substitution is highly sensitive to steric hindrance.[11–14] For example, it was shown that the ONSH reaction of substituted nitrobenzenes with phenylacetonitrile derivatives, proceeds exclusively in the *para* position to the nitro group, and no *ortho*-isomers were detected.[12] It was also reported that the S_NH reaction between nitrobenzene and aniline or substituted benzamides proceeds in high yield in the position *para* to the nitro group under mild conditions, without the need for an auxiliary leaving group or external oxidant.[15,16]

In our case, the amination of 2-chloro-3-nitropyridine (**5b**) with 3-bromo-2-(methylamino)pyridine (**4d**) proceeded with *para* selectivity to the nitro group and no further oxidizing reagent was necessary to isolate **6**.

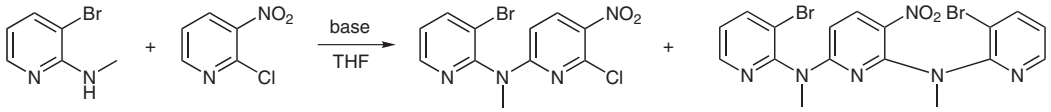
From these observations, we supposed that under these conditions, the amination of **5b** with **4d** proceeded with *para* selectivity to the nitro group via ONSH and the resulting compound **6** was formed accompanied, in small amounts, by the corresponding product of the S_NAr reaction (**7**).

Considering our preliminary results, we decided to study the scope and limitation of the amination of 3-nitropyridines in the position *para* to the nitro group by the ONSH reaction with several types of aminopyridines.

As a starting point, by modifying the parameters of this reaction, we tried to get higher yields of **6** and, if possible, to prevent the nucleophilic attack of **4d** on the ONSH resulting product. To this purpose, evaluation of the influences of experimental conditions of anion formation and of the ONSH reaction was carried out; a summary of the main results is presented in Table 1.

The preliminary experiments with LiHMDS showed that the anion formation could best be conducted using 2.2 equivalents of LiHMDS in THF, at 60 °C for three hours. Under these conditions, compound **6** was isolated in 32% yield, accompanied by 8% of the S_NAr product (**7**) (Table 1, entry 3). Replacement of LiHMDS by another base such as LDA, was not appropriate as only degrada-

Table 1 Optimization of the Experimental Conditions



4d **5b** **6** **7**

Entry	Anion formation (solvent = THF)				ONSH					
	Base	Equiv of base	Temp (°C)	Time (h)	Temp (°C)	Time (h)	Co-solvent	Recovered **4d** (%)	Yield of **6** (%)	Yield of **7** (%)
1	LiHMDS	1.1	60	3	r.t.	overnight	–	35	3	12
2		4.4	60	3	r.t.	overnight	–	15	35	10
3		2.2	60	3	r.t.	overnight	–	20	32	8
4		2.2	60	1	r.t.	overnight	–	41	27	12
5	LDA	2.2	60	3	r.t.	overnight	–	–[a]	–	–
6					50	overnight	–	14	37	8
7					50	3 h	–	15	34	5
8					50	3 h	$PhNO_2$	10	35	–
9	LiHMDS	2.2	60	3	50	1 h	$PhNO_2$	32	21	–
10					r.t.	1 h	–	25	30	10
11					r.t.	1 h	$PhNO_2$	trace	53	trace
12					r.t.	1 h	DMSO	–[a]	–	–
13	LDA	2.2	60	3	50	overnight	–	–[a]	–	–

[a] Only degradation of starting materials was observed.

tion of the reaction mixture was observed (Table 1, entries 5 and 13).

After anion formation and addition of 2-chloro-3-nitropyridine (**5b**), variation of the temperature and of the reaction times did not have a significant influence on the yields of the ONSH and S_NAr products (Table 1, entries 3,6 and 7).

Under similar conditions, the use of 2-fluoro-3-nitropyridine (**5a**) or 2-bromo-3-nitropyridine (**5c**) as substrate, did not improve the results described above. On the contrary, the former gave the ONSH product in very low yield and the latter brominated compound led to an inseparable mixture of products (results not shown).

Knowing that in many cases of 'spontaneous' ONSH (without external oxidant), the nitrobenzene could itself act as an oxidant,[17] thus increasing the yield of reaction, we also examined the influence of the solvent system. Indeed, the best yield of the ONSH was obtained by addition of nitrobenzene to the reaction mixture. As shown in Table 1 (entry 11), when the ONSH reaction of **5b** was carried out at room temperature for one hour, in the presence of 10 equivalents of nitrobenzene, we obtained a 53% yield of **6** and only traces of **7**. We believe that nitrobenzene may act as both an oxidant and a co-solvent in our reaction system (compare Table 1, entries 10, 11 and 12). To verify this hypothesis, nitrobenzene was replaced with DMSO, but in this case only degradation of the reaction mixture was observed (Table 1, entry 12).

For all the above reasons, we supposed that the formation of **6** arose through an ONSH mechanism: deprotonation of aminopyridine generates the amide ion, which is required for nucleophilic attack at the *para* position of nitropyridine, forming the expected σ-complex intermediate and the oxidative sequence then proceeded spontaneously.

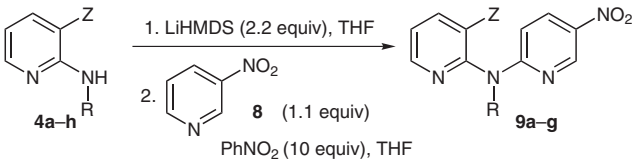
As a second part of our work, using the optimized reaction conditions developed for **5b**, we examined the possibility of introducing other commercial (**4a**, **4c**, **4g**) or synthetic (**4d**, **4e**, **4f**, **4h**) N-substituted aminopyridines to the *para* position of 3-nitropyridine (**8**). The results obtained are collected in Table 2 and Table 3.

As shown in Table 2 (entries 3–7), the reaction of 3-nitropyridine (**8**) with 2-N-substituted aminopyridines **4c**–**g**, under these optimized conditions, proceeded exclusively in the position *para* to the nitro group, giving the ONSH products **9c**–**g** in good yields that were even higher than in the case of the corresponding experiment of 2-chloro-3-nitropyridine **5b** with **4d**. Only the aminopyridines **4a** and **4b** led to the corresponding nitro-substituted *N*,*N*′-dipyridinylamines **9a** and **9b** in low yields (Table 2, entries 1 and 2). Compound **9a** was also generated in quantitative yield by refluxing **9g** in TFA.[18] Surprisingly, no reaction occurred in the case of **4h**; 60% of starting material was recovered and degradation was observed (Table 2, entry 8).

Under the same conditions, 3-nitropyridine (**8**) reacted similarly with 3-(methylamino)pyridine (**10**) and 4-(methylamino)pyridine (**12**), and the ONSH products **11** and **13** were obtained in 70% and 65% yields, respectively (Scheme 3).

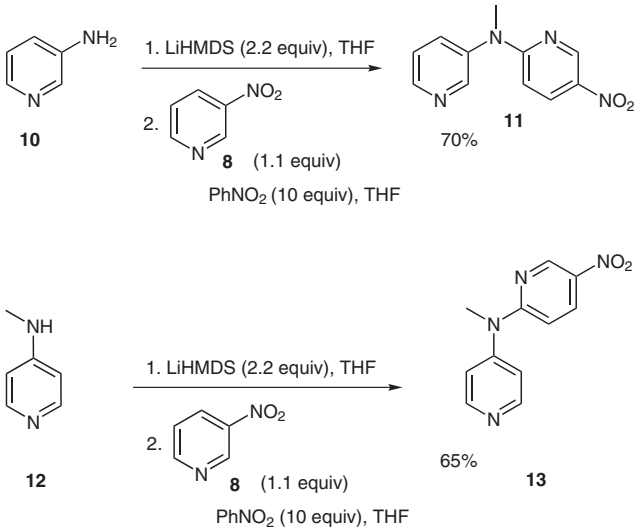
It is worth mentioning that, in order to prove the structure of compounds **9c**, **11** and **13**, the amination reactions were

Table 2 Reaction of N-Substituted Aminopyridines with 3-Nitropyridine

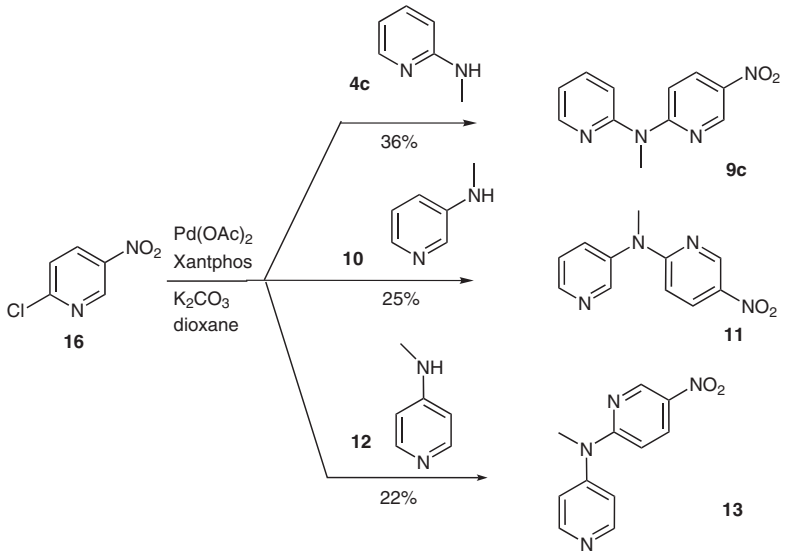


Entry	4	R	Z	Product	Yield (%)
1	**4a**	H	H	**9a**	30[a]
2	**4b**	H	Br	**9b**	38
3	**4c**	H	H	**9c**	86[b]
4	**4d**	Me	Br	**9d**	75
5	**4e**	Me	H	**9e**	88
6	**4f**	Bu	Br	**9f**	71
7	**4g**	Bu	H	**9g**	85
8	**4h**	PMB	Br	–[c]	–

[a] Compound **9a** was also generated in quantitative yield by refluxing **9g** in TFA.
[b] Compound **9c** was obtained in only 36% when the amination reaction was performed between **4c** and 2-chloro-5-nitropyridine using the methodology of palladium-catalyzed intermolecular coupling.
[c] No reaction occurred, 60% of starting material was recovered and degradation was observed; PMB = *p*-methoxybenzyl.



Scheme 3 ONSH reaction of 3-nitropyridine (**8**) with 3-(methylamino)pyridine (**10**) and 4-(methylamino)pyridine (**12**). Compounds **11** and **13** were obtained in 25% and 22% yields when the amination reaction was performed using the palladium-catalyzed intermolecular coupling (see Scheme 4).



Scheme 4 *Reagents and conditions*: amine (1.2 equiv), 2-chloro-5-nitropyridine (1 equiv), $Pd(OAc)_2$ (10%), Xantphos (20%), K_2CO_3 (1.5 equiv), 1,4-dioxane (solvent).

performed between amines **4c**, **10** and **12** as reactant and 2-chloro-5-nitropyridine (**16**) as substrates, using palladium-catalyzed intermolecular coupling. The reactions conducted under modified conditions described by Yin and Buchwald[19] and according to our optimized protocol[20] [1 equiv halide, 1.2 equiv amine, 10% $Pd(OAc)_2$, 20% Xantphos, 1.5 equiv K_2CO_3 and 1,4-dioxane as solvent], led to the expected products but in lower yields to those obtained by the ONSH process. As illustrated in Scheme 4, following this procedure, the products **9c**, **11** and **13** were obtained in only 36%, 25% and 22% yields, respectively.

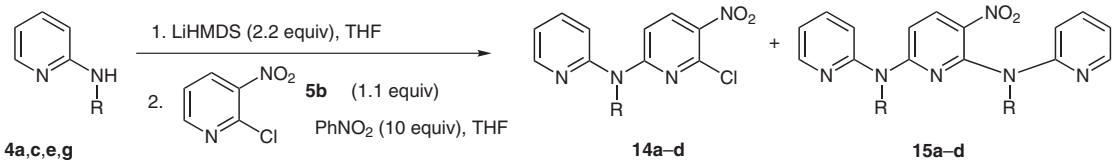
In order to probe the *para* selectivity of the amination reactions under our optimal reaction conditions, we also examined the reaction of 2-chloro-3-nitropyridine (**5b**) in the presence of 2-aminopyridines **4a**, **4c**, **4e** and **4g**. The results are summarized in Table 3.

We observed that the use of 2-chloro-3-nitropyridine (**5b**) as substrate in reactions with **4a**, **4c**, **4e** and **4g**, led to the expected ONSH compounds **14a–d** with yields ranging from 8% to 32% and the corresponding S_NAr derivatives **15a–d** (Table 3, entries 1–4).

When the amination reaction was performed between **5b** and 2-aminopyridine (**4a**), the ONSH compound **14a** was obtained in low yield (Table 3, entry 1) but only traces of the S_NAr product **15a** were observed. A similar low yield for the ONSH reaction was obtained when **4a** reacted with 3-nitropyridine (**8**) (Table 2, entry 1). These results suggest that 2-aminopyridine (**4a**) is not an appropriate amination agent for 3-nitropyridine (**8**) or 2-substituted-3-nitropyridine **5b** under these optimized reaction conditions.

It should be noted that, in the case of the reaction of **5b** with N-substituted 2-aminopyridine **4c**, **4e** and **4g**, the S_NAr reaction becomes a significant process (Table 3, entries 2–4). Moreover, in the case of 2-(methylamino)pyridine (**4c**), the main product is **15b**, resulting from an S_NAr reaction of the halogen, in 40% yield, while only 8% of the ONSH derived compound **14b** was isolated (Table 3, entry 2).

Table 3 Regioselectivity of the Amination Reactions



Entry	**4**	R	**14**	Yield (%)	**15**	Yield (%)
1	**4a**	H	**14a**	15	**15a**	trace
2	**4c**	Me	**14b**	8	**15b**	40
3	**4e**	Bu	**14c**	32	**15c**	20[a]
4	**4g**	PMB	**14d**	20	**15d**	20

[a] Compound **15c** was also generated in 49% yield when the amination reaction was performed between **4e** and **14c** using palladium-catalyzed intermolecular coupling.

In order to complete our studies on the formation of S_NAr products, we examined the Pd(0)-catalyzed amination of **14c** with amine **4e** under the previously described conditions (Scheme 4). As expected, this reaction led to the same compound **15c** in 49% yield.

In conclusion, in the present paper we have shown that interesting 3-nitro-substituted *N*,*N*′-dipyridinylamines may be easily obtained through oxidative nucleophilic substitution of hydrogen in the position *para* to the nitro group of 3-nitropyridine, using the metal amides of a range of aminopyridines as reactant. In the case of 2-chloro-3-nitropyridine, the amination reaction proceeded exclusively *para* to the nitro group, giving mainly the ONSH compounds with acceptable yields, accompanied with small amounts of the corresponding S_NAr derivative.

All air-sensitive experiments were performed under an inert atmosphere of argon. THF and dioxane were distilled from sodium benzophenone ketyl prior to use. MeOH was distilled over $CaCl_2$ and stored under an inert atmosphere over 3 Å molecular sieves. DMF was purified by distillation over CaH_2 and stored under an inert atmosphere over 4 Å molecular sieves. Petroleum ether (PE), where used, had a boiling range of 40–60 °C. All commercially available reagents were used without further purification. ^1H and ^{13}C NMR spectra were recorded on a Bruker Avance DPX 250 spectrometer (at 250 MHz and 63 MHz, respectively) or on a Bruker Avance II 400 spectrometer (at 400 MHz and 100 MHz, respectively) at 25 °C, using TMS as an internal standard. Chemical shifts (δ) are reported in parts per million (ppm) and the coupling constants (*J*) are reported in hertz (Hz). IR spectra were recorded on a Thermo-Nicolet AVATAR 320 AEK0200713 spectrometer using the ATR technique (germanium crystal) and reported in cm^{-1}. Mass spectra were recorded on a Perkin–Elmer mass spectrometer SCIEX API 300 using an ion spray (IS) ion source. Flash column chromatography was carried out with Merck Silica Gel 60 N (spherical, neutral, 63–200 μm) and analytical TLC on Merck Kieselgel 60 F_{254} sheets. HRMS (ESI-TOF) was performed on a Micromass LC TOF spectrometer. Melting points were determined on a Büchi 510 melting point apparatus in open capillaries and are uncorrected.

2-Amino-3-bromopyridine (4b)

2-Amino-3-bromopyridine was prepared via a modification of a literature procedure[21] described by Turner, using 1,2-dibromoethane as a brominating agent.

The analytical data were in accord with literature values.[8d]

3-Bromo-2-[(N-substituted)amino]pyridines 4d, 4f, 4g and 2-(Butylamino)pyridine (4e); General Procedure[8e] (GP 1)

To a suspension of NaH (60% in mineral oil, 1.1 equiv) in THF (**4d**, **4f**, **4e**) or DMF (**4g**) (0.4 mmol/mL solvent) was added slowly the appropriate aminopyridine (1 equiv) in THF or DMF (0.5 mmol/mL solvent) at 0 °C. The mixture was stirred at 40 °C for 30 min (or stirred at r.t. in DMF) and then the halogenated derivative (1.1 equiv) was added. The resulting mixture was heated to 60 °C (or stirred at r.t. in DMF). The reaction was monitored by TLC and, when complete consumption of starting material was achieved, quenched with H_2O (2.5 mL/mL solvent) and extracted with CH_2Cl_2 or EtOAc (3 × 2.5 mL/mL solvent). The combined organic layers were dried over $MgSO_4$ and the solvent was removed under reduced pressure to give a crude product which was purified by flash chromatography.

3-Bromo-2-(methylamino)pyridine (4d)

GP 1 was followed using 2-amino-3-bromopyridine (**4b**) and MeI as starting materials. Purification by flash chromatography (PE–EtOAc, 9:1→7:3) afforded **4d** (87%) as a yellow oil.

The analytical data were in accord with literature values.[8d]

2-(Butylamino)pyridine (4e)

GP 1 was followed using 2-aminopyridine and 1-bromobutane as starting materials. Purification by flash chromatography (PE–EtOAc, 9:1→8:2→7:3) afforded **4e** (70%) as beige crystals.

The analytical data were in accord with literature values.[22]

3-Bromo-2-(butylamino)pyridine (4f)

GP 1 was followed using 2-amino-3-bromopyridine (**4b**) and 1-bromobutane as starting materials. Purification by flash chromatography (PE–EtOAc, 9:1→7:3) afforded **4f** (80%) as a dark-yellow oil.

The analytical data were in accord with literature values.[8d]

3-Bromo-2-(4-methoxybenzyl)aminopyridine (4h)

GP 1 was followed using 2-amino-3-bromopyridine (**4b**) and 4-methoxybenzyl chloride as starting materials. Purification by flash chromatography (PE–EtOAc, 9:1→8:2→7:3) afforded **4h** (38%) as a yellow oil.

IR (ATR): 2931, 3425 cm^{-1}.

^1H NMR (250 MHz, $CDCl_3$): δ = 3.80 (s, 3 H, CH_3), 4.59 (d, *J* = 5.4 Hz, 2 H, CH_2), 5.24 (br s, 1 H, NH), 6.44 (dd, *J* = 4.9, 7.8 Hz, 1 H, H_{py}), 6.87 (d, *J* = 8.6 Hz, 2 H, 2 × H_{arom}), 7.28 (d, *J* = 8.6 Hz, 2 H, 2 × H_{arom}), 7.60 (dd, *J* = 1.5, 7.8 Hz, 1 H, H_{py}), 8.07 (dd, *J* = 1.5, 4.9 Hz, 1 H, H_{py}).

^{13}C NMR (63 MHz, $CDCl_3$): δ = 45.3 (CH_2), 55.4 (CH_3), 105.6 (C_q), 113.6 (CH_{py}), 114.1 (2 × CH_{arom}), 129.0 (2 × CH_{arom}), 131.3 (C_q), 139.6 (CH_{py}), 146.8 (CH_{py}), 154.5 (C_q), 159.0 (C_q).

MS (IS): *m*/*z* = 293.00 ([M + 1]$^+$, ^{79}Br), 295.00 ([M + 1]$^+$, ^{81}Br).

3-(Methylamino)pyridine (10)

This compound was prepared according to the methodology described in the literature.[23]

Yield: 79%; dark-yellow oil.

The analytical data were in accord with literature values.[24]

ONSH Reaction; General Procedure (GP 2)

To a stirred solution of amine (1 equiv) in anhydrous THF (0.2 mmol/mL) at r.t. was added LiHMDS (1M in THF, 2.2 equiv). The resulting mixture was heated at 60 °C for 3 h and then cooled to 0 °C. In a second round-bottom flask, nitrobenzene (10 equiv) was added to a solution of nitropyridine (1.1 equiv) in THF (0.5 mmol/mL). This last preparation was slowly added to the reaction mixture at 0 °C and then stirred at r.t. for 1 h before being hydrolyzed through the addition of H_2O (2.5 mL/mL THF). The mixture was extracted with EtOAc (3 × 2.5 mL/mL THF) and the combined organic phase was washed with brine (3 × 2.5 mL/mL THF) and dried over $MgSO_4$. The solvent was removed under reduced pressure and the residue was purified on a column of silica gel (PE–EtOAc).

***N*-(3-Bromopyridin-2-yl)-*N*-(6-chloro-5-nitropyridin-2-yl)-*N*-methylamine (6)**

Prepared according to GP 2 from 3-bromo-2-(methylamino)pyridine (**4d**) and 2-chloro-3-nitropyridine (**5b**). Purification by flash chromatography on silica gel (PE–EtOAc, 9:1→7:3) gave product **6**.

Yield: 53%; brown solid; mp 95 °C.

IR (ATR): 1321 cm^{-1}.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 3.53 (s, 3 H, CH_3), 6.10 (d, *J* = 9.1 Hz, 1 H, H_{py}), 7.24 (dd, *J* = 4.6, 7.9 Hz, 1 H, H_{py}), 8.06–8.13 (m, 2 H, H_{py}), 8.53 (dd, *J* = 1.6, 4.6 Hz, 1 H, H_{py}).

^{13}C NMR (63 MHz, $CDCl_3$): δ = 37.0 (CH_3), 106.5 (CH_{py}), 119.3 (C_q), 124.8 (CH_{py}), 135.1 (C_q), 136.3 (CH_{py}), 143.4 (CH_{py}), 144.6 (C_q), 149.0 (CH_{py}), 154.0 (C_q), 157.7 (C_q).

MS (IS): *m*/*z* = 343.0 ([M + 1]$^+$, ^{79}Br), 345.0 ([M + 1]$^+$, ^{81}Br).

HRMS (EI): *m*/*z* [M]$^+$ calcd for $C_{11}H_8N_4O_2{}^{35}Cl^{79}Br$: 341.95191; found: 341.9509.

N^2,*N*^{6}-Bis(3-bromopyridin-2-yl)-*N*^{2},*N*^{6}-dimethyl-3-nitropyridine-2,6-diamine (7)

LiHMDS (1M in THF, 0.3 mL, 0.294 mmol) was slowly added, under an Ar atmosphere, to a solution of 3-bromo-2-(methylamino)pyridine (**4d**; 25 mg, 0.134 mmol) in anhydrous THF (2 mL). The solution was stirred for 3 h at 60 °C and then cooled to 0 °C. A solution of *N*-(3-bromopyridin-2-yl)-*N*-(6-chloro-5-nitropyridin-2-yl)-*N*-methylamine (**6**; 50 mg, 0.147 mmol) in anhydrous THF (2 mL) was then slowly added. The resulting mixture was stirred at 45 °C for 17 h before cooling to r.t. and hydrolyzed with H_2O (10 mL). The aqueous solution was extracted with EtOAc (3 × 10 mL) and the combined organic phases are washed with brine (3 × 10 mL), dried ($MgSO_4$), filtered and concentrated under reduced pressure. Purification of the product by column chromatography (PE–EtOAc, 8:2→7:3→0:10) yielded product **7**.

Yield: 45%; yellow solid; mp 129 °C.

IR (ATR): 1320, 1414 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.43 (s, 3 H, CH_3), 3.51 (s, 3 H, CH_3), 5.88 (d, *J* = 8.9 Hz, 1 H, H_{py}), 6.94 (dd, *J* = 4.7, 7.8 Hz, 1 H, H_{py}), 7.18 (dd, *J* = 4.7, 7.9 Hz, 1 H, H_{py}), 7.94 (dd, *J* = 1.5, 7.8 Hz, 1 H, H_{py}), 8.02 (dd, *J* = 1.5, 7.9 Hz, 1 H, H_{py}), 8.10 (d, *J* = 8.9 Hz, 1 H, H_{py}), 8.16 (dd, *J* = 1.5, 4.7 Hz, 1 H, H_{py}), 8.52 (dd, *J* = 1.5, 4.7 Hz, 1 H, H_{py}).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 36.7 (CH_3), 38.5 (CH_3), 100.7 (CH_{py}), 117.1 (C_q), 119.8 (C_q), 122.3 (CH_{py}), 124.1 (CH_{py}), 127.1 (C_q), 137.3 (CH_{py}), 142.9 (CH_{py}), 143.2 (CH_{py}), 147.1 (CH_{py}), 148.7 (CH_{py}), 151.7 (C_q), 155.2 (C_q), 157.2 (C_q), 157.6 (C_q).

MS (IS): *m*/*z* = 495 ([M + 1]$^+$), 517 ([M + Na]$^+$).

HRMS (EI): *m*/*z* [M – NO_2]$^+$ calcd for $C_{17}H_{14}N_5{}^{79}Br_2$: 445.96159; found: 445.9600.

N-(5-Nitropyridin-2-yl)-*N*-(pyridin-2-yl)amine (9a)

Method I: Prepared according to GP 2 from 2-aminopyridine (**4a**) and 3-nitropyridine (**8**). Purification by flash chromatography on silica gel (PE–EtOAc: 9:1→8:2) afforded product **9a** (30%).

Method II:[17] Compound **9g** (50 mg, 0.15 mmol) was dissolved in TFA (3 mL) and the mixture was refluxed overnight. After cooling, the solvent was removed and the crude material was dissolved in EtOAc (10 mL), washed with a sat. $NaHCO_3$ (3 × 10 mL) and then with brine (3 × 10 mL). The organic extracts were dried ($MgSO_4$) and the solvent was removed under reduced pressure. The residue was purified by column chromatography over silica gel (PE–EtOAc, 8:2→7:3) to give **9a** (100%).

Yellow powder; mp 188–189 °C.

IR (ATR): 1215, 1338, 3019 cm^{-1}.

^{1}H NMR (250 MHz, DMSO-d_6): δ = 7.01–7.06 (m, 1 H, H_{py}), 7.71–7.79 (m, 2 H, H_{py}), 7.90 (d, *J* = 9.4 Hz, 1 H, H_{py}), 8.31 (d, *J* = 4.7 Hz, 1 H, H_{py}), 8.38 (dd, *J* = 2.8, 9.4 Hz, 1 H, H_{py}), 9.06 (d, *J* = 2.8 Hz, 1 H, H_{py}), 10.67 (br s, 1 H, NH).

^{13}C NMR (63 MHz, DMSO-d_6): δ = 110.6 (CH_{py}), 113.4 (CH_{py}), 118.1 (CH_{py}), 133.2 (CH_{py}), 137.1 (C_q), 138.1 (CH_{py}), 145.3 (CH_{py}), 147.6 (CH_{py}), 152.9 (C_q), 157.9 (C_q).

MS (IS): *m*/*z* = 216.50 [M + 1]$^+$.

HRMS (EI): *m*/*z* [M]$^+$ calcd for $C_{10}H_8N_4O_2$: 216.06473; found: 216.0644.

N-(3-Bromopyridin-2-yl)-*N*-(5-nitropyridin-2-yl)amine (9b)

Prepared according to GP 2 from 2-amino-3-bromopyridine (**4b**) and 3-nitropyridine (**8**). Purification by flash chromatography on silica gel (PE–EtOAc, 100:0→96:4→7:3) gave product **9b**.

Yield: 38%; yellow cotton-like solid; mp 178 °C.

IR (ATR): 1337, 1504, 3373 cm^{-1}.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 6.86 (dd, *J* = 4.7, 7.8 Hz, 1 H, H_{py}), 7.86 (dd, *J* = 1.6, 7.8 Hz, 1 H, H_{py}), 8.28 (dd, *J* = 1.6, 4.7 Hz, 1 H, H_{py}), 8.31 (br s, 1 H, NH); 8.43 (dd, *J* = 2.8, 9.4 Hz, 1 H, H_{py}), 8.65 (d, *J* = 9.4 Hz, 1 H, H_{py}), 9.13 (d, *J* = 2.8 Hz, 1 H, H_{py}).

^{13}C NMR (63 MHz, $CDCl_3$): δ = 108.0 (C_q), 110.8 (CH_{py}), 118.9 (CH_{py}), 133.7 (CH_{py}), 139.0 (C_q), 141.2 (CH_{py}), 145.3 (CH_{py}), 146.4 (CH_{py}), 149.5 (C_q), 157.7 (C_q).

MS (IS): *m*/*z* = 295.00 ([M + 1]$^+$, ^{79}Br), 297.00 ([M + 1]$^+$, ^{81}Br).

HRMS (EI): *m*/*z* [M]$^+$ calcd for $C_{10}H_7N_4O_2{}^{79}Br$: 293.97524; found: 293.9760.

Palladium-Catalyzed N-Arylation; General Procedure[18,19] (GP 3)

A round-bottom flask flushed with nitrogen was charged with Xantphos (20% mol) and anhydrous dioxane (0.02 mmol/mL). After degassing, $Pd(OAc)_2$ (10% mol) was introduced and the mixture was stirred under nitrogen for 10 min. In a second round-bottom flask, heteroaryl halide (1 equiv), amine (1.2 equiv) and K_2CO_3 (1.5 equiv) were poured into anhydrous dioxane (0.05 mmol, halide/mL). The the $Pd(OAc)_2$/Xantphos solution was transferred via a cannula and the resulted mixture was subsequently refluxed under Ar with vigorous stirring. The progress of reaction was monitored by TLC. After cooling, the residue was filtered off through a Celite pad and washed with CH_2Cl_2 and MeOH. The solvent was evaporated and the residue was purified by column chromatography.

N-Methyl-*N*-(5-nitropyridin-2-yl)-*N*-(pyridin-2-yl)amine (9c)

Method I: Prepared according to GP 2 from 2-(methylamino)pyridine (**4c**) and 3-nitropyridine (**8**). Purification by flash chromatography on silica gel (PE–EtOAc, 9:1→8:2) afforded product **9c** (86%).

Method II: Prepared according to GP 3 from 2-chloro-5-nitropyridine (**16**) and 2-(methylamino)pyridine (**4c**). Purification by flash chromatography on silica gel (PE–EtOAc, 9:1→7:3) afforded product **9c** (36%).

Yellow solid; mp 104–105 °C.

IR (ATR): 1337, 1495 cm^{-1}.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 3.68 (s, 3 H, CH_3), 6.96 (d, *J* = 9.5 Hz, 1 H, H_{py}), 7.15–7.20 (m, 1 H, H_{py}), 7.30 (d, *J* = 8.1 Hz, 1 H, H_{py}), 7.74 (ddd, *J* = 1.2, 7.5, 8.1 Hz, 1 H, H_{py}), 8.16 (dd, *J* = 2.8, 9.5 Hz, 1 H, H_{py}), 8.50 (dd, *J* = 1.2, 4.8 Hz, 1 H, H_{py}), 9.14 (d, *J* = 2.8 Hz, 1 H, H_{py}).

^{13}C NMR (63 MHz, $CDCl_3$): δ = 37.2 (CH_3), 109.1 (CH_{py}), 118.9 (CH_{py}), 121.1 (CH_{py}), 132.2 (CH_{py}), 137.0 (C_q), 138.5 (CH_{py}), 145.7 (CH_{py}), 149.1 (CH_{py}), 156.6 (C_q), 160.2 (C_q).

MS (IS): *m*/*z* = 230.8 [M + 1]$^+$.

HRMS (EI): *m*/*z* [M]$^+$ calcd for $C_{11}H_{10}N_4O_2$: 230.08038; found: 230.0791.

***N*-(3-Bromopyridin-2-yl)-*N*-methyl-*N*-(5-nitropyridin-2-yl)amine (9d)**

Prepared according to GP 2 from 3-bromo-2-(methylamino)pyridine (**4d**) and 3-nitropyridine (**8**). Purification by flash chromatography on silica gel (PE–EtOAc, 8:2→7:3) gave product **9d**.

Yield: 75%; dark-green solid; mp 103–105 °C.

IR (ATR): 1292, 1332, 1499 cm^{-1}.

^1H NMR (250 MHz, $CDCl_3$): δ = 3.55 (s, 3 H, CH_3), 6.27 (d, *J* = 9.3 Hz, 1 H, H_{py}), 7.23 (dd, *J* = 4.6, 7.9 Hz, 1 H, H_{py}), 8.06 (dd, *J* = 1.6, 7.9 Hz, 1 H, H_{py}), 8.15 (dd, *J* = 2.8, 9.3 Hz, 1 H, H_{py}), 8.55 (dd, *J* = 1.6, 4.6 Hz, 1 H, H_{py}), 9.10 (d, *J* = 2.8 Hz, 1 H, H_{py}).

^{13}C NMR (63 MHz, $CDCl_3$): δ = 36.9 (CH_3), 107.2 (CH_{py}), 119.6 (C_q), 124.6 (CH_{py}), 132.7 (CH_{py}), 136.9 (C_q), 143.3 (CH_{py}), 146.2 (CH_{py}), 149.0 (CH_{py}), 154.8 (C_q), 160.1 (C_q).

MS (IS): *m*/*z* = 309.3 ([M + 1]$^+$, ^{79}Br), 311.3 ([M + 1]$^+$, ^{81}Br).

HRMS (EI): *m*/*z* [M]$^+$ calcd for $C_{11}H_9N_4O_2{}^{79}Br$: 307.99089; found: 307.9908.

HRMS (EI): *m*/*z* [M – Br]$^+$ calcd for $C_{11}H_9N_4O_2$: 229.07255; found: 229.0718.

***N*-Butyl-*N*-(5-nitropyridin-2-yl)-*N*-(pyridin-2-yl)-amine (9e)**

Prepared according to GP 2 from 2-(butylamino)pyridine (**4e**) and 3-nitropyridine (**8**). Purification by flash chromatography on silica gel (PE–EtOAc, 100:0→9:1) gave product **9e**.

Yield: 88%; dark-red gum.

IR (ATR): 1331, 1467 cm^{-1}.

^1H NMR (250 MHz, $CDCl_3$): δ = 0.89 (t, *J* = 7.3 Hz, 3 H, CH_3), 1.32–1.44 (m, 2 H, CH_2), 1.62–1.74 (m, 2 H, CH_2), 4.18 (t, *J* = 7.6 Hz, 2 H, CH_2), 6.73 (d, *J* = 9.4 Hz, 1 H, H_{py}), 7.18–7.23 (m, 1 H, H_{py}), 7.27 (d, *J* = 8.0 Hz, 1 H, H_{py}), 7.75 (ddd, *J* = 1.9, 7.5, 8.0 Hz, 1 H, H_{py}), 8.09 (dd, *J* = 2.8, 9.4 Hz, 1 H, H_{py}), 8.52 (dd, *J* = 1.9, 4.8 Hz, 1 H, H_{py}), 9.12 (d, *J* = 2.8 Hz, 1 H, H_{py}).

^{13}C NMR (63 MHz, $CDCl_3$): δ = 13.9 (CH_3), 20.2 (CH_2), 30.2 (CH_2), 49.5 (CH_2), 109.0 (CH_{py}), 119.9 (CH_{py}), 121.4 (CH_{py}), 132.1 (CH_{py}), 136.7 (C_q), 138.6 (CH_{py}), 146.1 (CH_{py}), 149.6 (CH_{py}), 156.1 (C_q), 160.2 (C_q).

MS (IS): *m*/*z* = 273.00 ([M + 1]$^+$).

HRMS (EI): *m*/*z* [M]$^+$ calcd for $C_{14}H_{16}N_4O_2$: 272.12733; found: 272.1274.

HRMS (EI): *m*/*z* [M – C_2H_5]$^+$ calcd for $C_{12}H_{11}N_4O_2$: 243.08820; found: 243.0888.

***N*-(3-Bromopyridin-2-yl)-*N*-butyl-*N*-(5-nitropyridin-2-yl)amine (9f)**

Prepared according to GP 2 from 3-bromo-2-(butylamino)pyridine (**4f**) and 3-nitropyridine (**8**). Purification by flash chromatography on silica gel (PE–EtOAc, 9:1→8:2) gave product **9f**.

Yield: 71%; dark-red gum.

IR (ATR): 1330, 1491 cm^{-1}.

^1H NMR (250 MHz, $CDCl_3$): δ = 0.89 (t, *J* = 7.3 Hz, 3 H, CH_3), 1.34–1.43 (m, 2 H, CH_2), 1.64–1.76 (m, 2 H, CH_2), 4.04 (t, *J* = 7.7 Hz, 2 H, CH_2), 6.17 (d, *J* = 9.3 Hz, 1 H, H_{py}), 7.22 (dd, *J* = 4.6, 7.9 Hz, 1 H, H_{py}), 8.05 (dd, *J* = 1.6, 7.9 Hz, 1 H, H_{py}), 8.12 (dd, *J* = 2.8, 9.3 Hz, 1 H, H_{py}), 8.56 (dd, *J* = 1.6, 4.6 Hz, 1 H, H_{py}), 9.09 (d, *J* = 2.8 Hz, 1 H, H_{py}).

^{13}C NMR (63 MHz, $CDCl_3$): δ = 13.9 (CH_3), 20.3 (CH_2), 30.0 (CH_2), 49.9 (CH_2), 107.1 (CH_{py}), 120.3 (C_q), 124.3 (CH_{py}), 132.6 (CH_{py}), 136.6 (C_q), 143.2 (CH_{py}), 146.3 (CH_{py}), 148.9 (CH_{py}), 153.9 (C_q), 159.8 (C_q).

MS (IS): *m*/*z* = 351.00 ([M + 1]$^+$, ^{79}Br), 353.0 ([M + 1]$^+$, ^{81}Br).

HRMS (EI): *m*/*z* [M]$^+$ calcd for $C_{14}H_{15}N_4O_2{}^{79}Br$: 350.03784; found: 350.0367.

***N*-(4-Methoxybenzyl)-*N*-(5-nitropyridin-2-yl)-*N*-(pyridin-2-yl)amine (9g)**

Prepared according to GP 2 from 2-(4-methoxybenzylamino)pyridine (**4g**) and 3-nitropyridine (**8**). Purification by flash chromatography on silica gel (PE–EtOAc, 9:1→8:2→5:5) gave product **9g**.

Yield: 85%; brown-red gum.

IR (ATR): 1246, 1331, 1467 cm^{-1}.

^1H NMR (250 MHz, $CDCl_3$): δ = 3.75 (s, 3 H, CH_3), 5.44 (s, 2 H, CH_2), 6.78 (d, *J* = 8.5 Hz, 2 H, 2 × H_{arom}), 6.87 (d, *J* = 9.3 Hz, 1 H, H_{py}), 7.12 (dd, *J* = 5.0, 7.3 Hz, 1 H, H_{py}), 7.23–7.26 (m, 3 H, H_{py} and 2 × H_{arom}), 7.67 (ddd, *J* = 1.8, 7.3, 7.9 Hz, 1 H, H_{py}), 8.11 (dd, *J* = 2.8, 9.3 Hz, 1 H, H_{py}), 8.49 (dd, *J* = 1.8, 5.0 Hz, 1 H, H_{py}), 9.11 (d, *J* = 2.8 Hz, 1 H, H_{py}).

^{13}C NMR (63 MHz, $CDCl_3$): δ = 51.8 (CH_2), 55.2 (CH_3), 109.5 (CH_{py}), 113.9 (2 × CH_{arom}), 119.4 (CH_{py}), 121.2 (CH_{py}), 128.7 (2 × CH_{arom}), 129.5 (C_q), 132.3 (CH_{py}), 137.1 (C_q), 138.3 (CH_{py}), 145.8 (CH_{py}), 149.2 (CH_{py}), 155.7 (C_q), 158.7 (C_q), 160.0 (C_q).

MS (IS): *m*/*z* = 337.5 [M + 1]$^+$.

HRMS (EI): *m*/*z* [M]$^+$ calcd for $C_{18}H_{16}N_4O_3$: 336.12224; found: 336.1223.

***N*-Methyl-*N*-(5-nitropyridin-2-yl)-*N*-(pyridin-3-yl)amine (11)**

Method I: Prepared according to GP 2 from 3-(methylamino)pyridine (**10**) and 3-nitropyridine (**8**). Purification by flash chromatography on silica gel (PE–EtOAc, 9:1→7:3→6:4→4:6) gave product **11** (70%).

Method II: Prepared according to GP 3 from 2-chloro-5-nitropyridine (**16**) and 3-(methylamino)pyridine (**10**). Purification by flash chromatography on silica gel (CH_2Cl_2–MeOH, 100:0→98:2) gave product **11** (25%).

Dark-yellow crystals; mp 101–103 °C.

IR (ATR): 1297, 1336, 1507 cm^{-1}.

^1H NMR (250 MHz, $CDCl_3$): δ = 3.60 (s, 3 H, CH_3), 6.40 (d, *J* = 9.4 Hz, 1 H, H_{py}), 7.44 (dd, *J* = 4.7, 8.2 Hz, 1 H, H_{py}), 7.65–7.69 (m, 1 H, H_{py}), 8.08 (dd, *J* = 2.8, 9.4 Hz, 1 H, H_{py}), 8.60–8.62 (m, 2 H, H_{py}), 9.08 (d, *J* = 2.5 Hz, 1 H, H_{py}).

^{13}C NMR (63 MHz, $CDCl_3$): δ = 39.4 (CH_3), 106.7 (CH_{py}), 124.6 (CH_{py}), 132.5 (CH_{py}), 134.4 (CH_{py}), 136.3 (C_q), 141.3 (C_q), 146.2 (CH_{py}), 148.4 (CH_{py}), 148.6 (CH_{py}), 160.7 (C_q).

MS (IS): *m*/*z* = 231.00 [M + 1].

HRMS (EI): *m*/*z* [M – H]$^+$ calcd for $C_{11}H_9N_4O_2$: 229.07255; found: 229.0718.

***N*-Methyl-*N*-(5-nitropyridin-2-yl)-*N*-(pyridin-4-yl)amine (13)**

Method I: Prepared according to GP 2 from 4-(methylamino)pyridine (**12**) and 3-nitropyridine (**8**). Purification by flash chromatography on silica gel (PE–EtOAc, 1:9→0:100) gave product **13** (65%).

Method II: Prepared according to GP 3 from 2-chloro-5-nitropyridine (**16**) and 4-(methylamino)pyridine (**12**). Purification by flash chromatography on silica gel (PE–EtOAc, 5:5→3:7) gave product **13** (22%).

Yellow-beige powder; mp 155–156 °C.

IR (ATR): 1291, 1330, 1496 cm^{-1}.

^1H NMR (250 MHz, $CDCl_3$): δ = 3.64 (s, 3 H, CH_3), 6.82 (d, *J* = 9.4 Hz, 1 H, H_{py}), 7.25 (d, *J* = 6.0 Hz, 2 H, H_{py}), 8.16 (dd, *J* = 2.5, 9.4 Hz, 1 H, H_{py}), 8.65 (d, *J* = 6.0 Hz, 2 H, H_{py}), 9.12 (d, *J* = 2.5 Hz, 1 H, H_{py}).

^{13}C NMR (63 MHz, $CDCl_3$): δ = 38.3 (CH_3), 108.4 (CH_{py}), 119.4 (2 × CH_{py}), 132.6 (CH_{py}), 137.1 (C_q), 145.9 (CH_{py}), 151.6 (2 × CH_{py}), 151.9 (C_q), 159.9 (C_q).

MS (IS): *m*/*z* = 231.00 $[M + 1]^+$.

HRMS (EI): *m*/*z* $[M - NO_2]^+$ calcd for $C_{11}H_9N_4O_2$: 229.07255; found: 229.0718.

N-(6-Chloro-5-nitropyridin-2-yl)-*N*-(pyridin-2-yl)amine (14a)

Prepared according to GP 2 from 2-aminopyridine (**4a**) and 2-chloro-3-nitropyridine (**5b**). Purification by flash chromatography on silica gel (PE–EtOAc, 9:1) gave product **14a**.

Yield: 15%; yellow-beige powder; mp 139–140 °C.

IR (ATR): 1479, 1514, 3388 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.92 (d, *J* = 8.1 Hz, 1 H, H_{py}), 7.06 (dd, *J* = 5.0, 7.5 Hz, 1 H, H_{py}), 7.69 (ddd, *J* = 1.8, 7.5, 8.1 Hz, 1 H, H_{py}), 8.22 (d, *J* = 6.0 Hz, 1 H, H_{py}), 8.37–8.39 (m, 2 H, H_{py} and NH), 8.50 (d, *J* = 6.0 Hz, 1 H, H_{py}).

^{13}C NMR (63 MHz, $CDCl_3$): δ = 112.3 (CH_{py}), 114.0 (CH_{py}), 119.6 (CH_{py}), 133.4 (C_q), 138.7 (CH_{py}), 143.7 (C_q), 144.8 (C_q), 148.2 (CH_{py}), 150.3 (CH), 152.0 (C_q).

MS (IS): *m*/*z* = 251.3 ($[M + 1]^+$, ^{35}Cl), 253.3 ($[M + 1]^+$, ^{37}Cl).

HRMS (EI): *m*/*z* $[M]^+$ calcd for $C_{10}H_7N_4O_2{}^{35}Cl$: 250.02575; found: 250.025.

HRMS (EI): *m*/*z* $[M - NO_2]^+$ calcd for $C_{10}H_7N_3{}^{35}Cl$: 204.03285; found: 204.0320.

N-Methyl-*N*-(6-chloro-5-nitropyridin-2-yl)-*N*-(pyridin-2-yl)amine (14b)

Prepared according to GP 2 from 2-(methylamino)pyridine (**4c**) and 2-chloro-3-nitropyridine (**5b**). Purification by flash chromatography on silica gel (PE–EtOAc, 9:1→8:2) gave product **14b**.

Yield: 8%; beige solid; mp 120–121 °C.

IR (ATR): 1314, 1502 cm^{-1}.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 3.66 (s, 3 H, CH_3), 6.89 (d, *J* = 9.1 Hz, 1 H, H_{py}), 7.18–7.23 (m, 1 H, H_{py}), 7.27–7.33 (m, 1 H, H_{py}), 7.77 (ddd, *J* = 1.2, 7.5, 8.2 Hz, 1 H, H_{py}), 8.12 (d, *J* = 9.1 Hz, 1 H, H_{py}), 8.50 (dd, *J* = 1.2, 5.0 Hz, 1 H, H_{py}).

^{13}C NMR (63 MHz, $CDCl_3$): δ = 37.2 (CH_3), 108.2 (CH_{py}), 118.8 (CH_{py}), 121.5 (CH_{py}), 128.8 (C_q), 136.1 (CH_{py}), 138.7 (CH_{py}), 144.1 (C_q), 149.2 (CH), 156.1 (C_q), 157.9 (C_q).

MS (IS): *m*/*z* = 264.8 ($[M + 1]^+$, ^{35}Cl), 266.8 ($[M + 1]^+$, ^{37}Cl).

HRMS (EI): *m*/*z* $[M]^+$ calcd for $C_{11}H_9N_4O_2{}^{35}Cl$: 264.04140; found: 264.0422.

N-Butyl-*N*-(6-chloro-5-nitropyridin-2-yl)-*N*-(pyridin-2-yl)amine (14c)

Prepared according to GP 2 from 2-(butylamino)pyridine (**4e**) and 2-chloro-3-nitropyridine (**5b**). Purification by flash chromatography on silica gel (PE–EtOAc, 100:0→9:1→8:2) gave product **14c**.

Yield: 32%; dark-red gum.

IR (ATR): 1318, 1466 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.91 (t, *J* = 7.2 Hz, 3 H, CH_3), 1.32–1.42 (m, 2 H, CH_2), 1.63–1.71 (m, 2 H, CH_2), 4.16 (t, *J* = 7.6 Hz, 2 H, CH_2), 6.65 (d, *J* = 9.1 Hz, 1 H, H_{py}), 7.21–7.24 (m, 1 H, H_{py}), 7.27 (d, *J* = 8.0 Hz, 1 H, H_{py}), 7.78 (ddd, *J* = 2.0, 7.6, 8.0 Hz, 1 H, H_{py}), 8.09 (d, *J* = 9.1 Hz, 1 H, H_{py}), 8.53–8.54 (m, 1 H, H_{py}).

^{13}C NMR (63 MHz, $CDCl_3$): δ = 13.8 (CH_3), 20.0 (CH_2), 29.9 (CH_2), 49.5 (CH_2), 107.9 (CH_{py}), 119.8 (CH_{py}), 121.8 (CH_{py}), 132.7 (C_q), 136.0 (CH_{py}), 138.8 (CH_{py}), 144.2 (C_q), 149.6 (CH_{py}), 155.4 (C_q), 157.8 (C_q).

MS (IS): *m*/*z* = 307.00 ($[M + 1]^+$, ^{35}Cl), 309.00 ($[M + 1]^+$, ^{37}Cl).

HRMS (EI): *m*/*z* $[M]^+$ calcd for $C_{14}H_{15}N_4O_2{}^{35}Cl$: 306.08835; found: 306.0881.

N-(6-Chloro-5-nitropyridin-2-yl)-*N*-(4-methoxybenzyl)-*N*-(pyridin-2-yl)amine (14d)

Prepared according to GP 2 from 2-(4-methoxybenzylamino)pyridine (**4g**) and 2-chloro-3-nitropyridine (**5b**). Purification by flash chromatography on silica gel (PE–EtOAc, 9:1→7:3→5:5) gave product **14d**.

Yield: 20%; brown gum.

IR (ATR): 1320, 1466, 1151 cm^{-1}.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 3.76 (s, 3 H, CH_3), 5.37 (s, 2 H, CH_2), 6.72–6.81 (m, 3 H, H_{py} and 2 × H_{arom}), 7.16–7.27 (m, 4 H, 2 × H_{py} and 2 × H_{arom}), 7.69–7.75 (m, 1 H, H_{py}), 8.08 (d, *J* = 9.1 Hz, 1 H, H_{py}), 8.53–8.54 (m, 1 H, H_{py}).

^{13}C NMR (63 MHz, $CDCl_3$): δ = 52.2 (CH_2), 55.3 (CH_3), 108.3 (CH_{py}), 114.0 (2 × CH_{arom}), 119.7 (CH_{py}), 121.7 (CH_{py}), 129.1 (C_q), 129.4 (2 × CH_{arom}), 135.3 (C_q), 136.3 (CH_{py}), 138.6 (CH_{py}), 144.2 (C_q), 149.5 (CH_{py}), 155.2 (C_q), 157.6 (C_q), 159.0 (C_q).

MS (IS): *m*/*z* = 371.00 ($[M + 1]^+$, ^{35}Cl), 373.00 ($[M + 1]^+$, ^{37}Cl).

HRMS (EI): *m*/*z* $[M]^+$ calcd for $C_{18}H_{15}N_4O_3{}^{35}Cl$: 370.08327; found: 370.0844.

N^2,N^6-Dimethyl-3-nitro-N^2,N^6-dipyridin-2-ylpyridine-2,6-diamine (15b)

Prepared according to GP 2 from 2-(methylamino)pyridine (**4c**) and 2-chloro-3-nitropyridine (**5b**). Purification by flash chromatography on silica gel (PE–EtOAc, 9:1→8:2) gave product **15b**.

Yield: 40%; light-yellow solid; mp 157–159 °C.

IR (ATR): 1289, 1324, 1422 cm^{-1}.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 3.64 (2 × s, 6 H, 2 × CH_3), 6.59 (d, *J* = 9.1 Hz, 1 H, H_{py}), 6.80–6.85 (m, 1 H, H_{py}), 6.93 (d, *J* = 8.2 Hz, 1 H, H_{py}), 7.07–7.12 (m, 1 H, H_{py}), 7.32 (d, *J* = 8.2 Hz, 1 H, H_{py}), 7.55–7.62 (m, 1 H, H_{py}), 7.66–7.73 (m, 1 H, H_{py}), 8.08 (d, *J* = 9.1 Hz, 1 H, H_{py}), 8.12–8.15 (m, 1 H, H_{py}), 8.46–8.47 (m, 1 H, H_{py}).

^{13}C NMR (63 MHz, $CDCl_3$): δ = 36.7 (CH_3), 37.4 (CH_3), 103.6 (CH_{py}), 112.6 (CH_{py}), 117.9 (CH_{py}), 118.9 (CH_{py}), 120.4 (CH_{py}), 129.8 (C_q), 136.2 (CH_{py}), 137.9 (CH_{py}), 138.1 (CH_{py}), 147.9 (CH_{py}), 148.9 (CH_{py}), 150.2 (C_q), 156.7 (C_q), 157.7 (C_q), 157.9 (C_q).

MS (IS): *m*/*z* = 337.3 $[M + 1]^+$.

HRMS (EI): *m*/*z* $[M - NO_2]^+$ calcd for $C_{17}H_{16}N_5$: 290.14057; found: 290.1391.

N^2,N^6-Dibutyl-3-nitro-N^2,N^6-dipyridin-2-ylpyridine-2,6-diamine (15c)

Method I: Prepared according to GP 2 from 2-(butylamino)pyridine (**4e**) and 2-chloro-3-nitropyridine (**5b**). Purification by flash chromatography on silica gel (PE–EtOAc, 100:0→9:1→8:2) gave product **15c** (20%).

Method II: Prepared according to GP 3 from 2-(butylamino)pyridine (**4e**) and butyl(6-chloro-5-nitropyridin-2-yl)pyridin-2-ylamine (**14c**). Purification by flash chromatography on silica gel (PE–EtOAc, 9:1→8:2) gave product **15c** (49%).

Dark-red gum.

IR (ATR): 1414, 1466 cm^{-1}.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 0.89–0.95 (td, *J* = 2.2, 7.2, 7.5 Hz, 6 H, 2 × CH_3), 1.25–1.44 (m, 4 H, 2 × CH_2), 1.65–1.80 (m, 4 H, 2 × CH_2), 4.14–4.22 (m, 4 H, 2 × CH_2), 6.37 (d, *J* = 9.1 Hz, 1 H, H_{py}), 6.82–6.87 (m, 1 H, H_{py}), 6.94 (d, *J* = 7.5 Hz, 1 H, H_{py}), 7.12–7.17 (m, 1 H, H_{py}), 7.28 (d, *J* = 8.2 Hz, 1 H, H_{py}), 7.56–7.63 (m, 1 H,

H_{py}), 7.69–7.76 (m, 1 H, H_{py}), 8.03 (d, J = 9.1 Hz, 1 H, H_{py}), 8.15 (dd, J = 1.2, 4.7 Hz, 1 H, H_{py}), 8.50 (dd, J = 1.5, 5.0 Hz, 1 H, H_{py}).

^{13}C NMR (63 MHz, $CDCl_3$): δ = 14.0 (CH_3), 14.1 (CH_3), 20.4 (CH_2), 20.5 (CH_2), 30.6 (CH_2), 30.9 (CH_2), 49.4 (CH_2), 50.3 (CH_2), 103.3 (CH_{py}), 113.1 (CH_{py}), 118.1 (CH_{py}), 120.1 (CH_{py}), 120.9 (CH_{py}), 129.3 (C_q), 136.5 (CH_{py}), 138.1 (CH_{py}), 138.2 (CH_{py}), 148.3 (CH_{py}), 149.5 (CH_{py}), 150.2 (C_q), 156.5 (C_q), 157.5 (C_q), 158.0 (C_q).

MS (IS): m/z = 421.5 $[M + 1]^+$.

HRMS (EI): m/z $[M - NO_2]^+$ calcd for $C_{23}H_{28}N_5$: 374.23447; found: 374.2360.

N^2,N^6-Bis(4-methoxybenzyl)-3-nitro-N^2,N^6-dipyridin-2-ylpyridine-2,6-diamine (15d)

Prepared according to GP 2 from 2-(4-methoxybenzylamino)pyridine (**4g**) and 2-chloro-3-nitropyridine (**5b**). Purification by flash chromatography on silica gel (PE–EtOAc, 9:1→7:3→5:5) gave product **15d**.

Yield: 20%; brown gum.

IR (ATR): 1247, 1325, 1511 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.74 (s, 3 H, CH_3), 3.76 (s, 3 H, CH_3), 5.28 (s, 2 H, CH_2), 5.29 (s, 2 H, CH_2), 6.55 (d, J = 9.0 Hz, 1 H, H_{py}), 6.70 (d, J = 8.6 Hz, 2 H, 2 × H_{arom}), 6.76 (d, J = 8.6 Hz, 2 H, 2 × H_{arom}), 6.81 (dd, J = 5.1, 7.0 Hz, 1 H, H_{py}), 6.88 (d, J = 8.3 Hz, 1 H, H_{py}), 7.05–7.08 (m, 3 H, H_{py} and 2 × H_{arom}), 7.19–7.23 (m, 3 H, H_{py} and 2 × H_{arom}), 7.50–7.55 (m, 1 H, H_{py}), 7.58–7.62 (m, 1 H, H_{py}), 8.08 (d, J = 9.0 Hz, 1 H, H_{py}), 8.12 (dd, J = 1.2, 5.1 Hz, 1 H, H_{py}), 8.45 (dd, J = 1.2, 4.6 Hz, 1 H, H_{py}).

^{13}C NMR (63 MHz, $CDCl_3$): 51.8 (CH_2), 52.8 (CH_2), 55.3 (2 × CH_3), 104.0 (CH_{py}), 113.1 (CH_{py}), 113.9 (4 × CH_{arom}), 118.4 (CH_{py}), 119.5 (CH_{py}), 120.7 (CH_{py}), 127.9 (2 × CH_{arom}), 128.2 (2 × CH_{arom}), 129.9 (C_q), 130.2 (C_q), 130.6 (C_q), 136.6 (CH_{py}), 138.0 (CH_{py}), 138.4 (CH_{py}), 147.9 (CH_{py}), 149.2 (CH_{py}), 149.3 (C_q), 156.1 (C_q), 157.5 (C_q), 157.6 (C_q), 158.5 (C_q), 158.6 (C_q).

MS (IS): m/z = 549.5 $[M + 1]^+$.

HRMS (EI): m/z $[M - NO_2]^+$ calcd for $C_{31}H_{28}N_5O_2$: 502.22430; found: 502.2225.

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