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Efficient and Selective Method for the Synthesis of Dihydrodipyridopyrazines Based on the Pd-Catalysed Amination of Halopyridines

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Keywords: Dihydrodipyridopyrazines / Pd catalysis / Cross-coupling / Reduction / Cyclization

A novel methodology for the efficient and selective synthesis of isomers **A** and **B** of *N*-substituted dihydrodipyridopyrazines was developed. The key step is the intermolecular coupling of aminopyridines and halonitropyridines/dihalopyridines in the presence of a catalyst system composed of $Pd(OAc)_2$/Xantphos. This system displays good functional group compatibility and the desired C–N bond-forming process proceeds in good yields. Cyclization of suitable nitro-substituted *N*,*N*′-dipyridinylamines produces monosubstituted dihydrodipyridopyrazines, which can easily be alkylated to give a large variety of unsymmetrical 5,10-dialkyl-5,10-dihydrodipyrido[2,3-*b*:2′,3′-*e*]pyrazines (isomers **A**) and 5,10-dialkyl-5,10-dihydrodipyrido[2,3-*b*:3′,2′-*e*]pyrazines (isomers **B**).

Introduction

A few years ago a new family of planar nitrogen heterocycles – the dihydrodipyridopyrazines (DHDPPs) **1** and **2** (Figure 1) – was reported.[1,2]

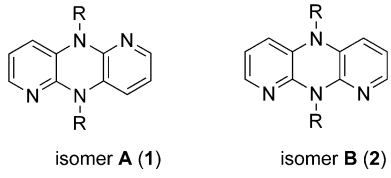
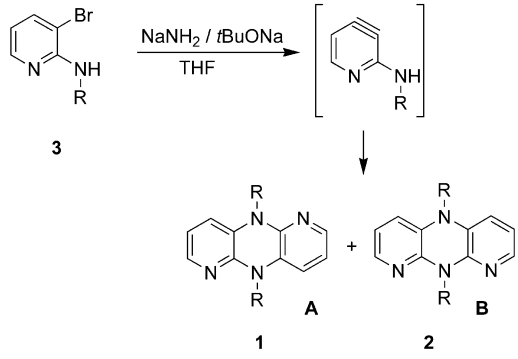


Figure 1. Dihydrodipyridopyrazine isomers **A** and **B**.

Hetarynic cyclizations of the corresponding 2-alkylamino-3-halogenopyridines **3** (Scheme 1) in the presence of the complex base $NaNH_2$/*t*BuONa make it possible to synthesize many symmetrical dihydrodipyridopyrazines without great difficulties of implementation, but with a major disadvantage lying in the production of mixtures of two isomers, together with total reaction yields that did not exceed 50%.[2,3]



Scheme 1.

These compounds show interesting chemical properties[4–6] and give very encouraging results with regard to their antitumor activity.[7] Wishing to avoid the disadvantages described above, we set out to synthesize each isomer separately.

In our efforts directed toward the construction of the dihydrodipyridopyrazine cycles (isomers **A** and **B**), we envisioned a sequence in which in either case a palladium-catalysed cross-coupling reaction or a nucleophilic aromatic substitution would provide an intermediate that would then be reduced and cyclized to give the desired dihydrodipyridopyrazine (see Schemes 2 and 3).

In connection with our interest in the preparation of dihydrodipyridopyrazine isomers **B** we have recently reported that the classical method through a nucleophilic displacement of a leaving group in the presence of LiHMDS as the

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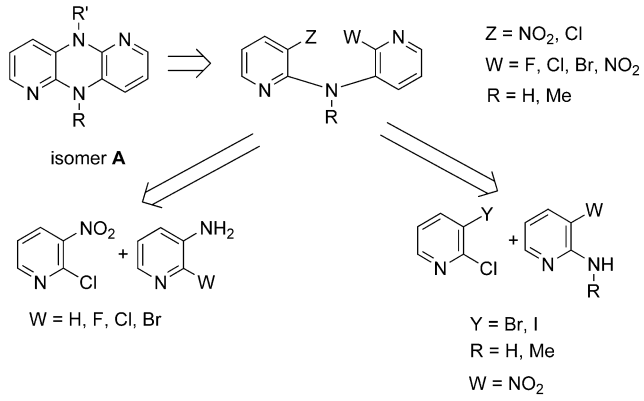
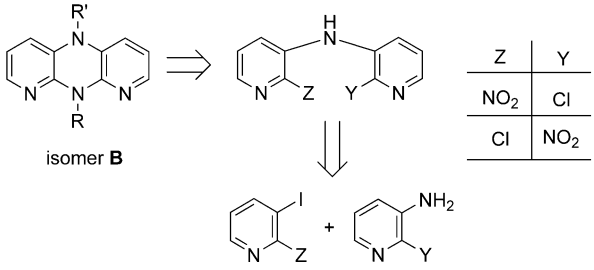


Scheme 2. Retrosynthetic analysis of the dihydrodipyridopyrazine isomers **A**.



Scheme 3. Retrosynthetic analysis of the dihydrodipyridopyrazine isomers **B**.

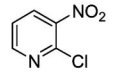
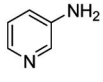
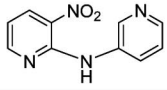
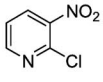
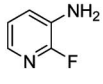
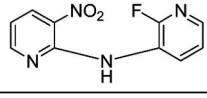
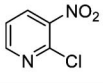
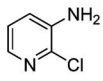
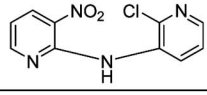
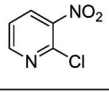
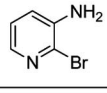
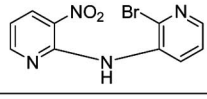
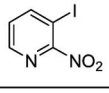
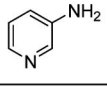
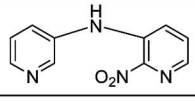
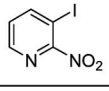
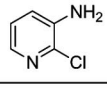
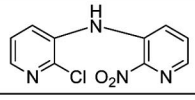
base and THF as the solvent led to the formation of the compound resulting from oxidative nucleophilic substitution of hydrogen (ONSH).[8]

For these reasons, in the field of aromatic C–N bond formation, we turned our attention to palladium-catalysed amination.

This paper presents a mild method for the efficient and selective synthesis of dihydrodipyridopyranizic isomers based on Pd^0-catalysed coupling of aminopyridines with substituted halonitropyridines and/or of aminopyridines with dihalopyridines.

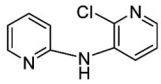
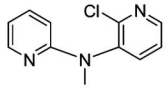
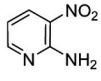
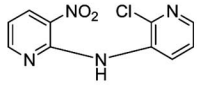
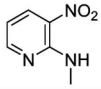
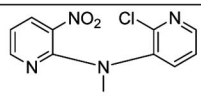
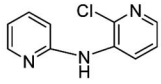
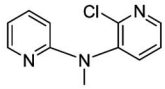
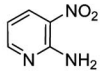
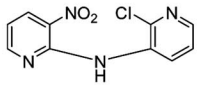
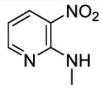
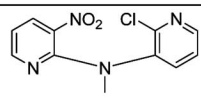
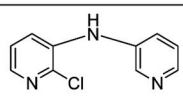
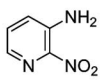
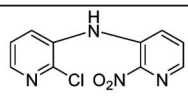
The catalytic amination of aryl halides reported by Buchwald[9] and Hartwig[10] represents an alternative to classical methods applied in the synthesis of a wide variety of potentially useful compounds and has allowed the preparation of compounds inaccessible by other known synthetic routes.[11] There are some examples of Pd-catalysed *N*-arylations with pyridinyl halides[12] achieved by use of DPPP, BINAP, DPPF, P(*t*Bu)$_3$ or Xantphos as ligands. In the case of electron-poor aminopyridines,[13] ligands such as DCHPDMAB or Xantphos are required. The couplings involving heteroaromatic cores represent a true challenge because the two partners involved are particularly deficient in electrons. However, only a few examples of *N*-arylation between two deactivated partners have been reported.[14] This underlines the difficulty in coupling electron-poor aminopyridines and hence shows the utility of particularly electron-rich ligands. On the other hand, our laboratory[15] has recently reported very efficient conditions for the amination of 2-chloropyridine with 3-amino-1,2,4-triazine in the presence of $Pd(OAc)_2$ as palladium source, Xantphos as the ligand and a large excess of K_2CO_3 as base in 1,4-dioxane with good results.

Table 1. Palladium-catalysed *N*-arylation of aminopyridines with halo-nitropyridines.

Entry	Halo-nitropyridine ArX		Aminopyridine $ArNH_2$		Product		Time [h]	Reaction conditions[a]	% Yield
1		**4**		**5**		**12**	5	A	94
2		**4**		**6a**		**13a**	3	A	86
3		**4**		**6b**		**13b**	4	A	67
4		**4**		**6c**		**13c**	24 24	A B	15[b] 20[b]
5		**7**		**5**		**14**	4	A	80
6		**7**		**6b**		**15**	5	A	43

[a] Method A: $Pd(OAc)_2$ (10 mol-%), Xantphos (20 mol-%), K_2CO_3 (1.5 equiv.), 1,4-dioxane, nitropyridine (1 equiv.), aminopyridine (1.2 equiv.). Method B: $Pd(OAc)_2$ (15 mol-%), Xantphos (30 mol-%), K_2CO_3 (1.5 equiv.), 1,4-dioxane, nitropyridine (1 equiv.), aminopyridine (1.2 equiv.). [b] 30% of starting amine was recovered.

Table 2. Palladium-catalysed amination of dihalopyridines.

Entry	Dihalopyridine		Aminopyridine $ArNH_2$		Product		Time [h]	Reaction conditions[a]	% Yield
1		**8a**		**9a**		**16**	8	A	44
2		**8a**		**9b**			24	A	–[b]
3		**8a**		**10a**		**13b**	24 24	A B	40[c] 42[c]
4		**8a**		**10b**		**20**	24	A	–[d]
5		**8b**		**9a**		**16**	24 24	A B	40[e] 76
6		**8b**		**9b**			24	A	–[f]
7		**8b**		**10a**		**13b**	24 24 48	A B C	48[g] 65[h] 90
8		**8b**		**10b**		**20**	24 24	A B	–[i] –[i]
9		**8b**		**5**		**17**	48 48	A C	30 56
10		**8b**		**11**		**15**	48 48 48	A B C	49[j] 69 85

[a] Method A: $Pd(OAc)_2$ (10 mol-%), Xantphos (20 mol-%), K_2CO_3 (1.5 equiv.), 1,4-dioxane, halopyridine (1 equiv.), aminopyridine (1.2 equiv.). Method B: $Pd(OAc)_2$ (15 mol-%), Xantphos (30 mol-%), K_2CO_3 (1.5 equiv.), 1,4-dioxane, halopyridine (1 equiv.), aminopyridine (1.2 equiv.). Method C: $Pd(OAc)_2$ (15 mol-%), Xantphos (30 mol-%), K_2CO_3 (1.5 equiv.), 1,4-dioxane, halopyridine (1.2 equiv.), aminopyridine (1 equiv.). [b] Starting amine (65%) was recovered. [c] Starting amine (35%) was recovered. [d] Starting amine (84%) was recovered. [e] Starting halopyridine (32%) was recovered. [f] Starting amine (75%) was recovered. [g] Starting amine (30%) was recovered. [h] Starting halopyridine (20%) was recovered. [i] Starting amine (72%) was recovered. [j] Starting amine (40%) was recovered.

Results and Discussion

Palladium-Catalysed Synthesis of Substituted *N*,*N*′-Dipyridinylamines

Our approach to *N*,*N*′-dipyridinylamines was inspired by the advances described above and is outlined in Tables 1 and 2.

Initially, halonitropyridines **4** and **7** react with aminopyridines **5** and **6a**–**c** (Table 1) in the presence of $Pd(OAc)_2$ (10 mol-%) as the palladium source, Xantphos (20 mol-%) as the ligand, K_2CO_3 (1.5 equiv.) as the base and 1,4-dioxane as the solvent (Method A).

Reaction times varied between 3–24 h with yields ranging from 15 to 94%.

The best results were obtained with 3-aminopyridine (**5**, Table 1, Entries 1 and 5), 3-amino-2-fluoropyridine (**6a**)[16] and 3-amino-2-chloropyridine (**6b**, Table 1, Entries 2 and 3) as amine source.

In the case of a coupling reaction with 3-amino-2-bromopyridine (**6c**) under conditions similar to those previously used with **4**, we observed the formation of the desired *N*-arylation product **13c**, but in poor yield (15%) and accompanied by the recovery of a proportion of the starting product. The reaction yield was not significantly improved after an increase in the amount of $Pd(OAc)_2$ to 15 mol-% with the same Xantphos/$Pd(OAc)_2$ ratio of 2:1 (Method B; Table 1, Entry 4).

It was possible to isolate single crystals of compounds **13a** and **15**, thus permitting their analysis by X-ray crystallography.

To complete our study of the palladium-catalysed amination, we also examined couplings of the dihalogenopyridines **8a** and **8b**[17] with a range of aminopyridines (**5**, **9a**, **9b**, **10a**, **10b** and **11**) under the same conditions. The most interesting results are shown in Table 2.

As would be expected, not all the dihalogenopyridines behave identically under the reaction conditions used. Treatment of 3-bromo-2-chloropyridine (**8a**) with 2-amino-3-nitropyridine (**10a**) in the presence either of 10 mol-% $Pd(OAc)_2$ (Method A) or 15 mol-% $Pd(OAc)_2$ (Method B) (Table 2, Entry 3) gave the coupling product **13b** in a moderate yield (42%).

Optimization of these reactions was attempted. Changing the bromide atom for an iodine atom did not lead to a higher yield of isolated **13b** (Table 2, Entry 3 vs. 7, Method A). To obtain the best results, high catalyst loadings [$Pd(OAc)_2$ 15 mol-%, Xantphos 30 mol-%] were used (Method B), but we observed only a slight optimization of the yield (Table 2, Entry 7). With use of an excess of halogenated substrate [1 equiv. of 2-amino-3-nitropyridine (**10a**) and 1.2 equiv. of 2-chloro-3-iodopyridine (**8b**)] with $Pd(OAc)_2$ (15 mol-%) as palladium source, Xantphos (30 mol-%) as ligand and K_2CO_3 (1.5 equiv.) as base in 1,4-dioxane (Method C), compound **13b** – the potential precursor of isomer **A** of DHDPP – was obtained in excellent yield (90%, Table 2, Entry 7).

Under the same conditions (Method C), replacement of 2-amino-3-nitropyridine (**10a**) with 3-amino-2-nitropyridine (**11**) as amine component gave compound **15**, the potential precursor of the dihydrodipyridopyrazine isomer **B**, in 85% yield (Table 2, Entry 10).

We observed that the Pd-catalysed amination reactions between 2-chloro-3-iodopyridine (**8b**) and the amino-nitropyridines **10a** and **11** led to **13b** and **15** in yields higher than those obtained in the coupling reactions of **4** with **6b** and of **7** with **6b**, respectively (Table 2, Entries 7 and 10 vs. Table 1, Entries 3 and 6).

It should be noted that no reaction occurred when the *N*-methylated aminopyridines **9b** and **10b** were used as amine sources, with the starting materials being recovered (Table 2, Entries 2, 4, 6 and 8).

This work confirms that both electron-withdrawing and -donating substituents are tolerated under these conditions.

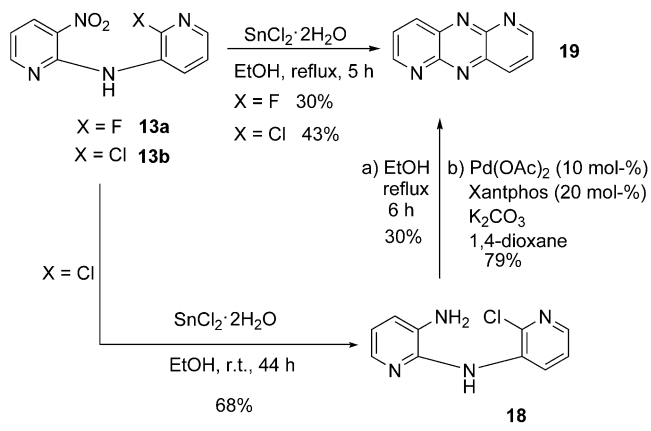
Compounds **13a**–**c** and **15** are potential substrates for the selective synthesis of dihydrodipyridopyrazine isomers **A** and **B**, respectively.

Synthesis of DHDPP Isomers A

As a second part of our work, using **13** and **15** as starting materials we examined the possibility of obtaining the *N*-substituted dihydrodipyridopyrazine isomers **A** and **B** selectively.

Because the 20% yield of **13c** made the use of this compound rather unattractive, however, we decided to employ **13a** and **13b** as starting substrates.

The nitro groups in **13a** and **13b**, the potential precursors of dihydrodipyridopyrazine isomers **A**, were subjected to reduction under Bellamy's conditions[18] ($SnCl_2 \cdot 2H_2O$, in ethanol at reflux for 5 h), but the corresponding amino derivative was not isolated. We directly obtained the aromatization product **19** in yields ranging from 30 to 43% (Scheme 4).



Scheme 4.

Amine **18** was isolated in 68% yield, however, when the reduction of the nitro group of **13b** in the presence of $SnCl_2 \cdot 2H_2O$ in ethanol was carried out at room temperature for 44 h. The structure of **18** was also confirmed by X-ray crystallography.

For the intramolecular cyclization, simple heating at reflux in ethanol was investigated. Under these conditions, though, compound **19** was isolated in only 30% yield. Pd-catalysed cyclization of **18** under the conditions of Method A [$Pd(OAc)_2$ (10 mol-%), Xantphos (20 mol-%), K_2CO_3 (1.5 equiv.) in 1,4-dioxane], however, gave access to **19** in good yield (79%) (Scheme 4).

The unambiguous assignment of the structure of aromatized compound **19** was established by X-ray crystallography (Figure 2).

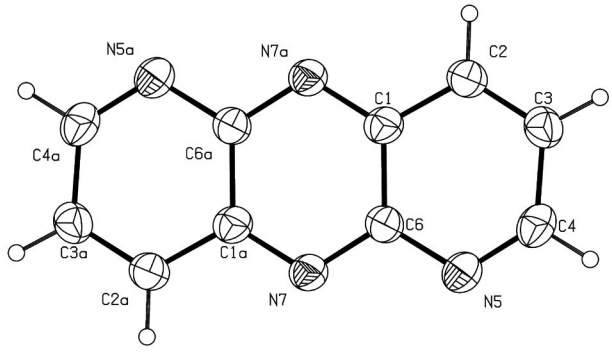
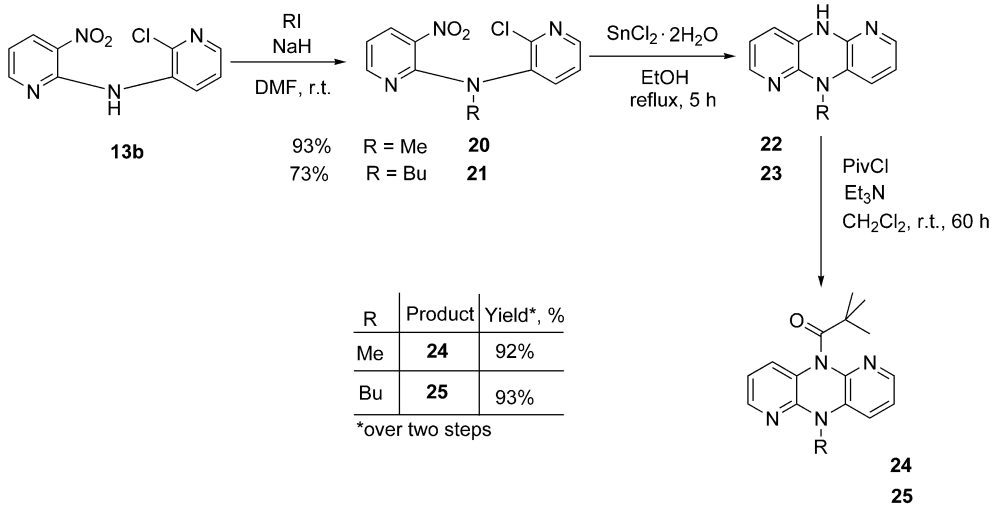


Figure 2. X-ray structure of compound **19**.

In view of the above results, we reasoned that a preliminary *N*-alkylation would be the most convenient method to stabilize the molecule before the reduction step. We therefore first allowed **13b** to react with methyl iodide or butyl iodide in the presence of sodium hydride in anhydrous DMF (Scheme 5). The alkylated products **20** and **21**, isolated in 93% and 73% yields, respectively, were than treated



R	Product	Yield*, %
Me	**24**	92%
Bu	**25**	93%

*over two steps

Scheme 5.

with $SnCl_2 \cdot 2H_2O$ in ethanol at reflux for 5 h to give the desired dihydrodipyridopyrazines **22** and **23**. However, because these compounds seem to be unstable to column chromatography, the monosubstituted isomers **22** and **23** were employed without preliminary purification in the next reactions.

It should be noted that the monosubstituted isomers **22** and **23** each possessed a free amine, and so were easily substitutable for the preparation of unsymmetrically substituted *N*,*N*-dialkyl dihydrodipyridopyrazines.

Compounds **22** and **23** were subjected, without prior purification, to a classic acylation procedure (PivCl, Et_3N, dichloromethane at room temperature). The pivaloyl derivatives **24** and **25** were synthesized in very good yields calculated over two steps (Scheme 5).

The structures of **21** and **24** were studied by X-ray crystallography (Figure 3).

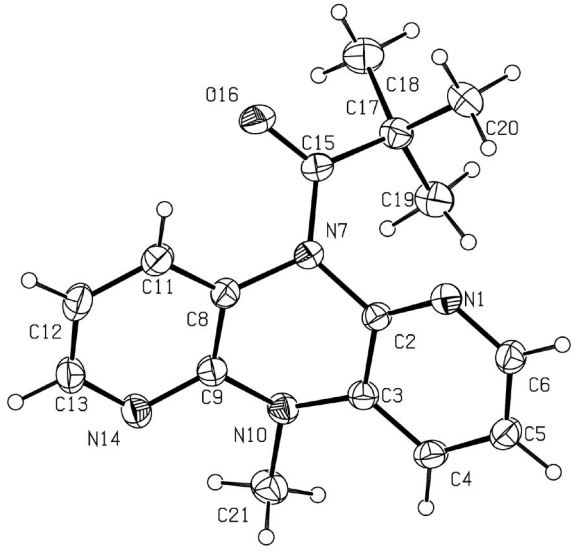
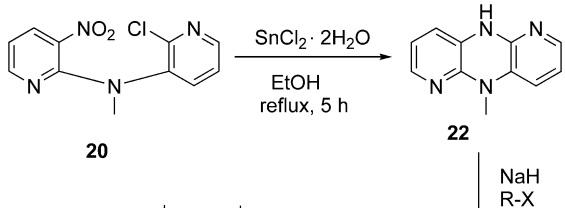


Figure 3. X-ray structure of compound **24**.

Treatment of crude **22** with sodium hydride in DMF and then with different halo derivatives resulted in the preparation of the various 5,10-dialkyl-5,10-dihydrodipyrido[2,3-*b*:2′,3′-*e*]pyrazines **26a**–**d** (DHDPP isomers **A**) in excellent yields (Scheme 6).



R-X	Product	Yield*, %
CH_3-I	**26a**	90
Br	**26b**	88
Br	**26c**	91
CH_2-Cl	**26d**	89

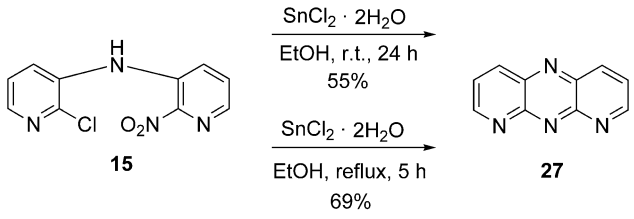
* over 2 steps

Scheme 6.

5,10-Dimethyl-5,10-dihydrodipyrido[2,3-*b*:2′,3′-*e*]pyrazine (**26a**), obtained in 90% yield over two steps, has the same spectroscopic data as those recorded for the compound isolated by an arynic sequence.[2]

Synthesis of DHDPP Isomers B

In the case of compound **15**, the potential precursor of dihydrodipyridopyrazine isomers **B**, similar treatment with $SnCl_2 \cdot 2H_2O$, in ethanol at room temperature or at reflux led directly to the corresponding aromatization product **27** in 55% and 69% yields, respectively (Scheme 7). In contrast with the successful reaction of **13b** at room temperature to give **18**, in the case of **15** the intermediate compound with a reduced nitro group was not detected.



Scheme 7.

This result and our success in the synthesis of isomers **A** encouraged us to proceed by the same methodology for the synthesis of isomers **B** from the starting compound **15**.

The 5,10-dialkyl-5,10-dihydrodipyrido[2,3-*b*:3′,2′-*e*]pyrazines **30a**–**d** were prepared as outlined in Scheme 8. *N*-Methylation of **15** with sodium hydride and methyl iodide in DMF provided product **28** in 83% yield. The structure of compound **28** was unambiguously established by X-ray crystallography. The desired DHDPP **B** isomers **30a**–**d** were isolated in good yields after reduction/cyclization of **28** in the presence of $SnCl_2 \cdot 2H_2O$ in ethanol at reflux for 5 h, which was followed by *N*-alkylation of crude **29** with various halo derivatives.

The spectroscopic data for product **30a**, obtained in 87% yield over two steps, are the same as those recorded for the 5,10-dimethyl-5,10-dihydrodipyrido[2,3-*b*:3′,2′-*e*]pyrazine synthesized by the arynic sequence.[2]

The structure of 10-benzyl-5-methyl-5,10-dihydrodipyrido[2,3-*b*:3′,2′-*e*]pyrazine (**30d**) was unambiguously established by X-ray crystallography. The ORTEP drawing of the crystal structure of compound **30d** (Figure 4) shows that two independent molecules exist in the unit. They present some differences in the plane angles' values between pyrazine moiety and phenyl group [67.1(2)° for up molecule and 71.6(2)° for down molecule].

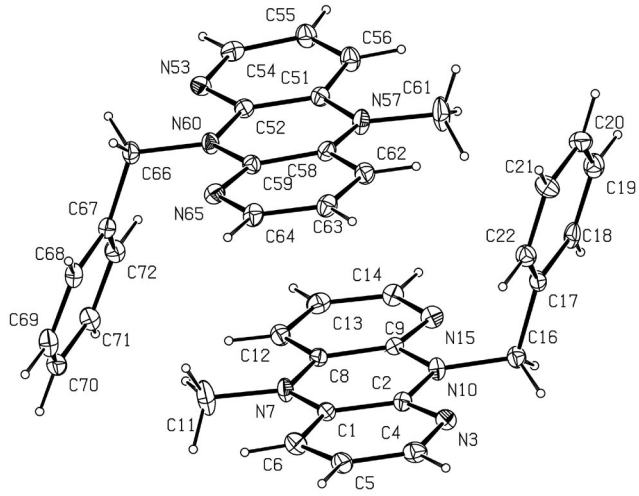


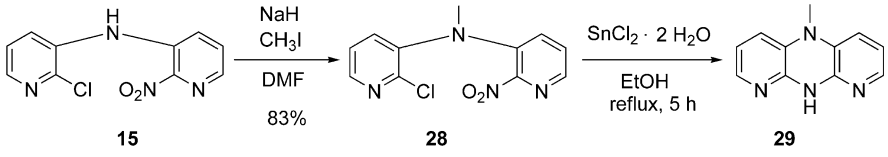
Figure 4. X-ray structure of compound **30d**.

Conclusions

Specific syntheses of each of the unsymmetrically substituted dihydrodipyridopyrazine isomers **A** and **B** have been completed. The novel strategy that was developed for their syntheses featured Pd-catalysed reactions as key steps.

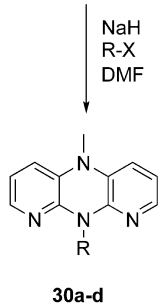
We found that palladium-catalysed coupling reactions between aminopyridines and either nitropyridines or dihalopyridines in the presence of $Pd(OAc)_2$ as catalyst and Xantphos as ligand, together with K_2CO_3 and dry 1,4-dioxane, provided various *N*,*N*′-dipyridinylamines in good yields. This method has reasonable generality and compatibility with base-sensitive functional group.

From suitable nitro-substituted *N*,*N*′-dipyridinylamines, a substitution–reduction–cyclization–substitution sequence allows easy and selective access to unsymmetrical 5,10-di-



R–X	Product	Yield*, %
CH_3-I	**30a**	87
Br	**30b**	82
Br	**30c**	84
CH_2–Cl	**30d**	82

* over 2 steps



Scheme 8.

alkyl-5,10-dihydrodipyrido[2,3-*b*:2′,3′-*e*]pyrazines and 5,10-dialkyl-5,10-dihydrodipyrido[2,3-*b*:3′,2′-*e*]pyrazines in very good yields.

Experimental Section

General: All air-sensitive experiments were performed under argon. Dioxane was distilled from sodium benzophenone ketyl prior to use. DMF was purified by distillation over CaH_2 and stored under an inert atmosphere over 4 Å molecular sieves. Dichloromethane was distilled from calcium hydride under argon prior to use. Petroleum ether, where used, had a boiling range of 40–60 °C. All commercially available reagents were used without further purification unless otherwise noted. ^{1}H 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), with 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 by the ATR technique (germanium crystal) and are reported in cm^{-1}. Flash column chromatography was carried out with Merck 40–70 nm (230–400 mesh) silica gel under nitrogen pressure. Thin-layer chromatography (TLC) was carried out on aluminium sheets precoated with silica gel (Merck 60 F254). Low-resolution mass spectra (MS) were recorded on a Perkin–Elmer SCIEX AOI 300 spectrometer. High-resolution mass spectra (ESI-TOF) were recorded on a Q-Tof micro waters spectrometer. Melting points were determined on a Büchi 510 melting point apparatus in open capillaries and are uncorrected. X-ray analyses were carried out on a Bruker Enraf Nonius CAD4 instrument with a Cu sealed tube for compounds **15**, **18**, **21** and **28**. Other X-ray analyses were carried out on a MSC-Rigaku R-axis MM007 instrument with a Cu rotating anode and an image plate[19] as detector for compounds **13a**, **19**, **24** and **30d**. The Shelxs[20] and Shelxl[21] programs were used for structures determination and refinement.

Starting Materials

Preparation of the Starting Materials: The halopyridines and aminopyridines were either commercially available (**4**, **5**, **6b**, **6c**, **8a**, **9a**, **9b**, **10a**, **11**) or were easily prepared from commercially available materials by literature procedures (**6a**,[16] **8b**[17]).

3-Iodo-2-nitropyridine (7): Compound **7** was prepared by a procedure reported by Kuethe[17] starting from 3-amino-2-nitropyridine (**11**). A 250 mL flask was charged with HCl (5 N, 10 mL) and 3-amino-2-nitropyridine (1.0 g, 7.188 mmol). This reaction mixture was cooled to –5 °C and sodium nitrite (0.744 g, 10.782 mmol) in H_2O (7 mL) was added dropwise while the internal temperature was maintained below 5 °C. After 10 min at –5 °C, KI (2.625 g, 15.841 mmol) in water (7 mL) was added dropwise while the internal temperature was maintained below 10 °C over the course of addition. The reaction mixture was allowed to warm to room temperature and EtOAc (15 mL) was added. The pH of the aqueous layer was adjusted to 11 by addition of NaOH solution (6 N), the layers were separated, and the organic layer was washed with $Na_2S_2O_3$ (0.3 M, 15 mL). The EtOAc layer was concentrated under reduced pressure and the residue was redissolved in DMF (10 mL). Water (30 mL) was added dropwise to the brown/reddish mixture and the slurry was stirred for 30 min and filtered. The filter cake was washed with water (2 × 10 mL) and dried under vacuum. The crude product was purified by column chromatography (petroleum ether/ethyl acetate 10:0→9:1) to provide the desired compound **7** (0.54 mg, 30% yield) as yellow crystals; m.p. 100–101 °C. ^{1}H NMR (250 MHz, $CDCl_3$, 27 °C): δ = 8.50 (dd, J = 4.6, 1.3 Hz, 1 H), 8.41 (dd, J = 7.9, 1.3 Hz, 1 H), 7.32 (dd, J = 7.9, 4.6 Hz, 1 H) ppm. ^{13}C NMR (62.9 MHz, $CDCl_3$, 27 °C): δ = 160.8 (Cq), 151.0 (CH), 147.9 (CH), 128.0 (CH), 81.6 (Cq) ppm. IR (ATR): $\tilde{\nu}$ = 1572, 1528 cm^{-1}. MS: m/z = 251.00 [M + H]$^+$. HRMS: calcd. for $C_5H_4IN_2O_2$ [M + H]$^+$ 250.9317; found 250.9321.

***N*-Methyl-3-nitropyridin-2-amine (10b):** A mixture of 2-chloro-3-nitropyridine (0.3 g, 1.89 mmol) and methylamine (20 mL, 39.74 mmol) in ethanol (20 mL) was heated at 130 °C for 8 h in an autoclave. The mixture was hydrolysed, extracted with ethyl acetate and dried with $MgSO_4$, and the solvent was removed under reduced pressure to give the crude product. This residue was purified by flash chromatography on silica gel (petroleum ether/ethyl acetate 8:2) and the desired product **10b** (0.26 g, 90% yield) was obtained as yellow crystals. ^{1}H NMR (250 MHz, $CDCl_3$, 27 °C): δ = 8.44–8.37 (m, 2 H), 8.19 (br s, 1 H, NH), 6.63 (dd, J = 8.3, 4.5 Hz, 1 H), 3.16 (d, J = 4.9 Hz, 3 H, CH_3) ppm. ^{13}C NMR (62.9 MHz, $CDCl_3$, 27 °C): δ = 155.9 (CH), 153.3 (Cq), 135.3 (CH), 128.4 (Cq), 111.6 (CH), 28.3 (CH_3) ppm. IR (ATR): $\tilde{\nu}$ = 3285, 1420 cm^{-1}. MS: m/z = 154.3 [M + H]$^+$. HRMS: calcd. for $C_6H_8N_3O_2$ [M + H]$^+$ 154.1466; found 154.1469.

General Procedure for the Palladium-Catalysed *N*-Arylations: A round-bottomed flask flushed with nitrogen was charged with Xantphos (20 mol-%) and anhydrous 1,4-dioxane (0.02 mmol mL^{-1}). After degassing, $Pd(OAc)_2$ (10 mol-%) was introduced and the mixture was stirred under nitrogen for 10 min. In a second round-bottomed flask, the heteroaryl halide (1 equiv.), the amine (1.2 equiv.) and K_2CO_3 (1.5 equiv.) were poured into anhydrous 1,4-dioxane (0.05 mmol halide per mL). The $Pd(OAc)_2$/Xantphos solution was transferred by cannula and the resulted mixture was subsequently heated at reflux under argon with vigorous stirring. The progress of the 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 flash chromatography on silica gel to afford the desired *N*,*N*′-dipyridinylamines.

Method A: $Pd(OAc)_2$ (10 mol-%), Xantphos (20 mol-%), K_2CO_3 (1.5 equiv.), 1,4-dioxane, halogenopyridine (1 equiv.), aminopyridine (1.2 equiv.).

Method B: $Pd(OAc)_2$ (15 mol-%), Xantphos (30 mol-%), K_2CO_3 (1.5 equiv.), 1,4-dioxane, halogenopyridine (1 equiv.), aminopyridine (1.2 equiv.).

Method C: $Pd(OAc)_2$ (15 mol-%), Xantphos (30 mol-%), K_2CO_3 (1.5 equiv.), 1,4-dioxane, halogenopyridine (1.2 equiv.), aminopyridine (1 equiv.).

***N*-(3-Nitropyridin-2-yl)-*N*-(pyridin-3-yl)amine (12):** This compound was obtained by the General Procedure for palladium-catalysed *N*-arylations – Method A, with 2-chloro-3-nitropyridine (**4**, 200 mg, 1.26 mmol) and 3-aminopyridine (**5**, 142 mg, 1.51 mmol). Purification by flash chromatography on silica gel (petroleum ether/ethyl acetate 7:3→5:5) afforded product **12** (256 mg, 94% yield) as dark orange crystals; m.p. 100–102 °C. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 10.09 (br s, 1 H, NH), 8.85 (d, J = 2.5 Hz, 1 H), 8.55 (dd, J = 8.3, 1.8 Hz, 1 H), 8.49 (dd, J = 4.5, 1.8 Hz, 1 H), 8.40 (dd, J = 4.7, 1.3 Hz, 1 H), 8.17–8.14 (m, 1 H), 7.33 (dd, J = 8.3, 4.7 Hz, 1 H), 6.91 (dd, J = 8.3, 4.5 Hz, 1 H) ppm. ^{13}C NMR (62.9 MHz, $CDCl_3$, 27 °C): δ = 155.0 (CH), 149.9 (Cq), 145.5 (CH), 143.8 (CH), 135.6 (CH), 134.9 (Cq), 129.2 (CH), 129.1 (Cq), 123.5 (CH), 114.9 (CH) ppm. IR (ATR): $\tilde{\nu}$ = 3327, 1604, 1573, 1497, 1478,

756 cm^{-1}. MS: *m/z* = 217.00 $[M + H]^+$. HRMS: calcd. for $C_{10}H_9N_4O_2$ $[M + H]^+$ 217.0726; found 217.0737.

***N*-(2-Fluoropyridin-3-yl)-*N*-(3-nitropyridin-2-yl)amine (13a):** This compound was obtained by the General Procedure for the palladium-catalysed *N*-arylations – Method A, with 2-chloro-3-nitropyridine (**4**, 1.07 g, 6.68 mmol) and 3-amino-2-fluoropyridine (**6a**, 0.91 g, 8.12 mmol). Purification by flash chromatography on silica gel (petroleum ether/ethyl acetate 9:1) afforded product **13a** (1.36 g, 86% yield) as orange crystals; m.p. 130 °C. ^1H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 10.30 (br s, 1 H, NH), 8.91 (ddd, *J* = 8.1, 7.9, 1.7 Hz, 1 H), 8.59 (dd, *J* = 8.3, 1.7 Hz, 1 H), 8.54 (dd, *J* = 4.5, 1.7 Hz, 1 H), 7.93 (dt, *J* = 4.8, 1.7 Hz, 1 H), 7.23 (dd, *J* = 7.9, 4.8 Hz, 1 H), 6.98 (dd, *J* = 8.3, 4.6 Hz, 1 H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$, 25 °C): δ = 154.7 (CH), 154.5 (d, Cq, *J* = 234.4 Hz), 149.4 (Cq), 140.7 (d, *J* = 14.1 Hz, CH), 135.7 (CH), 131.8 (d, *J* = 2.5 Hz, CH), 129.9 (Cq), 122.5 (d, *J* = 24.5 Hz, Cq), 121.8 (d, *J* = 4.0 Hz, CH), 115.4 (CH) ppm. IR (ATR): $\tilde{\nu}$ = 3315, 1610, 1429, 1227, 755 cm^{-1}. MS: *m/z* = 235.5 $[M + H]^+$. HRMS: calcd. for $C_{10}H_8FN_4O_2$ $[M + H]^+$ 235.0631; found 235.0627.

***N*-(2-Chloropyridin-3-yl)-*N*-(3-nitropyridin-2-yl)amine (13b):** This compound was obtained by the General Procedure for the palladium-catalysed *N*-arylations – Method C, with 2-amino-3-nitropyridine (**10a**, 1.00 g, 7.19 mmol) and 2-chloro-3-iodopyridine (**8b**, 2.065 g, 8.63 mmol). Purification by flash chromatography on silica gel (petroleum ether/ethyl acetate 9:1 → CH_2Cl_2/ethyl acetate 10:0, 9:1) afforded product **13b** (1.62 g, 90% yield) as a yellow-orange powder; m.p. 160 °C. ^1H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 10.66 (br s, 1 H, NH), 8.96 (dd, *J* = 8.2, 1.7 Hz, 1 H), 8.60 (dd, *J* = 8.3, 1.8 Hz, 1 H), 8.53 (dd, *J* = 4.6, 1.8 Hz, 1 H), 8.14 (dd, *J* = 4.6, 1.7 Hz, 1 H), 7.30 (dd, *J* = 8.2, 4.6 Hz, 1 H), 6.99 (dd, *J* = 8.3, 4.6 Hz, 1 H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$, 25 °C): δ = 160.1 (Cq), 154.5 (CH), 149.2 (Cq), 143.5 (CH), 141.9 (Cq), 135.8 (CH), 132.9 (Cq), 130.1 (CH), 122.9 (CH), 115.6 (CH) ppm. IR (ATR): $\tilde{\nu}$ = 3299, 1606, 1590, 1502, 775 cm^{-1}. MS: *m/z* = 253.00 (^{37}Cl) $[M + H]^+$, 251.00 (^{35}Cl) $[M + H]^+$. HRMS: calcd. for $C_{10}H_8N_4O_2{}^{35}Cl$ $[M + H]^+$ 251.0336; found 251.0329.

***N*-(2-Bromopyridin-3-yl)-*N*-(3-nitropyridin-2-yl)amine (13c):** This compound was obtained by the General Procedure for the palladium-catalysed *N*-arylations – Method B, with 2-chloro-3-nitropyridine (**4**, 100 mg, 0.63 mmol) and 3-amino-2-bromopyridine (**6c**, 131 mg, 0.76 mmol). Purification by flash chromatography on silica gel (petroleum ether/ethyl acetate 9:1 → 7:3) afforded product **13c** (37 mg, 20% yield) as a yellow powder: M.p. 83–85 °C. ^1H NMR (250 MHz, $CDCl_3$, 27 °C): δ = 10.60 (br s, 1 H, NH), 8.70 (dd, *J* = 8.1, 1.6 Hz, 1 H), 8.60 (dd, *J* = 8.3, 1.6 Hz, 1 H), 8.52 (dd, *J* = 4.6, 1.6 Hz, 1 H), 8.12 (dd, *J* = 4.6, 1.6 Hz, 1 H), 7.31 (dd, *J* = 8.1, 4.6 Hz, 1 H), 6.99 (dd, *J* = 8.3, 4.6 Hz, 1 H) ppm. ^{13}C NMR (62.9 MHz, $CDCl_3$, 27 °C): δ = 154.5 (CH), 149.1 (Cq), 144.3 (CH), 143.6 (Cq), 135.9 (CH), 135.2 (Cq), 134.7 (Cq), 130.1 (CH), 123.1 (CH), 115.6 (CH) ppm. IR (ATR): $\tilde{\nu}$ = 3276, 1590, 1495, 1459, 1425 cm^{-1}. MS: *m/z* = 297.00 (^{81}Br) $[M + H]^+$, 295.00 (^{79}Br) $[M + H]^+$. HRMS: calcd. for $C_{10}H_8N_4O_2{}^{79}Br$ $[M + H]^+$ 294.9831; found 294.9831.

***N*-(2-Nitropyridin-3-yl)-*N*-(pyridin-3-yl)amine (14):** This compound was obtained by the General Procedure for the palladium-catalysed *N*-arylations – Method A, with 3-iodo-2-nitropyridine (**7**, 100 mg, 0.4 mmol) and 3-aminopyridine (**5**, 45 mg, 0.48 mmol). Purification by flash chromatography on silica gel (petroleum ether/ethyl acetate 8:2 → 6:4) afforded product **14** (69 mg, 80% yield) as yellow crystals; m.p. 128–129 °C. ^1H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 9.14 (br s, 1 H, NH), 8.61 (d, *J* = 2.5 Hz, 1 H), 8.53 (dd, *J* = 4.7, 1.2 Hz, 1 H), 8.06 (dd, *J* = 4.0, 1.4 Hz, 1 H), 7.63–7.60 (m, 2 H), 7.44–7.38 (m, 2 H) ppm. ^{13}C NMR (62.9 MHz, $CDCl_3$, 27 °C): δ = 147.4 (CH), 146.2 (CH), 142.3 (Cq), 138.3 (CH), 138.1 (Cq), 134.7 (Cq), 131.7 (CH), 130.3 (CH), 125.3 (CH), 124.4 (CH) ppm. IR (ATR): $\tilde{\nu}$ = 3348, 1604, 1490, 1237 cm^{-1}. MS: *m/z* = 217.00 $[M + H]^+$. HRMS: calcd. for $C_{10}H_9N_4O_2$ $[M + H]^+$ 217.0726; found 217.0731.

***N*-(2-Chloropyridin-3-yl)-*N*-(2-nitropyridin-3-yl)amine (15):** This compound was obtained by the General Procedure for the palladium-catalysed *N*-arylations – Method C, with 3-amino-2-nitropyridine (**11**, 1.0 g, 7.19 mmol) and 2-chloro-3-iodopyridine (**8b**, 2.065 g, 8.63 mmol). Purification by flash chromatography on silica gel (petroleum ether/ethyl acetate 8:2 → 7:3) afforded product **15** (1.53 g, 85% yield) as a yellow-orange solid; m.p. 160–162 °C. ^1H NMR (400 MHz, $CDCl_3$, 27 °C): δ = 9.19 (br s, 1 H, NH), 8.29 (dd, *J* = 4.7, 1.6 Hz, 1 H), 8.14 (dd, *J* = 4.1, 1.4 Hz, 1 H), 7.74 (dd, *J* = 7.9, 1.6 Hz, 1 H), 7.61 (dd, *J* = 8.5, 1.4 Hz, 1 H), 7.48 (dd, *J* = 8.5, 4.1 Hz, 1 H), 7.34 (dd, *J* = 7.9, 4.7 Hz, 1 H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$, 27 °C): δ = 145.9 (Cq), 145.8 (CH), 143.3 (Cq), 139.2 (CH), 136.1 (Cq), 132.6 (Cq), 131.2 (CH), 130.2 (CH), 125.8 (CH), 123.2 (CH) ppm. IR (ATR): $\tilde{\nu}$ = 3323, 1601, 1493, 1415, 1247, 795 cm^{-1}. MS: *m/z* = 253.00 (^{37}Cl) $[M + H]^+$, 251.00 (^{35}Cl) $[M + H]^+$. HRMS: calcd. for $C_{10}H_8N_4O_2{}^{35}Cl$ $[M + H]^+$ 251.0336; found 251.0339.

***N*-(2-Chloropyridin-3-yl)-*N*-(pyridin-2-yl)amine (16):** This compound was obtained by the General Procedure for the palladium-catalysed *N*-arylations – Method B, with 2-chloro-3-iodopyridine (**8b**, 150 mg, 0.63 mmol) and 2-aminopyridine (**9a**, 70.7 mg, 0.75 mmol). Purification by flash chromatography on silica gel (petroleum ether/ethyl acetate 9:1 → 8:2 → 7:3) afforded product **16** (98 mg, 76% yield) as brown crystals; m.p. 120 °C (ref.[14e] 117 °C). The spectroscopic data (IR and NMR) were in accordance with the literature values.[14e]

***N*-(2-Chloropyridin-3-yl)-*N*-(pyridin-3-yl)amine (17):** This compound was obtained by the General Procedure for the palladium-catalysed *N*-arylations – Method C, with 3-aminopyridine (**5**, 40 mg, 0.42 mmol) and 2-chloro-3-iodopyridine (**8b**, 122.1 mg, 0.51 mmol). Purification by flash chromatography on silica gel (petroleum ether/ethyl acetate 9:1 → 7:3 → 4:6) afforded product **17** (49 mg, 56% yield) as a red-brown gum. ^1H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 8.52 (s, 1 H), 8.36 (d, *J* = 4.7 Hz, 1 H), 7.94 (dd, *J* = 4.6, 1.5 Hz, 1 H), 7.51 (dd, *J* = 8.2, 1.0 Hz, 1 H), 7.46 (dd, *J* = 8.1, 1.5 Hz, 1 H), 7.30 (dd, *J* = 8.2, 4.7 Hz, 1 H), 7.13 (dd, *J* = 8.1, 4.6 Hz, 1 H), 6.26 (br s, 1 H, NH) ppm. ^{13}C NMR (62.9 MHz, $CDCl_3$, 25 °C): δ = 144.8 (CH), 143.0 (CH), 140.5 (CH), 139.4 (Cq), 137.0 (Cq), 136.9 (Cq), 127.5 (CH), 124.1 (CH), 123.2 (CH), 121.8 (CH) ppm. IR (ATR): $\tilde{\nu}$ = 3407, 1582, 1485, 1216, 752 cm^{-1}. MS: *m/z* = 208.00 (^{37}Cl) $[M + H]^+$, 206.00 (^{35}Cl) $[M + H]^+$. HRMS: calcd. for $C_{10}H_9N_3{}^{35}Cl$ $[M + H]^+$ 206.0485; found 206.0486.

***N*²-(2-Chloropyridin-3-yl)pyridine-2,3-diamine (18):** This compound was obtained by the General Procedure for the reduction step, with **13b** (100 mg, 0.40 mmol) and stannous chloride dihydrate (450 mg, 2.00 mmol) in absolute ethanol at room temperature. Purification by flash chromatography on silica gel (petroleum ether/ethyl acetate 6:4) afforded product **18** (60 mg, 68% yield) as a beige-brown solid; m.p. 119–121 °C. ^1H NMR (250 MHz, $CDCl_3$, 27 °C): δ = 8.44 (dd, *J* = 8.2, 1.6 Hz, 1 H), 7.90 (dd, *J* = 4.7, 1.6 Hz, 1 H), 7.83 (dd, *J* = 5.0, 1.6 Hz, 1 H), 7.15 (dd, *J* = 8.2, 4.7 Hz, 1 H), 7.06 (dd, *J* = 7.5, 1.6 Hz, 1 H), 6.90 (s, 1 H, NH), 6.80 (dd, *J* = 7.5, 5.0 Hz, 1 H), 3.49 (br s, 2 H, NH_2) ppm. ^{13}C NMR (62.9 MHz, $CDCl_3$, 27 °C): δ = 144.6 (Cq), 140.3 (CH), 139.1 (CH), 139.0 (Cq), 135.2 (Cq), 131.4 (Cq), 125.5 (CH), 124.6 (CH), 123.2 (CH), 118.4

(CH) ppm. IR (ATR): ṽ = 3378, 3224, 1598, 1447, 751 cm^{-1}. MS: *m*/*z* = 223.5 (^{37}Cl) [M + H]$^+$, 221.5 (^{35}Cl) [M + H]$^+$. HRMS: calcd. for $C_{10}H_{10}N_4{}^{35}Cl$ [M + H]$^+$ 221.0594; found 221.0602.

Dipyrido[2,3-*b*:2′,3′-*e*]pyrazine (19): This compound was obtained by the General Procedure for the reduction/cyclization step, with **13b** (200 mg, 0.80 mmol) and stannous chloride dihydrate (900 mg, 4.00 mmol) at reflux in absolute ethanol. Purification by flash chromatography on silica gel (CH_2Cl_2/MeOH 100:0→98:2→95:5) afforded product **19** (62.5 mg, 43% yield) as a dark green solid; m.p. > 250 °C. ^1H NMR (250 MHz, $CDCl_3$, 27 °C): δ = 9.40 (dd, *J* = 3.8, 1.9 Hz, 2 H), 8.74 (dd, *J* = 8.8, 1.9 Hz, 2 H), 7.86 (dd, *J* = 8.5, 4.1 Hz, 2 H) ppm. ^{13}C NMR (62.9 MHz, $CDCl_3$, 27 °C): δ157.8 (2×CH), 149.9 (2×Cq), 141.1 (2×Cq), 139.4 (2×CH), 126.6 (2×CH) ppm. IR (ATR): ṽ = 1504 cm^{-1}. HRMS: calcd. for $C_{10}H_6N_4Na$ [M + Na]$^+$ 205.0490; found 205.0499.

General Procedure for Alkylations: The appropriate *N*,*N*′-dipyridinylamine (1 equiv.) in DMF was added under argon at 0 °C to a suspension of sodium hydride (60%, 1.1 equiv.) in DMF. The mixture was stirred at room temperature for 20 min and cooled to –78 °C, and the halo derivative (1.2 equiv.) was added dropwise. The reaction mixture was allowed to warm slowly to room temperature and stirred until the end of the reaction. The reaction was monitored by TLC for the disappearance of starting materials. The mixture was hydrolysed, extracted with ethyl acetate and dried with $MgSO_4$, and the solvent was removed under reduced pressure to give the crude product, which was purified by flash chromatography on silica gel to afford the desired product.

***N*-(2-Chloropyridin-3-yl)-*N*-methyl-*N*-(3-nitropyridin-2-yl)amine (20):** This compound was obtained by the General Procedure for alkylations, with compound **13b** (1.60 g, 6.38 mmol) and methyl iodide (476.9 μL, 7.66 mmol). The solution was stirred for 2 h at room temperature. Purification by flash chromatography on silica gel (petroleum ether/ethyl acetate 8:2) afforded product **20** (1.57 g, 93% yield) as a yellow solid; m.p. 79 °C. ^1H NMR (250 MHz, $CDCl_3$, 27 °C): δ = 8.48 (dd, *J* = 4.7, 1.6 Hz, 1 H), 8.28 (dd, *J* = 4.7, 1.9 Hz, 1 H), 7.92 (dd, *J* = 8.2, 1.6 Hz, 1 H), 7.51 (dd, *J* = 7.8, 1.9 Hz, 1 H), 7.19 (dd, *J* = 7.8, 4.7 Hz, 1 H), 6.91 (dd, *J* = 8.1, 4.7 Hz, 1 H), 3.54 (s, 3 H, CH_3) ppm. ^{13}C NMR (62.9 MHz, $CDCl_3$, 27 °C): δ = 151.6 (CH), 150.7 (Cq), 149.1 (Cq), 147.6 (CH), 140.1 (Cq), 135.7 (CH), 135.0 (Cq), 134.8 (CH), 123.5 (CH), 115.1 (CH), 39.9 (CH_3) ppm. IR (ATR): ṽ = 1512, 1407, 757 cm^{-1}. MS: *m*/*z* = 267.00 (^{37}Cl) [M + H]$^+$, 265.00 (^{35}Cl) [M + H]$^+$. HRMS: calcd. for $C_{11}H_{10}N_4O_2{}^{35}Cl$ [M + H]$^+$ 265.0492; found 265.0489.

***N*-Butyl-*N*-(2-chloropyridin-3-yl)-*N*-(3-nitropyridin-2-yl)amine (21):** This compound was obtained by the General Procedure, with compound **13b** (1.60 g, 6.38 mmol) and butyl iodide (875 μL, 7.66 mmol). The solution was stirred for 48 h at room temperature. Purification by flash chromatography on silica gel (petroleum ether/ethyl acetate 9:1) afforded product **21** (1.43 g, 73% yield) as a yellow solid; m.p. 101–102 °C. ^1H NMR (250 MHz, $CDCl_3$, 27 °C): δ = 8.47 (dd, *J* = 4.4, 1.9 Hz, 1 H), 8.27 (dd, *J* = 4.7, 1.6 Hz, 1 H), 7.92 (dd, *J* = 8.2, 1.9 Hz, 1 H), 7.50 (dd, *J* = 7.8, 1.6 Hz, 1 H), 7.25 (dd, *J* = 7.8, 4.7 Hz, 1 H), 6.89 (dd, *J* = 8.2, 4.4 Hz, 1 H), 4.01 (t, *J* = 7.8 Hz, 2 H, CH_2), 1.73–1.61 (m, 2 H, CH_2), 1.43–1.29 (m, 2 H, CH_2), 0.92 (t, *J* = 7.2 Hz, 3 H, CH_3) ppm. ^{13}C NMR (62.9 MHz, $CDCl_3$, 27 °C): δ = 151.5 (CH), 150.3 (Cq), 148.8 (Cq), 147.3 (CH), 138.6 (Cq), 137.0 (CH), 135.3 (Cq), 134.7 (CH), 123.4 (CH), 114.9 (CH), 51.9 (CH_2), 29.6 (CH_2), 20.2 (CH_2), 13.9 (CH_3) ppm. IR (ATR): ṽ = 754, 1422, 1480 cm^{-1}. MS: *m*/*z* = 309.50 (^{37}Cl) [M + H]$^+$, 307.50 (^{35}Cl) [M + H]$^+$. HRMS: calcd. for $C_{14}H_{16}N_4O_2{}^{35}Cl$ [M + H]$^+$ 307.0962; found 307.0966.

General Procedure for Reduction/Cyclization/Alkylation: A mixture of *N*,*N*′-dipyridinylamines and $SnCl_2{\cdot}2H_2O$ (5 equiv.) in absolute ethanol (0.07 g mL^{-1}) was heated to reflux for 5 h. After reduction, the starting material had disappeared and the solution was cooled down and then poured into ice. The pH was made basic by addition of a potassium carbonate solution before extraction with ethyl acetate and washing with brine. The organic layer was dried with magnesium sulfate and concentrated under reduced pressure. The obtained product was used in the next alkylation step without further purification by the General Procedure for alkylations (vide supra).

5-Methyl-5,10-dihydrodipyrido[2,3-*b*:2′,3′-*e*]pyrazine (22): This compound was obtained by the General Procedure for the reduction/cyclization step with compound **20** (1.54 g, 5.82 mmol) and stannous chloride dihydrate (6.56 g, 29.10 mmol) in absolute ethanol (25 mL). Product **22** (1.13 g), a yellow-green solid, was used in the next step without further purification; m.p. 218–220 °C. ^1H NMR (400 MHz, [D$_6$]DMSO, 25 °C): δ = 8.64 (br s, 1 H, NH), 7.23 (dd, *J* = 4.8, 1.6 Hz, 1 H), 7.16 (dd, *J* = 4.9, 1.3 Hz, 1 H), 6.42 (dd, *J* = 7.7, 1.3 Hz, 1 H), 6.39–6.32 (m, 3 H), 2.90 (s, 3 H, CH_3) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$, 25 °C): δ = 147.5 (Cq), 146.4 (Cq), 138.5 (CH), 138.0 (CH), 130.7 (Cq), 130.0 (Cq), 116.9 (CH), 116.5 (CH), 116.1 (CH), 115.6 (CH), 28.2 (CH_3) ppm. IR (ATR): ṽ = 3155, 1459, 1444 cm^{-1}. MS: *m*/*z* = 199.5 [M + H]$^+$. HRMS: calcd. for $C_{11}H_{11}N_4$ [M + H]$^+$ 199.0984; found 199.0978.

5-Butyl-5,10-dihydrodipyrido[2,3-*b*:2′,3′-*e*]pyrazine (23): This compound was obtained by the General Procedure for the reduction/cyclization step, with compound **21** (1.41 g, 4.60 mmol) and stannous chloride dihydrate (5.19 g, 23.00 mmol) in absolute ethanol (20 mL). Product **23** (1.08 g), a green solid, was used in the next step without further purification; m.p. 180–182 °C. ^1H NMR (250 MHz, [D$_6$]DMSO, 80 °C): δ = 8.33 (br s, 1 H, NH), 7.23–7.12 (m, 2 H), 6.38–6.30 (m, 4 H), 3.57 (t, *J* = 7.7 Hz, 2 H, CH_2), 1.52–1.32 (m, 4 H, 2 CH_2), 0.93 (t, *J* = 7.2 Hz, 3 H, CH_3) ppm. ^{13}C NMR (62.9 MHz, [D$_6$]DMSO, 80 °C): δ = 147.2 (Cq), 145.9 (Cq), 137.9 (CH), 137.7 (CH), 129.54 (Cq), 129.47 (Cq), 116.3 (CH), 116.0 (CH), 115.7 (CH), 115.0 (CH), 39.8 (CH_2), 26.7 (CH_2), 19.1 (CH_2), 13.3 (CH_3) ppm. IR (ATR): ṽ = 3150, 1453, 748 cm^{-1}. MS: *m*/*z* = 241.00 [M + H]$^+$. HRMS: calcd. for $C_{14}H_{17}N_4$ [M + H]$^+$ 241.1453; found 241.1455.

5-(2,2-Dimethylpropanoyl)-10-methyl-5,10-dihydrodipyrido[2,3-*b*:2′,3′-*e*]pyrazine (24): Triethylamine (263 μL, 1.89 mmol, 1.25 equiv.) was added under argon to a solution of non-purified compound **22** (300 mg, 1.51 mmol), resulting from the reduction/cyclization step, in dichloromethane (30 mL). After the mixture has been stirred for 5 min at room temperature, pivaloyl chloride (205 μL, 1.66 mmol, 1.1 equiv.) was added at 0 °C. After 60 h of stirring at room temperature, the reaction medium was hydrolysed, extracted with ethyl acetate and dried with $MgSO_4$, and the solvent was removed under reduced pressure to give the crude product. This residue was purified by flash chromatography on silica gel (petroleum ether/ethyl acetate 9:1) and the desired product **24** (400 mg, 92% yield calculated over two steps) was obtained as a yellow-green solid; m.p. 149–151 °C. ^1H NMR (250 MHz, $CDCl_3$, 27 °C): δ = 7.94–7.88 (m, 3 H), 7.06–7.05 (m, 2 H), 6.83 (dd, *J* = 7.7, 5.0 Hz, 1 H), 3.37 (s, 3 H, CH_3), 1.20 (s, 9 H, 3 CH_3-Piv) ppm. ^{13}C NMR (62.9 MHz, $CDCl_3$, 27 °C): δ = 181.6 (Cq, C=O), 150.0 (Cq), 143.8 (Cq), 142.8 (CH, C_{py}), 139.8 (CH, C_{py}), 135.3 (Cq), 128.4 (CH, C_{py}), 125.8 (Cq), 121.9 (CH, C_{py}), 119.1 (CH, C_{py}), 117.2 (CH, C_{py}), 42.9 (Cq, C-Piv), 30.0 (CH_3), 28.6 (3×CH_3-Piv) ppm. IR (ATR): ṽ = 1666, 1433 cm^{-1}. MS: *m*/*z* = 283.50 [M + H]$^+$. HRMS: calcd. for $C_{16}H_{19}N_4O$ [M + H]$^+$ 283.1559; found 283.1563.

5-Butyl-10-(2,2-dimethylpropanoyl)-5,10-dihydrodipyrido[2,3-*b*:2′,3′-*e*]-pyrazine (25): Triethylamine (217 μL, 1.56 mmol, 1.25 equiv.) was added under argon to a solution of non-purified compound **23** (300 mg, 1.25 mmol), resulting from the reduction/cyclization step, in dichloromethane (30 mL). After the mixture had been stirred for 5 min at room temperature, pivaloyl chloride (169 μL, 1.37 mmol, 1.1 equiv.) was added at 0 °C. After 60 h of stirring at room temperature, the reaction medium was hydrolysed, extracted with ethyl acetate and dried with $MgSO_4$, and the solvent was removed under reduced pressure to give the crude product. This residue was purified by flash chromatography on silica gel (petroleum ether/ethyl acetate 10:0→9:1) and the desired product **25** (385 mg, 93% yield calculated over two steps) was obtained as a brown-green solid; m.p. 111–113 °C. ^{1}H NMR (250 MHz, $CDCl_3$, 27 °C): δ = 7.89 (dd, J = 4.9, 1.6 Hz, 1 H), 7.85–7.80 (m, 2 H), 7.03–7.01 (m, 2 H), 6.79 (dd, J = 7.8, 4.9 Hz, 1 H), 4.00 (t, J = 7.5 Hz, 2 H, CH_2), 1.76–1.64 (m, 2 H, CH_2), 1.5–1.37 (m, 2 H, CH_2), 1.18 (s, 9 H, 3 × CH_3-Piv), 0.97 (t, J = 7.2 Hz, 3 H, CH_3-Bu) ppm. ^{13}C NMR (62.9 MHz, $CDCl_3$, 27 °C): δ = 181.7 (Cq, C=O), 149.5 (Cq), 143.9 (Cq), 142.8 (CH, C_{py}), 139.6 (CH, C_{py}), 134.2 (Cq), 128.2 (CH, C_{py}), 125.6 (Cq), 121.7 (CH, C_{py}), 119.2 (CH, C_{py}), 117.1 (CH, C_{py}), 42.9 (Cq, C-Piv), 41.7 (CH_2), 28.6 (3 CH_3), 28.1 (CH_2), 20.3 (CH_2), 14.0 (CH_3) ppm. IR (ATR): $\tilde{\nu}$ = 1728, 1433 cm^{-1}. MS: m/z = 325.61 [M + H]$^+$. HRMS: calcd. for $C_{19}H_{25}N_4O$ [M + H]$^+$ 325.2028; found 325.2030.

5,10-Dimethyl-5,10-dihydrodipyrido[2,3-*b*:2′,3′-*e*]pyrazine (26a): This compound was obtained by the General Procedure for reduction/cyclization/alkylation, with non-purified compound **22** (90 mg, 0.45 mmol), resulting from the reduction/cyclization step, and methyl iodide (34 μL, 0.54 mmol). The solution was stirred overnight at room temperature. Purification by flash chromatography on silica gel (petroleum ether/ethyl acetate 8:2) afforded product **26a** (89 mg, 90% yield calculated over two steps) as a green solid; m.p. 152–153 °C (ref.[2] 152 °C). The spectroscopic data (IR and NMR) were in accordance with the literature values.[2]

5-Butyl-10-methyl-5,10-dihydrodipyrido[2,3-b:2′,3′-e]pyrazine (26b): This compound was obtained by the General Procedure for reduction/cyclization/alkylation, with non-purified compound **22** (90 mg, 0.45 mmol), resulting from the reduction/cyclization step, and butyl bromide (60 μL, 0.54 mmol). The solution was stirred overnight at room temperature. Purification by flash chromatography on silica gel (petroleum ether/ethyl acetate 8:2) afforded product **26b** (104 mg, 88% yield calculated over two steps) as a green solid; m.p. 68–69 °C. ^{1}H NMR (250 MHz, $CDCl_3$, 27 °C): δ = 7.33–7.31 (m, 2 H), 6.38–6.33 (m, 2 H), 6.28–6.23 (m, 2 H), 3.60 (t, J = 7.3 Hz, 2 H, CH_2), 2.99 (s, 3 H, CH_3), 1.59–1.46 (m, 2 H, CH_2), 1.43–1.34 (m, 2 H, CH_2), 0.95 (t, J = 7.2 Hz, 3 H, CH_3) ppm. ^{13}C NMR (62.9 MHz, $CDCl_3$, 27 °C): δ = 147.8 (Cq), 147.4 (Cq), 138.4 (CH), 138.1 (CH), 132.1 (Cq), 131.3 (Cq), 116.6 (2 × CH), 115.1 (2 × CH), 41.1 (CH_2), 28.8 (CH_3), 27.1 (CH_2), 20.2 (CH_2), 14.0 (CH_3-Bu) ppm. IR (ATR): $\tilde{\nu}$ = 1598, 1466 cm^{-1}. MS: m/z = 255.50 [M + H]$^+$. HRMS: calcd. for $C_{15}H_{19}N_4$ [M + H]$^+$ 255.1610; found 255.1615.

5-Allyl-10-methyl-5,10-dihydrodipyrido[2,3-*b*:2′,3′-*e*]pyrazine (26c): This compound was obtained by the General Procedure for reduction/cyclization/alkylation, with non-purified compound **22** (90 mg, 0.45 mmol), resulting from the reduction/cyclization step, and allyl bromide (47 μL, 0.54 mmol). The solution was stirred overnight at room temperature. Purification by flash chromatography on silica gel (petroleum ether/ethyl acetate 8:2) afforded product **26c** (101 mg, 91% yield calculated over two steps) as a green solid; m.p. 62 °C. ^{1}H NMR (250 MHz, $CDCl_3$, 27 °C): δ = 7.34 (dd, J = 5.0, 1.6 Hz, 2 H), 6.44–6.27 (m, 4 H), 5.87–5.74 (m, 1 H, CH), 5.29–5.17 (m, 2 H, CH_{2b}), 4.28 (t, J = 2.2 Hz, 2 H, CH_{2a}), 3.04 (s, 3 H, CH_3) ppm. ^{13}C NMR (62.9 MHz, $CDCl_3$, 27 °C): δ = 147.5 (Cq), 147.0 (Cq), 138.4 (CH, C_{py}), 138.2 (CH, C_{py}), 131.9 (Cq), 131.6 (CH), 131.1 (Cq), 117.0 (CH, C_{py}), 116.6 (CH_{2b}), 116.2 (CH, C_{py}), 115.4 (2 × CH, 2 × C_{py}), 44.2 (CH_{2a}), 28.9 (CH_3) ppm. IR (ATR): $\tilde{\nu}$ = 1597, 1434 cm^{-1}. MS: m/z = 239.00 [M + H]$^+$. HRMS: calcd. for $C_{14}H_{15}N_4$ [M + H]$^+$ 239.1297; found 239.1297.

5-Benzyl-10-methyl-5,10-dihydrodipyrido[2,3-*b*:2′,3′-*e*]pyrazine (26d): This compound was obtained by the General Procedure for reduction/cyclization/alkylation, with non-purified compound **22** (90 mg, 0.45 mmol), resulting from the reduction/cyclization step, and benzyl chloride (63 μL, 0.54 mmol). The solution was stirred overnight at room temperature. Purification by flash chromatography on silica gel (petroleum ether/ethyl acetate 8:2) afforded product **26d** (119 mg, 89% yield calculated over two steps) as a green solid; m.p. 131–133 °C. ^{1}H NMR (250 MHz, $CDCl_3$, 27 °C): δ = 7.37–7.19 (m, 7 H, 2 H_{py} and 5 H_{arom}), 6.47 (dd, J = 7.5, 5.0 Hz, 1 H, H_{py}), 6.40 (dd, J = 7.5, 1.3 Hz, 1 H, H_{py}), 6.25 (dd, J = 7.5, 5.0 Hz, 1 H, H_{py}), 6.14 (dd, J = 7.5, 1.2 Hz, 1 H, H_{py}), 4.96 (s, 2 H, CH_2), 3.11 (s, 3 H, CH_3) ppm. ^{13}C NMR (62.9 MHz, $CDCl_3$, 27 °C): δ = 147.6 (Cq), 147.4 (Cq), 138.8 (CH_{py}), 137.8 (CH_{py}), 136.4 (Cq), 131.7 (Cq), 131.4 (Cq), 128.8 (2 × CH_{arom}), 127.1 (CH_{arom}), 126.6 (2 × CH_{arom}), 117.4 (CH_{py}), 116.7 (2 × CH_{py}), 116.0 (CH_{py}), 45.7 (CH_2), 29.3 (CH_3) ppm. IR (ATR): $\tilde{\nu}$ = 1454, 1434, 750 cm^{-1}. MS: m/z = 289.50 [M + H]$^+$. HRMS: calcd. for $C_{18}H_{17}N_4$ [M + H]$^+$ 289.1453; found 289.1465.

Dipyrido[2,3-*b*:3′,2′-*e*]pyrazine (27): This compound was obtained by the General Procedure for the reduction/cyclization step, with **15** (100 mg, 0.80 mmol) and stannous chloride dihydrate (450 mg, 2.00 mmol) in absolute ethanol (10 mL) at reflux. Purification by flash chromatography on silica gel (CH_2Cl_2/MeOH 100:0→98:2) afforded product **27** (50 mg, 69% yield) as a green solid; m.p. > 250 °C. ^{1}H NMR (250 MHz, CD_3OD, 27 °C): δ = 9.41 (dd, J = 3.8, 1.9 Hz, 2 H), 8.73 (dd, J = 8.8, 1.9 Hz, 2 H), 8.01 (dd, J = 8.8, 3.8 Hz, 2 H) ppm. ^{13}C NMR (62.9 MHz, $CDCl_3$, 27 °C): δ158.2 (2 × CH), 150.7 (2 × Cq), 140.3 (2 × Cq), 138.5 (2 × CH), 126.3 (2 × CH) ppm. IR (ATR): $\tilde{\nu}$ = 778 cm^{-1}. MS: m/z = 183.00 [M + H]$^+$. HRMS: calcd. for $C_{10}H_6N_4Na$ [M + Na]$^+$ 205.0490; found 205.0492.

***N*-(2-Chloropyridin-3-yl)-*N*-methyl-*N*-(2-nitropyridin-3-yl)amine (28):** This compound was obtained by the General Procedure for alkylations, with compound **15** (500 mg, 1.99 mmol) and methyl iodide (149 μL, 2.39 mmol). The solution was stirred for overnight at room temperature. Purification by flash chromatography on silica gel (petroleum ether/ethyl acetate 5:5) afforded product **28** (438 mg, 83% yield) as a yellow solid; m.p. 130 °C. ^{1}H NMR (250 MHz, $CDCl_3$, 27 °C): δ = 8.19 (dd, J = 4.7, 1.7 Hz, 1 H), 8.06 (dd, J = 4.3, 1.4 Hz, 1 H), 7.56 (dd, J = 8.3, 1.4 Hz, 1 H), 7.51–7.45 (m, 2 H), 7.21 (dd, J = 7.9, 4.7 Hz, 1 H), 3.30 (s, 3 H, CH_3) ppm. ^{13}C NMR (62.9 MHz, $CDCl_3$, 27 °C): δ = 150.1 (Cq), 147.8 (Cq), 146.6 (CH), 140.4 (CH), 140.3 (Cq), 137.0 (Cq), 134.9 (CH), 130.8 (CH), 128.2 (CH), 123.4 (CH), 41.0 (CH_3) ppm. IR (ATR): $\tilde{\nu}$ = 1422, 802 cm^{-1}. MS: m/z = 267.00 (^{37}Cl) [M + H]$^+$, 265.00 (^{35}Cl) [M + H]$^+$. HRMS: calcd. for $C_{11}H_{10}N_4O_2{}^{35}Cl$ [M + H]$^+$ 265.0492; found 265.0485.

5-Methyl-5,10-dihydrodipyrido[2,3-*b*:3′,2′-*e*]pyrazine (29): This compound was obtained by the General Procedure for the reduction/cyclization step, with compound **28** (360 mg, 1.36 mmol) and stannous chloride dihydrate (1.53 mg, 6.80 mmol) in absolute ethanol (25 mL). Product **29** (265 mg), a green-brown powder, was

used in the next step without further purification; m.p. 115–118 °C. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 7.34 (dd, J = 5.2, 0.8 Hz, 2 H), 6.49 (dd, J = 7.1, 5.2 Hz, 2 H), 6.34 (d, J = 7.1 Hz, 2 H), 2.84 (s, 3 H, CH_3) ppm. IR (ATR): $\tilde{\nu}$ = 3155, 1459, 1444 cm^{-1}. MS: m/z = 199.5 $[M + H]^+$. HRMS: calcd. for $C_{11}H_{11}N_4$ $[M + H]^+$ 199.0984; found 199.0989.

5,10-Dimethyl-5,10-dihydrodipyrido[2,3-*b*:3′,2′-*e*]pyrazine (30a): This compound was obtained by the General Procedure for reduction/cyclization/alkylation, with non-purified compound **29** (85 mg, 0.43 mmol), resulting from the reduction/cyclization step, and methyl iodide (32 μL, 0.51 mmol). The solution was stirred overnight at room temperature. Purification by flash chromatography on silica gel (petroleum ether/ethyl acetate 8:2) afforded product **30a** (80 mg, 87% yield calculated over two steps) as a yellow powder; m.p. 150–152 °C (ref.[2] 150 °C). The spectroscopic data (IR and NMR) were in accordance with the literature values.[2]

10-Butyl-5-methyl-5,10-dihydrodipyrido[2,3-*b*:3′,2′-*e*]pyrazine (30b): This compound was obtained by the General Procedure for reduction/cyclization/alkylation, with non-purified compound **29** (90 mg, 0.45 mmol), resulting from the reduction/cyclization step, and butyl bromide (60 μL, 0.54 mmol). The solution was stirred overnight at room temperature. Purification by flash chromatography on silica gel (petroleum ether/ethyl acetate 7:3) afforded product **30b** (96 mg, 82% yield calculated over two steps) as a green solid; m.p. 61 °C. ^{1}H NMR (250 MHz, [D$_6$]acetone, 27 °C): δ = 7.34 (dd, J = 4.4, 2.2 Hz, 2 H), 6.48–6.43 (m, 4 H), 3.93 (t, J = 7.5 Hz, 2 H, N–CH_2), 2.84 (s, 3 H, CH_3), 1.63–1.53 (m, 2 H, CH_2), 1.41–1.32 (m, 2 H, CH_2), 0.91 (t, J = 7.2 Hz, 3 H, CH_3) ppm. ^{13}C NMR (62.9 MHz, [D$_6$]acetone, 27 °C): δ = 148.8 (2 × Cq), 138.8 (2 × CH), 132.8 (2 × Cq), 117.9 (2 × CH), 115.7 (2 × CH), 40.1 (CH_2), 31.2 (CH_3), 29.4 (CH_2), 20.9 (CH_2), 14.3 (CH_3-Bu) ppm. IR (ATR): $\tilde{\nu}$ = 1425 cm^{-1}. MS: m/z = 255.50 $[M + H]^+$. HRMS: calcd. for $C_{15}H_{19}N_4$ $[M + H]^+$ 255.1610; found 255.1613.

10-Allyl-5-methyl-5,10-dihydrodipyrido[2,3-*b*:3′,2′-*e*]pyrazine (30c): This compound was obtained by the General Procedure for reduction/cyclization/alkylation, with non-purified compound **29** (90 mg, 0.45 mmol), resulting from the reduction/cyclization step, and allyl bromide (47 μL, 0.54 mmol). The solution was stirred overnight at room temperature. Purification by flash chromatography on silica gel (petroleum ether/ethyl acetate 7:3) afforded product **30c** (92 mg, 84% yield calculated over two steps) as a green solid; m.p. 93–94 °C. ^{1}H NMR (250 MHz, [D$_6$]acetone, 27 °C): δ = 7.33 (d, J = 3.1 Hz, 2 H), 6.48 (d, J = 3.1 Hz, 4 H), 5.97–5.83 (m, 1 H, CH), 5.21 (dd, J = 17.3, 1.6 Hz, 1 H, CH_a "*trans*"), 5.02 (dd, J = 10.3, 1.6 Hz, 1 H, CH_b "*cis*"), 4.63–4.61 (m, 2 H, N–CH_2), 2.87 (s, 3 H, CH_3) ppm. ^{13}C NMR (62.9 MHz, [D$_6$]acetone, 27 °C): δ = 148.4 (2 × Cq), 138.8 (2 × CH_{py}), 134.9 (CH), 132.8 (2 × Cq), 118.1 (2 × CH_{py}), 116.0 [CH_2, $CH_{2(a+b)}$], 115.9 (2 × CH_{py}), 42.1 (CH_2), 31.2 (CH_3) ppm. IR (ATR): $\tilde{\nu}$ = 1430 cm^{-1}. MS: m/z = 239.00 $[M + H]^+$. HRMS: calcd. for $C_{14}H_{15}N_4$ $[M + H]^+$ 239.1297; found 239.1296.

10-Benzyl-5-methyl-5,10-dihydrodipyrido[2,3-*b*:3′,2′-*e*]pyrazine (30d): This compound was obtained by the General Procedure for reduction/cyclization/alkylation, with non-purified compound **29** (84 mg, 0.42 mmol), resulting from the reduction/cyclization step, and benzyl bromide (61 μL, 0.51 mmol). The solution was stirred overnight at room temperature. Purification by flash chromatography on silica gel (petroleum ether/ethyl acetate 9:1) afforded product **30d** (101 mg, 82% yield calculated over two steps) as a green solid; m.p. 142–143 °C. ^{1}H NMR (250 MHz, [D$_6$]acetone, 27 °C): δ = 7.28 (d, J = 6.5 Hz, 2 H_{py}), 7.16–7.02 (m, 5 H_{arom}), 6.36 (s, 4 H_{py}), 5.12 (s, 2 H, CH_2), 2.73 (s, 3 H, CH_3) ppm. ^{13}C NMR (62.9 MHz, [D$_6$]acetone, 27 °C): δ = 148.6 (2 × Cq), 140.2 (Cq, C_{arom}), 138.7 (2 × CH_{py}), 132.8 (2 × Cq), 128.8 (2 × CH_{arom}), 128.4 (2 × CH_{arom}), 127.1 (CH_{arom}), 118.4 (2 × CH_{py}), 116.1 (2 × CH_{py}), 43.0 (CH_2), 31.3 (CH_3) ppm. IR (ATR): $\tilde{\nu}$ = 1425, 740 cm^{-1}. MS: m/z = 289.00 $[M + H]^+$. HRMS: calcd. for $C_{18}H_{17}N_4$ $[M + H]^+$ 289.1453; found 289.1465.

X-ray Crystallography: CCDC-720326 (for **13a**), -720327 (for **15**), -720328 (for **18**), -720329 (for **19**), -720330 (for **21**), -720331 (for **24**), -720332 (for **28**) and -720333 (for **30d**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Supporting Information (see also the footnote on the first page of this article): ^{1}H and ^{13}C NMR spectra for compounds **7**, **10b**, **12**, **13a**–**13c**, **14**, **15**, **17**, **18**–**25**, **26b**–**26d**, **27**, **28**, **30b**–**30d** and ^{1}H NMR spectrum for compound **29**; crystal data and structure refinement data for **13a**, **15**, **18**, **19**, **21**, **24**, **28** and **30d**.

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