From Quinoxaline, Pyrido[2,3-b]pyrazine and Pyrido[3,4-b]pyrazine to Pyrazino-Fused Carbazoles and Carbolines

Frédéric Lassagne, Timothy Langlais, Elsa Caytan, Emmanuelle Limanton, Ludovic Paquin, Manon Boullard, Coline Courtel, Idriss Curbet, Clément Gédéon, Julien Lebreton, et al.

To cite this version:
Frédéric Lassagne, Timothy Langlais, Elsa Caytan, Emmanuelle Limanton, Ludovic Paquin, et al.. From Quinoxaline, Pyrido[2,3-b]pyrazine and Pyrido[3,4-b]pyrazine to Pyrazino-Fused Carbazoles and Carbolines. Molecules, MDPI, 2018, 23 (11), pp.2961. 10.3390/molecules23112961. hal-01937243

HAL Id: hal-01937243
https://hal-univ-rennes1.archives-ouvertes.fr/hal-01937243
Submitted on 17 Jul 2019

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From Quinoxaline, Pyrido[2,3-b]pyrazine and Pyrido[3,4-b]pyrazine to Pyrazino-Fused Carbazoles and Carbolines

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Academic Editor: Richard A. Bunce
Received: 23 October 2018; Accepted: 11 November 2018; Published: 13 November 2018

Abstract: 2,3-Diphenylated quinoxaline, pyrido[2,3-b]pyrazine and 8-bromopyrido[3,4-b]pyrazine were halogenated in deprotometalation-trapping reactions using mixed 2,2,6,6-tetramethyl piperidino-based lithium-zinc combinations in tetrahydrofuran. The 2,3-diphenylated 5-iodo-quinoxaline, 8-iodopyrido[2,3-b]pyrazine and 8-bromo-7-iodopyrido[3,4-b]pyrazine thus obtained were subjected to palladium-catalyzed couplings with arylboronic acids or anilines, and possible subsequent cyclizations to afford the corresponding pyrazino[2,3-a]carbazole, pyrazino[2',3':5,6]pyrrodo[4,3-b]indole and pyrazino[2',3':4,5]pyridolo[2,3-d]indole, respectively. 8-Iodopyrido[2,3-b]pyrazine was subjected either to a copper-catalyzed C-N bond formation with azoles, or to direct substitution to introduce alkylamino, benzylamino, hydrazine and aryloxy groups at the 8 position. The 8-hydrazino product was converted into aryl hydrazones. Most of the compounds were evaluated for their biological properties (antiproliferative activity in A2058 melanoma cells and disease-relevant kinase inhibition).

Keywords: pyrazine; deprotometalation; coupling; N-arylation; palladium; copper

1. Introduction

Quinoxalines and pyridopyrazines are aromatic heterocycles present in compounds endowed with numerous interesting properties. Some derivatives are bioactive and are used as antimicrobial, anti-inflammatory, antimalarial, anticancer and antidepressant compounds [1,2]. Others are for example employed as organic dyes [3], electroluminescent materials [4], and organic semiconductors [5]. Quinoxaline and pyridopyrazine substrates can be readily synthesized by
condensation of 1,2-dicarbonyl compounds with 1,2-arylenediamines [6] and lend themselves to further elaboration. Deprotonative lithiation followed by interception of the arylmetals with electrophiles is an efficient way to functionalize aromatic compounds [7–12]. However, reactions with substrates sensitive to nucleophilic attack such as azines must be performed at very low temperatures to avoid secondary reactions between arylmetals and functions [13–15]. The use of in situ metal traps avoids the use of cryogenic conditions to achieve these reactions [16,17]. We have developed mixed lithium-zinc combinations based on TMP (TMP = 2,2,6,6-tetramethylpiperidino) capable of deprotonating sensitive substrates at temperatures close to rt [18–21]. In order to obtain original scaffolds such as pyrazino-fused carbazoles and carbolines, we decided to combine this deprotometalation under in situ trapping conditions with palladium- and copper-catalyzed coupling reactions.

2. Results and Discussion

2.1. Synthesis

To functionalize 2,3-diphenylquinoxaline (1a) and 2,3-diphenylpyrido[2,3-b]pyrazine (2a), two deprotonation methods were tested in tetrahydrofuran (THF) (Table 1, Method A and Method B).

Table 1. Deprotonative metalation of 2,3-diphenylquinoxaline (1a) and 2,3-diphenylpyrido[2,3-b]-pyrazine (2a) and conversion to the halogeno derivatives.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Method</th>
<th>Electrophile, Conditions</th>
<th>Product (E), Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1a (X = CH)</td>
<td>A</td>
<td>I2, THF, 0 °C, 1 h</td>
<td>1b (I), 74</td>
</tr>
<tr>
<td>2</td>
<td>1a (X = CH)</td>
<td>B</td>
<td>I2, THF, 0 °C, 1 h</td>
<td>1b (I), 70</td>
</tr>
<tr>
<td>3</td>
<td>2a (X = N)</td>
<td>A</td>
<td>I2, THF, 0 °C, 1 h</td>
<td>2b-I (I), 70</td>
</tr>
<tr>
<td>4</td>
<td>2a (X = N)</td>
<td>B</td>
<td>I2, THF, 0 °C, 1 h</td>
<td>2b-I (I), 62</td>
</tr>
<tr>
<td>5</td>
<td>2a (X = N)</td>
<td>B</td>
<td>Br2, −20 °C, 1 h</td>
<td>2b-Br (Br), 60</td>
</tr>
<tr>
<td>6</td>
<td>2a (X = N)</td>
<td>B</td>
<td>Cl, −20 °C, 1 h</td>
<td>2b-Cl (Cl), 62</td>
</tr>
</tbody>
</table>

1 After purification (see experimental part). 2 The rest is 5,8-diiodo-2,3-diphenylquinoxaline (1b′; 7% yield; see Figure 1). 1b′ was isolated in 70% yield by using ZnCl2·TMEDA (1 equiv) and LiTMP (3 equiv).

The lithium-zinc base of Method A is prepared from ZnCl2·TMEDA (TMEDA = N,N,N′,N′-tetramethylethlenediamine) and LiTMP in a 1:3 ratio. Previous studies have suggested that it
is a 1:1 LiTMP-Zn(TMP)$_2$ combination. While LiTMP deprotonates the substrate, Zn(TMP)$_2$ intercepts the generated aryllithium [18,19,22]. A recent computer study on anisole showed that the reactive species is solvated LiTMP. The effectiveness of the reaction derives from the stabilizing effect of the transmetalation step [21].

It is possible to replace Zn(TMP)$_2$ by ZnCl$_2$ provided that there is no contact between LiTMP and ZnCl$_2$ in the absence of the aromatic compound [23,24]. Thus, Method B is limited to activated substrates for which deprotonation is favored over reaction between LiTMP and ZnCl$_2$.

Whereas Method A should provide a lithium arylzincate, Method B should rather generate an arylzinc. Nevertheless, both species are known to react with iodine by aryl transfer. Thus, 2,3-diphenylquinoxaline (1a) and 2,3-diphenylpyrido[2,3-b]pyrazine (2a) were involved in Method A. After treatment at rt with the base for 2 h, addition of iodine led to iodoquinoxaline 1b and iodopyrido[2,3-b] pyrazine 2b-I in 74 and 70% yield, respectively (entries 1 and 3).

To evaluate Method B, 1a and 2a were mixed with ZnCl$_2$·TMEDA before addition of LiTMP at -20 °C and stirring for 0.5 h (Method B, entries 2 and 4). After subsequent interception with iodine, 1b and 2b-I were isolated in 70 and 62% yield, respectively (entries 2 and 4).

We explored the use of other electrophiles to intercept the heteroarylzinc chloride prepared from 2a by using Method B. Conversion to the corresponding bromide 2b-Br (60% yield, entry 5) and chloride 2b-Cl (62% yield, entry 6) was performed using bromine and trichloroisocyanuric acid, respectively, as the electrophile.

The deprotometalation-iodination sequence was successfully applied to 8-bromo-2,3-diphenyl pyrido[3,4-b]pyrazine (3a) [25,26], but failed with 7-bromo-2,3-diphenylpyrido[2,3-b]pyrazine (4a) due to significant degradation before trapping (Scheme 1). While the position of the iodo group in 3b was evidenced by subsequent reaction, it was studied by advanced NMR experiments in the case of 4b (see Supplementary Materials).

In order to prepare original pyrazino-fused carbazoles and carbolines, iodides 1b and 2b-I were subjected to in Suzuki couplings [27,28] under standard conditions (Table 2) [29]. Phenyl- (entry 1), 2-thienyl- (entries 2 and 3) and 2-aminophenyl- (entries 4 and 5) boronic acids led to the 5-arylated derivatives 1c-e and 2d,e in 42-97% yields. The more electron-rich arylboronic acids and the less electron-poor quinoxaline substrate 1b gave the best results.
Scheme 1. Deprotonative metalation of 8-bromo-2,3-diphenylpyrido[3,4-b]pyrazine (3a) and 7-bromo-2,3-diphenylpyrido[2,3-b]pyrazine (4a) followed by conversion to the halogeno derivatives.

Table 2. Suzuki coupling from 5-iodo-2,3-diphenylquinoxaline (1b) and 8-iodo-2,3-diphenylpyrido[2,3-b]pyrazine (2b-I).

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>ArB(OH)$_2$</th>
<th>Product (Ar), Yield (%) $^1$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1b (X = CH)</td>
<td>PhB(OH)$_2$</td>
<td>1c (Ph), 42</td>
</tr>
<tr>
<td>2</td>
<td>1b (X = CH)</td>
<td></td>
<td>1d (2-thienyl), 97</td>
</tr>
<tr>
<td>3</td>
<td>2b-I (X = N)</td>
<td></td>
<td>2d (2-thienyl), 75</td>
</tr>
<tr>
<td>4</td>
<td>1b (X = CH)</td>
<td></td>
<td>1e (2-aminophenyl), 92</td>
</tr>
<tr>
<td>5</td>
<td>2b-I (X = N)</td>
<td></td>
<td>2e (2-aminophenyl), 73</td>
</tr>
</tbody>
</table>

$^1$ After purification (see experimental part). $^2$ See Figure 1.

No intramolecular nitrene insertion into the corresponding diazino-fused carbazole and β-carboline was obtained for the azides coming from 1e and 2e [29]. We thus turned to the synthesis of the original pyrazino[2,3-a]carbazole 1g and the corresponding pyrazino-fused γ-carboline 2g isomers by combining intermolecular C-N bond formation [30–38] with intramolecular C-C bond formation (Scheme 2).

The first step, attempted from 1b by using catalytic palladium(II) acetate as transition metal source, Xantphos as ligand, and sodium tert-butoxide as base in toluene [39], yielded only 16% of diarylamine 1f. Applying to 1b and 2b-I the conditions reported by Maes and co-workers for related reactions [29], 1f and 2f were obtained in 92 and 67% yield, respectively (Scheme 2, left). Inspired by Pieters and co-workers, who cyclized 4-(2-chlorophenylamino)pyridine into 5H-pyrido[4,3-b]indole under these conditions [40], we successfully employed catalytic (Pd$_2$(dba)$_3$) and tri-tert-butylphosphine as catalyst precursors, diazabicyclo[5.4.0]undec-7-ene (DBU) as base, and dioxane as solvent for the second step. After 10 min at 180 °C under microwave irradiation, the pyrazino-fused carbazole 1g and γ-carboline 2g were isolated in moderate yields (Scheme 2, right).

We decided to combine both steps in an auto-tandem process under microwave irradiation (Table 3). Using (Pd$_2$(dba)$_3$), we selected Xantphos for its higher efficiency in comparison with tri-tert-butylphosphine. From 2b, best results were obtained with three equivalents of DBU as base (entries 1 and 2). In addition, a longer reaction time was required to ensure complete conversion and this afforded carboline 2g in 70% yield (entry 3).
The deprotometalation-iodination sequence was successfully applied to 5-iodo-2,3-diphenylquinoxaline (1b) and 8-iodo-2,3-diphenylpyrido[2,3-b]pyrazine (2b-I) into 2,3-diphenyl-11H-pyrazino[2,3-a]carbazole (1g) and 2,3-diphenyl-11H-pyrazino[2',3',5,6]pyrido[4,3-b]indole (2g), respectively. Dba = dibenzylideneacetone.

Table 3. Study of the conversion of the 8-halogenated 2,3-diphenylpyrido[2,3-b]pyrazines 2b into 2,3-diphenyl-11H-pyrazino[2',3',5,6]pyrido[4,3-b]indole (2g) under MW irradiation.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate (X)</th>
<th>n Equiv</th>
<th>Conditions 1</th>
<th>2f (%) 2</th>
<th>2g (%) 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2b-I (l)</td>
<td>1.2</td>
<td>180 °C, 20 min</td>
<td>80</td>
<td>20</td>
</tr>
<tr>
<td>2</td>
<td>2b-I (l)</td>
<td>3.0</td>
<td>180 °C, 20 min</td>
<td>41</td>
<td>59</td>
</tr>
<tr>
<td>3</td>
<td>2b-I (l)</td>
<td>3.0</td>
<td>180 °C, 60 min</td>
<td>&lt;5</td>
<td>&gt;95, 70</td>
</tr>
<tr>
<td>4</td>
<td>2b-I (l)</td>
<td>3.0</td>
<td>180 °C, 60 min 4</td>
<td>75</td>
<td>25</td>
</tr>
<tr>
<td>5</td>
<td>2b-I (l)</td>
<td>3.0</td>
<td>180 °C, 20 min 5</td>
<td>23</td>
<td>75</td>
</tr>
<tr>
<td>6 6</td>
<td>2b-I (l)</td>
<td>3.0</td>
<td>180 °C, 20 min</td>
<td>95</td>
<td>&lt;2</td>
</tr>
<tr>
<td>7 7</td>
<td>2b-I (l)</td>
<td>3.0</td>
<td>180 °C, 20 min</td>
<td>32</td>
<td>67</td>
</tr>
<tr>
<td>8</td>
<td>2b-I (l)</td>
<td>3.0</td>
<td>180 °C, 5 min 6</td>
<td>66</td>
<td>8</td>
</tr>
<tr>
<td>9</td>
<td>2b-Br (Br)</td>
<td>3.0</td>
<td>180 °C, 5 min 7</td>
<td>35 9</td>
<td>0</td>
</tr>
<tr>
<td>10</td>
<td>2b-Cl (Cl)</td>
<td>3.0</td>
<td>180 °C, 5 min 8</td>
<td>22 10</td>
<td>0</td>
</tr>
</tbody>
</table>

1 Maximum microwave power applied: 150–200 W at the beginning to reach the required temperature. 2 Evaluated from the NMR spectra of the crude. 3 Yield after purification. 4 Microwave profile of irradiation: The sequence ‘Maximum microwave power applied: 150–200 W to reach 180 °C then 2 min at 180 °C before cooling to 100 °C’ was repeated every 4 min. 5 Then classical heating at 180 °C for 40 min. 6 Without catalyst. 7 By using 12 mol% Pd2(dba)3 and 30 mol% Xantphos. 8 The rest was unreacted 2b-I (32%). 9 The rest was unreacted 2b-Br (38%) and 2a (28%). 10 The rest was unreacted 2b-Cl (78%).

By testing a profile to maximize the microwave power, we noticed that an increase of the applied power favored the formation of 2f over 2g (entry 4). By carrying out one third of the reaction time under microwave irradiation and the rest by classical heating at the same temperature, a small microwave effect was evidenced (entry 5). While 2g was not formed without catalyst, C-N bond formation giving 2f could take place (entry 6; see Figure 1). However, increasing the catalyst amount had no impact on the conversion to 2g (entry 7). Finally, we intentionally chose a short reaction time (5 min) in order to compare the palladium-catalyzed reactions under microwave irradiation from 2b-I (entry 7), 2b-Br (entry 7) and 2b-Cl (entry 10). The results clearly showed decreasing reactivity from 2b-I to 2b-Cl, and thus, we selected iodo as halogeno group to pursue our investigations.

We applied the optimized procedure to the synthesis of the pyrazino-fused α-carboline 3g from the bromoiodo substrate 3b and aniline. No trace of the expected product 3g was detected but the formation of 3g8 due to competitive debromination was noted, showing a less obvious intramolecular C-H arylation (Scheme 3, left). Consequently, we moved to the synthesis of the pyrazino-fused δ-carboline 3h. Upon treatment of 3b by 2-aminophenylboronic acid under standard conditions [29], coupling and subsequent cyclization occurred, providing 3h in 65% yield (Scheme 3, right).
We applied the optimized procedure to the synthesis of the pyrazino-fused indole 3h.

To take advantage of the iodo group on 2b-I, C-N bond formation with azoles was attempted under copper catalysis as reported previously [41,42] (Table 4). Thus, by treating 2b-I with pyrrole (entry 1; see Figure 1), indole (entry 2), pyrazole (entry 3), imidazole (entry 4) or 1,2,4-triazole (entry 5), in the presence of catalytic copper(I) oxide, cesium carbonate, and dimethylsulfoxide (DMSO) at 110 °C for 24 h, the expected N-arylated azoles were obtained in 51 to 79% yields.

As previously mentioned [22], such reactions work far less efficiently when performed on diiodides. Indeed, reacting the diiodide 1b′ with pyrazole only gave the monofunctionalized derivative 1k′, regardless of the amount of azole employed (Scheme 4).

Different amines and hydrazine reacted with 2b-I without recourse to catalyst (Table 5), affording the corresponding secondary amines 2n-p (entries 1-3) and arylhydrazine 2q (entry 4) in good yields. The latter was converted into the hydrazones 2r-u in the presence of aromatic aldehydes chosen for their ability to potentially interact with binding sites of biological interest [43] (Scheme 5). Finally, reaction of 2b-I with a phenol also proved possible without catalyst, giving the diaryl ether 2v in 64% yield (Scheme 6).
Table 4. Copper-catalyzed N-arylation of 8-iodo-2,3-diphenylpyrido[2,3-b]pyrazine (2b-I) using azoles.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Azole</th>
<th>Product, Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Pyrrole</td>
<td>2i, 67</td>
</tr>
<tr>
<td>2</td>
<td>Indole</td>
<td>2j, 51</td>
</tr>
<tr>
<td>3</td>
<td>Pyrazole</td>
<td>2k, 71</td>
</tr>
<tr>
<td>4</td>
<td>Imidazole</td>
<td>2l, 69</td>
</tr>
<tr>
<td>5</td>
<td>1,2,4-Triazole</td>
<td>2m, 79</td>
</tr>
</tbody>
</table>

1 After purification (see experimental part). The rest is starting material and the corresponding deiodinated compound.

Scheme 5. Conversion of 8-hydrazino-2,3-diphenylpyrido[2,3-b]pyrazine (2q) into aryl hydrazones.
Table 5. Conversion of 8-iodo-2,3-diphenylpyrido[2,3-b]pyrazine (2b-I) into corresponding amines and hydrazine.

<table>
<thead>
<tr>
<th>Entry</th>
<th>R-NH₂</th>
<th>Conditions</th>
<th>Product, Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>iPrNH₂ (1.2)</td>
<td>EtOH, 150 °C, 18 h</td>
<td>2n, 69</td>
</tr>
<tr>
<td>2</td>
<td>4-MeOC₆H₄CH₂NH₂ (1.2)</td>
<td>EtOH, 150 °C, 24 h</td>
<td>2o, 71</td>
</tr>
<tr>
<td>3</td>
<td>PhCH₂NH₂ (1.2)</td>
<td>EtOH, 150 °C, 24 h</td>
<td>2p, 79</td>
</tr>
<tr>
<td>4</td>
<td>NH₂NH₂·H₂O (10)</td>
<td>iPrOH, reflux, 4 h</td>
<td>2q, 92</td>
</tr>
</tbody>
</table>

Scheme 6. Conversion of 8-iodo-2,3-diphenylpyrido[2,3-b]pyrazine (2b-I) into ether 2v.

2.2. Biological Activity

Some of the synthesized compounds were tested [44] for their antiproliferative activity in A2058 melanoma cells and proved to exert a modest to good activity (Figure 2). The best results were obtained with the 4-(trifluoromethyl)benzaldehyde hydrazone 2u and the 8-benzylamino pyrido[2,3-b]pyrazine 2o which induced ~64% growth inhibition at 10⁻⁵ M.

Compounds 1c-e, 1g, 2d-g, 2i-v and 3h were evaluated [44] against a short panel of disease-relevant protein kinases. Protein kinases are drug targets often deregulated in diseases such as cancers and neurodegenerative disorders [45]. No significant inhibition of the following kinases was observed: Cyclin-dependent kinases 2 (CDK2/Cyclin A), 5 (CDK5/p25) and 9 (CDK9/Cyclin T), proto-oncogene kinase PIM1, CDC2-like kinase 1 (CLK1), dual specificity tyrosine phosphorylation regulated kinase 1A (DYRK1A), glycogen-synthase kinase 3 (GSK3; α/β or β), casein kinase 1 (CK1; δ/ε or ε), and mitotic kinase Haspin). Table S1 in Supplementary Materials shows the results obtained.
3. Materials and Methods

3.1. General Information

All the reactions were performed under a dry argon atmosphere. THF was distilled over sodium/benzophenone. Column chromatography separations were achieved on silica gel (40–63 μm). Melting points were measured on a Kofler apparatus. IR spectra were taken on an ATR Spectrum 100 spectrometer (Perkin-Elmer). 1H- and 13C-Nuclear Magnetic Resonance (NMR) spectra were recorded either on an Avance III spectrometer (291 K) at 300 MHz and 75 MHz, respectively, or on an Avance III HD spectrometer (298 K) at 500 MHz and 126 MHz, respectively (Bruker, Billeliva, Massachussets, USA). 1H chemical shifts (δ) are given in ppm relative to the solvent residual peak and 13C chemical shifts are relative to the central peak of the solvent signal [46]. 2,3-Diphenylpyrido[2,3-b]pyrazine (2a) [6], 8-bromo-2,3-diphenylpyrido[3,4-b]pyrazine (3a) [25,26] and 7-bromo-2,3-diphenylpyrido[2,3-b]pyrazine (4a) [6] were prepared as reported previously. The biological activity assays were performed as reported previously [44].

3.2. Crystallography

The X-ray diffraction data were collected either using an APEXII Bruker-AXS diffractometer (graphite monochromatized Mo-Kα radiation (λ = 0.71073 Å)) for the compounds 1b' and 2i, or using a D8 VENTURE Bruker AXS diffractometer (multilayer monochromatized Mo-Kα radiation (λ = 0.71073 Å)) equipped with a (CMOS) PHOTON 100 detector for 2f, 2p, 3h and 2d, at the temperature given in the crystal data. For 1b' and 2i, the structure was solved by direct methods using SIR97 [47]. For 2f, 2p, 3h and 2d, they were solved by dual-space algorithm using the SHELXT program [48]. Structural refinements were performed with full-matrix least-square methods based on F2 (SHELXL) [49]. In the case of 2f and 3h, the contribution of the disordered solvents to the calculated structure factors was estimated following the BYPASS algorithm [50], implemented as the SQUEEZE option in PLATON [51]; a new data set, free of solvent contribution, was then used in the final refinement. All non-hydrogen atoms were refined with anisotropic atomic displacement parameters. Except nitrogen linked hydrogen atom that was introduced in the structural model through Fourier difference maps analysis (2f, 2p, 3h), H atoms were finally included in their calculated positions and treated as riding on their parent atom with constrained thermal parameters. The molecular diagrams were generated by ORTEP-3 (version 2.02) [52].

3.3. Deprotonometalation Followed by Trapping with Electrophiles

3.3.1. General Procedure 1

To a solution of 2,2,6,6-tetramethylpiperidine (0.51 mL, 3.0 mmol) in THF (3 mL) at 0 °C were successively added BuLi (about 1.6 M hexanes solution, 3.0 mmol) and, 15 min later, ZnCl2·TMEDA [53] (0.25 g, 1.0 mmol). After 15 min at 0 °C, the pyrazine (2.0 mmol) was introduced, and the mixture was stirred for 2 h at rt before addition of I2 (0.76 g, 3.0 mmol) in THF (3 mL) at 0 °C. The mixture was
stirred at this temperature for 1 h before addition of an aqueous saturated solution of Na₂S₂O₃ (10 mL) and extraction with EtOAc (3 × 20 mL). The combined organic layers were dried over MgSO₄, filtered and concentrated under reduced pressure. The crude product was purified by chromatography over silica gel (the eluent is given in the product description).

3.3.2. 5-Iodo-2,3-diphenylquinoxaline (1b)

The general procedure 1 using 2,3-diphenylquinoxaline (1a, 0.56 g) gave 1b (elucent: heptane-CH₂Cl₂ 60:40; Rf = 0.55) in 74% yield as a pale yellow powder. Mp: 148 °C. IR: 486, 529, 551, 602, 689, 695, 701, 763, 776, 796, 892, 978, 1023, 1068, 1079, 1184, 1336, 1384, 1497, 1534, 3051 cm⁻¹. ¹H-NMR (CDCl₃): 7.31–7.41 (m, 6H), 7.48 (dd, 1H, J = 8.3 and 7.4 Hz), 7.54–7.57 (m, 2H), 7.64–7.67 (m, 2H), 8.15 (dd, 1H, J = 8.4 and 1.3 Hz), 8.36 (dd, 1H, J = 7.4 and 1.3 Hz). ¹³C-NMR (CDCl₃): 102.8 (C), 128.3 (2CH), 128.5 (2CH), 129.2 (CH), 129.3 (CH), 129.9 (2CH), 130.0 (CH), 130.5 (2CH), 131.0 (CH), 138.2 (C), 138.7 (C), 140.1 (CH), 140.9 (C), 141.3 (C), 153.9 (C), 154.1 (C). Anal. Calc. for C₂₀H₁₉IN₂: For 408.24: C 58.84, H 3.21, N, 6.86. Found: C 59.05, H 3.27, N, 6.70. 5,8-Diido-2,3-diphenylquinoxaline (1b') was similarly isolated (elucent: heptane-CH₂Cl₂ 60:40; Rf = 0.69) in 7% yield as a yellow powder. Mp: 222 °C. IR: 533, 572, 613, 649, 692, 771, 824, 893, 978, 1025, 1055, 1077, 1169, 1209, 1325, 1383, 1447, 2930, 3059 cm⁻¹. ¹H-NMR (CDCl₃): 7.34–7.45 (m, 6H), 7.64–7.76 (m, 4H), 8.02 (s, 2H). ¹³C-NMR (CDCl₃): 103.5 (2C), 128.4 (4CH), 129.7 (2CH), 130.4 (4CH), 137.7 (2C), 140.6 (2CH), 140.8 (2C), 154.5 (2C). Crystal data for 1b'. C₂₀H₁₂I₂N₂, M = 534.12, T = 150(2) K, monoclinic, P 2₁, a = 10.1153(9), b = 5.8725(5), c = 14.9603(14) Å, β = 98.489(4) °, V = 878.94(14) Å³, Z = 2, d = 2.018 g cm⁻³, μ = 3.581 mm⁻¹. A final least-squares refinement on F² with 3888 unique reflections and 217 parameters converged at ωR(F²) = 0.0701 (R(F) = 0.0343) for 3602 observed reflections with I > 2σ(I). CCDC 1858478.

3.3.3. 8-Iodo-2,3-diphenylpyrido[2,3-b]pyrazine (2b-I)

The general procedure 1 using 2,3-diphenylpyrido[2,3-b]pyrazine (2a, 0.57 g) gave 2b-I (elucent: CH₂Cl₂; Rf = 0.34) in 70% yield as a whitish powder. Mp: 220 °C. IR: 534, 562, 613, 624, 637, 699, 980, 1023, 1336, 1416, 1519, 1570, 3068 cm⁻¹. ¹H-NMR (CDCl₃): 7.32–7.44 (m, 6H), 7.64–7.69 (m, 4H), 8.28 (d, 1H, J = 4.5 Hz), 8.70 (d, 1H, J = 4.6 Hz). ¹³C-NMR (CDCl₃): 116.1 (C), 128.3 (2CH), 128.4 (2CH), 129.7 (CH), 129.8 (CH), 130.3 (2CH), 135.6 (CH), 136.6 (C), 137.6 (C), 149.1 (C), 153.6 (CH), 155.0 (C), 157.1 (C). Anal. Calc. for C₁₉H₁₂I₂N₂: 55.77, H 2.96, N, 10.27. Found: C 55.91, H 3.06, N, 10.03.

3.3.4. 8-Bromo-2,3-diphenylpyrido[2,3-b]pyrazine (2b-Br)

To a stirred mixture of 2,3-diphenyl pyrido[2,3-b]pyrazine (2a, 0.28 g, 1.0 mmol) and ZnCl₂-TMEDA [53] (0.26 g, 1.0 mmol) in THF (1 mL) at −20 °C was added dropwise a solution of LiTMP (about 1.6 M hexanes solution, 1.2 mmol) to a stirred, cooled (−20 °C) solution of 2,2,6,6-tetramethylpiperidinone (0.24 mL, 1.2 mmol) in THF (2 mL) and stirring for 15 min cooled at −20 °C. After 30 min at −20 °C, Br₂ (97 µL, 2.0 mmol) was introduced, and the mixture was stirred for 1 h before addition of an aqueous saturated solution of Na₂S₂O₃ (5 mL) and extraction with EtOAc (3 × 20 mL). The combined organic layers were dried over MgSO₄, filtered and concentrated under reduced pressure. The crude product was purified by chromatography over silica gel (elucent: CH₂Cl₂-EtOAc 90:10; Rf = 0.50) to give 2b-Br in 60% yield as a whitish powder. Mp: 183 °C. IR: 491, 538, 563, 615, 625, 649, 698, 767, 839, 985, 1021, 1049, 1090, 1179, 1241, 1336, 1387, 1421, 1460, 1524, 1584, 3067 cm⁻¹. ¹H-NMR (CDCl₃): 7.32–7.42 (m, 6H), 7.63–7.66 (m, 4H), 8.00 (d, 1H, J = 4.7 Hz), 8.91 (d, 1H, J = 4.7 Hz). ¹³C-NMR (CDCl₃): 128.3 (CH), 128.4 (CH), 128.7 (CH), 129.7 (CH), 129.8 (CH), 130.3 (CH), 133.7 (C), 136.3 (C), 137.7 (C), 137.9 (C), 150.1 (C), 153.4 (CH), 154.9 (C), 157.0 (C). Anal. Calc. for C₁₉H₁₂BrN₃ (362.23): C 63.00, H 3.34, N, 11.60. Found: C 63.24, H 3.58, N, 11.43.
3.3.5. 8-Chloro-2,3-diphenylpyrido[2,3-b]pyrazine (2b-Cl)

To a stirred mixture of 2,3-diphenyl pyrido[2,3-b]pyrazine (2a, 0.28 g, 1.0 mmol) and ZnCl₂-TMEDA [53] (0.26 g, 1.0 mmol) in THF (1 mL) at −20 °C was added dropwise a solution of LiTMP (prepared by adding BuLi (about 1.6 M hexanes solution, 1.2 mmol) to a stirred, cooled (−20 °C) solution of 2,2,6,6-tetramethylpiperidine (0.24 mL, 1.2 mmol) in THF (2 mL) and stirring for 15 min) cooled at −20 °C. After 30 min at −20 °C, trichloroisocyanuric acid (0.30 g, 1.3 mmol) was introduced (CAUTION: dissolution of trichloroisocyanuric acid in THF at a temperature above 0 °C produces intense heat), and the mixture was stirred at this temperature for 1 h before addition of water (5 mL) and extraction with EtOAc (3 × 20 mL). The combined organic layers were dried over MgSO₄, filtered and concentrated under reduced pressure. The crude product was purified by chromatography over silica gel (eluent: CH₂Cl₂-EtOAc 90:10; Rf = 0.60) to give 2b-Cl in 62% yield as a whitish powder. Mp: 180 °C. IR: 534, 544, 617, 658, 699, 770, 851, 991, 1025, 1055, 1193, 1242, 1314, 1388, 1422, 1452, 1532, 1583, 3034, 3060 cm⁻¹. ¹H-NMR (CDCl₃): 7.31–7.44 (m, 6H), 7.62–7.66 (m, 4H), 7.79 (d, 1H, J = 4.7 Hz), 9.02 (d, 1H, J = 4.7 Hz). ¹³C-NMR (CDCl₃): 125.1 (CH), 128.3 (CH), 128.5 (CH), 129.7 (C), 130.2 (CH), 130.3 (CH), 133.7 (C), 137.8 (C), 138.1 (C), 144.5 (C), 150.5 (C), 153.3 (CH), 154.8 (C), 157.1 (C). Anal. Calc. for C₃₉H₂₁Cl₃N₅ (513.73): C 46.75, H 2.27, N, 8.61. Found: C 46.93, H 2.49, N, 8.55.

3.3.6. General Procedure 2

To a stirred mixture of the pyrazine (1.0 mmol) and ZnCl₂-TMEDA [53] (0.26 g, 1.0 mmol) in THF (1 mL) at −20 °C was added dropwise a solution of LiTMP (prepared by adding BuLi (about 1.6 M hexanes solution, 1.2 mmol) to a stirred, cooled (−20 °C) solution of 2,2,6,6-tetramethylpiperidine (0.24 mL, 1.2 mmol) in THF (2 mL) and stirring for 15 min) cooled at −20 °C. After 30 min at −20 °C, I₂ (0.37 g, 1.5 mmol) in THF (2 mL) was introduced, and the mixture was stirred at this temperature for 1 h before addition of an aqueous saturated solution of Na₂S₂O₃ (5 mL) and extraction with EtOAc (3 × 20 mL). The combined organic layers were dried over MgSO₄, filtered and concentrated under reduced pressure. The crude product was purified by chromatography over silica gel (eluent: CH₂Cl₂-petroleum ether 80:20; Rf = 0.44) to give 2b-Cl in 67% yield as a red powder. Mp: 186–188 °C. IR: 493, 529, 559, 600, 658, 695, 765, 984, 1025, 1055, 1117, 1238, 1315, 1373, 1399, 1446, 1493, 1551, 3034, 3060 cm⁻¹. ¹H-NMR (CDCl₃): 7.34–7.47 (m, 6H), 7.54–7.57 (m, 2H), 7.62–7.65 (m, 2H), 9.27 (s, 1H). ¹³C-NMR (CDCl₃): 121.7 (C), 128.6 (2CH), 128.7 (2CH), 129.7 (C), 129.8 (2CH), 129.9 (2CH), 130.1 (CH), 130.5 (2CH), 130.6 (C), 137.4 (C), 137.7 (C), 142.3 (C), 152.5 (CH), 156.2 (C), 158.6 (C). Anal. Calc. for C₃₉H₂₁BrI₃N₅ (688.13): C 46.75, H 2.27, N, 8.61. Found: C 46.89, H 2.49, N, 8.55.

3.3.7. 8-Bromo-7-iodo-2,3-diphenylpyrido[3,4-b]pyrazine (3b)

The general procedure 2 using 8-bromo-2,3-diphenylpyrido[3,4-b]pyrazine (3a [25,26], 0.36 g) gave 3b (eluent: CH₂Cl₂-petroleum ether 80:20; Rf = 0.44) in 67% yield as a red powder. Mp: 186–188 °C. IR: 493, 529, 559, 600, 658, 695, 765, 984, 1025, 1055, 1117, 1238, 1315, 1373, 1399, 1446, 1493, 1551, 3034, 3060 cm⁻¹. ¹H-NMR (CDCl₃): 7.34–7.47 (m, 6H), 7.54–7.57 (m, 2H), 7.62–7.65 (m, 2H), 9.27 (s, 1H). ¹³C-NMR (CDCl₃): 121.7 (C), 128.6 (2CH), 128.7 (2CH), 129.7 (C), 129.8 (2CH), 130.1 (CH), 130.5 (2CH), 130.6 (C), 137.4 (C), 137.7 (C), 142.3 (C), 152.5 (CH), 156.2 (C), 158.6 (C). Anal. Calc. for C₃₉H₂₁BrI₃N₅ (688.13): C 46.75, H 2.27, N, 8.61. Found: C 46.89, H 2.49, N, 8.55.

3.3.8. 7-Bromo-6-iodo-2,3-diphenylpyrido[2,3-b]pyrazine (4b)

The general procedure 2 using 7-bromo-2,3-diphenylpyrido[2,3-b]pyrazine (4a [54], prepared in 90% yield [6], 0.36 g) gave 4b (eluent: CH₂Cl₂-heptane 70:30; Rf (heptane-CH₂Cl₂ 80:20) = 0.80) in 5% yield as a yellow powder. Mp: 150–152 °C. IR: 495, 547, 596, 615, 697, 731, 770, 778, 903, 937, 1025, 1060, 1107, 1178, 1274, 1332, 1390, 1448, 1502, 1562, 1603, 1699, 1768, 2734, 2940, 3064 cm⁻¹. ¹H-NMR (CDCl₃): 7.30–7.43 (m, 6H), 7.52–7.55 (m, 2H), 7.59–7.62 (m, 2H), 8.62 (s, 1H). ¹³C-NMR (CDCl₃): 128.3 (2CH), 128.6 (2CH), 128.7 (C), 129.9 (CH), 130.0 (CH), 130.0 (C), 130.3 (2CH), 135.5 (C), 137.6 (C), 138.0 (C), 139.5 (CH), 148.0 (C), 155.9 (C), 157.1 (C). Anal. Calc. for C₉₉H₉₁BrI₃N₉ (488.13): C 46.75, H 2.27, N, 8.61. Found: C 46.93, H 2.38, N, 8.49.
3.4. Suzuki Coupling Reactions

3.4.1. General Procedure 3

To a stirred mixture of the iodide (0.50 mmol) and Pd(PPh$_3$)$_4$ (29 mg, 25 µmol) in degassed 1,2-dimethoxyethane (5 mL) was added the boronic acid (0.60 mmol) and NaHCO$_3$ (2.0 mmol) in degassed water (1.6 mL). The resulting mixture was heated at 80 °C for 3 h and cooled to rt before addition of water (5 mL) and extraction with EtOAc (3 × 10 mL). The combined organic layers were washed with brine (10 mL), dried over MgSO$_4$, filtered and concentrated under reduced pressure. The crude product was purified by chromatography over silica gel (the eluent is given in the product description).

3.4.2. 2,3,5-Triphenylquinoxaline (1c)

The general procedure 3 using 5-iodo-2,3-diphenyl quinoxaline (1b, 0.20 g) and phenylboronic acid (73 mg) gave 1c (eluent: CH$_2$Cl$_2$-heptane 60:40; R$_f$ = 0.35) in 42% yield as a white powder. 

Mp: 150 °C. IR: 763, 804, 841, 927, 984, 1023, 1081, 1128, 1233, 1336, 1388, 1433, 1444, 1491, 1566, 2858, 2927, 2965, 3064 cm$^{-1}$. 

$^1$H-NMR (CDCl$_3$): 7.26–7.34 (m, 3H), 7.36–7.48 (m, 4H), 7.52–7.64 (m, 6H), 7.81–7.89 (m, 4H), 8.21 (dd, 1H, $J$ = 7.3 and 2.5 Hz).

$^{13}$C-NMR (CDCl$_3$): 127.7 (CH), 128.0 (2CH), 128.1 (2CH), 128.5 (2CH), 128.7 (CH), 129.0 (CH), 129.8 (CH), 129.9 (2CH), 130.3 (2CH), 130.4 (CH), 131.1 (2CH), 138.4 (C), 139.0 (C), 139.1 (C), 139.4 (C), 140.6 (C), 141.3 (C), 152.4 (C), 152.9 (C).

Anal. Calc. for C$_{26}$H$_{18}$N$_2$ (358.44): C 87.12, H 5.06, N, 7.82. Found: C 87.25, H 5.22, N, 7.70.

3.4.3. 2,3-Diphenyl-5-(2-thienyl)quinoxaline (1d)

The general procedure 3 using 5-iodo-2,3-diphenylquinoxaline (1b, 0.20 g) and 2-thienylboronic acid (77 mg) gave 1d (eluent: CH$_2$Cl$_2$-heptane 60:40; R$_f$ = 0.20) in 97% yield as a yellow powder.

Mp: 210 °C. IR: 738, 766, 796, 828, 854, 916, 933, 969, 1025, 1053, 1083, 1163, 1238, 1336, 1390, 1442, 1495, 1562, 1592, 3064 cm$^{-1}$. 

$^1$H-NMR (CDCl$_3$): 7.18 (dd, 1H, $J$ = 5.1 and 3.7 Hz), 7.32–7.40 (m, 6H), 7.51 (dd, 1H, $J$ = 5.1 and 1.2 Hz), 7.58–7.61 (m, 2H), 7.67–7.70 (m, 2H), 7.76 (dd, 1H, $J$ = 8.3 and 7.4 Hz), 7.88 (dd, 1H, $J$ = 3.7 and 1.2 Hz), 8.08 (dd, 1H, $J$ = 8.3 and 1.3 Hz), 8.13 (dd, 1H, $J$ = 7.4 and 1.3 Hz).

$^{13}$C-NMR (CDCl$_3$): 126.7 (CH), 126.9 (CH), 127.5 (CH), 128.1 (CH), 128.2 (2CH), 128.5 (2CH), 128.8 (CH), 129.0 (CH), 129.9 (2CH), 130.4 (CH), 131.1 (2CH), 138.4 (C), 139.0 (C), 139.1 (C), 139.4 (C), 140.6 (C), 141.3 (C), 152.4 (C), 152.9 (C).

Anal. Calc. for C$_{24}$H$_{16}$N$_2$S (364.47): C 79.09, H 4.43, N, 7.69. Found: C 79.11, H 4.48, N, 7.72.

3.4.4. 2,3-Diphenyl-8-(2-thienyl)pyrido[2,3-b]pyrazine (2d)

The general procedure 3 using 8-iodo-2,3-diphenylpyrido[2,3-b]pyrazine (2b-I, 0.20 g) and 2-thienylboronic acid (77 mg) gave 2d (eluent: CH$_2$Cl$_2$-EtOAc 95:5; R$_f$ = 0.20) in 97% yield as a pale yellow powder. 

Mp: 215 °C. IR: 540, 695, 744, 1025, 1096, 1182, 1238, 1336, 1384, 1435, 1480, 1551, 1568, 2927, 2965, 3060 cm$^{-1}$. 

$^1$H-NMR (CDCl$_3$): 7.23 (dd, 1H, $J$ = 5.1 and 3.8 Hz), 7.32–7.45 (m, 6H), 7.66–7.72 (m, 5H), 7.98 (d, 1H, $J$ = 4.8 Hz), 8.10 (dd, 1H, $J$ = 3.8 and 1.2 Hz), 9.10 (d, 1H, $J$ = 4.8 Hz).

$^{13}$C-NMR (CDCl$_3$): 120.3 (CH), 127.2 (CH), 128.3 (2CH), 128.4 (2CH), 129.2 (CH), 129.4 (CH), 129.5 (CH), 130.3 (2CH), 132.4 (CH), 132.4 (C), 136.0 (C), 138.2 (C), 138.3 (C), 140.9 (C), 150.2 (C), 153.1 (C), 153.9 (CH), 155.8 (C).

Crystal data for 2d. C$_{23}$H$_{15}$N$_3$S, M = 365.44, T = 150(2) K, triclinic, P 1, a = 6.6311(18), b = 9.939(3), c = 13.655(4) Å, $\alpha = 81.914(12)$, $\beta = 80.405(11)$, $\gamma = 89.955(10)$ °, $V = 878.3(4)$ Å$^3$, $Z = 2$, $d = 1.382$ g cm$^{-3}$, $\mu = 0.197$ mm$^{-1}$. A final refinement on $F^2$ with 7113 unique intensities and 236 parameters converged at $\omega R(F^2) = 0.3351$ ($R(F) = 0.1327$) for 6147 observed reflections with $I > 2\sigma(I)$. CCDC 1858479.


3.4.5. 5-(2-Aminophenyl)-2,3-diphenylquinoxaline (1e)

The general procedure 3 using 5-iodo-2,3-diphenylquinoxaline (1b, 0.20 g) and 2-aminophenylboronic acid (82 mg) gave 1e (eluent: heptane-CH$_2$C$_2$ 70:30; R$_f$ = 0.31) in 92% yield as a yellow powder. Mp: 178 °C. IR: 689, 702, 740, 771, 977, 1307, 1342, 1492, 1626, 3025, 3060, 3212, 3328, 3468 cm$^{-1}$. $^1$H-NMR (CDCl$_3$): 3.87 (br s, 2H, NH$_2$), 6.85 (br s, 2H, NH$_2$), 6.92 (td, 1H, J = 7.4 and 1.2 Hz), 7.21–7.30 (m, 5H), 7.35–7.40 (m, 3H), 7.47–7.50 (m, 2H), 7.50–7.58 (m, 2H), 7.78–7.86 (m, 2H), 8.20 (dd, 1H, J = 7.8 and 2.1 Hz). $^{13}$C-NMR (CDCl$_3$): 116.5 (CH), 118.8 (CH), 125.7 (C), 128.1 (2CH), 128.5 (2CH), 128.9 (CH), 129.0 (CH), 129.0 (CH), 129.0 (CH), 129.0 (CH), 129.5 (CH), 130.1 (2CH), 130.2 (CH), 132.3 (CH), 138.8 (C), 139.2 (C), 139.3 (C), 139.6 (C), 141.3 (C), 145.0 (C), 152.5 (C), 153.2 (C). Anal. Calc. for C$_{26}$H$_{19}$N$_3$ (373.46): C 83.62, H 5.13, N, 11.25. Found: C 83.81, H 5.26, N, 11.17.

3.4.6. 8-(2-Aminophenyl)-2,3-diphenylpyrido[2,3-b]pyrazine (2e)

The general procedure 3 using 8-iodo-2,3-diphenylpyrido[2,3-b]pyrazine (2b-I, 0.20 g) and 2-aminophenylboronic acid (82 mg) gave 2e (eluent: CH$_2$Cl$_2$-EtOAc 70:30; R$_f$ = 0.50) in 73% yield as a yellow powder. Mp: 205 °C. IR: 687, 742, 766, 854, 981, 1015, 1047, 1237, 1307, 1382, 1489, 1623, 3024, 3055, 3345 cm$^{-1}$. $^1$H-NMR (CDCl$_3$): 3.99 (br s, 2H, NH$_2$), 6.87 (br s, 2H, NH$_2$), 6.94 (td, 1H, J = 7.4 and 1.2 Hz), 7.25–7.40 (m, 8H), 7.50–7.60 (m, 6H), 8.45 (d, 1H, J = 4.4 Hz), 9.19 (d, 1H, J = 4.4 Hz). $^{13}$C-NMR (CDCl$_3$): 116.9 (CH), 118.7 (CH), 122.6 (C), 126.3 (CH), 128.2 (2CH), 128.2 (2CH), 129.3 (CH), 129.5 (CH), 130.1 (CH), 130.1 (2CH), 130.2 (CH), 130.3 (C), 130.4 (C), 130.8 (C), 130.8 (C), 130.8 (C), 130.9 (C), 134.0 (C), 134.0 (C), 134.9 (C), 142.8 (C), 142.8 (C), 151.4 (C), 155.7 (C). Anal. Calc. for C$_{25}$H$_{18}$N$_4$ (374.45): C 80.19, H 4.85, N, 14.96. Found: C 80.07, H 4.87, N, 14.85.

3.4.7. 2,3-Diphenyl-1H-pyrazino[2′,3′,4,5]pyrido[2,3-b]indole (3h)

In a tube containing a stirred mixture of 8-bromo-7-iodo-2,3-diphenylpyrido[3,4-b]pyrazine (3b, 0.24 g, 0.50 mmol) and Pd(PPh$_3$)$_4$ (29 mg, 25 µmol) in degassed 1,2-dimethoxyethane (5 mL) was introduced 2-aminophenylboronic acid (82 mg, 0.60 mmol) and Na$_2$CO$_3$ (2.0 mmol) in degassed water (1.6 mL). The sealed tube was heated overnight at 140 °C and cooled to rt before addition of saturated aqueous NaHCO$_3$ (5 mL) and extraction with EtOAc (3 × 10 mL). The combined organic layers were washed with brine (10 mL), dried over MgSO$_4$, filtered and concentrated under reduced pressure. The crude product was purified by chromatography over silica gel (eluent: CH$_2$Cl$_2$-EtOAc 90:10; R$_f$ = 0.28) to give 3h in 65% yield as a yellow powder. Mp: 284–286 °C. IR: 695, 748, 763, 1025, 1092, 1190, 1236, 1315, 1328, 1336, 1376, 1446, 1495, 1540, 1624, 3034, 3064, 3420 cm$^{-1}$. $^1$H-NMR (CDCl$_3$): 7.30–7.42 (m, 7H), 7.50–7.60 (m, 6H), 8.45 (d, 1H, J = 7.9 Hz), 9.47 (s, 1H), 9.78 (br s, 1H). $^{13}$C-NMR (CDCl$_3$): 111.9 (CH), 120.6 (CH), 121.3 (CH), 123.1 (C), 126.7 (C), 127.2 (CH), 128.4 (2CH), 128.5 (2CH), 129.2 (CH), 129.6 (CH), 130.0 (2CH), 130.1 (2CH), 132.4 (C), 134.9 (C), 138.4 (C), 138.6 (C), 138.8 (C), 139.5 (C), 146.5 (CH), 153.6 (C), 155.9 (C). Crystal data for 3h. C$_{25}$H$_{18}$N$_4$, M = 372.42, T = 150(2) K, orthorhombic, $Pbca$, $a = 7.1524(9)$, $b = 16.3313(17)$, $c = 33.798(4)$ Å, $V = 3947.9(8)$ Å$^3$, $Z = 8$, $d = 1.253$ g cm$^{-3}$, $µ = 0.076$ mm$^{-1}$. A final refinement on $F^2$ with 4429 unique intensities and 265 parameters converged at $R(F^2) = 0.1564$ ($R(F) = 0.0739$) for 3511 observed reflections with $I > 2\sigma(I)$. CCDC 1858477. This compound was also obtained in 64% yield under microwave irradiation (300 W; Monowave 300, Anton Paar, Graz, Austria) for 30 min at 150 °C.

3.5. 8-(2-Azidophenyl)-2,3-diphenylpyrido[2,3-b]pyrazine

To a stirred solution of 8-(2-aminophenyl)-2,3-diphenylpyrido[2,3-b]pyrazine (2e, 94 mg, 0.25 mmol) in acetic acid (1.5 mL) at 0 °C was added 1M aqueous NaNO$_2$ (0.35 mL, 0.35 mmol). After stirring for 1 h at rt, the solution was cooled to 0 °C before addition of 1M aqueous Na$_3$CO$_3$ (0.35 mL, 0.35 mmol). After stirring overnight at rt, 3 mL of saturated aqueous NaHCO$_3$ were added. Extraction with EtOAc (3 × 10 mL), washing of the combined organic layers with brine (10 mL),
drying over MgSO₄, filtration and concentration under reduced pressure afforded a brown powder which was purified by chromatography over silica gel (eluuent: CH₂Cl₂-EtOAc 95:5; Rₛ = 0.50) to afford the azide in 64% yield. IR: 685, 745, 1288, 1440, 1577, 2088, 2124, 3064 cm⁻¹. ¹H-NMR (CDCl₃): 7.23–7.40 (m, 8H), 7.45–7.57 (m, 4H), 7.66–7.69 (m, 3H), 9.18 (d, 1H, J = 4.4 Hz). ¹³C-NMR (CDCl₃): 118.8 (CH), 124.7 (CH), 126.0 (CH), 127.9 (C), 128.2 (2CH), 128.2 (2CH), 129.2 (CH), 129.5 (CH), 130.1 (2CH), 130.3 (2CH), 130.4 (CH), 132.5 (CH), 134.5 (C), 138.3 (C), 138.5 (C), 138.7 (C), 146.7 (C), 149.8 (C), 153.5 (CH), 153.7 (C), 155.8 (C).

3.6. Palladium-Catalyzed N-arylation

3.6.1. General Procedure 4

To a stirred mixture of the halide (0.50 mmol) and Cs₂CO₃ (0.48 g, 1.5 mmol) in 2-chloroaniline (63 µL, 0.60 mmol) was added a solution of the catalyst prepared by stirring Pd₂(dba)₃ (11 mg, 12.5 µmol) and Xantphos (16 mg, 27.5 µmol) in degassed dioxane (2 mL) for 10 min at rt. The resulting mixture was heated at 110 °C for 24 h and cooled to rt before addition of water (5 mL) and extraction with EtOAc (3 × 10 mL). The combined organic layers were washed with brine (10 mL), dried over MgSO₄, filtered and concentrated under reduced pressure. The crude product was purified by chromatography over silica gel (the eluent is given in the product description).

3.6.2. 5-(2-Chlorophenylamino)-2,3-diphenylquinoxaline (1f)

The general procedure 4 using 5-iodo-2,3-diphenylquinoxaline (1b, 0.20 g) gave 1f (eluuent: heptane-CH₂Cl₂ 60:40; Rₛ = 0.42) in 92% yield as a yellow powder. Mp: 182 °C. IR: 695, 729, 748, 959, 1021, 1055, 1072, 1098, 1182, 1218, 1317, 1343, 1356, 1394, 1442, 1454, 1497, 1534, 1562, 1579, 1594, 1613, 3060, 3347 cm⁻¹. ¹H-NMR (CDCl₃): 6.95 (td, 1H, J = 7.7 and 1.4 Hz), 7.27–7.39 (m, 7H), 7.46–7.52 (m, 2H), 7.55–7.62 (m, 4H), 7.64–7.66 (m, 2H), 7.71 (dd, 1H, J = 8.2 and 1.4 Hz), 8.56 (br s, 1H). ¹³C-NMR (CDCl₃): 109.1 (CH), 118.9 (CH), 118.9 (CH), 122.6 (CH), 125.1 (C), 127.6 (CH), 128.2 (2CH), 128.4 (2CH), 128.9 (CH), 128.9 (CH), 129.9 (2CH), 130.1 (2CH), 130.2 (CH), 130.9 (CH), 132.1 (C), 138.4 (C), 138.9 (C), 139.2 (C), 139.3 (C), 141.9 (C), 150.4 (C), 153.9 (C). Anal. Calc. for C₂₆H₁₈ClN₃: C 76.89, H 4.58, N, 10.13.

3.6.3. 8-(2-Chlorophenylamino)-2,3-diphenylpyrido[2,3-b]pyrazine (2f)

The general procedure 4 using 8-iodo-2,3-diphenylpyrido[2,3-b]pyrazine (2b-1, 0.20 g) gave 2f (eluuent: CH₂Cl₂-EtOAc 90:10; Rᵣ = 0.32) in 67% yield as a yellow powder. Mp: 202 °C. IR: 542, 699, 755, 1021, 1102, 1242, 1313, 1336, 1356, 1437, 1452, 1534, 1558, 1583, 1646, 3060, 3322, 3631 cm⁻¹. ¹H-NMR (CDCl₃): 7.13–7.19 (m, 2H), 7.30–7.41 (m, 7H), 7.53 (dd, 1H, J = 8.0 and 1.5 Hz), 7.57–7.65 (m, 4H), 7.68 (dd, 1H, J = 8.1 and 1.5 Hz), 8.77 (br s, 1H, NH), 8.81 (d, 1H, J = 5.4 Hz, H₆). ¹³C-NMR (CDCl₃): 102.8 (CH), 122.2 (CH), 125.5 (CH), 127.2 (C), 127.5 (C), 127.8 (CH), 128.2 (2CH), 128.4 (2CH), 129.2 (CH), 129.4 (CH), 130.0 (2CH), 130.3 (2CH), 130.5 (CH), 136.2 (C), 138.4 (C), 138.5 (C), 147.0 (C), 150.3 (C), 151.1 (C), 155.0 (CH), 156.5 (C). Crystal data for 2f. C₂₅H₁₇ClN₄, M = 408.88, T = 150(2) K, orthorhombic, P c a 2₁, a = 15.3485(15), b = 18.8937(16), c = 6.9936(7) Å, V = 2028.1(3) Å³, Z = 4, d = 1.339 g cm⁻³, μ = 0.208 mm⁻¹. A final refinement on F² with 4578 unique intensities and 274 parameters converged at wR(F²) = 0.1478 (R(F) = 0.0583) for 4133 observed reflections with I > 2σ(I). CCDC 1858474.

3.7. Palladium-Catalyzed N-arylation

2,3-Diphenyl-11H-pyrazino[2,3-a]carbazole (1g) was prepared by adapting a reported procedure [40]. To a stirred mixture of 5-(2-chlorophenylamino)-2,3-diphenylquinoxaline (1f, 0.24 g, 0.60 mmol) and 1,8-diazabicyclo[5.4.0]undec-7-ene (0.13 mL, 0.90 mmol), was added a solution of the catalyst prepared by stirring Pd₂(dba)₃ (14 mg, 15 µmol) and P(tBu)₃ (12 mg, 60 µmol) in degassed dioxane (1 mL) for 10 min at rt. The resulting mixture was heated by microwave irradiation (300 W; Monowave 300, Anton Paar, Graz, Austria) for 10 min at 180 °C before addition of water (5 mL)
and extraction with EtOAc (3 × 10 mL). The combined organic layers were washed with brine (10 mL), dried over MgSO₄, filtered and concentrated under reduced pressure. The crude product was purified by chromatography over silica gel (eluents: heptane-CH₂Cl₂ 60:40; Rᵢ = 0.48) to give 1g in 62% yield as a yellow powder. Mp: 260 °C. IR: 1025, 1087, 1102, 1175, 1242, 1326, 1347, 1362, 1384, 1444, 1459, 1624, 1731, 2854, 2922, 3420 cm⁻¹. 

1H-NMR ((CD₃)₂SO): 6.86 (ddd, 1H, J = 8.0, 7.1 and 1.0 Hz), 6.91–6.97 (m, 6H), 7.01–7.10 (m, 3H), 7.14–7.17 (m, 2H), 7.28 (d, 1H, J = 8.3 Hz), 7.39 (d, 1H, J = 8.7 Hz), 8.14 (d, 1H, J = 8.7 Hz), 12.13 (br s, 1H).

13C-NMR ((CD₃)₂SO): 112.2 (CH), 118.8 (CH), 119.7 (CH), 120.3 (CH), 120.7 (C), 122.7 (C), 124.2 (CH), 125.6 (CH), 128.0 (2CH), 128.0 (2CH), 128.5 (CH), 129.7 (2CH), 129.9 (2CH), 130.0 (C), 134.3 (C), 139.0 (C), 139.2 (C), 139.8 (C), 139.9 (C), 150.7 (C), 151.4 (C). Anal. Calc. for C₂₆H₁₇N₃ (371.44): C 84.07, H 4.61, N, 11.31. Found: C 84.19, H 4.52, N, 11.12.

3.8. One-Pot Palladium-Catalyzed N-arylation/C-H Arylation

3.8.1. General Procedure 5

To a mixture of the halide (0.25 mmol), 1,8-diazabicyclo[5.4.0]undec-7-ene (118 µL, 0.75 mmol), 2-chloroaniline (38 mg, 0.30 mmol), Pd₂(dba)₃ (9.2 mg, 10 µmol) and Xantphos (13 mg, 22 µmol), was added degassed 1,4-dioxane (1 mL). The mixture was heated by microwave irradiation (150 W; Monowave 300, Anton Paar, Graz, Austria) under the conditions given in the product description. The cooled residue was taken up with EtOAc (20 mL). The organic layer was washed with brine (10 mL), dried over MgSO₄, filtered and concentrated under reduced pressure. The crude product was purified by chromatography over silica gel (the eluent is given in the product description).

3.8.2. 2,3-Diphenyl-1H-pyrazino[2′,3′:5,6]pyrido[4,3-b]indole (2g)

The general procedure 5 (1 h at 180 °C) using 8-iodo-2,3-diphenylpyrido[2,3-b]pyrazine (2b-I, 0.10 g) gave 2g (eluents: CH₂Cl₂–EtOAc 90:10; Rᵢ = 0.43) in 70% yield as a white powder. Mp > 260 °C. IR: 525, 542, 551, 626, 699, 750, 768, 1025, 1045, 1075, 1100, 1236, 1339, 1444, 1555, 1736, 2665, 3056 cm⁻¹. 

1H-NMR ((CD₃)₂SO): 7.40–7.45 (m, 7H), 7.55–7.63 (m, 5H), 7.77 (dd, 1H, J = 8.2 and 0.9 Hz), 8.42 (dt, 1H, J = 7.8 and 1.0 Hz), 9.87 (s, 1H), 13.19 (s, 1H).

13C-NMR ((CD₃)₂SO): 112.6 (CH), 118.2 (C), 120.7 (CH), 121.3 (CH), 121.4 (C), 126.4 (C), 126.5 (CH), 128.0 (CH), 128.0 (2CH), 128.1 (2CH), 128.8 (CH), 129.8 (2CH), 129.9 (2CH), 130.0 (C), 134.3 (C), 139.0 (C), 139.2 (C), 139.8 (C), 150.7 (C), 151.4 (C). Anal. Calc. for C₂₅H₁₆N₄ (372.43): C 80.63, H 4.33, N, 15.04. Found: C 80.54, H 4.28, N, 14.89.

3.8.3. 7-(Phenylamino)-2,3-diphenylpyrido[3,4-b]pyrazine (3g')

The general procedure 5 (40 min at 180 °C) using 8-bromo-7-iodo-2,3-diphenylpyrido[3,4-b]pyrazine (3b, 0.12 g) gave 3g' (eluents: CH₂Cl₂-MeOH 99:1; Rᵢ = 0.27) in 32% yield as a yellow powder. Mp: 224–226 °C. IR: 699, 750, 770, 978, 1025, 1057, 1077, 1169, 1217, 1336, 1349, 1435, 1450, 1527, 1555, 1588, 1613, 2854, 2927, 2961, 3025, 3232 cm⁻¹. 

1H-NMR (CDCl₃): 7.14 (p, 1H, J = 4.4 Hz), 7.23 (br s, 1H), 7.29–7.49 (m, 15H), 9.26 (s, 1H). 

13C-NMR (CDCl₃): 158.3 (C), 155.8 (C), 154.0 (CH), 151.4 (C), 146.3 (C), 139.8 (C), 138.8 (C), 138.7 (C), 132.4 (C), 129.8 (2CH), 129.7 (2CH), 129.5 (CH), 128.9 (CH), 128.4 (2CH), 128.4 (2CH), 124.1 (CH), 121.4 (2CH), 98.3 (CH). Anal. Calc. for C₃₅H₁₈N₄ (374.45): C 80.19, H 4.85, N, 14.96. Found: C 80.17, H 4.99, N, 14.84.

3.9. Copper-Catalyzed N-arylation

3.9.1. General Procedure 6

A mixture containing the iodide (0.50 mmol) and azole (1.0 mmol), Cu₂O (6.0 mg, 0.10 mmol), Cs₂CO₃ (0.33 g, 1.0 mmol) and DMSO (0.5 mL) was stirred at 110 °C for 24 h. The cooled residue was taken up with EtOAc (20 mL) and filtered through a Celite pad. The organic layer was washed with water (10 mL) and brine (10 mL), dried over MgSO₄, filtered and concentrated under reduced pressure.
The crude product was purified by chromatography over silica gel (the eluent is given in the product description).

3.9.2. 2,3-Diphenyl-8-(N-pyrrolyl)pyrido[2,3-b]pyrazine (2i)

The general procedure 6 using 8-iodo-2,3-diphenylpyrido[2,3-b]pyrazine (2b-I, 0.20 g) and pyrrole (67 mg) gave 2i (eluent: CH₂Cl₂-CH₂OEt 90:10; Rᵣ = 0.47) in 67% yield as a yellow powder. Mp: 210 °C. IR: 946, 1025, 1072, 1096, 1107, 1173, 1238, 1289, 1328, 1362, 1388, 1433, 1454, 1482, 1549, 1588, 3025, 3060, 3111, 3141, 3180 cm⁻¹. 1H-NMR (CDCl₃): 6.39–6.40 (m, 2H), 7.24–7.35 (m, 6H), 7.49–7.53 (m, 3H), 7.59–7.62 (m, 2H), 7.65–7.66 (m, 2H), 9.01 (d, 1H, J = 5.0 Hz). 13C-NMR (CDCl₃): 112.0 (2CH), 115.1 (CH), 122.7 (2CH), 128.3 (2CH), 128.4 (2CH), 129.4 (C), 129.5 (CH), 129.8 (CH), 130.0 (2CH), 130.2 (2CH), 137.8 (C), 138.1 (C), 144.6 (C), 150.7 (C), 153.2 (C), 153.9 (CH), 156.0 (C). Crystal data for 2i. C₁₃H₁₆Ν₄, M = 348.40, T = 150(2) K, orthorhombic, P 2₁ 2₁ 2₁, a = 6.3672(5), b = 13.0997(10), c = 21.537(18) Å, V = 1796.4(2) Å³, Z = 4, d = 1.288 g cm⁻³, μ = 0.079 mm⁻¹. A final refinement on F² with 2367 unique intensities and 245 parameters converged at ωR(F²) = 0.1207 (R(F) = 0.0498) for 1679 observed reflections with I > 2σ(I). CCDC 1858475.

3.9.3. 8-(N-indolyl)-2,3-diphenylpyrido[2,3-b]pyrazine (2j)

The general procedure 6 using 8-iodo-2,3-diphenylpyrido[2,3-b]pyrazine (2b-I, 0.20 g) and indole (0.12 g) gave 2j (eluent: CH₂Cl₂; Rᵣ = 0.36) in 51% yield as a red powder. Mp: 136 °C. IR: 1023, 1154, 1208, 1236, 1324, 1356, 1379, 1442, 1454, 1478, 1519, 1555, 1577, 1592, 3240, 3339, 3639 cm⁻¹. 1H-NMR (CDCl₃): 6.82 (d, 1H, J = 3.4 Hz), 7.22–7.44 (m, 8H), 7.53–7.56 (m, 2H), 7.67 (d, 1H, J = 8.3 Hz), 7.70–7.72 (m, 3H), 7.86 (dd, 1H, J = 4.9 and 1.2 Hz), 7.94 (d, 1H, J = 3.4 Hz), 9.17 (d, 1H, J = 4.9 Hz). 13C-NMR (CDCl₃): 106.1 (CH), 111.4 (CH), 118.0 (CH), 121.5 (CH), 122.1 (CH), 123.2 (CH), 128.4 (2CH), 128.5 (C), 129.7 (CH), 129.9 (CH), 130.1 (2CH), 130.3 (C), 130.3 (2CH), 130.5 (C), 130.8 (CH), 136.2 (C), 137.8 (C), 138.0 (C), 144.8 (C), 150.8 (C), 153.6 (CH), 156.4 (C). Anal. Calc. for C₂₂H₁₈N₄ (398.47): C 81.39, H 4.55, N, 14.06. Found: C 81.26, H 4.67, N, 13.84.

3.9.4. 2,3-Diphenyl-8-(N-pyrazoylethylidene)pyrido[2,3-b]pyrazine (2k)

The general procedure 6 using 8-iodo-2,3-diphenylpyrido[2,3-b]pyrazine (2b-I, 0.20 g) and pyrazole (68 mg) gave 2k (eluent: CH₂Cl₂; Rᵣ = 0.36) in 51% yield as a red powder. Mp: 136 °C. IR: 1027, 1032, 1092, 1164, 1229, 1324, 1356, 1388, 1532, 1549, 1592, 3034, 3060, 3159 cm⁻¹. 1H-NMR (CDCl₃): 6.55 (d, 1H, J = 2.2 Hz), 7.30–7.41 (m, 6H), 7.55–7.58 (m, 2H), 7.64–7.66 (m, 2H), 8.52 (s, 1H), 9.02 (dd, 1H, J = 5.3 and 2.4 Hz), 9.12 (dd, 1H, J = 5.2 and 2.2 Hz), 9.46 (t, 1H, J = 2.5 Hz). 13C-NMR (CDCl₃): 109.2 (CH), 115.0 (CH), 127.9 (C), 128.3 (2CH), 128.6 (2CH), 129.6 (CH), 129.8 (CH), 129.9 (2CH), 130.3 (2CH), 134.4 (CH), 137.6 (C), 138.3 (C), 142.5 (CH), 143.2 (C), 150.5 (C), 153.4 (C), 154.3 (CH), 156.1 (C). Anal. Calc. for C₂₂H₁₅N₅ (349.40): C 75.63, H 4.33, N, 20.04. Found: C 75.71, H 4.42, N, 19.86.

3.9.5. 8-(N-imidazolyl)-2,3-diphenylpyrido[2,3-b]pyrazine (2l)

The general procedure 6 using 8-iodo-2,3-diphenylpyrido[2,3-b]pyrazine (2b-I, 0.20 g) and imidazole (68 mg) gave 2l (eluent: EtOAc-MeOH 95:5; Rᵣ = 0.48) in 69% yield as a yellow powder. Mp: 209 °C. IR: 1019, 1053, 1075, 1105, 1115, 1169, 1236, 1319, 1334, 1379, 1429, 1446, 1459, 1482, 1549, 1594, 3064, 3124, 3639 cm⁻¹. 1H-NMR (CDCl₃): 7.32–7.45 (m, 7H), 7.56 (s, 1H, J = 6.6 Hz), 7.65–7.71 (m, 3H), 7.80 (br s, 1H), 8.82 (br s, 1H), 9.20 (d, 1H, J = 4.8 Hz). 13C-NMR (CDCl₃): 115.6 (CH), 119.5 (CH), 128.3 (2CH), 128.4 (2CH), 128.9 (C), 129.7 (CH), 129.9 (CH), 129.9 (2CH), 130.1 (2CH), 130.3 (CH), 137.5 (C), 137.6 (C), 138.8 (CH), 141.4 (C), 150.7 (C), 154.1 (C), 154.2 (CH), 156.6 (C). Anal. Calc. for C₂₂H₁₅N₅ (349.40): C 75.63, H 4.33, N, 20.04. Found: C 75.74, H 4.37, N, 19.92.
3.9.6. 2,3-Diphenyl-8-[1-(1,2,4-triazolyl)]pyrido[2,3-b]pyrazine (2m)

The general procedure 6 using 8-iodo-2,3-diphenylpyrido[2,3-b]pyrazine (2b-I, 0.20 g) and 1,2,4-triazole (69 mg) gave 2m (eluent: CH₂Cl₂-EtOAc 80:20; Rf = 0.35) in 79% yield as an orange powder. Mp: 205 °C. IR: 708, 995, 1025, 1049, 1079, 1124, 1158, 1223, 1242, 1276, 1332, 1386, 1403, 1459, 1508, 1551, 1590, 3064, 3146 cm⁻¹. ¹H-NMR (CDCl₃): 7.35–7.49 (m, 6H), 7.59 (d, 2H, J = 7.0 Hz), 7.68 (d, 2H, J = 7.2 Hz), 8.22 (s, 1H), 8.37 (br s, 1H), 9.27 (br s, 1H), 10.16 (br s, 1H). ¹³C-NMR (CDCl₃): 115.1 (CH), 127.3 (C), 128.2 (2CH), 128.5 (2CH), 129.8 (CH), 129.8 (2CH), 129.9 (2CH), 130.1 (2CH), 137.3 (C), 137.7 (C), 140.4 (C), 147.2 (CH), 150.4 (C), 152.0 (CH), 154.1 (C), 154.5 (CH), 156.7 (C). Anal. Calc. for C₂₃H₁₄N₆ (350.39): C 71.99, H 4.03, N, 23.99. Found: C 72.19, H 4.15, N, 23.81.

3.9.7. 5-Iodo-2,3-diphenyl-8-(N-pyrazolyl)quinoxaline (1k′)

The general procedure 6 using 5-iodo-2,3-diphenylquinoxaline (1b′, 0.27 g) and pyrazole (68 mg) gave 1k′ (eluent: CH₂Cl₂-heptane 80:20; Rf = 0.45) in 50% yield as a pale yellow powder. Mp: 200–202 °C. IR: 536, 585, 602, 692, 696, 755, 843, 894, 946, 1040, 1092, 1182, 1193, 1221, 1336, 1397, 1465, 1519, 1543, 1592, 3060, 3159 cm⁻¹. ¹H-NMR (CDCl₃): 6.56 (dd, 1H, J = 2.6, 1.8 Hz), 7.35–7.45 (m, 6H), 7.57–7.60 (m, 2H), 7.70–7.73 (m, 2H), 7.82 (d, 1H, J = 1.8 Hz), 8.12 (d, 1H, J = 8.2 Hz), 8.43 (d, 1H, J = 8.3 Hz), 8.97–8.98 (m, 1H). ¹³C-NMR (CDCl₃): 99.3 (C), 107.6 (CH), 123.7 (CH), 128.4 (2CH), 128.5 (2CH), 129.5 (CH), 129.6 (CH), 130.0 (2CH), 130.4 (2CH), 133.2 (C), 133.5 (CH), 137.1 (C), 137.8 (C), 138.2 (C), 139.7 (CH), 140.7 (C), 141.1 (CH), 153.0 (C), 153.6 (C). Anal. Calc. for C₂₃H₁₄N₆ (474.31): C 58.24, H 3.19, N, 11.81. Found: C 58.33, H 3.26, N, 11.68.

3.10. Nucleophilic Substitution Using Amines

3.10.1. General Procedure 7

A sealed tube containing the iodide (0.50 mmol) and amine (amount given in the product description) in ethanol (2 mL) was heated (conditions given in the product description). The cooled residue was concentrated before chromatography over silica gel (eluent given in the product description).

3.10.2. 8-(Isopropylamino)-2,3-diphenylpyrido[2,3-b]pyrazine (2n)

The general procedure 7 (150 °C, 18 h) using 8-iodo-2,3-diphenylpyrido[2,3-b]pyrazine (2b-I, 0.20 g) and isopropylamine (51 µL, 0.60 mmol) gave 2n (eluent: CH₂Cl₂-EtOAc 50:50; Rf = 0.20) in 69% yield as a beige powder. Mp: 179 °C. IR: 699, 703, 772, 804, 1156, 1178, 1236, 1313, 1336, 1538, 1564, 1592, 2965, 3038, 3064, 3390 cm⁻¹. ¹H-NMR (CDCl₃): 1.27 (d, 6H, J = 6.4 Hz, Me), 3.77 (dp, 1H, J = 7.9 and 6.4 Hz, CHMe₂), 6.40 (br d, 1H, J = 8.0 Hz, NH), 6.45 (d, 1H, J = 5.5 Hz), 7.15–7.28 (m, 6H), 7.39–7.42 (m, 2H), 7.46–7.49 (m, 2H), 8.59 (dd, 1H, J = 5.4, 0.6 Hz). ¹³C-NMR (CDCl₃): 22.3 (2CH₂), 44.1 (CH), 100.7 (CH), 127.1 (C), 128.0 (2CH), 128.2 (2CH), 128.7 (CH), 129.0 (CH), 129.9 (2CH), 130.2 (2CH), 138.5 (C), 138.8 (C), 150.0 (C), 150.2 (C), 150.9 (CH), 154.9 (CH), 155.9 (C), 159.2 (C). Anal. Calc. for C₃₂H₂₃N₄O (418.50): C 77.49, H 5.30, N, 13.39. Found: C 77.49, H 5.30, N, 13.39.

3.10.3. 8-(4-Methoxybenzylamino)-2,3-diphenylpyrido[2,3-b]pyrazine (2o)

The general procedure 7 (150 °C, 24 h) using 8-iodo-2,3-diphenylpyrido[2,3-b]pyrazine (2b-I, 0.20 g) and 4-methoxybenzylamine (78 µL, 0.60 mmol) gave 2o (eluent: CH₂Cl₂-EtOAc 50:50; Rf = 0.48) in 71% yield as a yellow powder. Mp: 190 °C. IR: 697, 832, 1175, 1236, 1302, 1341, 1437, 1459, 1510, 1585, 2828, 2910, 3064, 3232 cm⁻¹. ¹H-NMR (CDCl₃): 3.81 (s, 3H, OMe), 4.55 (d, 2H, J = 5.9 Hz), 6.58 (d, 1H, J = 5.3 Hz), 6.90 (d, 2H, J = 8.7 Hz), 7.02 (t, 1H, J = 5.7 Hz), 7.27–7.35 (m, 8H), 7.49–7.51 (m, 2H), 7.58–7.61 (m, 2H), 8.69 (d, J = 5.3 Hz, 1H). ¹³C-NMR (CDCl₃): 46.5 (CH₂), 55.3 (CH₃), 101.1 (CH), 114.3 (2CH), 127.2 (C), 128.0 (2CH), 128.2 (2CH), 128.6 (2CH), 128.8 (CH), 129.1 (CH), 129.1 (C), 129.9 (2CH), 130.3 (2CH), 138.5 (C), 138.8 (C), 150.0 (C), 150.2 (C), 150.9 (CH), 154.9 (CH), 155.9 (C), 159.2 (C). Anal. Calc. for C₂₇H₂₂N₄O (418.50): C 77.49, H 5.30, N, 13.39. Found: C 77.58, H 5.44, N, 13.20.
3.10.4. 8-(Benzy lamino)-2,3-diphenylpyrido[2,3-b]pyrazine (2p)

The general procedure 7 (150 °C, 24 h) using 8-iodo-2,3-diphenylpyrido[2,3-b]pyrazine (2b-I, 0.20 g) and benzy lamine (66 µL, 0.60 mmol) gave 2p (eluent: CH₂Cl₂-CHCl₃ 50:50; R₆ = 0.50) in 79% yield as a yellow powder. Mp: 238 °C. IR: 697, 768, 873, 1150, 1238, 1300, 1324, 1339, 1439, 1538, 1593, 2910, 3064, 3201 cm⁻¹. ¹H-NMR (CDCl₃): 4.63 (d, 2H, J = 6.0 Hz), 6.56 (d, 1H, J = 5.4 Hz), 7.11 (t, 1H, J = 6.0 Hz), 7.27–7.39 (m, 11H), 7.49–7.52 (m, 2H), 7.58–7.61 (m, 2H), 8.68 (d, 1H, J = 5.4 Hz). ¹³C-NMR (CDCl₃): 47.0 (CH), 101.2 (CH), 127.2 (2CH), 127.2 (C), 127.8 (CH), 128.1 (2CH), 128.3 (2CH), 128.9 (CH), 129.8 (2CH), 129.9 (CH), 130.3 (2CH), 137.2 (C), 138.3 (C), 138.8 (C), 150.0 (C), 150.3 (C), 151.0 (C), 154.9 (CH), 156.0 (C). Crystal data for 2p. C₂₆H₂₀N₄O, M = 388.46, T = 150(2) K, monoclinic, P 2₁/a, a = 12.8640(10), b = 23.6400(20), c = 25.4600(2) Å, β = 91.436(4)°, V = 1988.1(3) Å³, Z = 4, d = 1.298 g cm⁻³, μ = 0.078 mm⁻¹. A final refinement on F² with 4438 unique intensities and 274 parameters converged at ωR(F²) = 0.1432 (R(F) = 0.0626) for 3710 observed reflections with I > 2(I(I)). CCDC 1858476.

3.11. Nucleophilic Substitution using Hydrazine Hydrate: 8-Hydrazino-2,3-diphenylpyrido[2,3-b]pyrazine (2q)

A solution of 8-iodo-2,3-diphenyl pyrido [2,3-b]pyrazine (2b-I, 0.20 g, 0.50 mmol) and hydrazine hydrate (0.25 mL, 5.0 mmol) in iso propanol (2 mL) was heated under reflux for 4 h. The cooled residue was concentrated and taken up with CH₂Cl₂ (20 mL). The organic layer was washed with water (10 mL), dried over MgSO₄, filtered and concentrated under reduced pressure to give the title compound 2q in 92% yield as a red powder. Mp > 250 °C. IR: 797, 1038, 1150, 1238, 1300, 1324, 1339, 1439, 1538, 1590, 1618, 3201 cm⁻¹. ¹H-NMR (CDCl₃): 4.63 (d, 2H, J = 5.6 Hz), 7.22–7.36 (m, 7H), 7.40–7.43 (m, 2H), 7.48–7.51 (m, 2H), 8.60 (d, 1H, J = 5.6 Hz). ¹³C-NMR (CDCl₃): 101.2 (CH), 126.2 (C), 128.2 (2CH), 128.3 (2CH), 129.0 (CH), 129.2 (CH), 129.9 (2CH), 130.3 (2CH), 138.4 (C), 138.7 (C), 149.7 (C), 150.3 (C), 153.0 (C), 155.0 (CH), 156.1 (C). Anal. Calc. for C₁₉H₁₅N₅ (313.36): C 72.83, H 4.83, N, 22.35. Found: C 72.96, H 4.89, N, 22.31.

3.12. Condensation Reactions from the Hydrazine 2q

3.12.1. General Procedure 8

A sealed tube containing 8-hydrazino-2,3-diphenylpyrido[2,3-b]pyrazine (2q, 0.16 g, 0.50 mmol) and the aldehyde (0.55 mmol) in ethanol (2 mL) was heated at 110 °C overnight. The cooled residue was concentrated under vacuum, washed with methanol and isolated by filtration.

3.12.2. 2-Hydroxybenzaldehyde 2-[8-(2,3-diphenylpyrido[2,3-b]pyrazinyl)hydrazone (2r)

General Procedure 8 using 2-hydroxybenzaldehyde (67 mg) gave 2r (R₄ (CH₂Cl₂-CHCl₃ 80:20) = 0.44) in 60% yield as a yellow powder. Mp > 260 °C. IR: 952, 1019, 1096, 1163, 1239, 1270, 1309, 1328, 1422, 1540, 1562, 1594, 1618, 3064, 3317 cm⁻¹. ¹H-NMR (CDCl₃): 6.91 (d, 1H, J = 5.6 Hz), 7.23–7.44 (m, 9H), 7.51–7.54 (m, 2H), 7.58–7.62 (m, 2H), 8.26 (s, 1H), 8.91 (d, 1H, J = 5.3 Hz), 9.71 (br s, 1H), 10.60 (br s, 1H). The ¹³C spectra could not be recorded due to low solubility in CDCl₃ and DMSO. Anal. Calc. for C₂₉H₂₀N₅O (417.47): C 74.80, H 4.59, N, 16.78. Found: C 74.72, H 4.89, N, 16.78.

3.12.3. Piperonal 2-[8-(2,3-diphenylpyrido[2,3-b]pyrazinyl)hydrazone (2s)

General Procedure 8 using piperonal (83 mg) gave 2s (R₄ (CH₂Cl₂-CHCl₃ 80:20) = 0.37) in 70% yield as a yellow powder. Mp: 254 °C. IR: 933, 1038, 1150, 1255, 1339, 1450, 1489, 1501, 1545, 1568, 1590, 2901, 3060, 3322, 3648 cm⁻¹. ¹H-NMR (CDCl₃): 6.03 (s, 2H), 6.84 (d, 1H, J = 8.0 Hz), 7.07 (dd, 1H, J = 8.1 and 1.6 Hz), 7.28–7.42 (m, 7H), 7.50 (t, 3H, J = 6.6 Hz), 7.59 (d, 2H, J = 6.8 Hz), 7.97 (s, 1H), 8.85 (d, 1H, J = 5.3 Hz), 9.66 (s, 1H). ¹³C-NMR ((CD₃)₂SO): 101.5 (CH₂), 103.5 (CH), 104.9 (CH), 108.5 (CH), 120.3 (CH), 125.6 (C), 128.1 (2CH), 128.2 (2CH), 128.8 (CH), 129.1 (CH), 129.2 (C), 129.7 (2CH), 130.1 (2CH),
138.3 (C), 138.6 (C), 145.1 (CH), 147.7 (C), 148.1 (C), 148.8 (C), 149.6 (C), 150.0 (C), 154.5 (CH), 155.5 (C). Anal. Calc. for C$_{27}$H$_{19}$N$_2$O$_2$ (445.48): C 72.80, H 4.30, N, 15.72. Found: C 72.95, H 4.44, N, 15.83.

3.12.4. 2-Hydroxy-4-methoxybenzaldehyde 2-[8-(2,3-diphenylpyrido[2,3-b]pyrazinyl)]hydrazone (2t)

General Procedure 8 using 2-hydroxy-4-methoxybenzaldehyde (84 mg) gave 2t (R$_f$ (CH$_2$Cl$_2$-EtOAc 80:20) = 0.58) in 80% yield as a yellow powder. Mp $> 260$ °C. IR: 1017, 1066, 1109, 1124, 1145, 1236, 1300, 1321, 1512, 1545, 1562, 1588, 3060, 3184, 3317, 3652 cm$^{-1}$. $^1$H-NMR (CDCl$_3$): 3.85 (s, 3H), 6.52 (dd, 1H, $J$ = 8.5 and 2.5 Hz), 6.58 (d, 1H, $J$ = 2.5 Hz), 7.15 (d, 1H, $J$ = 8.6 Hz), 7.19 (d, 1H, $J$ = 5.2 Hz), 7.28–7.43 (m, 6H), 7.50–7.54 (m, 2H), 7.58–7.61 (m, 2H), 8.19 (s, 1H), 8.88 (br s, 1H), 9.59 (br s, 1H), 10.81 (s, 1H). The $^{13}$C spectra could not be recorded due to low solubility in CDCl$_3$ and DMSO. Anal. Calc. for C$_{27}$H$_{21}$N$_2$O$_2$ (447.50): C 72.47, H 4.73, N, 15.65. Found: C 72.53, H 4.89, N, 15.60.

3.12.5. 4-(Trifluoromethyl)benzaldehyde 2-[8-(2,3-diphenylpyrido[2,3-b]pyrazinyl)]hydrazone (2u)

General Procedure 8 using 4-(trifluoromethyl)benzaldehyde (87 mg) gave 2u (R$_f$ (CH$_2$Cl$_2$-EtOAc 80:20) = 0.51) in 73% yield as a yellow powder. Mp: 206–260 °C. IR: 1032, 1135, 1163, 1238, 1291, 1339, 1431, 1439, 1461, 1510, 1543, 1566, 1631, 2845, 2931, 3004, 3056, 3176, 3317 cm$^{-1}$. $^1$H-NMR (CDCl$_3$): 7.28–7.43 (m, 6H), 7.50–7.54 (m, 2H), 7.58–7.61 (m, 2H), 8.19 (s, 1H), 8.88 (br s, 1H), 9.59 (br s, 1H), 10.81 (s, 1H). The $^{13}$C spectra could not be recorded due to low solubility in CDCl$_3$ and DMSO. Anal. Calc. for C$_{27}$H$_{19}$N$_2$O$_2$ (445.48): C 72.80, H 4.30, N, 15.72. Found: C 72.95, H 4.44, N, 15.83.

3.13. Nucleophilic Substitution Using a Phenolate: Methyl 2-[8-(2,3-diphenylpyrido[2,3-b]pyrazinyl)]oxy-5-methoxybenzoate (2v)

A mixture of 8-iodo-2,3-diphenylpyrido[2,3-b]pyrazine (2b-I, 0.20 g, 0.50 mmol), methyl 2-hydroxy-5-methoxy-benzoate (0.10 g, 0.55 mmol), K$_2$CO$_3$ (77 mg, 0.55 mmol) and DMSO (1 mL) was heated at 110 °C for 2 h. The cooled residue was treated by an aqueous solution of Na$_2$CO$_3$ and DMSO before extraction with Et$_2$O (3 × 10 mL). The organic layer was dried over MgSO$_4$, filtered and concentrated under reduced pressure, and the residue was chromatographed over silica gel (eluent: CH$_2$Cl$_2$-MeOH 95:5; RF (CH$_2$Cl$_2$-EtOAc 95:5) = 0.50) to give the title compound 2v in 64% yield as a beige powder. Mp: 206 °C. IR: 542, 698, 773, 856, 1021, 1072, 1109, 1205, 1235, 1263, 1333, 1350, 1434, 1468, 1496, 1554, 1719, 2845, 2956, 3041 cm$^{-1}$. $^1$H-NMR (CDCl$_3$): 3.65 (s, 3H), 3.90 (s, 3H), 6.64 (d, $J$ = 5.2 Hz, 1H), 7.19 (dd, 1H, $J$ = 8.9, 3.0 Hz), 7.24 (d, 1H, $J$ = 9.5 Hz), 7.30–7.40 (m, 6H), 7.55–7.58 (m, 3H), 7.61–7.64 (m, 2H), 8.86 (d, 1H, $J$ = 5.2 Hz). $^{13}$C-NMR (CDCl$_3$): 52.4 (CH$_3$), 56.0 (CH$_3$), 107.6 (CH), 116.3 (CH), 120.6 (CH), 124.6 (C), 125.0 (CH), 128.2 (2CH), 128.4 (2CH), 129.0 (C), 129.1 (CH), 129.4 (CH), 130.2 (2CH), 130.3 (2CH), 138.2 (C), 138.7 (C), 147.0 (C), 151.1 (C), 153.6 (C), 154.4 (CH), 156.6 (C), 157.4 (C), 163.0 (C), 164.7 (C). Anal. Calc. for C$_{28}$H$_{21}$N$_3$O$_4$ (463.49): C 72.56, H 4.57, N, 9.07. Found: C 72.49, H 4.65, N, 9.01.

4. Conclusions

Original pyrazino-fused polycyclic scaffolds were synthesized by combining deproto-metallation-iodolysis with palladium- or copper-catalyzed couplings or direct substitution reactions. This study highlights the interest in preparing iodo derivatives of sensitive aromatic heterocycles by using lithium-zinc basic combinations to access scaffolds of potential biological interest. Interestingly, bromine and trichloroisocyanuric acid were successfully employed as electrophiles to intercept the intermediate heteroarylzinc halides.

Supplementary Materials: Supplementary materials are available online.
Author Contributions: F.L., T.L., M.B., C.C., I.C., C.G. and J.L. synthesized and analyzed all compounds presented in this article; E.C. contributed to the identification of some synthesized compounds by NMR; E.L. and L.P. contributed with the experiments performed under microwave irradiation; L.P., M.S., B.B. and S.B. performed the bioassays; T.R. collected the X-ray diffraction data and solved the structures. F.M. wrote the paper with the help of E.C., L.P.; V.T., S.R., S.B. and T.R.; F.L. started the project, designed the molecules and revised the paper.

Funding: This research received no external funding.

Acknowledgments: O. Lozach and T. Robert (KISSf screening facility) are acknowledged for their excellent technical support, and William Erb for his relevant advice. F.M. and F.L. thank the Université de Rennes 1. L.P. and V.T. thank the French Cancer League (Comité 17) for financial support and the Cancéropôle Grand Ouest (axis: natural sea products in cancer treatment) for scientific support. S.B. and S.R. thank the Cancéropôle Grand Ouest (axis: natural sea products in cancer treatment), IBiSA (French Infrastructures en sciences du vivant: biologie, santé et agronomie) and Biogenouest (Western France life science and environment core facility network) for supporting KISSf screening facility. We acknowledge FEDER founds (D8 VENTURE Bruker AXS diffractometer) and Thermofisher (generous gift of 2,2,6,6-tetramethylpiperidine).

Conflicts of Interest: The authors declare no conflict of interest.

References
41. Teo, Y.-C.; Yong, F.-F.; Sim, S. Ligand-free Cu$_2$O-catalyzed cross coupling of nitrogen heterocycles with iodopyridines. Tetrahedron 2013, 69, 7279–7284. [CrossRef]

Sample Availability: Samples of the synthesized compounds are available from the corresponding authors.

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