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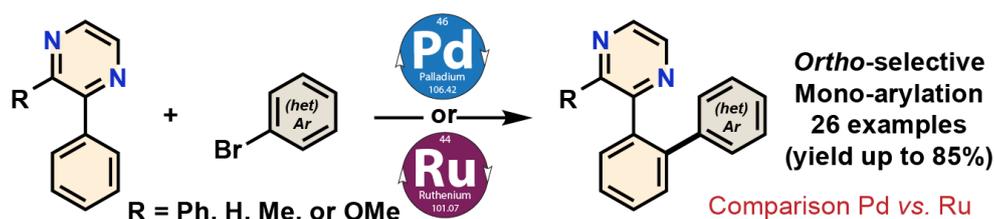
Palladium – Ruthenium Catalyst Complementarity Strengthens *Ortho*-Directed C–H bond Arylation of 2-Arylpyrazines

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Abstract: We report the Pd- or Ru-catalyzed C–H bond arylation at the *ortho*-position of the aryl unit of 2-arylpyrazines. The reaction proceeds with complete regioselectivity using phosphine-free Pd(OAc)₂ or [RuCl₂(*p*-cymene)]₂ as the catalysts and potassium acetate as an inexpensive base. In all cases, the mono-arylation of 2-arylpyrazines was obtained even with 2,3-diphenylpyrazine. Moreover, the reaction is not sensitive to the pyrazine substitution. By selecting the proper catalytic system, a wide variety of electron-rich and -poor (hetero)aryl bromides, including bromopyridine derivatives, has been successfully employed.

Introduction

Pyrazines (1,4-diazines) are an essential class of aza-heteroarenes in medicinal chemistry.^[1] For example, Selexipag is an approved drug for the treatment of pulmonary arterial hypertension (Figure 1). Berzosertib is currently under investigation in the treatment of various neoplasms and tumors (Figure 1). Besides, 2-arylpyrazines are currently used as ligands to prepare organometallic materials such as the luminescent iridium(III) complex [Ir(DPP)₂Pic, Figure 1].^[2] Therefore, the development of straightforward methods to diversify such structures is an important research area.

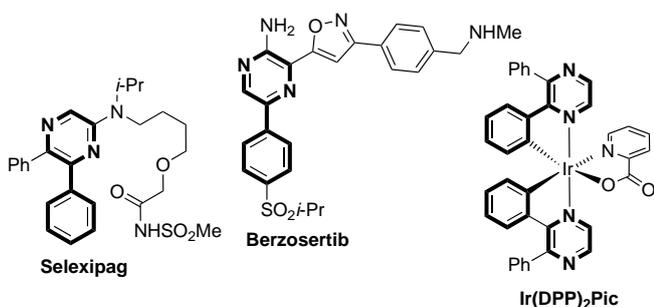


Figure 1. Examples of Pharmaceuticals and Materials Containing a 2-Arylpyrazine Scaffold.

Since a few decades, transition metal-catalyzed C–H bond functionalizations have become very appealing transformations for the construction of intermediates, drugs, and materials or to modify complex structures quickly.^[3] Among C–H bond transformations, the direct arylation has drawn particular attention, as it allows the one-step formation of (hetero)biaryls.^[4] Nitrogen heterocycles are often employed to control the regioselectivity in the C–H bond arylation of benzene rings.^[5] Among them, the most commonly employed contains a pyridine unit.^[5] Conversely, the use of diazine as directing group remains scarce in the literature. It is mainly limited to 1,3-diazines, such as 2-arylpyrimidines^[6] and 6-arylpyrimines.^[7]

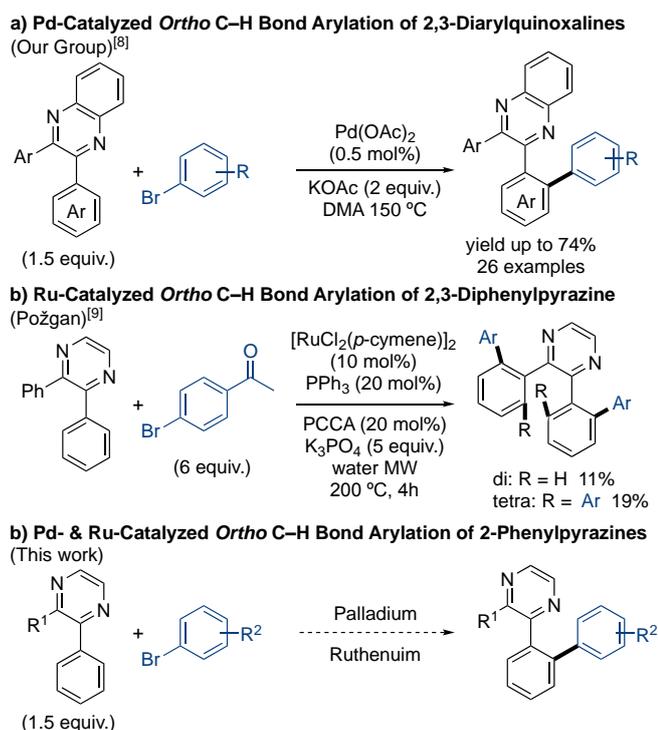
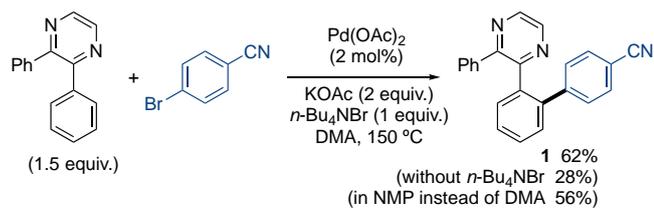
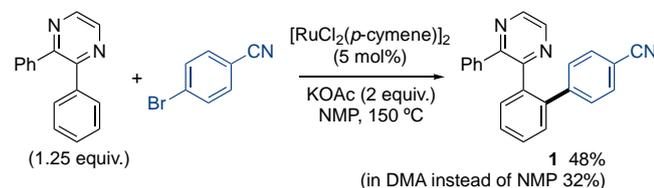
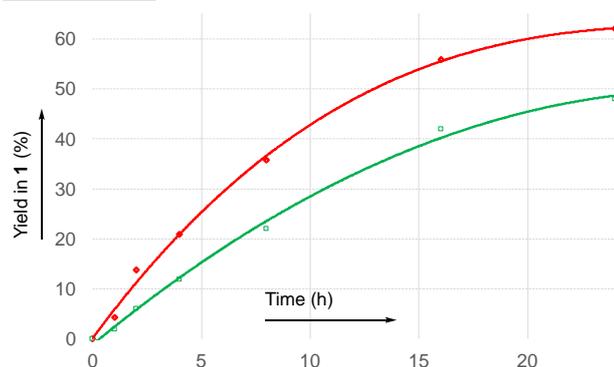


Figure 2. Previous Examples of Pd- or Ru-catalyzed *ortho* C–H bond Arylation of Aryl Rings Using a 1,4-Diazine as Directing Group.

In 2018, our group employed quinoxaline as an active directing group in the Pd-catalyzed C–H bond arylation at the *ortho*-position of the aryl unit of 2-arylquinoxalines (Figure 2a).^[8] In contrast to previously employed directing groups, quinoxaline only promotes *ortho* mono-arylation affording the (hetero)biaryl products in moderate to good yields without the formation of bis-arylated products. In 2020, Požgan and co-workers described only one example of direct polyarylation of 2,3-diphenylpyrazine using Ru(II)/carboxylate/PPh₃ as the catalytic system in water under microwave irradiation (Figure 2b).^[9] However, their work focused only on multiple C–H bond functionalizations using a large excess of the aryl bromide (4-bromoacetophenone). The reaction was not selective and a mixture of diarylated and tetraarylated products was produced in poor yields. To the best of our knowledge, there is no example of the use of pyrazine as a directing group for the mono C–H bond arylation. However, it could provide a practical methodology to prepare a variety of biologically active compounds and active materials in a single operation. Therefore, we have investigated the reactivity of palladium and ruthenium for the C–H bond arylation of arenes using a pyrazine as directing group (Figure 2c).

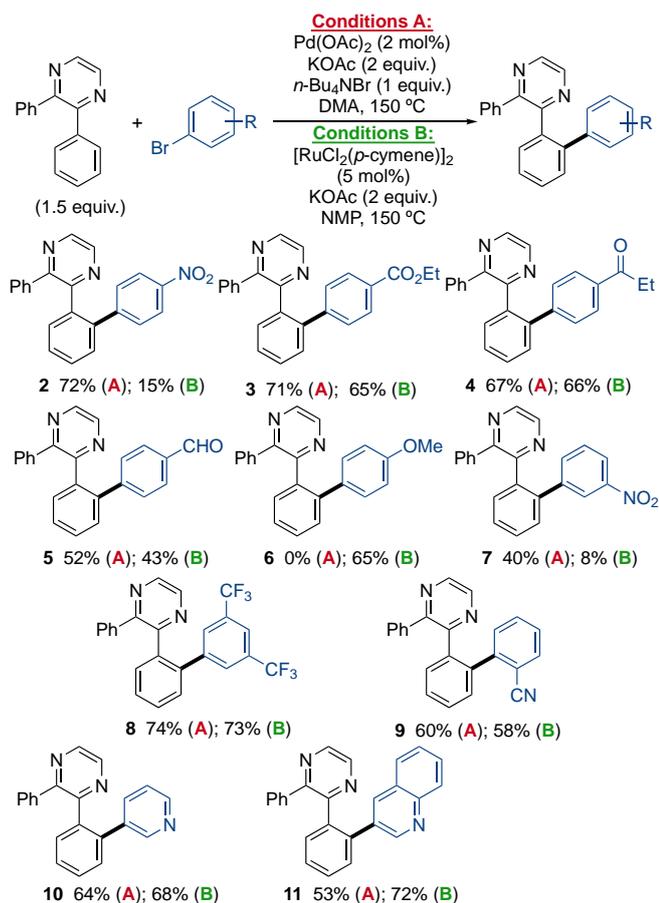
Results and Discussion

We began our investigations by evaluating the reactivity of a palladium catalyst for the C–H bond arylation of 2,3-diphenylpyrazine (Scheme 1, top). Using our previous conditions for the C–H bond arylation of 2,3-diphenylquinoxaline,^[8] (namely Pd(OAc)₂ as catalyst associated with KOAc as the base in DMA at 150 °C with 1.5 equivalents of 2,3-diphenylpyrazine) we were pleased to find that only mono-arylation of one of the two phenyl rings occurred, although the desired arylated product **1** was isolated in a very poor 28% yield due to the formation of Ullmann-type aryl bromide homocoupling as the main side-product.^[10] Tetraalkylammonium salts have been highly successful in enhancing the reactivity and selectivity in Pd-catalyzed cross-coupling reactions,^[11] including in C–H bond arylations.^[12] Reetz and co-workers have demonstrated that they stabilize the *in-situ* generated nanosized Pd colloids in phosphine-free catalysis based on simple Pd(OAc)₂ salts.^[13] When 1 equivalent of (*n*-Bu)₄NBr was employed in our reaction, the desired arylated pyrazine **1** was obtained in 62% yield. Next, we also investigated the reactivity of Ru(II) catalytic system toward the mono-C–H bond arylation using 1.5 equivalents of 2,3-diphenylpyrazine with 1 equivalent of 4-bromobenzonitrile using our previous conditions for C–H bond arylation of 2-arylpyridine derivatives,^[14] namely 5 mol% [RuCl₂(*p*-cymene)₂] associated with KOAc as the base in NMP at 150 °C (Scheme 1, middle). These phosphine-free ruthenium conditions afforded the desired product **1** in 48% yield without the formation of di- or multi-arylated products. It should be noted that the efficiency of palladium and ruthenium catalysis is dependent on the choice of solvent: DMA for palladium and NMP for ruthenium, as the solvent's flip gave lower yields in **1**. The kinetic profiles of palladium and ruthenium reactions show that the reaction proceeds slightly faster with Pd(OAc)₂ (Scheme 1, bottom). Based on our previous observations,^[15] we know that phosphine-free palladium catalysis is very sensitive to the electronic nature of the aryl bromide: almost no reaction occurred with electron-rich aryl bromides owing to a slower rate in the oxidative addition. *Ortho*-directed C–H bond arylation with ruthenium(II) catalysis often involves C–H bond cleavage – oxidative addition of aryl bromides – reductive elimination sequence,^[16] while palladium(0) catalysis involves oxidative addition of aryl bromides – C–H bond cleavage – reductive elimination sequence.^[17] The interconversion between the first two elementary steps could lead to different reactivities depending on the substitution of both aryl bromides and 2-arylpyrazines. Therefore, we decided to explore the scope of the reaction with both catalytic systems to expand the scope of aryl bromide that can be efficiently coupled with 2-arylpyrazine derivatives.

Conditions A:**Conditions B:****Reaction Profiles**

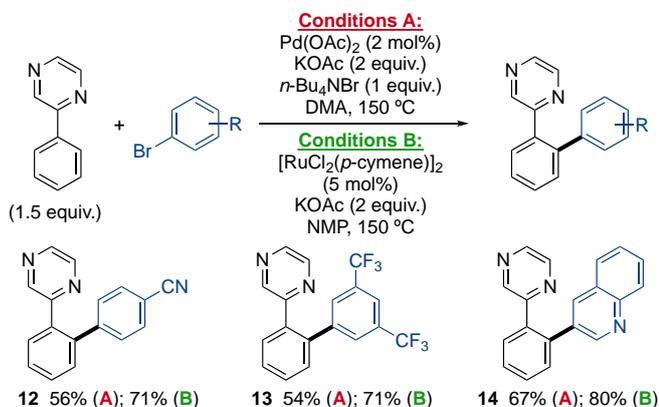
Scheme 1. Pd and Ru-Catalyzed C-H Bond Arylation of 2,3-Diphenylpyrazine with 4-Bromobenzonitrile: Reaction Conditions and Kinetic Profiles for the Formation of **1**.

Having found two sets of conditions for the selective mono C–H bond arylation 2,3-diphenylpyrazine, we firstly study the reactivity of diversely substituted aryl bromides to probe the difference between palladium and ruthenium catalysts (Scheme 2). In most cases, the *ortho*-directed arylation of 2,3-diphenylpyrazine using palladium catalysis outperformed the ruthenium system. In particular, this is true for 4-bromonitrobenzene with which the palladium conditions afforded the *ortho* mono-arylated 2,3-diphenylpyrazine **2** in 72% yield, while ruthenium gave only a poor conversion. From ethyl 4-bromobenzoate, 4-bromopropiophenone, and 4-bromobenzaldehyde, the arylated pyrazines **3–5** were isolated in good yields using palladium conditions. The reactivity of phosphine-free palladium catalysis strongly depends on the electronic nature of the aryl bromide. When the reaction was carried out with 4-bromoanisole, no reaction occurred using Pd(OAc)₂. This limitation can be overcome using [RuCl₂(*p*-cymene)]₂ affording the desired product **6** in 65% yield. Similarly to 4-bromonitrobenzene, 3-bromonitrobenzene can be efficiently coupled with 2,3-diphenylpyrazine using palladium-based conditions, suggesting that the NO₂ group is incompatible with Ru(II) catalysis. 1-Bromo-3,5-bis(trifluoromethyl)benzene displayed a similar reactivity with palladium or ruthenium catalysis affording the arylated pyrazine **8** in similar yields whatever the catalytic system. The compound **9** resulting from the C–H bond arylation with 2-bromobenzonitrile was obtained in 60% yield using palladation and 58% yield using ruthenium. Interestingly, nitrogen-containing heteroaryl bromides, such as 3-bromopyridine and 3-bromoquinoline, reacted in better yields using ruthenium catalyst affording the coupling products **10** and **11** in 68% and 72% yield, respectively.



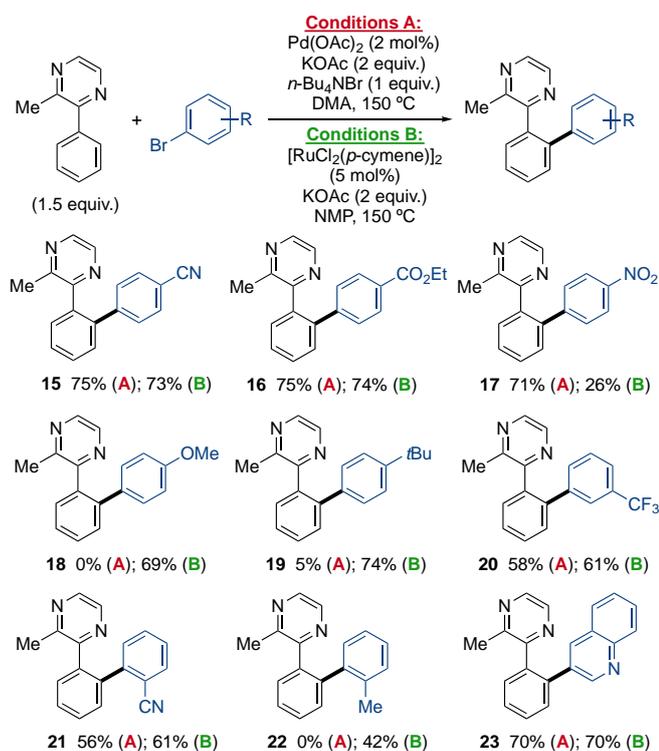
Scheme 2. Pd- vs. Ru-Catalyzed C–H Bond Arylation of 2,3-Diphenylpyrazine

Surprisingly, C–H bond functionalizations of 2-phenylpyrazine have been limited to direct cyanation using rhodium,^[18] direct alkenylation using ruthenium,^[19] and direct fluorination using palladium.^[20] Heck-type arylation aside,^[21] there is no previous example of direct arylation. Therefore, we decided to investigate the reactivity of 2-phenylpyrazine under both palladium- and ruthenium-based conditions (Scheme 3). The ruthenium-based system is more efficient for the C–H bond arylation with 4-bromobenzonitrile, 1-bromo-3,5-bis(trifluoromethyl)benzene, and 3-bromoquinoline affording **12–14** in 71–80% yields.



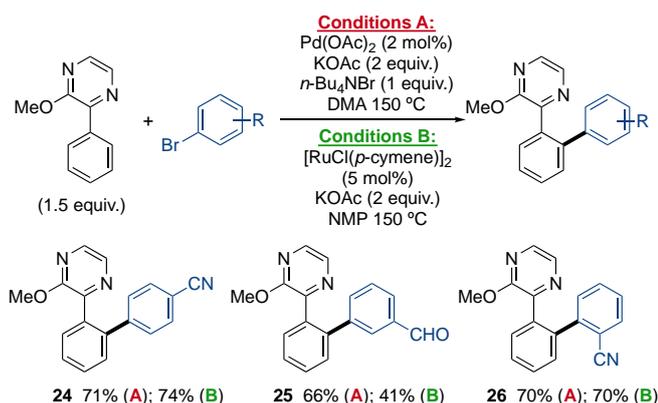
Scheme 3. Pd- vs. Ru-Catalyzed C–H Bond Arylation of 2-Phenylpyrazine

Next, we investigated the reactivity of 2-methyl-3-phenylpyrazine in transition-metal-catalyzed C–H bond arylation with aryl bromides as aryl sources (Scheme 4). Both palladium- and ruthenium-based conditions gave only the monoarylated products resulting from the *ortho*-directed of C(sp²)–H bond cleavage without the formation of arylated products arising from the functionalization of the C(sp³)–H methyl bond.^[22] The coupling reactions between 2-methyl-3-phenylpyrazine and 4-bromobenzonitrile or ethyl 4-bromobenzoate were carried out with the same efficiency whatever the catalytic system used, affording the arylated products **15** and **16** in 75% yields. Again with 4-bromonitrobenzene, the conditions employing Pd(OAc)₂ should be preferred to isolate **17** in 71% yield. For the reactions with electron-rich aryl bromides (e.g., 4-bromoanisole or 1-bromo-4-*tert*-butylbenzene), Ru-based conditions have to be employed as the arylated pyrazine **18**, and **19** were obtained in 69% and 74% yields with [RuCl₂(*p*-cymene)₂], while Pd(OAc)₂ catalyst gave those coupling products in trace amounts. The coupling products **20** and **21** were isolated in slightly better yields using ruthenium conditions from 3-bromobenzotrifluoride and 2-bromobenzonitrile, respectively. Pd-catalyzed C–H bond arylation with bromoarenes bearing an electron-donating substituent at *ortho*-position, such as 2-bromotoluene, are often sluggish, especially under phosphine-free conditions. However, the reaction using Ru-based catalyst afforded **22** in 42% yield. The coupling of 3-bromoquinoline afforded the pyrazine **23** in a similar yield using either palladium or ruthenium catalysis.



Scheme 4. Pd- vs. Ru-Catalyzed C–H Bond Arylation of 2-Methyl-3-phenylpyrazine

We next tried to functionalize 2-methoxy-3-phenylpyrazine (Scheme 5). The methoxy substituent does not have a strong influence on the reactivity or the regioselectivity similarly to the methyl substituent. The reaction with 4-bromobenzonitrile afforded the pyrazine **23** in 71% or 74% yield with palladium or ruthenium catalysis, respectively. The ruthenium-based conditions were less tolerant to a formyl substituent than palladium-based conditions, as **25** was isolated in only 41% with [RuCl₂(*p*-cymene)₂ owing to the formation of deformed side-product. Finally, **26** resulting from the coupling of 2-methoxy-3-phenylpyrazine and 2-bromobenzonitrile was obtained in similar yield with both reaction conditions.



Scheme 5. Pd- vs. Ru-Catalyzed C–H Bond Arylation of 2-Methoxy-3-phenylpyrazine

Conclusion

In summary, we have shown that pyrazine is an efficient directing group in *ortho*-C–H bond arylation of phenyl rings. From 2,3-diphenylpyrazine, the reaction was regioselective in favor of the formation of the mono-arylated product, in contrast to the previously reported results using a pyridine as directing group. The reaction is not very sensitive to the substitution on the pyrazine ring as 2-phenylpyrazine, 2-methyl-3-phenylpyrazine, and 2-methoxy-3-phenylpyrazine display similar reactivity. The development of two sets of conditions –one palladium-based and the other ruthenium-based– allowed complementarity in functional group tolerance. Indeed, the reactions with electron-rich aryl bromides can only be achieved in good yields using ruthenium-based conditions, while formyl and nitro substituted aryl bromides required the use of palladium catalysis. Through the selection of the appropriate catalyst, a broad range of well-decorated 2-(pyrazin-2-yl)biphenyl derivatives has been prepared.

Experimental Section

General Methods: All reactions were carried out under argon atmosphere with standard Schlenk techniques. DMA was not purified before use. NMP was distilled over CaH₂. ¹H and ¹³C NMR spectra were recorded on Bruker AV III 400 MHz NMR spectrometer equipped with BBFO probehead. Chemical shifts (δ) were reported in parts per million relative to residual chloroform (7.28 ppm for ¹H; 77.23 ppm for ¹³C), constants were reported in Hertz. ¹H NMR assignment abbreviations were the following: singlet (s), doublet (d), triplet (t), quartet (q), doublet of doublets (dd), doublet of triplets (dt), and multiplet (m). All reagents were weighed and handled in air.

Procedure A (Palladium-catalyzed direct arylation): To a 15 mL oven dried Schlenk tube, phenylpyrazine derivative (1.5 mmol), aryl bromide (1 mmol), KOAc (196 mg, 2 mmol), *n*-Bu₄NBr (193 mg, 1 mmol), Pd(OAc)₂ (4.5 mg, 0.02 mmol, 2 mol%) and DMA (5 mL) were successively added. The atmosphere was replaced with argon *via* vacuum-argon cycles (5 times) and stirred at 150 °C for 18 hours. After cooling the reaction to room temperature, the solvent was removed under vacuum. The crude mixture was purified by silica or alumina oxide column chromatography to afford the desired arylated products.

Procedure B (Ruthenium-catalyzed direct arylation): To a 15 mL oven dried Schlenk tube, phenylpyrazine derivative (1.5 mmol), aryl bromide (1 mmol), KOAc (196 mg, 2 mmol), NMP (5 mL) and $[\text{Ru}_2(\text{p-cymene})\text{Cl}_2]_2$ (46 mg, 0.075 mmol, 7.5 mol%) were successively added. The atmosphere was replaced with argon *via* vacuum-argon cycles (5 times) and stirred at 150 °C (oil bath temperature) for 48 hours (see tables and schemes). After cooling the reaction to room temperature, the solvent was removed under vacuum. The crude mixture was purified by silica or alumina oxide column chromatography to afford the desired arylated products.

2'-(3-Phenylpyrazin-2-yl)-[1,1'-biphenyl]-4-carbonitrile (1): Following general Procedure **A** using 2,3-diphenylpyrazine (348 mg, 1.5 mmol) and 4-bromobenzonitrile (182 mg, 1 mmol), the residue was purified by flash chromatography on silica gel (Heptane-EtOAc, 70-30) to afford the desired compound **1** (207 mg, 62%) as a pale white solid (Mp = 186-188 °C): ^1H NMR (400 MHz, CDCl_3) δ 8.65 (d, J = 2.4 Hz, 1H), 8.60 (d, J = 2.4 Hz, 1H), 7.80 (d, J = 7.7 Hz, 1H), 7.62 (td, J = 7.5, 1.3 Hz, 1H), 7.52 (td, J = 7.6, 1.4 Hz, 1H), 7.27 (d, J = 8.0 Hz, 2H), 7.22 (t, J = 7.4 Hz, 1H), 7.17 (d, J = 7.7 Hz, 1H), 7.08 (d, J = 7.8 Hz, 2H), 6.83 (d, J = 8.2 Hz, 2H), 6.54 (d, J = 8.4 Hz, 2H). ^{13}C NMR (101 MHz, CDCl_3) δ 153.1, 152.6, 144.9, 142.8, 142.2, 139.1, 137.6, 137.3, 131.5, 131.5, 129.6, 129.5, 129.4, 129.1, 128.9, 128.5, 127.9, 118.8, 110.1. MS (EI, 70 eV) m/z (%): 103 (34), 333 (100) $[\text{M}]^+$.

2'-(4'-Nitro-[1,1'-biphenyl]-2-yl)-3-phenylpyrazine (2): Following general Procedure **A** using 2,3-diphenylpyrazine (348 mg, 1.5 mmol) and 4-bromobenzonitrile (202 mg, 1 mmol), the residue was purified by flash chromatography on aluminium oxide (Heptane-EtOAc, 70-30) to afford the desired compound **2** (254 mg, 72%) as a pale yellow solid (Mp = 178-180 °C): ^1H NMR (400 MHz, CDCl_3) δ 8.67 (d, J = 2.4 Hz, 1H), 8.61 (d, J = 2.4 Hz, 1H), 7.85 (d, J = 8.8 Hz, 2H), 7.82 (dd, J = 7.7, 0.9 Hz, 1H), 7.64 (td, J = 7.6, 1.1 Hz, 1H), 7.54 (td, J = 7.6, 1.2 Hz, 1H), 7.23 (dd, J = 16.0, 7.6 Hz, 2H), 7.08 (t, J = 7.8 Hz, 2H), 6.83 (d, J = 7.2 Hz, 2H), 6.60 (d, J = 8.8 Hz, 2H). ^{13}C NMR (101 MHz, CDCl_3) δ 153.1, 152.5, 146.9, 146.3, 142.9, 142.3, 138.7, 137.7, 137.3, 131.5, 129.6, 129.5, 129.5, 129.3, 128.9, 128.5, 128.0, 123.0. MS (EI, 70 eV) m/z (%): 103 (49), 306 (30), 353 (100) $[\text{M}]^+$.

Ethyl 2'-(3-Phenylpyrazin-2-yl)-[1,1'-biphenyl]-4-carboxylate (3): Following general Procedure **A** using 2,3-diphenylpyrazine (348 mg, 1.5 mmol) and ethyl 4-bromobenzoate (229 mg, 1 mmol), the residue was purified by flash chromatography on aluminium oxide (Heptane-EtOAc, 80-20) to afford the desired compound **3** (270 mg, 71%) as a pale white solid (Mp = 146-148 °C): ^1H NMR (400 MHz, CDCl_3) δ 8.99 (d, J = 2.4 Hz, 1H), 8.58 (d, J = 2.4 Hz, 1H), 7.78 (dd, J = 7.6, 0.9 Hz, 1H), 7.67 (d, J = 8.4 Hz, 2H), 7.58 (td, J = 7.5, 1.1 Hz, 1H), 7.50 (td, J = 7.6, 1.3 Hz, 1H), 7.22 (dd, J = 7.5, 5.6 Hz, 2H), 7.06 (dd, J = 7.8 Hz, 2H), 6.81 (d, J = 7.2 Hz, 2H), 6.52 (d, J = 8.4 Hz, 2H), 4.38 (q, J = 7.1 Hz, 2H), 1.41 (t, J = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, CDCl_3) δ 166.5, 153.4, 153.2, 144.7, 142.6, 142.0, 140.0, 137.6, 137.4, 131.2, 129.8, 129.3, 129.0, 128.9, 128.7, 128.5, 128.3, 127.8, 60.9, 14.3. MS (EI, 70 eV) m/z (%): 103 (28), 351 (44), 380 (100) $[\text{M}]^+$.

1-(2'-(3-Phenylpyrazin-2-yl)-[1,1'-biphenyl]-4-yl)propan-1-one (4): Following general Procedure **A** using 2,3-diphenylpyrazine (348 mg, 1.5 mmol) and 4-bromopropiophenone (213 mg, 1 mmol), the residue was purified by flash chromatography on aluminium oxide (Heptane-EtOAc, 85-15) to afford the desired compound **4** (244 mg, 67%) as a yellow oil: ^1H NMR (400 MHz, CDCl_3) δ 8.64 (d, J = 2.3 Hz, 1H), 8.58 (d, J = 2.3 Hz, 1H), 7.78 (d, J = 7.4 Hz, 1H), 7.60 – 7.55 (m, 3H), 7.51 (t, J = 7.2 Hz, 1H), 7.21 (d, J = 6.8 Hz, 2H), 7.05 (d, J = 6.8 Hz, 2H), 6.80 (d, J = 7.5 Hz, 2H), 6.54 (d, J = 8.2 Hz, 2H), 2.95 (q, J = 7.2 Hz, 2H), 1.23 (t, J = 7.2 Hz, 3H). ^{13}C NMR (101 MHz, CDCl_3) δ 200.5, 153.3, 153.1,

144.8, 142.6, 142.1, 139.9, 137.6, 137.5, 134.6, 131.3, 129.7, 129.3, 128.9, 128.9, 128.6, 128.3, 127.8, 127.5, 31.8, 8.3. MS (EI, 70 eV) m/z (%): 103 (18), 335 (100), 364 (90) [M]⁺.

2'-(3-phenylpyrazin-2-yl)-[1,1'-biphenyl]-4-carbaldehyde (5): Following general Procedure **A** using 2,3-diphenylpyrazine (348 mg, 1.5 mmol) and 4-bromobenzaldehyde (185 mg, 1 mmol), the residue was purified by flash chromatography on silica gel (Heptane-EtOAc, 80-20) to afford the desired compound **5** (174 mg, 52%) as a yellow solid (Mp = 165-167 °C): ¹H NMR (300 MHz, CDCl₃) δ 9.94 (s, 1H), 8.65 (d, *J* = 2.4 Hz, 1H), 8.58 (d, *J* = 2.4 Hz, 1H), 7.80 (dd, *J* = 7.6, 1.2 Hz, 1H), 7.61 (td, *J* = 7.5, 1.3 Hz, 1H), 7.55 – 7.47 (m, 2H), 7.24 – 7.17 (m, 3H), 7.04 (dd, *J* = 10.6, 4.9 Hz, 2H), 6.80 (d, *J* = 7.9 Hz, 2H), 6.61 (d, *J* = 8.2 Hz, 2H). ¹³C NMR (101 MHz, CDCl₃) δ 191.9, 153.3, 152.9, 146.5, 142.7, 142.1, 139.7, 137.7, 137.4, 134.3, 131.4, 129.7, 129.4, 129.4, 129.2, 128.9, 128.9, 128.4, 127.8. MS (EI, 70 eV) m/z (%): 103 (28), 336 (100) [M]⁺.

2-(4'-Methoxy-[1,1'-biphenyl]-2-yl)-3-phenylpyrazine (6): Following general Procedure **B** using 2,3-diphenylpyrazine (348 mg, 1.5 mmol) and 1-bromo-4-methoxybenzene (187 mg, 1 mmol), the residue was purified by flash chromatography on aluminium oxide (Heptane-EtOAc, 90-10) to afford the desired compound **6** (220 mg, 65%) as a pale white solid (Mp = 114-116 °C): ¹H NMR (400 MHz, CDCl₃) δ 8.63 (d, *J* = 2.4 Hz, 1H), 8.56 (d, *J* = 2.4 Hz, 1H), 7.73 (dd, *J* = 7.5, 1.1 Hz, 1H), 7.50 – 7.46 (m, 2H), 7.23 – 7.15 (m, 2H), 7.07 (dd, *J* = 7.7 Hz, 2H), 6.87 (d, *J* = 7.3 Hz, 2H), 6.54 (d, *J* = 8.7 Hz, 2H), 6.37 (d, *J* = 8.7 Hz, 2H), 3.76 (s, 3H). ¹³C NMR (101 MHz, CDCl₃) δ 158.3, 153.9, 153.5, 142.2, 141.9, 140.6, 137.7, 137.4, 132.7, 130.9, 130.0, 129.8, 129.1, 128.8, 128.1, 127.6, 127.5, 113.4, 55.3. MS (EI, 70 eV) m/z (%): 103 (18), 323 (32), 338 (100) [M]⁺.

2-(3'-Nitro-[1,1'-biphenyl]-2-yl)-3-phenylpyrazine (7): Following general Procedure **A** using 2,3-diphenylpyrazine (348 mg, 1.5 mmol) and 1-bromo-3-nitrobenzene (202 mg, 1 mmol), the residue was purified by flash chromatography on silica gel (Heptane-EtOAc, 90-10) to afford the desired compound **7** (141 mg, 40%) as a pale brown solid (Mp = 127-129 °C): ¹H NMR (400 MHz, CDCl₃) δ 8.67 (d, *J* = 2.2 Hz, 1H), 8.58 (d, *J* = 2.2 Hz, 1H), 7.97 (d, *J* = 7.3 Hz, 1H), 7.84 (d, *J* = 7.4 Hz, 1H), 7.64 (t, *J* = 7.3 Hz, 1H), 7.54 (t, *J* = 7.3 Hz, 1H), 7.24 – 7.17 (m, 3H), 7.13 (t, *J* = 7.9 Hz, 1H), 7.03 (dd, *J* = 7.7 Hz, 2H), 6.76 (dd, *J* = 12.4, 7.7 Hz, 3H). ¹³C NMR (101 MHz, CDCl₃) δ 153.1, 152.6, 148.1, 142.9, 142.4, 141.8, 138.4, 137.8, 137.1, 134.7, 131.5, 129.7, 129.2, 128.8, 128.4, 127.8, 123.8, 121.3. MS (EI, 70 eV) m/z (%): 103 (100), 306 (55), 353 (95) [M]⁺.

2-(3',5'-Bis(trifluoromethyl)-[1,1'-biphenyl]-2-yl)-3-phenylpyrazine (8): Following general Procedure **A** using 2,3-diphenylpyrazine (348 mg, 1.5 mmol) and 1-bromo-3,5-bis(trifluoromethyl)benzene (293 mg, 1 mmol), the residue was purified by flash chromatography on aluminium oxide (Heptane-EtOAc, 85-15) to afford the desired compound **8** (329 mg, 74%) as a pale white solid (Mp = 144-146 °C): ¹H NMR (300 MHz, CDCl₃) δ 8.69 (t, *J* = 3.8 Hz, 1H), 8.61 (d, *J* = 2.4 Hz, 1H), 7.89 (dd, *J* = 7.6, 1.3 Hz, 1H), 7.68 (td, *J* = 7.6, 1.3 Hz, 1H), 7.62 (s, 1H), 7.56 (td, *J* = 7.6, 1.4 Hz, 1H), 7.22 (ddd, *J* = 7.4, 3.7, 1.3 Hz, 2H), 7.05 (dd, *J* = 10.7, 4.8 Hz, 2H), 6.84 (s, 2H), 6.77 (dd, *J* = 8.3, 1.3 Hz, 2H). ¹³C NMR (101 MHz, CDCl₃) δ 153.1, 152.3, 142.9, 142.3, 141.9, 138.0, 137.7, 137.0, 131.9 (q, *J* = 33.1 Hz), 131.6, 129.7, 129.5, 129.4, 128.8 (m), 128.7, 128.6, 128.0, 122.9 (q, *J* = 276.2 Hz), 120.2 (m). MS (EI, 70 eV) m/z (%): 103 (55), 231 (38), 444 (100) [M]⁺.

2'-(3-Phenylpyrazin-2-yl)-[1,1'-biphenyl]-2-carbonitrile (9): Following general Procedure **A** using 2,3-diphenylpyrazine (348 mg, 1.5 mmol) and 2-bromobenzonitrile (182 mg, 1 mmol), the residue was

purified by flash chromatography on silica gel (Heptane-EtOAc, 75-25) to afford the desired compound **9** (200 mg, 60%) as a white solid (Mp = 200-202 °C): ¹H NMR (300 MHz, CDCl₃) δ 8.65 (d, *J* = 2.4 Hz, 1H), 8.56 (d, *J* = 2.4 Hz, 1H), 7.88 (dd, *J* = 7.6, 1.3 Hz, 1H), 7.66 (td, *J* = 7.6, 1.4 Hz, 1H), 7.57 (td, *J* = 7.6, 1.4 Hz, 1H), 7.41 (dd, *J* = 7.5, 1.3 Hz, 2H), 7.36 – 7.29 (m, 1H), 7.24 (dd, *J* = 7.5, 1.5 Hz, 1H), 7.21 – 7.19 (m, 1H), 7.19 – 7.16 (m, 1H), 7.15 (dd, *J* = 3.1, 1.7 Hz, 1H), 6.96 – 6.90 (m, 2H), 6.50 (dd, *J* = 6.7, 1.1 Hz, 1H). ¹³C NMR (101 MHz, CDCl₃) δ 153.2, 152.3, 143.2, 142.5, 142.0, 138.4, 137.4, 136.6, 133.4, 131.6, 131.3, 130.9, 130.5, 129.5, 129.1, 129.1, 128.7, 128.4, 127.0, 117.7, 112.3. MS (EI, 70 eV) *m/z* (%): 103 (48), 231 (30) 333 (100) [M]⁺.

2-Phenyl-3-(2-(pyridin-3-yl)phenyl)pyrazine (10): Following general Procedure **B** using 2,3-diphenylpyrazine (348 mg, 1.5 mmol) and 3-bromopyridine (158 mg, 1 mmol), the residue was purified by flash chromatography on silica gel (EtOAc 100%) to afford the desired compound **10** (210 mg, 68%) as a yellow oil : ¹H NMR (400 MHz, CDCl₃) δ 8.66 (d, *J* = 2.4 Hz, 1H), 8.60 (d, *J* = 2.4 Hz, 1H), 8.36 (dd, *J* = 4.8, 1.3 Hz, 1H), 7.81 (dd, *J* = 7.7, 1.1 Hz, 1H), 7.68 (d, *J* = 1.8 Hz, 1H), 7.62 (td, *J* = 7.6, 1.3 Hz, 1H), 7.53 (td, *J* = 7.6, 1.4 Hz, 1H), 7.24 (t, *J* = 7.4 Hz, 1H), 7.19 (dd, *J* = 7.6, 1.0 Hz, 1H), 7.09 (dd, *J* = 10.6, 4.9 Hz, 2H), 6.93 (dd, *J* = 7.4, 4.8 Hz, 1H), 6.82 (dd, *J* = 8.3, 1.1 Hz, 2H), 6.76 – 6.72 (m, 1H). ¹³C NMR (101 MHz, CDCl₃) δ 153.2, 152.8, 149.4, 147.5, 142.8, 142.2, 137.9, 137.4, 137.4, 135.7, 131.4, 129.9, 129.5, 128.8, 128.5, 127.9, 122.6. MS (EI, 70 eV) *m/z* (%): 103 (22), 205 (43) 309 (100) [M]⁺.

3-(2-(3-Phenylpyrazin-2-yl)phenyl)-quinoline (11): Following general Procedure **B** using 2,3-diphenylpyrazine (348 mg, 1.5 mmol) and 3-bromoquinoline (208 mg, 1 mmol), the residue was purified by flash chromatography on aluminium oxide (Heptane-EtOAc, 80-20) to afford the desired compound **11** (259 mg, 72%) as a yellow oil : ¹H NMR (400 MHz, CDCl₃) δ 8.68 (d, *J* = 2.4 Hz, 1H), 8.57 (d, *J* = 2.4 Hz, 1H), 8.02 – 7.98 (m, 2H), 7.86 (dd, *J* = 7.6, 1.0 Hz, 1H), 7.71 – 7.61 (m, 2H), 7.57 (td, *J* = 7.6, 1.3 Hz, 1H), 7.48 (d, *J* = 5.5 Hz, 2H), 7.29 (d, *J* = 6.2 Hz, 1H), 7.20 (t, *J* = 7.4 Hz, 1H), 7.16 (d, *J* = 1.9 Hz, 1H), 6.95 (dd, *J* = 7.8 Hz, 2H), 6.64 (d, *J* = 7.2 Hz, 2H). ¹³C NMR (101 MHz, CDCl₃) δ 153.2, 152.8, 150.5, 146.4, 142.9, 142.3, 138.0, 137.5, 135.1, 133.3, 131.5, 130.2, 129.6, 129.4, 129.0, 128.8, 128.7, 128.5, 127.8, 127.6, 126.6. MS (EI, 70 eV) *m/z* (%): 103 (14), 255 (43) 359 (100) [M]⁺.

2'-(Pyrazin-2-yl)-[1,1'-biphenyl]-4-carbonitrile (12): Following general Procedure **B** using 2-phenylpyrazine (234 mg, 1.5 mmol) and 4-bromobenzonitrile (182 mg, 1 mmol), the residue was purified by flash chromatography on aluminium oxide (Heptane-EtOAc, 90-10) to afford the desired compound **12** (182 mg, 71%) as a pale yellow solid (Mp = 142-144 °C): ¹H NMR (400 MHz, CDCl₃) δ 8.54 (s, 1H), 8.41 (d, *J* = 2.3 Hz, 1H), 8.24 (s, 1H), 7.71 (dd, *J* = 5.6, 3.4 Hz, 1H), 7.60 – 7.52 (m, 4H), 7.45 (dd, *J* = 5.6, 3.4 Hz, 1H), 7.24 (d, *J* = 8.2 Hz, 2H). ¹³C NMR (101 MHz, CDCl₃) δ 154.5, 145.9, 145.7, 144.2, 142.5, 139.3, 136.1, 132.2, 131.0, 130.6, 130.4, 129.8, 129.1, 118.7, 111.1. MS (EI, 70 eV) *m/z* (%): 257 (100) [M]⁺.

2'-(3,5'-Bis(trifluoromethyl)-[1,1'-biphenyl]-2-yl)pyrazine (13): Following general Procedure **B** using 2-phenylpyrazine (234 mg, 1.5 mmol) and 1-bromo-3,5-bis(trifluoromethyl)benzene (293 mg, 1 mmol), the residue was purified by flash chromatography on aluminium oxide (Heptane-EtOAc, 90-10) to afford the desired compound **13** (261 mg, 71%) as a pale white solid (Mp = 134-136 °C): ¹H NMR (400 MHz, CDCl₃) δ 8.53 (dd, *J* = 2.4, 1.6 Hz, 1H), 8.43 (d, *J* = 2.5 Hz, 1H), 8.30 (d, *J* = 1.3 Hz, 1H), 7.76 (s, 1H), 7.74 – 7.69 (m, 1H), 7.63 – 7.57 (m, 4H), 7.54 – 7.49 (m, 1H). ¹³C NMR (101 MHz, CDCl₃) δ 154.3, 145.7, 144.1, 142.9, 142.7, 138.2, 136.4, 131.7 (q, *J* = 33.4 Hz), 131.0, 130.7, 130.0, 129.91 (q, *J* = 2.7 Hz), 129.4, 123.2 (q, *J* = 272.8 Hz), 120.9 (m). MS (EI, 70 eV) *m/z* (%): 347 (85), 368 (100) [M]⁺.

3-(2-(Pyrazin-2-yl)phenyl)quinoline (14): Following general Procedure **B** using 2-phenylpyrazine (234 mg, 1.5 mmol) and 3-bromoquinoline (208 mg, 1 mmol), the residue was purified by flash chromatography on aluminium oxide (Heptane-EtOAc, 80-20) to afford the desired compound **14** (226 mg, 80%) as a white solid (Mp = 136-138 °C): ¹H NMR (400 MHz, CDCl₃) δ 8.58 (d, *J* = 2.0 Hz, 1H), 8.51 (s, 1H), 8.36 (d, *J* = 2.4 Hz, 1H), 8.31 (d, *J* = 0.9 Hz, 1H), 8.05 (d, *J* = 7.8 Hz, 2H), 7.79 – 7.73 (m, 2H), 7.69 (t, *J* = 7.6 Hz, 1H), 7.62 – 7.57 (m, 3H), 7.53 (t, *J* = 7.5 Hz, 1H). ¹³C NMR (101 MHz, CDCl₃) δ 154.6, 151.5, 146.9, 145.9, 144.3, 142.6, 137.5, 136.5, 135.8, 133.9, 131.4, 131.0, 129.9, 129.7, 129.4, 128.9, 127.9, 127.8, 127.1. MS (EI, 70 eV) *m/z* (%): 229 (28), 255 (60), 283 (100) [M]⁺.

2'-(3-Methylpyrazin-2-yl)-[1,1'-biphenyl]-4-carbonitrile (15): Following general Procedure **A** using 2-methyl-3-phenylpyrazine (255 mg, 1.5 mmol) and 4-bromobenzonitrile (182 mg, 1 mmol), the residue was purified by flash chromatography on aluminium oxide (Heptane-EtOAc, 90-10) to afford the desired compound **15** (204 mg, 75%) as a yellow solid (Mp = 136-138 °C): ¹H NMR (400 MHz, CDCl₃) δ 8.43 (d, *J* = 2.2 Hz, 1H), 8.39 (d, *J* = 2.5 Hz, 1H), 7.58 – 7.54 (m, 2H), 7.49 (d, *J* = 8.4 Hz, 2H), 7.47 – 7.44 (m, 2H), 7.18 (d, *J* = 8.4 Hz, 2H), 2.08 (s, 3H). ¹³C NMR (101 MHz, CDCl₃) δ 154.2, 152.4, 145.4, 142.9, 141.5, 139.2, 137.5, 132.0, 130.3, 130.0, 129.9, 129.5, 128.9, 118.7, 111.0, 22.1. MS (EI, 70 eV) *m/z* (%): 81 (70), 256 (55), 271 (100) [M]⁺.

Ethyl 2'-(3-methylpyrazin-2-yl)-[1,1'-biphenyl]-4-carboxylate (16): Following general Procedure **A** using 2-methyl-3-phenylpyrazine (255 mg, 1.5 mmol) and ethyl 4-bromobenzoate (229 mg, 1 mmol), the residue was purified by flash chromatography on aluminium oxide (Heptane-EtOAc, 90-10) to afford the desired compound **16** (228 mg, 75%) as a yellow solid (Mp = 90-92 °C): ¹H NMR (400 MHz, CDCl₃) δ 8.44 (d, *J* = 2.3 Hz, 1H), 8.36 (d, *J* = 2.5 Hz, 1H), 7.87 (d, *J* = 8.4 Hz, 2H), 7.59 – 7.49 (m, 3H), 7.44 (dd, *J* = 8, 1.6 Hz, 1H), 7.13 (d, *J* = 8.4 Hz, 2H), 4.34 (q, *J* = 7.1 Hz, 2H), 2.03 (s, 3H), 1.36 (t, *J* = 7.1 Hz, 3H). ¹³C NMR (101 MHz, CDCl₃) δ 166.4, 154.7, 152.5, 145.2, 142.6, 141.4, 140.1, 137.6, 130.2, 130.0, 129.5, 129.4, 129.3, 129.2, 128.4, 61.1, 22.1, 14.4. MS (EI, 70 eV) *m/z* (%): 81 (35), 289 (52), 318 (100) [M]⁺.

2-Methyl-3-(4'-nitro-[1,1'-biphenyl]-2-yl)pyrazine (17): Following general Procedure **A** using 2-methyl-3-phenylpyrazine (255 mg, 1.5 mmol) and 1-bromo-4-nitrobenzene (202 mg, 1 mmol), the residue was purified by flash chromatography on aluminium oxide (Heptane-EtOAc, 90-10) to afford the desired compound **17** (207 mg, 71%) as a brown solid (Mp = 96-98 °C): ¹H NMR (400 MHz, CDCl₃) δ 8.43 (d, *J* = 2.2 Hz, 1H), 8.40 (d, *J* = 2.4 Hz, 1H), 8.06 (d, *J* = 8.8 Hz, 2H), 7.60 – 7.55 (m, 2H), 7.53 – 7.45 (m, 2H), 7.24 (d, *J* = 8.8 Hz, 2H), 2.10 (s, 3H). ¹³C NMR (101 MHz, CDCl₃) δ 154.2, 152.4, 147.4, 146.9, 142.9, 141.5, 138.9, 137.6, 130.4, 130.2, 130.0, 129.5, 129.1, 123.5, 22.2. MS (EI, 70 eV) *m/z* (%): 81 (70), 244 (40), 291 (100) [M]⁺.

2-(4'-Methoxy-[1,1'-biphenyl]-2-yl)-3-methylpyrazine (18): Following general Procedure **B** using 2-methyl-3-phenylpyrazine (255 mg, 1.5 mmol) and 1-bromo-4-methoxybenzene (187 mg, 1 mmol), the residue was purified by flash chromatography on aluminium oxide (Heptane-EtOAc, 90-10) to afford the desired compound **18** (190 mg, 69%) as a yellow oil: ¹H NMR (400 MHz, CDCl₃) δ 8.45 (d, *J* = 2.2 Hz, 1H), 8.35 (d, *J* = 2.5 Hz, 1H), 7.57 – 7.34 (m, 4H), 6.97 (d, *J* = 8.8 Hz, 2H), 6.72 (d, *J* = 8.8 Hz, 2H), 3.74 (s, 3H), 2.00 (s, 3H). ¹³C NMR (101 MHz, CDCl₃) δ 158.9, 155.4, 152.7, 142.3, 141.3, 140.7, 137.5, 133.0, 130.4, 130.0, 129.9, 129.2, 127.3, 113.8, 55.2, 22.0. MS (EI, 70 eV) *m/z* (%): 143 (55), 261 (100), 276 (90) [M]⁺.

2-(4'-(Tert-butyl)-[1,1'-biphenyl]-2-yl)-3-methylpyrazine (19): Following general Procedure **B** using 2-methyl-3-phenylpyrazine (255 mg, 1.5 mmol) and 1-*tert*-butyl-4-bromobenzene (213 mg, 1 mmol), the residue was purified by flash chromatography on aluminium oxide (Heptane-EtOAc, 90-10) to afford the desired compound **19** (224 mg, 74%) as a brown oil: ^1H NMR (400 MHz, CDCl_3) δ 8.46 (d, $J = 2.3$ Hz, 1H), 8.36 (d, $J = 2.5$ Hz, 1H), 7.52 – 7.39 (m, 4H), 7.20 (d, $J = 8.4$ Hz, 2H), 6.99 (d, $J = 8.4$ Hz, 2H), 1.98 (s, 3H), 1.26 (s, 9H). ^{13}C NMR (101 MHz, CDCl_3) δ 155.4, 152.7, 150.1, 142.3, 141.3, 141.0, 137.6, 137.5, 130.1, 130.0, 129.2, 129.0, 127.4, 125.2, 34.5, 31.4, 22.0. MS (EI, 70 eV) m/z (%): 136 (18), 287 (100), 302 (58) $[\text{M}]^+$.

2-Methyl-3-(3'-(trifluoromethyl)-[1,1'-biphenyl]-2-yl)pyrazine (20): Following general Procedure **B** using 2-methyl-3-phenylpyrazine (255 mg, 1.5 mmol) and 1-bromo-3-(trifluoromethyl)benzene (225 mg, 1 mmol), the residue was purified by flash chromatography on aluminium oxide (Heptane-EtOAc, 90-10) to afford the desired compound **20** (191 mg, 61%) as a yellow oil: ^1H NMR (400 MHz, CDCl_3) δ 8.48 (d, $J = 2.1$ Hz, 1H), 8.39 (dd, $J = 7.2, 2.5$ Hz, 1H), 7.62 – 7.57 (m, 1H), 7.57 – 7.51 (m, 2H), 7.50 – 7.46 (m, 2H), 7.35 (d, $J = 7.1$ Hz, 2H), 7.31 (d, $J = 8.0$ Hz, 1H), 2.04 (s, 3H). ^{13}C NMR (101 MHz, CDCl_3) δ 154.5, 152.5, 142.7, 141.4, 141.4, 139.6, 137.7, 132.6, 130.8, 130.2, 130.0, 129.5, 128.8, 128.5, 126.7 (q, $J = 248.5$ Hz), 126.4 (q, $J = 3.8$ Hz), 123.91 (q, $J = 3.8$ Hz), 22.0. MS (EI, 70 eV) m/z (%): 81 (45), 279 (80) 314 (100) $[\text{M}]^+$.

2'-(3-Methylpyrazin-2-yl)-[1,1'-biphenyl]-2-carbonitrile (21): Following general Procedure **B** using 2-methyl-3-phenylpyrazine (255 mg, 1.5 mmol) and 2-bromobenzonitrile (182 mg, 1 mmol), the residue was purified by flash chromatography on aluminium oxide (Heptane-EtOAc, 90-10) to afford the desired compound **21** (166 mg, 61%) as a yellow oil: ^1H NMR (400 MHz, CDCl_3) δ 8.34 (d, $J = 3.2$ Hz, 2H), 7.64 (dd, $J = 7.4, 1.5$ Hz, 1H), 7.61 – 7.55 (m, 3H), 7.53 – 7.48 (m, 1H), 7.35 – 7.28 (m, 2H), 7.04 (dd, $J = 7.5, 1.3$ Hz, 1H), 2.26 (s, 3H). ^{13}C NMR (101 MHz, CDCl_3) δ 153.8, 152.9, 144.3, 142.6, 141.1, 137.9, 137.4, 133.3, 131.9, 131.7, 130.8, 130.2, 129.2, 129.1, 127.7, 118.3, 112.4, 22.3. MS (EI, 70 eV) m/z (%): 169 (55), 271 (100) $[\text{M}]^+$.

2-Methyl-3-(2'-methyl-[1,1'-biphenyl]-2-yl)pyrazine (22): Following general Procedure **B** using 2-methyl-3-phenylpyrazine (255 mg, 1.5 mmol) and 1-bromo-2-methylbenzene (171 mg, 1 mmol), the residue was purified by flash chromatography on aluminium oxide (Heptane-EtOAc, 85-15) to afford the desired compound **22** (109 mg, 42%) as a white solid (Mp = 138-140 °C): ^1H NMR (400 MHz, CDCl_3) δ 8.36 (d, $J = 2.0$ Hz, 1H), 8.30 (d, $J = 2.4$ Hz, 1H), 7.55 – 7.48 (m, 2H), 7.47 – 7.43 (m, 1H), 7.41 – 7.36 (m, 1H), 7.11 (d, $J = 4.2$ Hz, 2H), 6.98 (dd, $J = 10.1, 5.8$ Hz, 1H), 6.92 (d, $J = 7.5$ Hz, 1H), 2.20 (s, 3H), 2.16 (s, 3H). ^{13}C NMR (101 MHz, CDCl_3) δ 154.8, 152.5, 142.3, 141.0, 140.7, 139.8, 138.3, 135.9, 130.8, 130.6, 130.2, 129.8, 128.5, 127.5, 127.5, 125.1, 22.3, 20.4. MS (EI, 70 eV) m/z (%): 178 (38), 245 (100), 260 (60) $[\text{M}]^+$.

3-(2-(3-Methylpyrazin-2-yl)phenyl)quinoline (23): Following general Procedure **A** using 2-methyl-3-phenylpyrazine (255 mg, 1.5 mmol) and 3-bromoquinoline (208 mg, 1 mmol), the residue was purified by flash chromatography on aluminium oxide (Heptane-EtOAc, 70-30) to afford the desired compound **23** (208 mg, 70%) as a brown oil: ^1H NMR (400 MHz, CDCl_3) δ 8.65 (d, $J = 2.2$ Hz, 1H), 8.44 (d, $J = 2.3$ Hz, 1H), 8.36 (d, $J = 2.5$ Hz, 1H), 8.03 (d, $J = 8.6$ Hz, 1H), 7.90 (d, $J = 2.0$ Hz, 1H), 7.69 (dd, $J = 12.2, 4.3$ Hz, 2H), 7.63 – 7.55 (m, 3H), 7.52 (dd, $J = 10.4, 4.2$ Hz, 2H), 2.10 (s, 3H). ^{13}C NMR (101 MHz, CDCl_3) δ 154.4, 152.4, 151.1, 146.9, 143.0, 141.6, 138.0, 137.5, 135.8, 133.6, 130.6, 130.3, 129.8, 129.6, 129.3, 128.7, 128.0, 127.6, 127.1, 22.2. MS (EI, 70 eV) m/z (%): 229 (25), 282 (78), 297 (100) $[\text{M}]^+$.

2'-(3-Methoxypyrazin-2-yl)-[1,1'-biphenyl]-4-carbonitrile (24): Following general Procedure **B** using 2-methoxy-3-phenylpyrazine (279 mg, 1.5 mmol) and 4-bromobenzonitrile (182 mg, 1 mmol), the residue was purified by flash chromatography on aluminium oxide (Heptane-EtOAc, 90-10) to afford the desired compound **24** (213 mg, 74%) as a white solid (Mp = 132-134 °C): ¹H NMR (400 MHz, CDCl₃) δ 8.18 (d, *J* = 2.7 Hz, 1H), 8.03 (d, *J* = 2.7 Hz, 1H), 7.60 (dd, *J* = 5.8, 3.2 Hz, 1H), 7.56 – 7.53 (m, 2H), 7.51 (d, *J* = 8.4 Hz, 2H), 7.42 (dd, *J* = 5.7, 3.2 Hz, 1H), 7.19 (d, *J* = 8.4 Hz, 2H), 3.47 (s, 3H). ¹³C NMR (101 MHz, CDCl₃) δ 157.5, 146.5, 144.9, 140.2, 139.9, 136.4, 135.1, 131.8, 130.9, 129.5, 129.5, 128.8, 118.9, 110.7, 53.2. MS (EI, 70 eV) *m/z* (%): 190 (40), 258 (68), 287 (100) [M]⁺.

2'-(3-Methoxypyrazin-2-yl)-[1,1'-biphenyl]-3-carbaldehyde (25): Following general Procedure **A** using 2-methoxy-3-phenylpyrazine (279 mg 1.5 mmol) and 3-bromobenzaldehyde (185 mg, 1 mmol), the residue was purified by flash chromatography on aluminium oxide (Heptane-EtOAc, 90-10) to afford the desired compound **25** (191 mg, 66%) as a brown oil: ¹H NMR (400 MHz, CDCl₃) δ 9.90 (s, 1H), 8.19 (d, *J* = 2.7 Hz, 1H), 7.99 (d, *J* = 2.7 Hz, 1H), 7.73 (dd, *J* = 5.2, 3.6 Hz, 1H), 7.65 (s, 1H), 7.59 (dt, *J* = 7.2, 3.2 Hz, 1H), 7.56 – 7.52 (m, 2H), 7.50 – 7.46 (m, 1H), 7.36 (t, *J* = 7.5 Hz, 1H), 7.34 – 7.30 (m, 1H), 3.43 (s, 3H) ¹³C NMR (101 MHz, CDCl₃) δ 192.1, 157.5, 145.4, 142.7, 140.3, 140.0, 136.4, 136.3, 135.3, 134.7, 130.6, 130.4, 129.6, 129.5, 128.6, 128.4, 127.9, 53.2. MS (EI, 70 eV) *m/z* (%): 165 (28), 175 (40), 290 (100) [M]⁺.

2'-(3-Methoxypyrazin-2-yl)-[1,1'-biphenyl]-2-carbonitrile (26): Following general Procedure **A** using 2-methoxy-3-phenylpyrazine (279 mg, 1.5 mmol) and 2-bromobenzonitrile (182 mg, 1 mmol), the residue was purified by flash chromatography on aluminium oxide (Heptane-EtOAc, 90-10) to afford the desired compound **26** (201 mg, 70%) as a white solid (Mp = 120-122 °C): ¹H NMR (400 MHz, CDCl₃) δ 8.15 (d, *J* = 2.7 Hz, 1H), 7.97 (d, *J* = 2.7 Hz, 1H), 7.71 (d, *J* = 5.8 Hz, 1H), 7.65 (dd, *J* = 8.6, 3.6 Hz, 1H), 7.60 – 7.54 (m, 2H), 7.53 – 7.49 (m, 1H), 7.33 – 7.27 (m, 2H), 6.97 – 6.92 (m, 1H), 3.57 (s, 3H). ¹³C NMR (101 MHz, CDCl₃) δ 157.5, 145.2, 144.7, 140.0, 137.9, 136.2, 135.6, 133.1, 131.6, 130.8, 130.7, 130.1, 129.2, 129.1, 127.4, 118.5, 112.7, 53.2. MS (EI, 70 eV) *m/z* (%): 165 (28), 258 (40), 287 (100) [M]⁺.

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