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Palladium-Catalyzed Regioselective Direct Arylation of Benzofurazans at C4 Position

Imane Idris,^{a,b} Fazia Derridj,^{a,b} Jean-François Soulé,^a* and Henri Doucet^a*

^a Institut des Sciences Chimiques de Rennes, UMR 6226 CNRS-Université de Rennes 1 "Organometalliques, Materiaux et Catalyse", Campus de Beaulieu, 35042 Rennes, France. Fax: (+33)-(0)2-2323-6939, jean-framcois.soule@univ-rennes1.fr and henri.doucet@univ-rennes1.fr

^b Laboratoire de physique et chimie des Matériaux (LPCM), UMMTO University, BP 17 RP, 15000 Tizi-Ouzou, Algeria.

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Abstract. The palladium-catalyzed direct arylation of	Palladium-catalyzed one-pot C4,C7-diarylation of
benzofurazans with aryl bromides to access 4-	benzofurazane was also described using a larger amount of
arylbenzofurazans proceeds in moderate-to-high yields using	aryl bromide. Moreover, the derivatization of 4-
phosphine-free palladium acetate as the catalyst and	arylbenzofurazans into 4-arylquinaxolines is also reported.
potassium acetate as an inexpensive base. A wide variety of	
(hetero)aryl bromides, including bromopyridine and	Keywords: Benzofurazans; C–H activation; Catalysis;
bromothiophene derivatives has been successfully employed.	
	-

Introduction

Benzofurazan is an important unit, which found applications in materials sciences. Especially C4 or/and C7 (hetero)aryl benzofurazans are involved in the molecular design of photovoltaic materials (Figure 1).^[1] Some 4-arylbenzofurazans also displayed important biological activities such as I, which inhibits the PAS-B domain of the hypoxia 2α ;^[2] inducible factor the or benzo[c][1,2,5]oxadiazole-1-oxide **II**, which has been synthetized for its antimicrobial properties.^[3] Recently, electron donor-acceptor type organic semiconductors were designed based on 4heteroarylbenzofurazan (Th-BO-Th) for application as organo-photocatalysts (Figure 1).^[4]

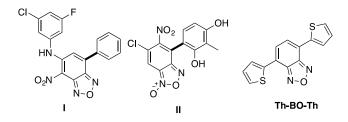
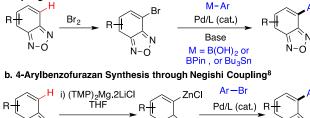
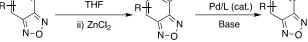


Figure 1. Examples of Useful Molecules Containing a 4-Arylbenzofurazan Unit.

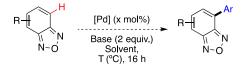
One of the most 4 common access to arylbenzofurazan derivatives through is а bromination of benzofurazan followed by palladium Suzuki^[5] or Stille^[6] cross-coupling catalyzed reactions (Scheme 1a). Oligomers have also been synthetized from 4,7-dibromofurazan and an organometallic reagent.^[7] Negishi reactions with an organozinc reagent prepared from benzofurazan through magnesiation а with bis(2.2.6.6tetramethylpiperidin-1-yl)magnesium-lithium chloride complex (TMP2Mg·2LiCl) followed by transmetalation with zinc chloride, have also been reported (Scheme 1b).^[8] Since the discovery by Nakamura^[9] and Otha^[10] of the Pd-catalyzed C-H bond arylation of heteroarenes using aryl halides, this technology has emerged as one of the most powerful method for the formation of C-C bonds for the access to a wide variety of arylated heterocycles as no prefunctionalization is required.^[11] However, examples of palladium-catalyzed non-directed C-H bond arylation of 6-membered rings remains scarce.^[12] Recent examples on the arylation of activated benzothiadiazole via C-H bond activation have been reported using palladium catalysis.^[13] To the best of our knowledge there is no example of direct arylation of benzofurazan in the literature, to date (Scheme 1c).

a. 4-Arylbenzofurazan Synthesis through Suzuki-Miyaura or Stille Couplings⁵⁻⁷





c. Palladium-Catalyzed Direct Arylation of Benzofurazan (this work)



Scheme 1. Previous Strategies Synthetize 4to Arylbenzofurazans.

As part of our continuing efforts concerning the functionalization of benzene rings fused to heterocycles via palladium-catalyzed C-H bond arylation, we recently reported an efficient protocol for the synthesis of benzothiazoles and benzoxazoles arylated at the C7 position.^[14] Based on these results, we examined the reactivity of benzofurazan in palladium-catalyzed direct arylation using aryl bromides as aryl source.

Results and Discussion

We began our investigations by fine-tuning the conditions using benzofurazan and 4bromobenzonitrile as model substrates in 1.5:1 ratio (Table 1). We were pleased to find that the reaction occurred regioselectively at the C4 position to afford 1 in good yields using 2 mol% of a diphosphinepalladium catalyst in the presence of KOAc as base in DMA at 150 °C or even at 120 °C (Table 1, entries 1 and 2). More interestingly, we found that the reaction is also operative using 2 mol% of phosphine-free $Pd(OAc)_2$ catalyst in a comparable yield (Table 1, entry 3). A lower catalyst loading of 1 mol% of $Pd(OAc)_2$ gave 1 in 85% yield; while partial conversion was obtained if only 0.5 mol% catalyst loading was used (Table 1, entries 4 and 5). Other inorganic bases, such as PivOK, K₂CO₃ or Cs₂CO₃ did not allow to improve the yield in 1 (Table 1, entries 6-8). When the reaction was performed using 1 mol% Pd(OAc)₂ at 120 °C, the C4-arylated benzofurazan 1 was obtained in 87% yield (Table 1, Under these conditions, the excess of entry 9). benzofurazan can be decreased up to 1.15 equivalents, as the desired product 1 was isolated in 89% yield (Table 1, entry 10). Then, we employed greener solvents than DMA such as cyclopentylmethyl ether, 1-pentanol or diethylcarbonate,^[15] but no reaction occurred (Table 1, entries 11-13). No reaction occurred when 4-chlorobenzonitrile was used as aryl

source (Table 1, entry 14). It should also be mentioned that using the optimized reaction conditions, benzothiadiazole was unreactive.

Table 1. Optimization of the Reaction Conditions

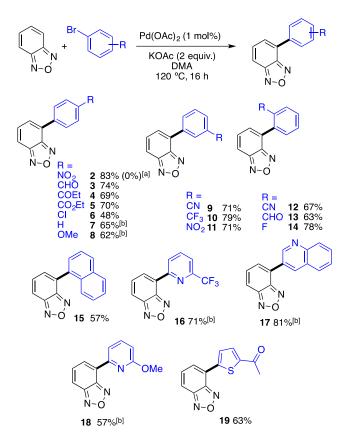
CN [Pd] (x mol%) Base (2 equiv.) N-Ò Solvent, 150 °C, 16 h (1.5 equiv.) Ó 1 Pd Solve Conv. Yield Entry Base $(\%)^{[a]}$ in **1** $(\%)^{[a]}$ (x mol%)nt PdCl(C₃H₅) 1 KOAc DMA 100 75 (dppb) (2) $PdCl(C_3H_5)$ $2^{[b]}$ 74 KOAc DMA 100 (dppb) (2) Pd(OAc)₂ 3 KOAc DMA 100 82 (2)Pd(OAc)₂ 4 KOAc DMA 100 85 (1)Pd(OAc)₂ DMA 79 5 KOAc 83 (0.5)Pd(OAc)₂ 6 **PivOK** DMA 80 53 (1)Pd(OAc)₂ 7 K₂CO₃ DMA 95 12 (1)Pd(OAc)₂ 8 Cs₂CO₃ DMA 67 0 (1)Pd(OAc)₂ **9**[b] KOAc DMA 100 87 (1)Pd(OAc)₂ 10^[b,c] KOAc DMA 100 89 (1)Pd(OAc)₂ CPM $11^{[b]}$ KOAc 0 0 E (1)Pd(OAc)₂ pentan- $12^{[b]}$ KOAc 0 0 (1)1-ol Pd(OAc)₂ 13^[b] KOAc DEC 0 0 (1)Pd(OAc)₂ 14^[d] DMA KOAc 0 0 (1)

[a] Determined by GC-MS analysis using dodecane as internal standard. [b] Reaction performed at 120 °C. [c] Reaction performed using 1.15 equiv. of benzofurazan. [d] 4-Chlorobenzonitrile was used instead of 4-bromobenzonitrile. DMA = Dimethylacetamide; CPME = Cyclopentylmethyl ether; DEC = Diethylcarbonate

With the best conditions in hands, namely 1 mol% phosphine-free Pd(OAc)₂ associated to KOAc as base in DMA at 120 °C, we turned our attention to the scope of the reaction (Scheme 2). First, we examined the reactivity of *para*-substituted aryl bromides. The coupling of benzofurazan with 4-bromonitrobenzene, 4-bromobenzaldehyde, 4-bromopropiophenone, and ethyl 4-bromobenzoate proceeded nicely to afford 2-5 in 69–83% yields. A moderate yield in the desired 4-aryl benzofurazan 6 was obtained from the less electron-deficient 4-bromochlorobenzene owing a partial conversion of this aryl bromide. For bromobenzene and electron-rich 4-bromoanisole, as their oxidative addition to palladium is more challenging,^[16] the reactions were conducted at a more elevated temperature of 150 °C to afford the

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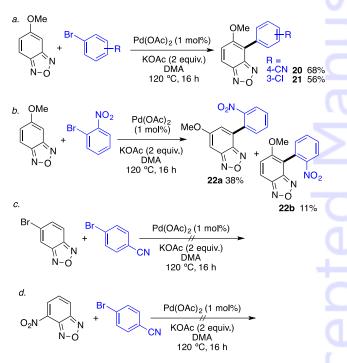
desired products 7 and 8 in 65% and 62% yields, respectively. It should be noted that no additional phosphine ligand is required to perform such couplings. The electron-deficient meta-substituted arvl bromides 3-bromobenzonitrile, 3-(trifluoromethyl)bromobenzene 3and bromonitrobenzene were also very reactive using 1 mol% Pd(OAc)₂ as the catalyst at 120 °C and afforded 9-11 in yields of 71-79%. Then, we investigated the effect of an ortho substituent on the aryl bromide. 2-Nitrile-, 2-formyl-, and 2-fluorobromobenzenes allowed the formation of the desired 4-arylated benzofurazans 12-14 in good yields. Under the standard reaction conditions, more sterically demanding 1-bromonaphthalene was also efficiently coupled with benzofurazan to deliver 15 in 57% yield. N-containing heteroaryl bromides (e.g., 2-bromo-6-(trifluoromethyl)pyridine, 2-bromo-6-methoxypyridine) bromoquinoline, or nicely reacted in the presence of 1 mol% $Pd(OAc)_2$ at 150 °C to afford the desired products 16-18 in good yields. In addition, this methodology allowed the synthesis 4-thiophen-2-ylfurazan 19, which is a useful intermediate in the design of organic materials, in 63% yield.



Scheme 2. Scope of Aryl Bromides in Palladium-Catalyzed Direct C4 Arylation of Benzofurazan. [a] 4-Chloronitrobenzene was used instead of 4-bromonitrobenzene. [b] Reaction performed at 150 °C.

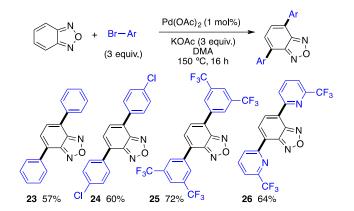
Next, we investigated the reactivity of 4- and 5substituted benzofurazans (Scheme 3). Benzofurazan

substituted by an electron-donating group such as a methoxy at C5 position underwent Pd(OAc)₂catalyzed direct arylation. The reaction was completely regioselective with 4-bromobenzonitrile or 3-chlorobromobenzene and the arylation took place exclusively at the C4 position to afford products 20 and 21 in 68% and 56% yields, respectively (Scheme 3a). Conversely, the reaction was not regioselective using 2-bromonitrobenzene, probably because of its greater steric hindrance. The major regioisomer 22a was isolated in 38% yield and resulted from the C-H bond activation at the less sterically hindered C7 position of the benzofurazan (Scheme 1b); whereas, the C4-arylation regioisomer 22b was formed in less than 11% yield, making its In contrast, benzofurazans isolation difficult. substituted by an electron-withdrawing group such as 5-bromobenzofurazan or 4-nitrobenzofurazan were not reactive under our reaction conditions, even at 150 °C or in the presence of $PdCl(C_3H_5)(dppb)$ catalyst (Scheme 3c and 3d).



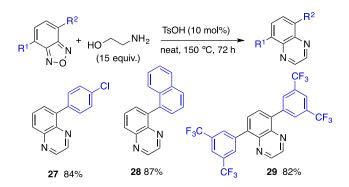
Scheme 3. Reactivities of Substituted Benzofurazans in Palladium-Catalyzed Direct Arylation.

Using the same reaction conditions, but in the presence of an excess amount of aryl bromides and base (3 equivalents), benzofurazan has been diarylated at both C4 and C7 carbons in one pot (Scheme From 4). bromobenzene, 4chlorobromobenzene and 3.5bis(trifluoromethyl)bromobenzene the diarylated products 23-26 were isolated in a range of yield of 57–72%. Again, it is important to note that this procedure did not required the use of a phosphine ligand.



Scheme 4. Scope of Palladium-Catalyzed C4,C7 Diarylation of Benzofurazan

It is known that furazan unit of benzofurazans can easily undergo a ring opening in the presence of ethanolamines under acidic conditions to yield quinoxaline derivatives.^[17] Quinoxaline is an important motif, which is present in many pharmaceuticals.^[18] Therefore, we investigated the synthesis of some quinoxalines from arylated benzofurazans. Using the Samsonov conditions,^[17] namely, 10 mol% para-toluenesulfonic acid in the presence 1-aminoethanol, of the arylated benzofurazans 6, 15 and 25 were converted into 5aryl quinoxalines 27-29 in 82-87% yields.



Scheme 5. Synthesis of 5-Arylated cc from Arylated Benzofurazans

Conclusion

In summary, we disclose here an elegant route to access 4-arylated benzofurazans from commercially available benzofurazan through palladium-catalyzed regioselective C–H bond arylation. Our phosphine-free procedure using Pd(OAc)₂ catalyst, KOAc as inexpensive base in the presence of aryl bromides as coupling partners promotes the C4 arylation or the C4,C7-diarylation of benzofurazan depending of the aryl bromide stoichiometry. A wide range of functions such as methoxy, fluoro, formyl, propionyl, carboxylate, nitrile or nitro on the aryl bromide is tolerated. Some sterically hindered aryl bromides,

and sulfur or nitrogen containing heteroaromatic substrates have also been employed successfully. In addition, some of these 4-arylated benzofurazans were successfully transformed into quinoxaline derivatives.

Experimental Section

General Methods: All reactions were carried out under argon atmosphere with standard Schlenk techniques. DMA was purchased from Acros Organics and were not purified before use. Benzofurazans were purchased from Sigma-Aldrich. ¹H NMR spectra were recorded on Bruker GPX (400 MHz) spectrometer. 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). ¹³C NMR spectra were recorded at 100 MHz on the same spectrometer and reported in ppm. All reagents were weighed and handled in air.

Procedure A (Palladium-catalyzed direct C4 arylation): To a 5 mL oven dried Schlenk tube, benzofurazan derivative (1.15 mmol), aryl bromide (1 mmol), AcOK (196 mg, 2 mmol), DMA (4 mL) and Pd(OAc)₂ (2.2 mg, 0.01 mmol, 2 mol%) were successively added. The reaction mixture was evacuated by vacuum-argon cycles (5 times) and stirred at 120-150 °C (oil bath temperature) for 16 hours (see tables and schemes). After cooling the reaction at room temperature and concentration, the crude mixture was purified by silica column chromatography to afford the desired arylated products.

4-(Benzo[c][1,2,5]oxadiazol-4-yl)benzonitrile (1): general procedure A using Following the 4bromobenzonitrile (182 mg, 1 mmol) and benzofurazan (138 mg, 1.15 mmol), the residue was purified by flash chromatography on silica gel (pentane-CH₂Cl₂, 60-40) to afford the desired compound 1 (197 mg, 89%) as a white solid (Mp = 180-184 °C). ¹H NMR (400 MHz, CDCl₃) δ (ppm) 8.13 (d, J = 8.5 Hz, 2H), 7.91 (d, J = 8.9 Hz, 1H), 7.82 (d, J = 8.5 Hz, 2H), 7.66 (d, J = 7.0 Hz, 1H), 7.56 (dd, J = 7.0, 9.0 Hz, 1H).¹³C NMR (100 MHz, CDCl₃) δ (ppm) 149.7, 148.1, 139.4, 132.7, 131.6, 129.3, 128.9, 128.4, 118.5, 116.8, 112.8.Elemental analysis: calcd (%) for C₁₃H₇N₃O (221.22): C 70.58, H 3.19; found: C 70.85, H 3.46.

4-(4-Nitrophenyl)benzo[c][1,2,5]oxadiazole (2): Following the general procedure **A** using 4bromonitrobenzene (202 mg, 1 mmol) and benzofurazan (138 mg, 1.15 mmol), the residue was purified by flash chromatography on silica gel (pentane-EtOAc, 90-10) to afford the desired compound **2** (200 mg, 83%) as a yellow solid (MP = 198-202 °C). ¹H NMR (400 MHz, CDCl₃) δ (ppm) 8.42 (d, *J* = 8.9 Hz, 2H), 8.23 (d, *J* = 8.9 Hz, 2H), 7.96 (d, *J* = 9.0 Hz, 1H), 7.73 (d, *J* = 6.8 Hz, 1H), 7.60 (dd, *J* = 6.8, 9.0 Hz, 1H).

¹³C NMR (100 MHz, CDCl₃) δ (ppm) 149.7, 148.2, 148.1, 141.2, 131.5, 129.7, 129.2, 128.1, 124.2, 117.1.Elemental analysis: calcd (%) for $C_{12}H_7N_3O_3$ (241.21): C 59.75, H 2.93; found: C 59.81, H 3.19.

4-(Benzo[c][1,2,5]oxadiazol-4-yl)benzaldehyde (3): procedure A using Following the general 4bromobenzaldehyde (185 mg, 1 mmol) and benzofurazan (138 mg, 1.15 mmol), the residue was purified by flash chromatography on silica gel (pentane-Et₂O, 70-30) to afford the desired compound 3 (166 mg, 74%) as a pale yellow solid (MP = 128-130 °C). ¹H NMR (400 MHz, CDCl₃) δ (ppm) 10.14 (s, 1H), 8.22 (d, J = 8.4 Hz, 2H), 8.07 (d, J = 8.4 Hz, 2H), 7.93 (d, J = 9.0 Hz, 1H), 7.72 (d, J = 6.8 Hz, 1H), 7.58 (dd, J = 6.8, 9.0 Hz, 1H).¹³C NMR (100 MHz, CDCl₃) δ (ppm) 191.6, 149.8, 148.3, 140.9, 136.5, 131.6, 130.2, 129.3, 129.1, 129.0, 116.5.Elemental analysis: calcd (%) for C13H8N2O2 (224.21): C 69.64, H 3.60: found: C 69.52, H 3.75.

1-(4-(Benzo[c][1,2,5]oxadiazol-4-

yl)phenyl)propan-1-one (4): Following the general procedure **A** using 4-bromopropiophenone (213 mg, 1 mmol) and benzofurazan (138 mg, 1.15 mmol), the residue was purified by flash chromatography on silica gel (pentane-CH₂Cl₂, 50-50) to afford the desired compound **4** (174 mg, 69%) as a white solid (MP = 161-165 °C). ¹H NMR (400 MHz, CDCl₃) δ (ppm) 8.14 (s, 4H), 7.90 (d, *J* = 9.0 Hz, 1H), 7.69 (d, *J* = 6.8 Hz, 1H), 7.57 (dd, *J* = 6.8, 9.0 Hz, 1H), 3.09 (q, *J* = 7.3 Hz, 2H), 1.29 (t, *J* = 7.2 Hz, 3H).¹³C NMR (100 MHz, CDCl₃) δ (ppm) 200.2, 149.8, 148.4, 139.3, 137.1, 131.6, 129.3, 128.9, 128.6, 128.5, 116.1, 32.0, 8.2.Elemental analysis: calcd (%) for C₁₅H₁₂N₂O₂ (252.27): C 71.42, H 4.79; found: C 71.56, H 3.81.

Ethyl 4-(benzo[*c***][1,2,5]oxadiazol-4-yl)benzoate (5):** Following the general procedure **A** using ethyl 4bromobenzoate (229 mg, 1 mmol) and benzofurazan (138 mg, 1.15 mmol), the residue was purified by flash chromatography on silica gel (pentane-CH₂Cl₂, 40-60) to afford the desired compound **5** (188 mg, 70%) as an orange solid (MP = 105-108 °C). ¹H NMR (400 MHz, CDCl₃) δ (ppm) 8.22 (d, *J* = 8.2 Hz, 2H), 8.11 (d, *J* = 8.2 Hz, 2H), 7.89 (d, *J* = 9.0 Hz, 1H), 7.68 (d, *J* = 6.8 Hz, 1H), 7.56 (dd, *J* = 6.8, 9.0 Hz, 1H), 4.45 (q, *J* = 7.1 Hz, 2H), 1.46 (t, *J* = 7.1 Hz, 3H).¹³C NMR (100 MHz, CDCl₃) δ (ppm) 166.1, 149.8, 148.4, 139.3, 131.6, 131.0, 130.1, 129.4, 128.9, 128.3, 116.0, 61.2, 14.4.

Elemental analysis: calcd (%) for C₁₅H₁₂N₂O₃ (268.27): C 67.16, H 4.51; found: C 66.98, H 4.79.

4-(4-Chlorophenyl)benzo[c][1,2,5]oxadiazole (6): Following the general procedure **A** using 1-bromo-4chlorobenzene (191 mg, 1 mmol) and benzofurazan (138 mg, 1.15 mmol), the residue was purified by flash chromatography on silica gel (pentane- CH₂Cl₂, 80-20) to afford the desired compound **6** (111 mg, 48%) as a yellow solid (MP = 95-97 °C). ¹H NMR (400 MHz, CDCl₃) δ (ppm) 7.98 (d, J = 8.5 Hz, 2H), 7.85 (d, J = 8.9 Hz, 1H), 7.59 (d, J = 6.8 Hz, 1H), 7.57 – 7.44 (m, 3H).¹³C NMR (100 MHz, CDCl₃) δ (ppm) 149.8, 148.4, 135.4, 133.6, 131.7, 129.6, 129.2, 129.2, 128.0, 115.5. Elemental analysis: calcd (%) for C₁₂H₇ClN₂O (230.65): C 62.49, H 3.06; found: C 62.53, H 3.00.

4-(Phenyl)benzo[c][1,2,5]oxadiazole (7): Following the general procedure **A** using bromobenzene (157 mg, 1 mmol) and benzofurazan (138 mg, 1.15 mmol), the residue was purified by flash chromatography on silica gel (pentane-toluene, 80-20) to afford the desired compound **7** (127 mg, 65%) as a yellow solid (MP = 58-60 °C). ¹H NMR (400 MHz, CDCl₃) δ (ppm) 8.04 – 7.98 (m, 2H), 7.87 – 7.80 (m, 1H), 7.60 (td, *J* = 1.0, 6.8 Hz, 1H), 7.57 –

7.46 (m, 4H).¹³C NMR (100 MHz, CDCl₃) δ (ppm) 149.8, 148.6, 135.3, 131.8, 130.5, 129.3, 129.0, 128.4, 128.0, 115.0. Elemental analysis: calcd (%) for C₁₂H₈N₂O (196.21): C 73.46, H 4.11; found: C 73.69, H 3.90.

4-(4-methoxyphenyl)benzo[c][1,2,5]oxadiazole (8): Following the general procedure **A** using 4-bromoanisole (187 mg, 1 mmol) and benzofurazan (138 mg, 1.15 mmol), the residue was purified by flash chromatography on silica gel (pentane-toluene, 80-20) to afford the desired compound **8** (140 mg, 62%) as an orange solid (MP = 118-121 °C). ¹H NMR (400 MHz, CDCl₃) δ (ppm) 8.00 (d, J = 8.8 Hz, 2H), 7.77 (dd, J = 1.3, 8.5 Hz, 1H), 7.58 – 7.47 (m, 2H), 7.08 (d, J = 8.8 Hz, 2H), 3.92 (s, 3H).¹³C NMR (100 MHz, CDCl₃) δ (ppm) 160.5, 149.9, 148.7, 131.9, 130.1, 129.7, 127.7, 126.7, 114.4, 114.1, 55.4. This is a known compound and the spectral data are identical to those reported in literature.^[5a]

3-(Benzo[c][1,2,5]oxadiazol-4-yl)benzonitrile (9): Following the general procedure Α using 3bromobenzonitrile (182 mg, 1 mmol) and benzofurazan (138 mg, 1.15 mmol), the residue was purified by flash chromatography on silica gel (pentane-toluene, 80-20) to afford the desired compound 9 (157 mg, 71%) as a yellow solid (MP = 156-159 °C). ¹H NMR (400 MHz, CDCl₃) δ (ppm) $\delta 8.34 - 8.24$ (m, 2H), 7.92 (d, J = 8.9 Hz, 1H), 7.78 (dt, J = 1.4, 7.7 Hz, 1H), 7.69 (d, J = 7.8 Hz, 1H), 7.67 -7.63 (m, 1H), 7.58 (dd, J = 6.8, 8.9 Hz, 1H). ¹³C NMR (100 MHz, CDCl₃) δ (ppm) 149.7, 148.2, 136.4, 132.6, 132.5, 131.8, 131.6, 129.9, 128.9, 128.1, 118.4, 116.5, 113.4. Elemental analysis: calcd (%) for C₁₃H₇N₃O (221.22): C 70.58, H 3.19; found: C 70.41, H 3.29.

4-(3-

(Trifluoromethyl)phenyl)benzo[c][1,2,5]oxadiazole

(10): Following the general procedure A using 1-bromo-3-(trifluoromethyl)benzene (225 mg, 1 mmol) and benzofurazan (138 mg, 1.15 mmol), the residue was purified by flash chromatography on silica gel (pentanetoluene, 90-10) to afford the desired compound **10** (209 mg, 79%) as pale yellow oil. ¹H NMR (400 MHz, CDCl₃) δ (ppm) 8.28 – 8.24 (m, 2H), 7.90 (d, *J* = 8.9 Hz, 1H), 7.77 – 7.73 (m, 1H), 7.70 (d, *J* = 7.9 Hz, 1H), 7.67 (d, *J* = 6.8 Hz, 1H), 7.57 (dd, *J* = 6.8, 9.0 Hz, 1H). ¹³C NMR (100 MHz, CDCl₃) δ (ppm) 149.7, 148.4, 135.9, 131.7, 131.6, 131.5 (q, *J* = 32.8 Hz), 129.5, 129.0, 128.7, 125.9 (q, *J* = 4.1 Hz),125.0 (q, *J* = 4.1 Hz), 123.9 (q, *J* = 272.4), 116.1. Elemental analysis: calcd (%) for C₁₃H₇F₃N₂O (264.21): C 59.10, H 2.67; found: C 59.33, H 2.51.

4-(3-Nitrophenyl)benzo[c][1,2,5]oxadiazole (11): general procedure A using Following the 3bromonitrobenzene (202 mg, 1 mmol) and benzofurazan (138 mg, 1.15 mmol), the residue was purified by flash chromatography on silica gel (pentane-EtOAc, 90-1510 to afford the desired compound 11 (171 mg, 71%) as a brown solid (MP = 150-153 °C). ¹H NMR (400 MHz, CDCl₃) δ (ppm) 8.86 (s, 1H), 8.45 (d, J = 7.5 Hz, 1H), 8.35 (d, J =7.9 Hz, 1H), 7.94 (d, J = 9.1 Hz, 1H), 7.81 – 7.68 (m, 2H), 7.64 - 7.53 (m, 1H). ¹³C NMR (100 MHz, CDCl₃) δ (ppm) 149.7, 148.8, 148.2, 136.7, 134.4, 131.6, 130.1, 129.1, 127.9, 123.8, 123.0, 116.7. Elemental analysis: calcd (%) for C₁₂H₇N₃O₃ (241.21): C 59.75, H 2.93; found: C 59.98, H 3.07.

2-(Benzo[c][1,2,5]oxadiazol-4-yl)benzonitrile (12): Following the general procedure **A** using 2bromobenzonitrile (182 mg, 1 mmol) and benzofurazan (138 mg, 1.15 mmol), the residue was purified by flash chromatography on silica gel (pentane-CH₂Cl₂, 60-40) to afford the desired compound **12** (148 mg, 67%) as a white solid (MP = 164-166 °C). ¹H NMR (400 MHz, CDCl₃) δ (ppm) 7.97 (d, *J* = 9.1 Hz, 1H), 7.93 (d, *J* = 7.8 Hz, 1H), 7.90 (d, *J* = 7.2 Hz, 1H), 7.79 (dt, *J* = 1.4, 7.7 Hz, 1H), 7.72 (d, *J* = 6.7 Hz, 1H), 7.65 – 7.57 (m, 2H). ¹³C NMR (100 MHz, CDCl₃) δ (ppm) 149.5, 148.6, 138.7, 134.1, 133.0, 131.7, 131.4, 131.1, 129.3, 126.9, 118.0, 117.0, 111.7. Elemental analysis: calcd (%) for C₁₃H₇N₃O (221.22): C 70.58, H 3.19; found: C 70.39, H 3.30.

2-(Benzo[c][1,2,5]oxadiazol-4-yl)benzaldehyde

(13): Following the general procedure **A** using 2bromobenzaldehyde (185 mg, 1 mmol) and benzofurazan (138 mg, 1.15 mmol), the residue was purified by flash chromatography on silica gel (pentane-Et₂O, 70-30) to afford the desired compound **13** (141 mg, 63%) as an orange solid (MP = 140-143 °C). ¹H NMR (400 MHz, CDCl₃) δ (ppm) 9.97 (s, 1H), 8.12 (d, *J* = 7.9 Hz, 1H), 7.94 (d, *J* = 9.0 Hz, 1H), 7.77 (dt, *J* = 1.5, 7.5 Hz, 1H), 7.71 – 7.63 (m, 2H), 7.57 (dd, *J* = 6.6, 9.1 Hz, 1H), 7.36 (d, *J* = 6.6 Hz, 1H). ¹³C NMR (100 MHz, CDCl₃) δ (ppm) 190.8, 149.6, 149.1, 138.1, 134.4, 133.9, 131.8, 131.3, 131.2, 129.7, 129.5, 128.0, 116.4. Elemental analysis: calcd (%) for C₁₃H₈N₂O₂ (224.21): C 69.64, H 3.60; found: C 69.72, H 3.88.

4-(2-Fluorophenyl)benzo[c][1,2,5]oxadiazole (14): Following the general procedure A using 1-bromo-2fluorobenzene (175 mg, 1 mmol) and benzofurazan (138 mg, 1.15 mmol), the residue was purified by flash chromatography on silica gel (pentane-toluene, 90-10) to afford the desired compound 14 (167 mg, 78%) as a yellow solid (MP = 119-121 °C). ¹H NMR (400 MHz, CDCl₃) δ (ppm) 7.91 - 7.84 (m, 2H), 7.62 (d, J = 6.9 Hz, 1H), 7.54(dd, J = 6.8, 9.0 Hz, 1H), 7.51 - 7.44 (m, 1H), 7.34 (td, J =1.2, 7.6 Hz, 1H), 7.30 – 7.24 (m, 1H). 13 C NMR (100 MHz, CDCl₃) δ (ppm) 159.9 (d, J = 249.5 Hz), 149.5, 148.7, 131.5, 131.2 (d, J = 5.4 Hz), 130.8 (d, J = 8.6 Hz), 124.9, 124.5, 124.5, 123.1 (d, J = 12,8 Hz), 116.4 (d, J = 20.9 Hz), 115.8. Elemental analysis: calcd (%) for C₁₂H₇FN₂O (214.20): C 67.29, H 3.29; found: C 67.18, H 3.45.

4-(Naphthalen-1-yl)benzo[c][1,2,5]oxadiazole (15): Following the general procedure A using 1bromonaphthalene (207 mg, 1 mmol) and benzofurazan (138 mg, 1.15 mmol), the residue was purified by flash chromatography on silica gel (pentane-toluene, 95-15) to afford the desired compound 15 (140 mg, 57%) as a yellow solid (MP = 68-71 °C). ¹H NMR (400 MHz, CDCl₃) δ (ppm) 8.03 – 7.96 (m, 2H), 7.94 (d, J = 8.9 Hz, 1H), 7.74 (d, J = 8.9 Hz, 1H), 7.69 – 7.63 (m, 1H), 7.63 – 7.56 (m, 2H), 7.55 - 7.50 (m, 2H), 7.50 - 7.43 (m, 1H). ¹³C NMR (100 MHz, CDCl₃) δ (ppm) 149.9, 149.5, 133.9, 133.5, 131.6, 131.6, 131.3, 130.1, 129.5, 128.6, 127.9, 126.6, 126.2, 125.3, 125.3, 115.5. Elemental analysis: calcd (%) for C₁₆H₁₀N₂O (246.27): C 78.03, H 4.09; found: C 78.45, H 4.19.

4-(6-(Trifluoromethyl)pyridin-2-

yl)benzo[c][1,2,5]oxadiazole (16): Following the general procedure **A** using 2-bromo-6-(trifluoromethyl)pyridine (225 mg, 1 mmol) and benzofurazan (138 mg, 1.15 mmol), the residue was purified by flash chromatography on silica gel (pentane-toluene, 80-20) to afford the desired compound **16** (188 mg, 71%) as a yellow solid (MP = 148-150 °C). ¹H NMR (400 MHz, CDCl₃) δ (ppm) 8.89 (d, *J* = 8.0 Hz, 1H), 8.64 (d, *J* = 6.9 Hz, 1H), 8.15 – 8.05 (m, 1H),

7.97 (dd, J = 0.8, 8.9 Hz, 1H), 7.74 (dd, J = 0.9, 7.8 Hz, 1H), 7.64 (dd, J = 6.9, 9.0 Hz, 1H).

¹³C NMR (100 MHz, CDCl₃) δ (ppm) 152.1, 149.9, 148.3 (q, J = 34.9 Hz), 147.7, 138.8, 131.9, 131.2, 126.8, 126.5, 121.4 (q, J = 274.7 Hz), 119.9, 117.7. Elemental analysis: calcd (%) for C₁₂H₆F₃N₃O (265.20): C 54.35, H 2.28; found: C 64.43, H 2.37.

4-(Quinolin-3-yl)benzo[c][1,2,5]oxadiazole (17): Following the general procedure A using 3bromoquinoline (208 mg, 1 mmol) and benzofurazan (138 mg, 1.15 mmol), the residue was purified by flash chromatography on silica gel (pentane-EtOAc, 70-30) to afford the desired compound 17 (200 mg, 81%) as an orange solid (MP = 143-145 °C). ¹H NMR (400 MHz, DMSO- d_6) δ (ppm) 9.53 (d, J = 2.4 Hz, 1H), 9.06 (d, J =2.0 Hz, 1H), 8.18 - 8.10 (m, 4H), 7.87 (ddd, J = 1.4, 6.9, 8.4 Hz, 1H), 7.81 (dd, J = 6.8, 9.0 Hz, 1H), 7.72 (ddd, J =1.2, 6.9, 8.1 Hz, 1H). ¹³C NMR (100 MHz, DMSO-*d*₆) δ (ppm) 150.1, 150.0, 148.7, 147.8, 135.9, 133.6, 131.0, 130.9, 129.3, 129.2, 128.3, 127.9, 127.7, 126.3, 116.3. Elemental analysis: calcd (%) for C₁₅H₉N₃O (247.26): C 72.87, H 3.67; found: C 72.98, H 3.54.

4-(6-Methoxypyridin-2-

yl)benzo[*c*][1,2,5]oxadiazole (18): Following the general procedure **A** using 2-bromo-6-methoxypyridine (188 mg, 1 mmol) and benzofurazan (138 mg, 1.15 mmol), the residue was purified by flash chromatography on silica gel (pentane-toluene, 90-10) to afford the desired compound **18** (130 mg, 57%) as a yellow solid (MP = 140-143 °C). ¹H NMR (400 MHz, CDCl₃) δ (ppm) 8.53 (d, *J* = 6.9 Hz, 1H), 8.32 (d, *J* = 7.5 Hz, 1H), 7.89 (d, *J* = 8.9 Hz, 1H), 7.79 (dd, *J* = 7.4, 8.3 Hz, 1H), 7.60 (dd, *J* = 6.9, 9.0 Hz, 1H), 6.85 (d, *J* = 8.3 Hz, 1H), 4.09 (s, 3H). ¹³C NMR (100 MHz, CDCl₃) δ (ppm) 163.5, 150.0, 148.8, 147.9, 139.6, 131.8, 129.5, 128.1, 117.7, 116.4, 111.7, 53.3. Elemental analysis: calcd (%) for C₁₂H₉N₃O₂ (227.22): C 63.43, H 3.99; found: C 63.68, H 4.13.

1-(5-(Benzo[*c***][1,2,5]oxadiazol-4-yl)thiophen-2yl)ethan-1-one (19):** Following the general procedure **A** using 1-(5-bromothiophen-2-yl)ethan-1-one (205 mg, 1 mmol) and benzofurazan (138 mg, 1.15 mmol), the residue was purified by flash chromatography on silica gel (pentane-EtOAc, 80-20) to afford the desired compound **19** (154 mg, 63%) as a yellow solid (MP = 205-207 °C). ¹H NMR (400 MHz, CDCl₃) δ (ppm) 8.17 (d, *J* = 4.0 Hz, 1H), 7.90 – 7.83 (m, 1H), 7.78 (d, *J* = 4.0 Hz, 1H), 7.75 (d, *J* = 6.8 Hz, 1H), 7.51 (dd, *J* = 6.8, 9.0 Hz, 1H), 2.64 (s, 3H). ¹³C NMR (100 MHz, CDCl₃) δ (ppm) 190.6, 149.5, 147.3, 145.1, 144.7, 133.3, 131.6, 129.8, 127.6, 123.3, 116.3, 26.8. Elemental analysis: calcd (%) for C₁₂H₈N₂O₂S (244.26): C 59.01, H 3.30; found: C 58.87, H 3.11.

4-(5-Methoxybenzo[c][1,2,5]oxadiazol-4yl)benzonitrile (20): Following the general procedure **A** using 4-bromobenzonitrile (182 mg, 1 mmol) and 6methoxybenzofurazan (173 mg, 1.15 mmol), the residue was purified by flash chromatography on silica gel (pentane-Et₂O, 60-40) to afford the desired compound **20** (172 mg, 68%) as an orange solid (MP = 195-197 °C). ¹H NMR (300 MHz, CD₂Cl₂) δ (ppm) 8.02 – 7.89 (m, 3H), 7.81 (d, *J* = 8.7 Hz, 2H), 7.58 (d, *J* = 9.8 Hz, 1H), 4.02 (s, 3H). ¹³C NMR (100 MHz, CD₂Cl₂) δ (ppm) 156.4, 150.0, 146.9, 137.3, 131.8, 131.0, 123.6, 118.7, 117.9, 111.5, 110.0, 57.6. Elemental analysis: calcd (%) for C₁₄H₉N₃O₂ (251.25): C 66.93, H 3.61; found: C 67.05, H 3.88.

4-(3-Chlorophenyl)-5-

methoxybenzo[*c*][1,2,5]**oxadiazole** (21): Following the general procedure **A** using 1-bromo-3-chlorobenzene (191 mg, 1 mmol) and 6-methoxybenzofurazan (173 mg, 1.15 mmol), the residue was purified by flash chromatography on silica gel (pentane-Et₂O, 90-10) to afford the desired compound **21** (169 mg, 65%) as a yellow solid (MP = 76-79 °C). ¹H NMR (400 MHz, CDCl₃) δ (ppm) 7.89 (d, *J* = 9.7 Hz, 1H), 7.79 (d, *J* = 1.5 Hz, 1H), 7.69 (td, *J* = 1.5, 7.5 Hz, 1H), 7.51 (d, *J* = 9.7 Hz, 1H), 7.48 – 7.42 (m, 1H), 7.42 – 7.38 (m, 1H), 3.98 (s, 3H). ¹³C NMR (100 MHz, CDCl₃) δ (ppm) 155.7, 150.3, 146.9, 134.1, 133.9, 130.3, 129.4, 128.5, 128.3, 123.9, 117.1, 111.3, 57.7. Elemental analysis: calcd (%) for C₁₃H₉ClN₂O₂ (260.68): C 59.90, H 3.48; found: C 60.12, H 3.27.

6-Methoxy-4-(2-

nitrophenyl)benzo[c][1,2,5]oxadiazole (22a): Following the general procedure A using 2-bromonitrobenzene (191 mg, 1 mmol) and 6-methoxybenzofurazan (173 mg, 1.15 mmol), the residue was purified by flash chromatography on silica gel (pentane-Et₂O, 60-40) to afford the desired compound 22a (103 mg, 38%) as a yellow solid (MP = 200-202 °C). ¹H NMR (400 MHz, CDCl₃) δ (ppm) 8.20 (d, J = 8.1 Hz, 1H), 7.77 (t, J = 7.6 Hz, 1H), 7.68 (t, J = 7.9Hz, 1H), 7.59 (d, *J* = 7.6 Hz, 1H), 7.10 (d, *J* = 2.0 Hz, 1H), 6.92 (d, J = 2.0 Hz, 1H), 3.99 (s, 3H). ¹³C NMR (100 MHz, CDCl₃) δ (ppm) 161.4, 150.1, 146.6, 133.5, 132.0, 130.3, 130.2, 128.8, 127.2, 125.2, 89.6, 56.2. Elemental analysis: calcd (%) for C₁₃H₉N₃O₄ (271.23): C 57.57, H 3.34; found: C 57.21, H 3.56. 22b ¹H NMR (400 MHz, CDCl₃) δ (ppm) 8.10 (d, J = 8.1 Hz, 1H), 7.95 (d, J = 9.7 Hz, 1H), 7.75 (t, J = 7.5 Hz, 1H), 7.70 (d, J = 7.5 Hz, 1H), 7.61 (t, J = 7.7 Hz, 1H), 7.46 (d, J = 9.7 Hz, 1H), 3.90 (s, 3H).

Procedure B (Palladium-catalyzed one-pot direct C4,C7-diarylation): To a 5 mL oven dried Schlenk tube, benzofurazan derivative (1 mmol), aryl bromide (3 mmol), AcOK (294 mg, 3 mmol), DMA (4 mL) and Pd(OAc)₂ (2.2 mg, 0.01 mmol, 2 mol%) were successively added. The reaction mixture was evacuated by vacuum-argon cycles (5 times) and stirred at 150 °C (oil bath temperature) for 16 hours. After cooling the reaction at room temperature and concentration, the crude mixture was purified by silica column chromatography to afford the desired diarylated products.

4,7-Diphenylbenzo[*c*][**1,2,5**]**oxadiazole** (23): Following the general procedure **B** using 1-bromobenzene (471 mg, 3 mmol) and benzofurazan (120 mg, 1 mmol), the residue was purified by flash chromatography on silica gel (pentane-Et₂O, 95-5) to afford the desired compound **23** (155 mg, 57%) as a yellow solid (MP = 190-191 °C). ¹H NMR (400 MHz, CDCl₃) δ (ppm) 8.11 – 8.03 (m, 4H), 7.71 (s, 2H), 7.62 – 7.54 (m, 4H), 7.53 – 7.47 (m, 2H). ¹³C NMR (100 MHz, CDCl₃) δ (ppm) 149.3, 135.3, 129.2, 129.0, 128.9, 128.7, 128.4. Elemental analysis: calcd (%) for C₁₈H₁₂N₂O (272.31): C 79.39, H 4.44; found: C 79.57, H 4.60.

4,7-Bis(4-chlorophenyl)benzo[c][1,2,5]oxadiazole

(24): Following the general procedure **B** using 1-bromo-4chlorobenzene (574 mg, 3 mmol) and benzofurazan (120 mg, 1 mmol), the residue was purified by flash chromatography on silica gel (pentane-CH₂Cl₂, 80-20) to afford the desired compound **24** (205 mg, 60%) as a yellow solid (MP = 230-232 °C). ¹H NMR (400 MHz, CDCl₃) δ (ppm) 8.02 (d, *J* = 8.3 Hz, 4H), 7.69 (s, 2H), 7.55 (d, *J* = 8.3 Hz, 4H).

¹³C NMR (100 MHz, CDCl₃) δ (ppm) 149.0, 135.4, 133.5, 129.6, 129.2, 128.5, 128.0. Elemental analysis: calcd (%) for $C_{18}H_{10}Cl_2N_2O$ (341.19): C 63.37, H 2.95; found: C 63.18, H 3.09.

4,7-Bis(3,5-

bis(trifluoromethyl)phenyl)benzo[*c*][1,2,5] **oxadiazole** (25): Following the general procedure **B** using 1-bromo-3,5-bis(trifluoromethyl)benzene (879 mg, 3 mmol) and benzofurazan (120 mg, 1 mmol), the residue was purified by flash chromatography on silica gel (pentane-toluene, 90-10) to afford the desired compound **25** (392 mg, 72%) as a yellow solid (MP = 156-159 °C). ¹H NMR (300 MHz, CDCl₃) δ (ppm) 8.53 (s, 4H), 8.02 (s, 2H), 7.86 (s, 2H). ¹³C NMR (100 MHz, CDCl₃) δ (ppm) 148.6, 136.5, 132.7 (q, *J* = 33.6 Hz), 129.6, 128.4 (d, *J* = 2.6 Hz), 127.7, 123.2 (m), 123.1 (q, *J* = 270.1 Hz). Elemental analysis: calcd (%) for C₂₂H₈F₁₂N₂O (544.30): C 48.55, H 1.48; found: C 48.62, H 1.54.

4,7-Bis(6-(trifluoromethyl)pyridin-2-

yl)benzo[*c*][1,2,5]oxadiazole (26): Following the general procedure **B** using 2-bromo-6-(trifluoromethyl)pyridine (678 mg, 3 mmol) and benzofurazan (120 mg, 1 mmol), the residue was purified by flash chromatography on silica gel (pentane-toluene, 80-20) to afford the desired compound **26** (263 mg, 64%) as a yellow solid (MP = 209-211 °C). ¹H NMR (300 MHz, CDCl₃) δ (ppm) 8.96 (d, *J* = 8.0 Hz, 2H), 8.84 (s, 2H), 8.14 (d, *J* = 8.0 Hz, 2H), 7.78 (d, *J* = 8.0 Hz, 2H). ¹³C NMR (100 MHz, CDCl₃) δ (ppm) 150.7, 147.5, 147.4 (q, *J* = 34.9 Hz), 137.8, 130.8, 126.2, 126.0, 120.3 (q, *J* = 275.7 Hz), 119.2.Elemental analysis: calcd (%) for C₁₈H₈F₆N₄O (410.28): C 52.70, H 1.97; found: C 52.89, H 1.63.

Procedure C (acid-promoted the formation of quinoxalines): To a 5 mL oven dried Schlenk tube, arylated benzofurazan derivative (0.5 mmol), *p*-toluenesulfonic acid (8.6 mg, 0.05 mmol), 2-aminoethan-1-ol (0.45 mL, 7.5 mmol) were successively added. The reaction mixture wasstirred at 150 °C (oil bath temperature) for 72 hours. After cooling the reaction at room temperature and concentration, the crude mixture was purified by silica column chromatography to afford the desired arylated products.

5-(4-Chlorophenyl)quinoxaline (27): Following the general procedure С using 4-(4chlorophenyl)benzo[c][1,2,5]oxadiazole (6) (115 mg, 0.5 mmol), the residue was purified by flash chromatography on silica gel (pentane-CH₂Cl₂, 70-30) to afford the desired compound 27 (101 mg, 84%) as a brown solid (MP = 109-111 °C). ¹H NMR (400 MHz, CDCl₃) δ (ppm) 8.97 – 8.85 (m, 2H), 8.20 (dd, J = 1.6, 8.3 Hz, 1H), 7.88 (t, J = 7.1 Hz, 1H), 7.82 (dd, J = 1.6, 7.2 Hz, 1H), 7.63 (d, J = 8.5 Hz, 2H), 7.51 (d, J = 8.5 Hz, 2H). ¹³C NMR (100 MHz, CDCl₃) δ (ppm) 144.9, 144.7, 143.1, 140.9, 140.0, 136.5, 134.1, 131.9, 130.5, 129.9, 129.3, 128.4. Elemental analysis: calcd (%) for C₁₄H₉ClN₂ (240.69): C 69.86, H 3.77; found: C 69.90, H 4.02.

5-(Naphthalen-1-yl)quinoxaline (28): Following the general procedure **C** using 4-(naphthalen-1-yl)benzo[*c*][1,2,5]oxadiazole (**15**) (123 mg, 0.5 mmol), the residue was purified by flash chromatography on silica gel (pentane-CH₂Cl₂, 70-30) to afford the desired compound **28** (111 mg, 87%) as a brown solid (MP = 100-103 °C). ¹H NMR (400 MHz, CDCl₃) δ (ppm) 8.88 (d, *J* = 1.8 Hz, 1H),

8.77 (d, J = 1.8 Hz, 1H), 8.28 (dd, J = 1.5, 8.4 Hz, 1H), 8.01 – 7.91 (m, 3H), 7.86 (dd, J = 1.5, 7.1 Hz, 1H), 7.63 (dd, J = 7.0, 8.2 Hz, 1H), 7.53 (dd, J = 1.3, 7.0 Hz, 1H), 7.49 (ddd, J = 2.0, 6.0, 8.1 Hz, 1H), 7.38 – 7.30 (m, 2H). ¹³C NMR (100 MHz, CDCl₃) δ (ppm) 144.9, 142.9, 142.3, 140.5, 136.5, 133.5, 132.7, 132.0, 129.7, 129.4, 128.5, 128.3, 128.1, 126.3, 125.9, 125.7, 125.2. Elemental analysis: calcd (%) for C₁₈H₁₂N₂ (256.31): C 84.35, H 4.72; found: C 84.14, H 4.96.

5,8-Bis(3,5-bis(trifluoromethyl)phenyl)quinoxaline (**29**): Following the general procedure C using 4,7-bis(3,5bis(trifluoromethyl)phenyl)benzo[*c*][1,2,5] oxadiazole (**25**) (272 mg, 0.5 mmol), the residue was purified by flash chromatography on silica gel (pentane-CH₂Cl₂, 80-20) to afford the desired compound **29** (227 mg, 82%) as a brown solid (MP = 200-203 °C). ¹H NMR (400 MHz, CDCl₃) δ (ppm) 8.98 (s, 2H), 8.30 – 8.16 (m, 4H), 8.01 (s, 2H), 8.00 (s, 2H). ¹³C NMR (100 MHz, CDCl₃) δ (ppm) 145.3, 140.7, 139.6, 138.9, 131.5 (q, *J* = 33.7 Hz), 130.8, 130.3, 123.4 (q, *J* = 273.4 Hz), 121.8. Elemental analysis: calcd (%) for C₂₄H₁₀F₁₂N₂ (554.34): C 52.00, H 1.82; found: C 52.18, H 2.07.

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I. Idris, F. Derridj, J.-F. Soulé,* H. Doucet*

