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Synthesis of quinoxalines and pyrido[2,3-*b*]pyrazines by Suzuki–Miyaura cross-coupling reaction

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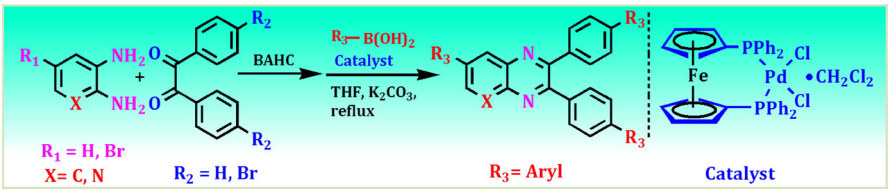
Abstract Bromo-substituted quinoxalines and pyrido[2,3-*b*]pyrazines were synthesized by condensation reactions of aromatic 1,2-diamino and 1,2-diketone compounds. These compounds were used as common intermediates for postcondensation modification by Suzuki–Miyaura coupling reaction to form aryl-substituted quinoxalines and pyrido[2,3-*b*]pyrazines. High-efficiency with improved product yield of aryl-substituted quinoxalines and pyrido[2,3-*b*]pyrazine derivatives was achieved by conducting a coupling reaction in presence of Pd(dppf)Cl_2·CH_2Cl_2 in tetrahydrofuran (THF) using K_2CO_3 as base at reflux temperature.

Graphical abstract



Keywords Suzuki–Miyaura reaction · Quinoxalines · Pyrido[2,3-*b*]pyrazines · Pd(dppf)Cl_2·CH_2Cl_2

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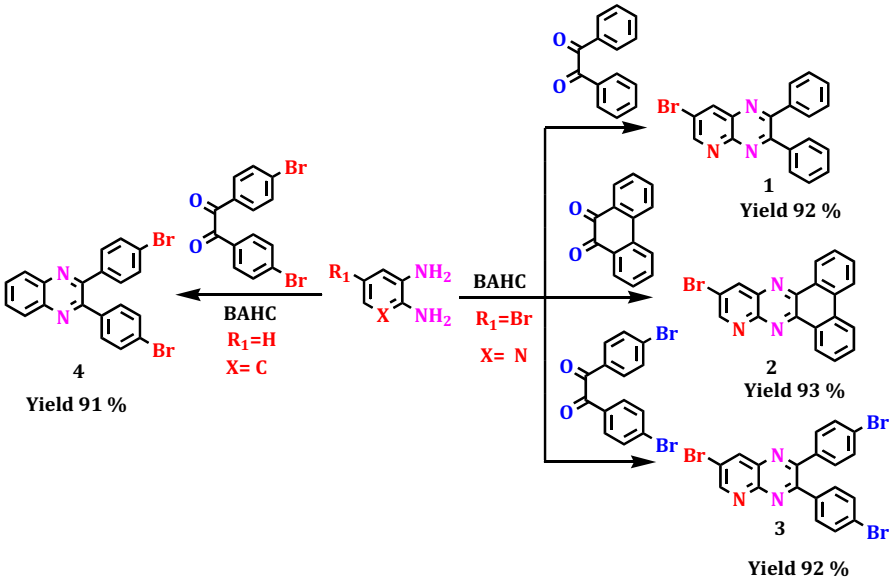
Introduction

The biological activity manifested by many polycyclic nitrogen-containing heterocyclic compounds makes them attractive targets for organic chemists for synthesis of pharmaceutical motifs [1–4]. Annulated pteridines such as quinoxaline and pyrazine derivatives are versatile intermediates for preparation of various nitrogen-containing compounds. They represent key structural motif in many medicinally important compounds, including quinoxaline anticancer drugs such as chloroquinoxaline sulfonamide (CQS) and XK469 [5, 6]. Both of these compounds exhibit activity against solid tumors and are known to be antineoplastic quinoxaline topoisomerase II poisons [7–10]. It is also noteworthy that, by virtue of their thermal stability, intense luminescence, and other desirable properties, they have been widely used in organic semiconductors, and electroluminescent materials for manufacture of highly efficient organic light-emitting diodes (OLEDs) [11–14]. Pyrazines are also useful precursors utilized in a number of synthetic platforms and starting materials for construction of heteroaromatic systems.

In recent years, transition-metal-catalyzed cross-coupling has been used as an efficient process in the chemist's toolbox for construction of many heterocyclic compounds [15–17]. Among such approaches, palladium-catalyzed Suzuki–Miyaura coupling is a powerful, versatile, and popular method for construction of a variety of pharmaceutically active heterocyclic compounds [18–20].

In this work, synthesis of π-extended quinoxaline and pyrazine derivatives was carried out in a two-step reaction. In the first step, as described in Scheme 1,



Scheme 1 Synthesis of key precursors of quinoxaline and pyrido[2,3-*b*]pyrazines

appropriate quinoxaline and pyrazine derivatives containing one or more bromo substituents were synthesized from corresponding 1,2-diamino and 1,2-diketone compounds. Secondly, the classical Suzuki–Miyaura cross-coupling protocol between bromo compounds and arylboronic acids was employed to obtain the desired products in quantitative yield.

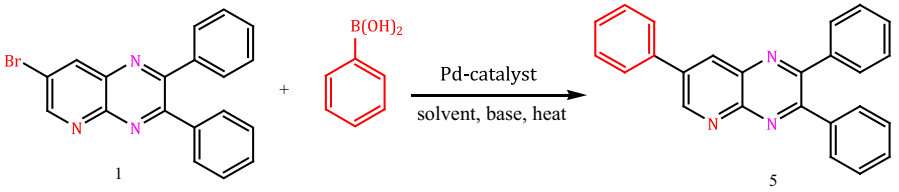
In continuation of our work related to heterogeneous Pd catalysis [21–24], we report herein a concise synthesis of pyrazine and quinoxaline derivatives that further demonstrates the synthetic power of coupling two or three nucleophiles to bromo compounds as an extension. This methodology furnishes an elegant entry to diverse pteridine analogues, using Suzuki–Miyaura cross-coupling based on readily accessible, commercial starting materials.

Results and discussion

Our work began with the intention of developing general reaction conditions for palladium-catalyzed arylation of pyrido[2,3-*b*]pyrazines and quinoxalines. As shown in Scheme 1, four precursors used for Pd-catalyzed Suzuki–Miyaura coupling reactions were synthesized following the literature procedure [25]. The key required starting compounds **1**, **2**, and **3** were obtained from condensation reactions of commercially available 5-bromo-2,3-diaminopyridine with benzil or 9,10-phenanthraquinone or 4,4′-dibromobenzil, respectively, in good to excellent yields using Brønsted acid hydrotrope combined catalyst (BAHC) in water. Meanwhile, **4** was prepared from 1,2-diaminobenzene and 4,4′-dibromobenzil by adopting the same reaction procedure. All compounds were solids and well soluble in chlorinated solvents and THF, but insoluble in ethanol. Their chemical structures were confirmed by ^{1}H and ^{13}C nuclear magnetic resonance spectroscopy (NMR), and mass-spectrometric analysis. The spectral data are in harmony with data reported in literature [25].

It is known that uncatalyzed substitution at 7-position of 7-bromo-2,3-diphenylpyrido[2,3-*b*]pyrazine (**1**) is problematic, because these reactions provide low yield with the formation of a mixture of regioisomeric products due to the elimination/addition mechanism, as addition often competes with substitution [26]. Considering these problems, palladium-catalyzed cross-coupling reaction can expected to be one of the most advantageous alternatives to introduce functionalized side-chains and other substituents into 7-bromo-2,3-diphenylpyrido[2,3-*b*]pyrazine (**1**) without facing the problems found in uncatalyzed transformation as disclosed by Liebscher and Yin [27]. To optimize the reaction conditions, we began our studies by examining the coupling reaction of compound **1** with phenyl boronic acid, as shown in Table 1. Initial studies were carried out at 1 mmol scale and reflux temperature using different palladium sources such as $Pd(OAc)_2$, $PdCl_2$, and $Pd(dppf)Cl_2{\cdot}CH_2Cl_2$ with K_2CO_3 as base in THF. We found that $Pd(OAc)_2$ and $PdCl_2$ were less effective (Table 1, entries 2 and 3), while $Pd(dppf)Cl_2{\cdot}CH_2Cl_2$ [28] gave 89 % yield of the desired product in 4 h at reflux temperature (Table 1, entry 1). The next, important goal of our investigation was to identify an optimum base. It was observed that organic bases such as triethylamine (TEA) and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) did not work satisfactorily (Table 1,

Table 1 Optimization of reaction conditions for Pd-catalyzed arylation of **1** with phenyl boronic acid[a]



Entry	Catalyst (1 mol%)	Ligand (3 mol%)	Base	Solvent	Time (h)	Yield[b] (%)
1	$Pd(dppf)Cl_2{\cdot}CH_2Cl_2$	–	K_2CO_3	THF	4	89
2	$Pd(OAc)_2$	PPh_3	K_2CO_3	THF	14	62
3	$PdCl_2$	PPh_3	K_2CO_3	THF	14	58
4	$Pd(dppf)Cl_2{\cdot}CH_2Cl_2$	–	Na_2CO_3	THF	5	84
5	$Pd(dppf)Cl_2{\cdot}CH_2Cl_2$	–	K_3PO_4	THF	10	59
6	$Pd(dppf)Cl_2{\cdot}CH_2Cl_2$	–	TEA	THF	15	51
7	$Pd(dppf)Cl_2{\cdot}CH_2Cl_2$	–	DBU	THF	15	53
8	$Pd(dppf)Cl_2{\cdot}CH_2Cl_2$	–	K_2CO_3	EtOH	16	37
9	$Pd(dppf)Cl_2{\cdot}CH_2Cl_2$	–	K_2CO_3	DMF	9	70[c]
10	$Pd(dppf)Cl_2{\cdot}CH_2Cl_2$	–	K_2CO_3	1,4-Dioxane	9	69[c]
11	$Pd(dppf)Cl_2{\cdot}CH_2Cl_2$	–	K_2CO_3	Toluene	10	66[c]

[a] Reaction conditions: compound **1** (1.0 mmol), phenyl boronic acid (1.2 mmol), Pd catalyst (1 mol%), PPh_3 (3 mmol), base (2.0 mmol), solvent (5 ml), reflux under aerobic conditions

[b] Isolated yields after purification

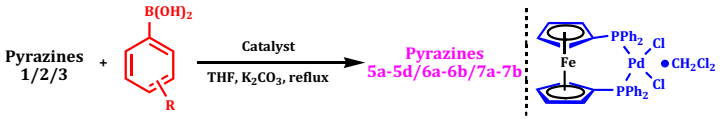
[c] Reactions at 80 °C

entries 6 and 7). Upon screening commonly used inorganic bases, it was found that K_2CO_3 played a crucial role (Table 1, entry 1), while K_3PO_4 was considerably less effective (Table 1, entry 5). Comparable conversion was obtained using Na_2CO_3 or K_2CO_3 (Table 1, entry 4). Having determined the best base, the effect of various solvents on the reaction were surveyed. Among the various solvents used, we found that THF provided the optimal yield of the desired product (Table 1, entry 1) as compared with other solvents (Table 1, entries 8–11), similar to our previously reported Pd-DABCO@SiO_2 catalyst [29].

To probe the generality of the method, the reaction of 7-bromo-2,3-diphenylpyrido[2,3-*b*]pyrazine (**1**) with different substituted arylboronic acids were conducted (Table 2). It was observed that the reactions of compound **1** with phenyl, 4-acetylphenyl, and (3,5-dimethyl-4-methoxy)phenyl boronic acids afforded the desired products in good yields (78–89 %) in 4–17 h (Table 2, entries 1–3). The reaction of sterically hindered naphthyl boronic acid with compound **1** could also be effected in 84 % yield in 14 h (Table 2, entry 4). Similarly, compound **2** was also reactive against phenyl and 4-methylphenyl boronic acids with good product yield (Table 2, entries 5 and 6).

Encouraged by these findings, we sought to ascertain the coupling of tribromo-substituted pyrazine (**3**) with phenyl boronic acid under the same optimized

Table 2 Suzuki–Miyaura coupling of pyrido[2,3-*b*]pyrazines with arylboronic acids[a]



Catalyst

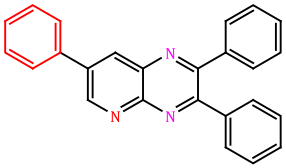
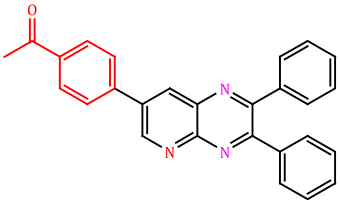
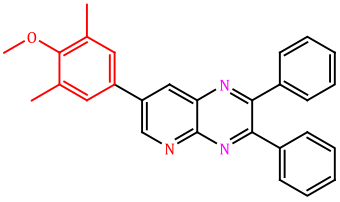
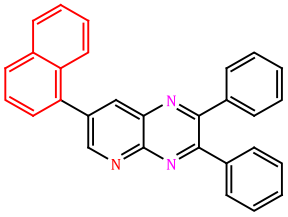
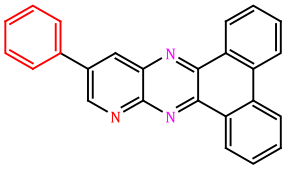
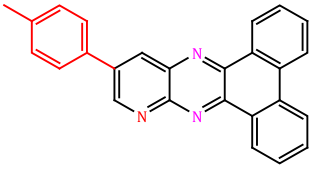
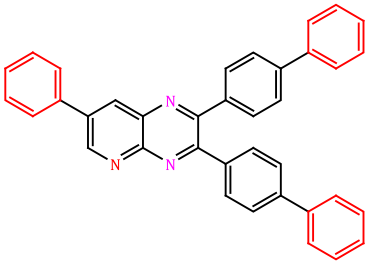
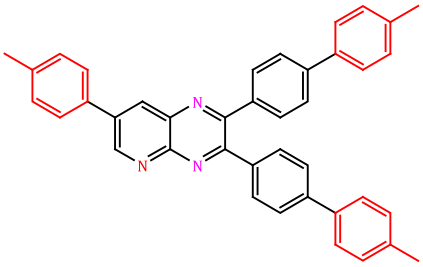
Entry	Pyrazine	Product	Time (h)	Yield[b] (%)
1	**1**	 **5a**	4	89[27]
2	**1**	 **5b**	17	78[27]
3	**1**	 **5c**	12	89[29]
4	**1**	 **5d**	14	84[29]
5	**2**	 **6a**	18	72

Table 2 continued

Entry	Pyrazine	Product	Time (h)	Yield[b] (%)
6	**2**	 **6b**	10	66
7	**3**	 **7a**	14	81[c]
8	**3**	 **7b**	14	78[c]

[a] Reaction conditions: compound **1** or **2** (1.0 mmol), arylboronic acid (1.2 mmol), $Pd(dppf)Cl_2{\cdot}CH_2Cl_2$ (1 mol%), K_2CO_3 (2.0 mmol), THF (5 ml), reflux under aerobic conditions

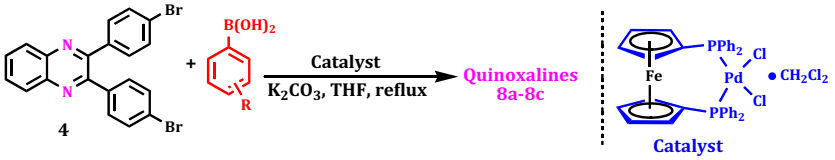
[b] Isolated yields after purification

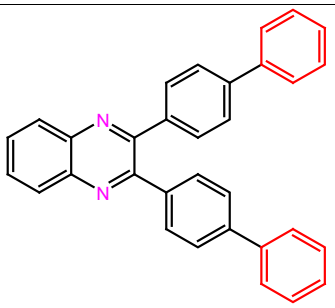
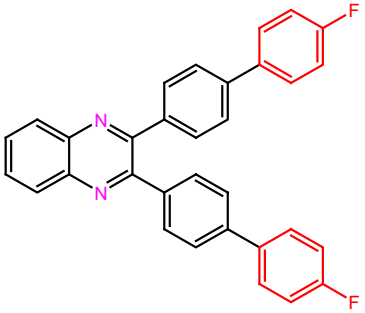
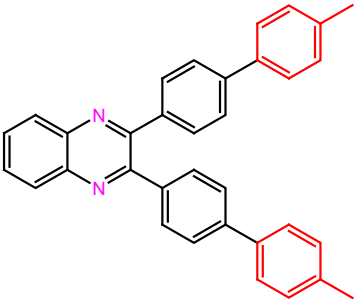
[c] Reaction conditions: compound **3** (1.0 mmol), phenyl boronic acid (3.2 mmol), $Pd(dppf)Cl_2{\cdot}CH_2Cl_2$ (3 mol%), K_2CO_3 (6.0 mmol), THF (5 ml), reflux under aerobic conditions

conditions; For example, we were also able to couple tribromide with phenyl and 4-methylphenyl boronic acid, which proceeded with good yields (Table 2, entries 7 and 8) using 3 mol% catalyst.

As an expansion of this study, we next explored preparation of structurally related quinoxaline derivatives. For this study, precursor compound **4** was applied for Suzuki–Miyaura coupling under conditions similar to those used for pyrazines; the reactions are detailed in Table 3. Three different arylboronic acids were successfully coupled with compound **4** using 2 mol% catalyst. In all cases

Table 3 Suzuki–Miyaura coupling of quinoxaline with arylboronic acids[a]



Entry	Quinoxaline	Product	Time (h)	Yield[b] (%)
1	**4**	 **8a**	16	90
2	**4**	 **8b**	20	88
3		 **8c**	16	90

[a] Reaction conditions: compound **4** (1.0 mmol), arylboronic acid (2.2 mmol), Pd(dppf)Cl_2·CH_2Cl_2 (2 mol%), K_2CO_3 (4.0 mmol), THF (5 ml), reflux under aerobic conditions

[b] Isolated yields after purification

examined, compound **4** was efficiently transformed into the desired coupling products with good yields (88–90 %) in 16–20 h.

Conclusions

In conclusion, bromo-substituted quinoxalines and pyrido[2,3-*b*]pyrazines generated from condensation reactions of aromatic 1,2-diamino and 1,2-diketone compounds were efficiently obtained using green BAHC catalyst in water at room temperature. These compounds were used as common intermediates for postcondensation modification by Suzuki–Miyaura cross-coupling reaction. The highly active $Pd(dppf)Cl_2{\cdot}CH_2Cl_2$ catalyst was used for synthesis of novel pyrido[2,3-*b*]pyrazine and quinoxaline derivatives with a variety of arylboronic acids in good yields.

Experimental

General remarks

^1H and ^{13}C NMR spectra were recorded on a Bruker AC spectrometer at 300 and 75 MHz, respectively, using $CDCl_3$ as solvent and tetramethylsilane (TMS) as internal standard. Melting points were determined with a DBK melting point apparatus and are uncorrected. All chemicals were obtained from Aldrich and Spectrochem and used without further purification.

General procedure for Suzuki–Miyaura coupling reaction of pyrido[2,3-*b*]pyrazine and quinoxaline derivatives

An oven-dried Schlenk flask, equipped with a magnetic stir bar, septum, and condenser, was charged with compound **1/2/3/4** (1.0 mmol), arylboronic acid (1.2/2.2/3.2 mmol), K_2CO_3 (2/4/6 mmol), $Pd(dppf)Cl_2{\cdot}CH_2Cl_2$ (1/2/3 mol%), and 5 ml THF. The reaction mixture was refluxed, and after complete consumption of starting materials as determined by thin-layer chromatography (TLC) analysis, the reaction mixture was filtered and water (20 ml) was added. The filtrate was extracted with diethyl ether (3 × 10 ml). The combined organic layers were collected, dried over anhydrous Na_2SO_4, and concentrated in vacuum to afford product, which was purified by silica gel column chromatography (eluent: *n*-hexane/ethyl acetate = 9/1).

Physical and spectroscopic data for selected compounds

Compound 6a; Yellow solid, m.p. 255–256 °C; ^1H NMR (300 MHz, $CDCl_3$): δ_H (ppm) 7.49–7.63 (m, 3H), 7.74–7.90 (m, 6H), 8.57–8.60 (m, 2H), 8.82 (d, 1H, $J = 2.4$ Hz), 9.37 (d, 1H, $J = 7.8$ Hz), 9.56 (d, 2H, $J = 9.3$ Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ_C (ppm) 120.5, 123.0, 127.5, 128.1, 128.9, 129.1, 129.6, 131.3, 132.5, 137.3, 143.9, 154.8; ESI–MS (M.F. = $C_{25}H_{15}N_3$; $M^+ = 357.12$).

Compound 6b; Yellow solid, m.p. 296–298 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ_H (ppm) 1.26 (s, 3H), 7.19–7.35 (m, 2H), 7.75–7.90 (m, 6H), 8.56–8.60 (m, 2H), 8.86 (d, 1H, $J = 2.4$ Hz), 9.35 (d, 1H, $J = 7.8$ Hz), 9.55 (d, 2H, $J = 9.3$ Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ_C (ppm) 29.6, 120.4, 124.1, 126.5, 128.0, 128.6, 129.1, 130.9, 132.4, 137.1, 143.9, 154.5; ESI–MS (M.F. = $C_{26}H_{17}N_3$; $M^+ = 371.14$).

Compound 7a; Yellow solid, m.p. 333 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ_H (ppm) 7.34–7.82 (m, 23H), 8.66 (d, 1H, $J = 7.8$ Hz), 9.45 (d, 1H, $J = 3.6$ Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ_C (ppm) 127.1, 128.7, 129.4, 130.3, 130.8, 134.4, 136.0, 136.6, 137.0, 137.5, 138.0, 140.2, 142.1, 142.3, 153.3, 154.5, 155.3; ESI–MS (M.F. = $C_{37}H_{25}N_3$; $M^+ = 511.20$).

Compound 7b; Yellow solid, m.p. >300 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ_H (ppm) 2.48 (s, 9H), 7.24–7.34 (m, 4H), 7.37 (d, 2H, $J = 7.5$ Hz), 7.50–7.80 9 m, 14H), 8.65 (d, 1H, $J = 3.0$ Hz), 9.44 (d, 1H, $J = 2.4$ Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ_C (ppm) 29.6, 126.6. 126.8, 126.9, 127.3, 129.4, 129.5, 130.1, 130.5, 130.7, 131.7, 133.6, 134.2, 137.3, 139.0, 142.0, 142.3, 153.3, 154.7, 155.1; ESI–MS (M.F. = $C_{40}H_{31}N_3$; $M^+ = 553.16$).

Compound 8a; Yellow solid, m.p. 235–237 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ_H (ppm) 7.31–7.36 (m, 2H), 7.41–7.45 (m, 4H), 7.59–7.63 (m, 8H), 7.67–7.70 (m, 4H), 7.79 (dd, 2H, $J = 3.3$ and 6.3 Hz), 8.21 (dd, 2H, $J = 3.6$ and 6.3 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ_C (ppm) 126.9, 127.0, 127.5, 128.7, 129.1, 129.8, 130.4, 132.6, 137.9, 140.4, 141.2, 141.8, 152.7; ESI–MS (M.F. = $C_{32}H_{22}N_2$; $M^+ = 434.17$).

Compound 8b; Yellow solid, m.p. 217–219 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ_H (ppm) 7.10–7.15 (m, 4H), 7.53–7.60 (m, 8H), 7.65 (d, 4H, $J = 8.1$ Hz), 7.78 (dd, 2H, $J = 3.3$ and 6.3 Hz), 8.18 (dd, 2H, $J = 3.3$ and 6.3 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ_C (ppm) 126.7, 127.1, 127.7, 129.0, 129.5, 130.6, 133.0, 138.1, 140.4, 141.9, 154.0, 160.0); ESI–MS (M.F. = $C_{32}H_{20}F_2N_2$; $M^+ = 471.16$).

Compound 8c; Yellow solid, m.p. 249–151 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ_H (ppm) 2.42 (s, 6H), 7.10–7.13 (m, 4H), 7.55–7.62 (m, 6H), 7.66 (m, 4H), 7.76 (d, 2H, $J = 3.3$ Hz), 8.10 (d, 2H, $J = 3.3$ Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ_C (ppm) 28.2, 126.5, 127.0, 128.0, 129.3, 129.5, 130.5, 132.9, 138.1, 140.3, 142.0, 154.1, 159.7; ESI–MS (M.F. = $C_{34}H_{26}N_2$; $M^+ = 462.20$).

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