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Synthesis of 2,5-Diarylpyrroles by Ligand-Free Palladium-Catalyzed CH Activation of Pyrroles in Ionic Liquids

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The palladium-catalyzed CH activation and arylation of *N*-methylpyrrole and *N*-phenylpyrrole allowed a convenient synthesis of diarylpyrroles. The reactions were performed by using tetrabutylammonium acetate as an ionic solvent, which allowed for the application of a ligand-free catalytic system by using simple palladium salts or polyvinylpyrrolidone-stabilized palladium nanoparticles as the catalyst.

Introduction

Arylated pyrroles are important compounds in chemical research with applications ranging from natural product chemistry to materials science (Figure 1).[1] Arylpyrroles have found many applications in pharmaceutical chemistry as they can bind to a variety of different receptors. For example, they have been reported to act as lipoxygenase, myosin ATPase, and β-secretase inhibitors.[2] Owing to the widespread applications of arylated pyrroles, the development of new and more convenient synthetic methods is a topic of ongoing interest.[3] In this context, palladium-catalyzed cross-coupling reactions, such as Suzuki–Miyaura, Stille, or Negishi coupling reactions, play an important role.[4] In recent years, palladium-catalyzed CH activations have been established as an interesting alternative to common cross-coupling reactions.[5] The application of this methodology avoids the drawbacks of stoichiometrically employed organometallic reagents (that have a relatively high price, toxicity, and sensitivity to air and moisture). On the other hand, activation of a comparatively inert CH bond often requires high temperatures and toxic solvents, such as DMF, dimethylamine (DMA), or *N*-methylpyrrolidone (NMP).[6] The functionalization of electron-rich heterocycles has become a major topic in the field of palladium-catalyzed CH activation reactions based on a Pd^{II}/Pd^{0} catalytic cycles.[7] Owing to the polarization of the molecule by the heteroatom, the catalyst generally attacks selectively on the position with the lowest electron density. The potential of palladium(0)-catalyzed CH arylation reactions has intensively been studied by several research groups, especially by the groups of Doucet,[8] Fagnou,[9] and Daugulis.[10]

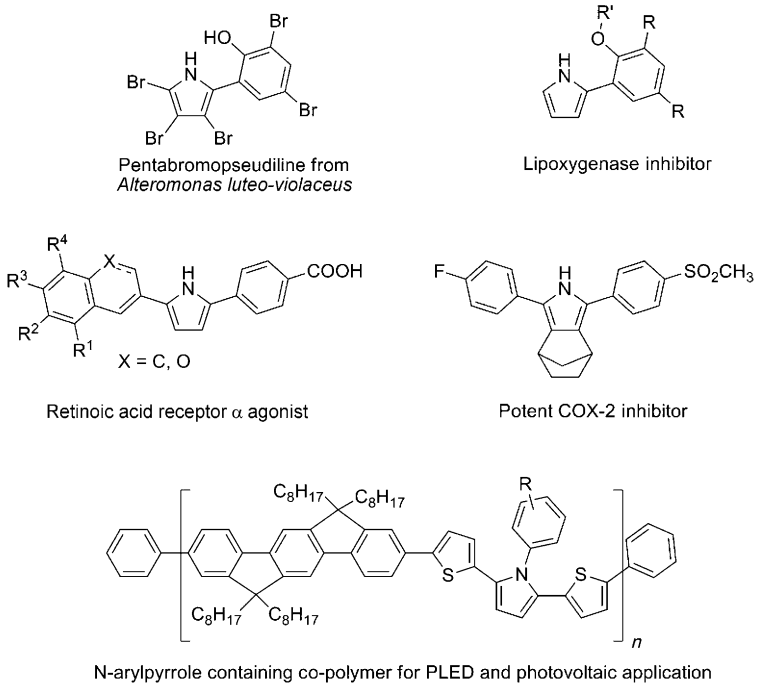

Figure 1. Applications of different arylpyrroles. PLED = Polymer light-emitting diodes.

Most of the reported studies directed towards direct arylation reactions of heterocycles are related to monoarylations.[8–11] In contrast, multiple CH activation is rare.[12] For that

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reason, we examined the possibility of double CH activation reactions of different N-substituted pyrroles. In 2009, Doucet reported the monoarylation of different functionalized pyrroles under phosphine-free conditions using KOAc or K_2CO_3 as the base and DMA as the solvent.[13] During writing this manuscript we became aware that Doucet et al. also very recently published the synthesis of diarylpyrroles through palladium-catalyzed CH activation.[14] Nevertheless, our target was to establish a ligand-free method and to avoid the use of toxic solvents, such as DMA or NMP (Figure 2). In this context, we studied the use of ionic liquids and palladium nanoparticles as the solvent

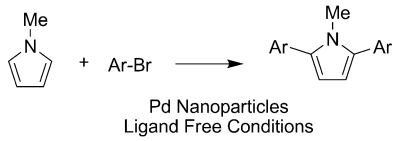


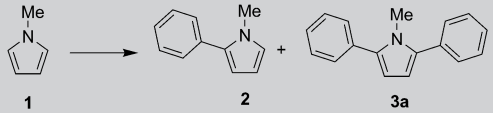
Figure 2. Target reaction: Palladium-catalyzed ligand-free synthesis of 2,5-diarylpyrroles.

and catalyst, respectively. Therefore, we believe that, despite the report of Doucet, our work presented herein will be interesting for a wide range of organic and medicinal chemists.

Results and Discussion

For initial tests we chose the reaction of *N*-methylpyrrole with bromobenzene under typical ligand-free conditions (Table 1). First, palladium(II) acetate and potassium acetate were used as the catalyst precursor and base, respectively. The yields and the ratio between mono- and diarylated products were highly influenced by the choice of the solvent (entries 1–3). Whereas

Table 1. Optimization of the synthesis of *N*-methyl-2,5-diphenylpyrrole (**3a**).[a]



1 2 3a

Entry	PdX_2	Base	Solvent	Additive	Ratio **2**/**3a**[b]	Yield **3a** [%][c]
1	$Pd(OAc)_2$	KOAc	NMP	–	2:1	21
2	$Pd(OAc)_2$	KOAc	DMA	–	3:1	7
3	$Pd(OAc)_2$	KOAc	PEG-400	–	1:2	41
4	$Pd(OAc)_2$	KOAc	PEG-400	TBA-Ac	1:1	34
5	$Pd(OAc)_2$	KOAc	TBA-Ac	–	1:37	75
6	$Pd(OAc)_2$	KOAc	TBA-Br	–	1:1	28
7	$Pd(OAc)_2$	KOAc	$[C_2MIM][BF_4]$[d]	–	0	0
8	$Pd(OPiv)_2$	CsOPiv	TBA-Ac	–	0:1	79
9	$Pd(OPiv)_2$	CsOPiv	TBA-OPiv	–	0:1	63
10	$Pd(OPiv)_2$	–	TBA-Ac	–	0:1	43
11	–	KOAc	TBA-Ac	–	–	0
12	$Pd(OPiv)_2$	CsOPiv	$[C_2MIM][OAc]$	–	–	0

[a] Reaction conditions: $Pd(X)_2$ (1 mol%), base (3.0 equiv.), Ph–Br (3.0 equiv.), solvent, additive, 140 °C, 20 h. [b] Determined by ^{1}H NMR-spectroscopy of the crude product. [c] Yield of isolated products. [d] $[C_2MIM][BF_4]$ = (1-ethyl-3-methylimidazolium tetrafluoroborate.

the use of DMA gave diarylpyrrole **3a** in a low yield along with monoarylated pyrrole **2** as the major product, employment of the biodegradable polymer poly(ethylene glycol) (PEG-400) as the solvent resulted in the formation of **3a** as the major product, which was isolated in 41% yield. Recently, it was reported that phase-transfer catalysts may have a positive impact on CH activation reactions.[15] It is known that the acetate ion can act as integral part of the reaction mechanism.[16] Therefore, we selected tetrabutylammonium acetate (TBA-Ac) as the phase-transfer catalyst and obtained product **3a** in 34% yield (entry 4). Subsequently, we used TBA-Ac as the solvent, which resulted in a dramatic increase of the isolated yield of **3a** (75%). Analysis of the crude product revealed that **3a** was predominantly formed (**3a**/**2a** = 31:1, entry 5).

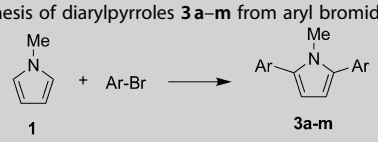
We next studied the use of other palladium catalysts and bases. Employment of palladium pivaloate $[Pd(OPiv)_2]$ as a catalyst precursor and cesium pivaloate as the base led to a further slight increase of the yield of **3a**, which was now exclusively formed (79%, entry 8). Other ionic liquids derived from ammonium or imidazolium salts were less efficient, which highlights the importance of the employed ammonium cations and acetate anions (entries 6, 7, 9, 12).

Having optimized conditions in our hands, we next studied the scope of the reaction and prepared a variety of diarylpyrroles from various aryl bromides. The results are presented in Table 2. Electron-poor aryl bromides gave good yields of the diarylated products, whereas the electron-rich aryl bromides were converted in moderate yields. Sterically hindered *ortho*-substituted aryl bromides were less reactive in the reaction (products **3d** and **3k**). The moderate yield of compound **3f** can be explained by a second arylation through the chloro substituent. The employment of 2-bromothiophene resulted in the formation of a complex mixture, owing to additional CH activation reactions of the thiophene moiety. The relatively low yield of product **3i** (in comparison to the yields of products derived from other electron-poor substrates) can be explained by the formation of reasonable amounts of triarylated pyrrole.

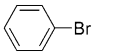
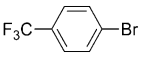
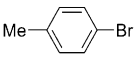
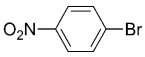
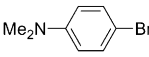
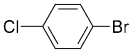
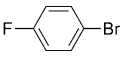
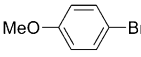
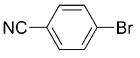
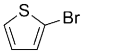
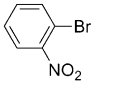
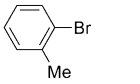
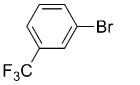
Aryl chlorides are often much cheaper than aryl bromides, because they represent industrial products that are prepared on a large scale. Therefore, we studied the applicability of our methodology to aryl chlorides. The results are presented in Table 3. Aryl chlorides containing electron-withdrawing groups were successfully employed and gave the desired products in moderate yields. In contrast, the use of electron-rich 4-chloroanisole failed (no product was formed). However, addition of XPhos allowed the isolation of the desired product **3h**, albeit in low yield.

Our next step was to elucidate the impact of the N-protecting group of pyrrole to get insight into the scope and limitations of the developed catalytic system. Thus, we tested *N*-*tert*-butoxycarbonyl (*N*-Boc)-protected pyrrole and *N*-phenylpyrrole under the established conditions. Whereas *N*-Boc protected pyrrole gave no reasonable yields of diarylated products, *N*-phenylpyrrole reacted smoothly to give the appropriate diarylated pyrroles in moderate yields (Table 4). As expected, electron-poor aryl bromides were more reactive than electron-rich aryl bromides. Aryl chlorides gave lower yields than the corre-

Table 2. Synthesis of diarylpyrroles **3a–m** from aryl bromides.[a]

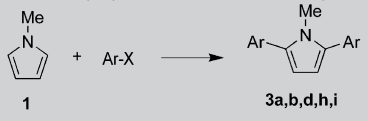


1 **3a-m**

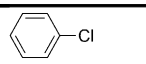
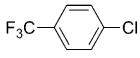
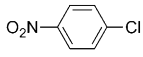
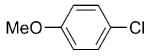
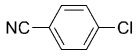
3	Ar–Br	Yield **3** [%][b]
a		79
b		82
c		67
d		71
e		54
f		44
g		62
h		36
i		38
j		0
k		26
l		51
m		30

[a] Reaction conditions: $Pd(OPiv)_2$ (1 mol%), **1** (1 mmol), CsOPiv (3.0 equiv.), Ar–Br (3.0 equiv.), TBA-Ac (1.5 g), 140 °C, 20 h. [b] Yield of isolated products.

Table 3. Synthesis of diarylpyrroles **3a,b,d,h,i** from aryl chlorides.[a]

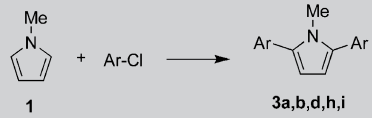


1 **3a,b,d,h,i**

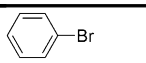
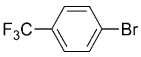
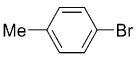
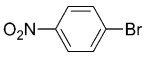
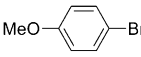
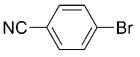
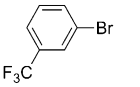
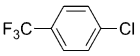
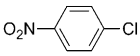
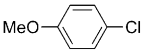
3	Ar–Cl	Yield **3** [%][b]
a		46
b		53
d		45
h		18[c]
i		43

[a] Reaction conditions: $Pd(OPiv)_2$ (1 mol%), **1** (1 mmol) Cs(OPiv) (3.0 equiv.), Ar–Cl (3.0 equiv.), TBA-Ac (1.5 g), 140 °C, 20 h. [b] Yield of isolated products. [c] Addition of 2 mol% of XPhos required.

Table 4. Synthesis of *N*-phenyl-2,5-diarylpyrroles **6a–j** from arylbromides and arylchlorides.[a]



1 **3a,b,d,h,i**

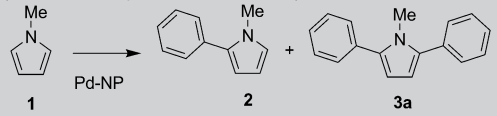
6	Ar–X	Yield **6** [%][b]
a		52
b		40
c		37
d		33
e		15
f		63
g		31
h		22
i		35
j		5[c]

[a] Reaction conditions: $Pd(OPiv)_2$ (1 mol%), **5** (1 mmol), CsOPiv (2.4 equiv.), Ar–X (2.4 equiv.), TBA-Ac (1.5 g), 140 °C, 20 h. [b] Yield of isolated products. [c] Addition of 2 mol% of XPhos required.

sponding aryl bromides. Despite the addition of X-Phos, the reaction of **5** with 4-chloroanisole afforded product **6j** in only 5% yield. In agreement with the findings of Doucet et al.,[14] the reactions of *N*-phenylpyrrole (**5**) proceeded with generally lower yields than those of *N*-methylpyrrole (**1**). This can be explained by the steric demand of the phenyl group.

There are several reports related to the formation of palladium nanoparticles (Pd-NP) in ligand-free palladium-catalyzed reactions using DMF, DMA, or PEG as solvents.[17] In particular, this is observed in Heck reactions using ammonium salts as additives (Jeffrey conditions).[18] Thus, we examined the mode of action of our catalyst system. In a typical experiment, we added an excess of mercury to the reaction after 2 h. The isolated yield of product **3a**, using mercury as an additive and stirring of the reaction mixture for 20 h, reached the range of yield as observed for the mercury-free reaction which was quenched after 2 h. This result clearly indicated the participation of a palladium(0) species in the catalytic cycle.[19] However, the analysis of the reaction mixture after 20 h, using small-angle X-ray scattering (SAXS) spectroscopy under standard conditions, provided no clear evidence of the presence of nanoparticles. Therefore, we tested preformed Pd-NP as heterogeneous catalysts. Surprisingly, polyvinylpyrrolidone (PVP)-stabilized Pd-NP provided the desired products only if TBA-Ac was used as the solvent, whereas in other solvents no product could be detected (Table 5). This is in sharp contrast to the re-

Table 5. Application of PVP-stabilized Pd-NP for the syntheses of 2,5-diphenylpyrrole **3a** using Pd-NP as the catalyst.[a]



1 2 3a

	NP radius [nm]	Solvent	Ratio **2**/**3a**[b]	Yield **3a** [%]
1	1.1 ±0.1	DMA	–	0
2	1.1 ±0.1	propylene carbonate	–	0
3	1.1 ±0.1	PEG-400	–	0
4	1.1 ±0.1	NMP	–	0
5	1.1 ±0.1	dimethyl sulfoxide	–	0
6	1.1 ±0.1	xylene	–	0
7	1.1 ±0.1	TBA-Ac	0.0:1.0	49[c]
8	3.1 ±0.3	TBA-Ac	1.0:0.8	17[b]
9	2.4 ±0.5	TBA-Ac	1.0:1.1	23[b]

[a] Reaction conditions: Pd-NP (1 mol%), KOAc (3 equiv.), **1** (0.5 mmol), Ph–Br (3 equiv.), solvent, 140 °C, 20 h. [b] Determined by ^{1}H NMR-spectroscopy of the crude product. [c] Yield of isolated products.

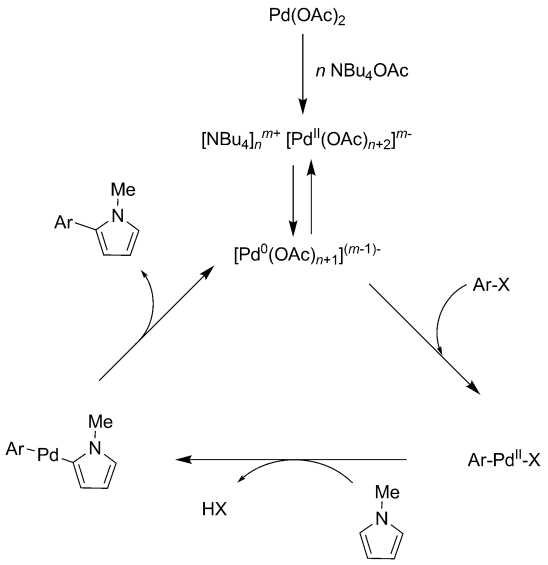
sults obtained by using Pd^{II} salts as the catalyst precursors (Table 1). Furthermore, the reaction involving preformed Pd-NP proved to be dependent on the size of the nanoparticles. Small nanoparticles showed higher activities than larger ones, because of their larger surface. In general, Pd^{II} salts gave higher yields than the employed nanoparticles.

In various publications, the groups of Trzeciak and Muzart showed that $Pd(OAc)_2$ forms anionic palladates in the presence of ammonium salts.[20] In particular, Trzeciak et al. observed the reduction of these palladates to palladium(0) in the presence of acetate anions at elevated temperatures.[21] Moreover, it was reported that PVP-stabilized Pd-NP are oxidized to related palladates in the presence of ammonium salts,[22] which explains the activity of the nanoparticles in the presence of ammonium acetate. As a consequence of our experimental data and the results published by Trzeciak and others, we proposed a catalytic cycle based on a Pd^0/Pd^{II} mechanism (Scheme 1).

The reaction of the ammonium salt with the employed palladium(II) salt or with the Pd-NP resulted in the formation of anionic palladate complexes. At elevated temperatures, traces of tributylamine were formed from the employed ammonium salt by Hofmann elimination. Tributylamine subsequently reduced the palladate to the catalytically active palladium(0) species.[23] On the one hand the ammonium salt stabilized the active palladium(0) species by preventing the formation of "palladium black". On the other hand, it increased the solubility of the organometallic complex. The formed ammonium palladate species represented a resting state of the catalytically active palladium(0) complex.

Conclusions

We developed a catalytic system for the diarylation of *N*-methyl- and *N*-phenylpyrrole. The reactions proceeded under "ligand-free" conditions. The best yields were obtained if tetrabutylammonium acetate, an environmentally friendly ionic liquid, was used as the solvent. A variety of aryl bromides and electron-poor aryl chlorides were successfully employed in this reaction. In addition, we examined the application of palladium nanoparticles as heterogeneous catalysts in this reaction. Supported by further experimental results, we proposed a possible mechanism and discussed the crucial role of tetrabutylammonium acetate as a solvent.



Scheme 1. Proposed reaction mechanism; species such as Ar–Pd^{II}–X are coordinated by acetate anions and assumed to be negatively charged.[24]

Experimental Section

General

All reactions were performed under argon atmosphere. TBA-Ac was either purchased from Sigma Aldrich or synthesized according to a known procedure.[25] Unless otherwise cited, all chemicals are commercially available and were used without further purification. Column chromatography was performed by using Merck Silicagel 60 (0.043–0.06 mm). NMR data were recorded on Bruker ARX 300 and Bruker ARX 400 spectrometers. ^{13}C and ^{1}H NMR spectra were referenced to signals of deuterated solvents and residual protonated solvents, respectively. IR spectra were recorded on a Nicolet 550 FT-IR spectrometer with ATR sampling technique for solids as well as liquids. GC–MS was performed on an Agilent HP-5890 instrument with an Agilent HP-5973 Mass Selective Detector (EI) and HP-5 capillary column using helium carrier gas. ESI-HRMS measurements were performed on an Agilent 1969A TOF mass spectrometer. For High Resolution MS (HRMS) a Finnigan MAT 95 XP was used. Only the measurements with an average deviation from the theoretical mass of ±2 mDa were accounted as correct. Elemental analyses (EA) were performed with a Leco Mikroanalysator–TrueSpec CHNS Micro. Melting points were determined on a Micro-Hot-Stage GalenTM III Cambridge Instruments. The melting points were not corrected. SAXS measurements were performed with a Kratky-type instrument (SAXSess, Anton Paar, Austria) operated at 40 kV and 50 mA in slit collimation by using a 2D CCD detector (T = −40 °C). The 2D scattering pattern was converted into a 1D scattering curve as a function of the magnitude of the scattering vector with SAXSQuant Software (Anton Paar). A Göbel mirror was used to convert the divergent polychromatic X-ray beam into a col-

limated line-shaped beam of $Cu_{K\alpha}$ radiation ($\lambda = 0.154$ nm). Slit collimation of the primary beam was applied in order to increase the flux and to improve the signal quality. The liquid sample cell consisted of a quartz capillary (internal diameter: 1 mm) stacked in a metal body with two windows for the X-ray beam. Using this sample cell, an identical volume of the solution was always irradiated. Scattering profiles of Pd-NP were obtained by subtraction of the detector current and the scattering profile of the solvent from the scattering profiles of the Pd-NP solutions. From the scattering curves then both the Guinier radius and the volume-weighted size distribution by indirect Fourier transformation were obtained.

Preparation of Pd/PVP nanoparticles

The following values are for a 20 mL approach with a Pd concentration of 20 mM. Na_2PdCl_4 (117.7 mg, 0.4 mmol) and PVP K-30 (133.4 mg, 1.2 mmol of repeating unit) were dissolved in ethylene glycol (18 mL). The solution was stirred at 100 °C under argon atmosphere. Subsequently, an ethylene glycol solution of sodium hydroxide (2 mL, 0.5 M) was rapidly added. The color changed within seconds from orange over yellow to dark brown. After stirring for 3 h at 100 °C, the mixture was cooled to RT.

Syntheses of 2,5-diarylpyrroles

$Pd(OPiv)_2$ (0.01 mmol, 1.0 mol%), *N*-methyl- or *N*-phenylpyrrole (**1** or **5**, 1.0 mmol), the appropriate amount of aryl bromide or aryl chloride, and CsOPiv were placed in an argon-flushed glass pressure tube, followed by tetrabutylammonium acetate (1.5 g). The pressure tube was closed with a Teflon cap and the reaction mixture was stirred at 140 °C for 20 h. Afterwards, the mixture was cooled to RT and diluted with distilled water and ethyl acetate. The water layer was extracted 2 times with ethyl acetate and the combined organic layers were washed with brine. The combined organic layers were dried with sodium sulfate and filtered. The solvent of the filtrate was evaporated and the product was purified by column chromatography.

N-Methyl-2,5-diphenylpyrrole (**3a**): According to the general procedure, **3a** was isolated as a light yellow solid by using Ar–Br or Ar–Cl (3.0 mmol) with CsOPiv (3.0 mmol) as the base (Ar–Br: 185 mg, 79%; Ar–Cl: 107 mg, 46%), m.p. 165–167 °C. ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 3.61$ (s, 3H, CH_3), 6.32 (s, 2H, CH), 7.27–7.47 ppm (m, 10H, CH). ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 34.3$ (CH_3), 108.7, 126.8, 128.4, 128.7 (CH), 133.5, 136.9 ppm (C). IR (ATR): $\tilde{\nu} = 3058$ (w), 2918 (w), 2850 (w), 1597 (w), 1464 (m), 1331 (w), 1076 (m), 918 (w), 750 (s), 697 (s), 506 cm^{-1} (m). MS (EI, 70 eV): *m/z* (%) = 233 (M^+, 100), 232 (19), 219 (11), 217 (14), 115 (9). HRMS (EI, 70 eV): calcd. for $C_{17}H_{15}N$: 233.11990; found: 233.11997.

N-Methyl-2,5-di(4-trifluoromethylphenyl)pyrrole (**3b**): According to the general procedure, **3b** was isolated as a white solid by using Ar–Br or Ar–Cl (3.0 mmol) with CsOPiv (3.0 mmol) as the base (Ar–Br: 306 mg, 82%; Ar–Cl: 195 mg, 53%), m.p. 155 °C. ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 3.66$ (s, 3H, CH_3), 6.45 (s, 2H, CH), 7.61 (d, 4H, $^3J = 8.2$ Hz, CH), 7.72 ppm (d, 4H, $^3J = 8.2$ Hz, CH). ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 34.5$ (CH_3), 110.3 (CH), 124.3 (q, $^1J = 272.3$ Hz, CF_3), 125.5 (q, $^3J = 3.9$ Hz, CH), 128.6 (CH), 128.9 (q, $^2J = 32.2$ Hz, C), 136.5, 136.6 ppm (C). IR (ATR): $\tilde{\nu} = 1930$ (w), 1609 (m), 1455 (w), 1320 (s), 1107 (s), 1067 (s), 750 (s), 1013 (m), 845 (s), 764 (m), 598 (m), 505 cm^{-1} (m). MS (EI, 70 eV): *m/z* (%) = 369 (M^+, 100), 368 (15), 350 (9), 285 (4), 259 (2), 185 (3). HRMS (EI, 70 eV): calcd. for $C_{19}H_{13}F_6N$: 369.09467; found: 369.09442. EA: calcd. for $C_{19}H_{13}F_6N$ (369.29): C, 61.79; H, 3.55; N, 3.79; found: C, 61.94; H, 3.57; N, 3.64.

N-Methyl-2,5-di(*p*-tolyl)pyrrole (**3c**): According to the general procedure, **3c** was isolated as a light yellow solid by using Ar–Br (3.0 mmol, 177 mg, 67%) with CsOPiv (3.0 mmol) as the base, m.p. 161 °C. ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 2.30$ (s, 6H, CH_3), 3.49 (s, 3H, CH_3), 6.19 (s, 2H, CH), 7.13 (d, 4H, $^3J = 7.9$ Hz, CH), 7.25–7.29 ppm (m, 4H, CH). ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 21.2$ (CH_3), 34.2 (CH_3), 108.2, 128.6, 129.1 (CH), 130.7, 136.5, 136.6 ppm (C). IR (ATR): $\tilde{\nu} = 3018$ (w), 2915 (w), 2853 (w), 1914 (w), 1446 (m), 1326 (m), 1113 (m), 820 (s), 766 (s), 510 (s), 487 cm^{-1} (m). MS (EI, 70 eV): *m/z* (%) = 261 (M^+, 100), 260 (14), 246 (10), 130 (5), 128 (5). HRMS (EI, 70 eV): calcd. for $C_{19}H_{19}N$: 261.15120; found: 261.15120. Elemental analysis calcd. for $C_{19}H_{19}N$ (261.35): C, 87.31; H, 7.33; N, 5.36; found: C, 87.41; H, 7.30; N, 5.08.

N-Methyl-2,5-di(4-nitrophenyl)pyrrole (**3d**): According to the general procedure, **3d** was isolated as an orange-red solid using Ar–Br or Ar–Cl (3.0 mmol) with CsOPiv (3.0 mmol) as the base (Ar–Br: 232 mg, 71%; Ar–Cl: 144 mg, 45%), m.p. 193 °C. ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 3.70$ (s, 3H, CH_3), 6.52 (s, 2H, CH), 7.59–7.63 (m, 4H, CH), 8.26–8.31 ppm (m, 4H, CH). ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 35.1$ (CH_3), 112.0 (CH), 124.1, 128.5, (CH), 137.0, 138.9, 146.4 ppm (C). IR (ATR): $\tilde{\nu} = 3096$ (w), 2929 (w), 1936 (w), 1589 (s), 1509 (s), 1332 (s), 1104 (m), 850 (s), 752 (s), 695 (m), 496 cm^{-1} (m). MS (EI, 70 eV): *m/z* (%) = 323 (M^+, 100), 293 (10), 277 (9), 247 (10), 231 (22), 230 (17). HRMS (EI, 70 eV): calcd. for $C_{17}H_{13}N_3O_4$: 323.09006; found: 323.09005.

N-Methyl-2,5-di(4-(*N*,*N*-dimethylamino)phenyl)pyrrole (**3e**): According to the general procedure, **3e** was isolated as a yellow solid using Ar–Br (3.0 mmol, 174 mg, 54%) with CsOPiv (3.0 mmol) as the base, m.p. 189–190 °C. ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 2.97$ (s, 12H, NMe_2), 3.54 (s, 3H, CH_3), 6.18 (s, 2H, CH), 6.74–6.79 (m, 4H, CH), 7.30–7.35 ppm (m, 4H, CH). ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 33.9$ (CH_3), 40.6 (NMe_2), 107.1, 112.3 (CH), 122.2 (C), 129.7 (CH), 136.2, 149.4 ppm (C). IR (ATR): $\tilde{\nu} = 2954$ (m), 2927 (m), 2870 (m), 2792 (m), 1903 (w), 1610 (s), 1506 (s), 1442 (s), 1341 (s), 1226 (m), 1163 (s), 1060 (m), 945 (m), 820 (s), 756 (s), 532 cm^{-1} (m). MS (EI, 70 eV): *m/z* (%) = 319 (M^+, 100), 304 (33), 303 (10), 288 (10), 160 (12), 152 (11). HRMS (EI, 70 eV): calcd. for $C_{21}H_{25}N_3$: 319.20430; found: 319.20429.

N-Methyl-2,5-di(4-chlorophenyl)pyrrole (**3f**): According to the general procedure, **3f** was isolated as a yellow solid by using Ar–Br (3.0 mmol, 135 mg, 44%) with CsOPiv (3.0 mmol) as the base, m.p. 174 °C. ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 3.56$ (s, 3H, CH_3), 6.30 (s, 2H, CH), 7.38 ppm (s, 8H, CH). ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 34.2$ (CH_3), 109.1, 128.7, 129.8 (CH), 131.7, 132.9, 136.0 ppm (C). IR (ATR): $\tilde{\nu} = 3915$ (w), 1909 (w), 1672 (w), 1448 (m), 1405 (w), 1336 (w), 1092 (m), 1007 (m), 834 (s), 758 (s), 714 (m), 513 (s), 480 cm^{-1} (m). MS (EI, 70 eV): *m/z* (%) = 301 (M^+, 100), 303 (64), 304 (13), 305 (11), 300 (9), 286 (11), 251 (7), 151 (9). HRMS (EI, 70 eV): calcd. for $C_{17}H_{13}Cl_2N$: 301.04196; found: 301.04203. Elemental analysis calcd. for $C_{17}H_{13}Cl_2N$ (302.18): C, 67.57; H, 4.34; N, 4.63; found: C, 67.50; H, 4.45; N, 4.34.

N-Methyl-2,5-di(4-fluorophenyl)pyrrole (**3g**): According to the general procedure, **3g** was isolated as a white solid by using Ar–Br (3 mmol, 167 mg, 62%) with CsOPiv (3 mmol) as the base, m.p. 194–196 °C. ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 3.53$ (s, 3H, CH_3), 6.25 (s, 2H, CH), 7.06–7.14 (m, 4H, CH), 7.37–7.43 ppm (m, 4H, CH). ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 34.0$ (CH_3), 108.6 (CH), 115.4 (d, $^2J = 21.4$ Hz, CH), 129.6 (d, $^4J = 3.3$ Hz, C), 130.4 (d, $^3J = 8.4$ Hz, CH), 135.7 (C), 162.0 ppm (d, $^2J = 246.6$ Hz, CF). IR (ATR): $\tilde{\nu} = 2950$ (w), 1902 (w), 1665 (w), 1600 (w), 1548 (w), 1493 (s), 1329 (w), 1222 (s), 1156 (m), 1098 (m), 837 (s), 812 (s), 765 (s), 636 (m), 523 (s), 429 cm^{-1} (w). MS (EI, 70 eV): *m/z* (%) = 269 (M^+, 100), 268 (17), 254

(19), 253 (13), 227 (6), 133 (8). HRMS (EI, 70 eV): calcd. for $C_{17}H_{13}F_2N$: 269.10106; found: 269.10098.

N-Methyl-2,5-di(4-methoxyphenyl)pyrrole (**3h**): According to the general procedure, **3h** was isolated as a yellow solid using Ar–Br or Ar–Cl (3.0 mmol) with CsOPiv (3.0 mmol) as the base and the XPhos ligand (2 mol%) (Ar–Br: 107 mg, 36%; Ar–Cl: 52 mg, 18%), m.p. 156 °C. ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 3.54$ (s, 3H, CH_3), 3.84 (s, 6H, OCH_3), 6.22 (s, 2H, CH), 6.93–6.97 (m, 4H, CH), 7.35–7.40 ppm (m, 4H, CH). ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 33.9$ (CH_3), 55.3 (OCH_3), 107.7, 113.8 (CH), 126.4 (C), 130.0 (CH), 136.1, 158.7 ppm (C). IR (ATR): $\tilde{\nu} = 3013$ (w), 2954 (w), 2932 (w), 2836 (w), 1904 (w), 1677 (w), 1606 (m), 1572 (m), 1463 (m), 1242 (s), 1174 (s), 1112 (m), 1026 (s), 833 (s), 757 (s), 632 (m), 531 cm^{-1} (m). MS (EI, 70 eV): *m/z* (%) = 293 (M^+, 100), 279 (15), 278 (75), 147 (11). HRMS (EI, 70 eV): calcd. for $C_{19}H_{19}NO_2$: 293.14103; found: 293.14116.

N-Methyl-2,5-di(4-cyanophenyl)pyrrole (**3i**): According to the general procedure, **3i** was isolated as a yellow solid by using Ar–Br or Ar–Cl (3.0 mmol) with CsOPiv (3.0 mmol) as the base (Ar–Br: 109 mg, 38%; Ar–Cl: 121 mg, 43%), m.p. 195–197 °C. ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 3.63$ (s, 3H, CH_3), 6.43 (s, 2H, CH), 7.52–7.56 (m, 4H, CH) 7.67–7.71 ppm (m, 4H, CH). ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 34.9$ (CH_3), 110.2 (CH), 111.3, 118.8 (C), 128.6, 132.4 (CH), 136.9, 137.1 ppm (C). IR (ATR): $\tilde{\nu} = 2960$ (w), 2873 (w), 2224 (m), 1689 (w), 1603 (m), 1445 (m), 1246 (m), 840 (s), 768 (s), 730 (m), 546 cm^{-1} (s). MS (EI, 70 eV): *m/z* (%) = 283 (M^+, 100), 282 (16), 268 (7), 267 (9). HRMS (EI, 70 eV): calcd. for $C_{19}H_{13}N_3$: 283.11040; found: 283.11005.

N-Methyl-2,5-bis(2-nitrophenyl)pyrrole (**3k**): According to the general procedure, **3k** was isolated as a highly viscous oil by using Ar–Br (3.0 mmol, 85 mg, 26%) with CsOPiv (3.0 mmol) as the base. ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 3.20$ (s, 3H, CH_3), 6.21 (s, 2H, CH), 7.53–7.56 (m, 4H, CH) 7.63–7.66 (m, 2H, CH), 7.95–7.98 ppm (m, 2H, CH). ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 32.4$ (CH_3), 109.4 (CH), 124.2 (CH), 127.8 (C), 129.0 (CH), 129.2, 130.3 (C), 132.5, 133.7 ppm (CH). IR (ATR): $\tilde{\nu} = 2923$ (w), 1607 (m), 1519 (s), 1341 (s), 1238 (m), 1085 (w), 852 (m), 750 (s), 511 cm^{-1} (m). MS (EI, 70 eV): *m/z* (%) = 323 (M^+, 62), 234 (21), 218 (40), 202 (22), 189 (19), 163 (32), 147 (31). HRMS (ESI): calcd for $C_{17}H_{14}N_3O_4$ ($[M+H]^+$): 324.09788; found: 324.09778.

N-Methyl-2,5-di(*o*-tolyl)pyrrole (**3l**): According to the general procedure, **3l** was isolated as a viscous oil by using Ar–Br (3.0 mmol, 133 mg, 51%) with CsOPiv (3.0 mmol) as the base. ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 2.34$ (s, 6H, CH_3), 3.17 (s, 3H, CH_3), 6.23 (s, 2H, CH), 7.28–7.42 ppm (m, 8H, CH). ^{13}C NMR (75 MHz, $CDCl_3$): $\delta =$ 20.0 (CH_3), 31.8 (CH_3), 107.7, 125.5, 127.9, 129.9, 131.3 (CH), 133.5, 133.7, 138.1 ppm (C). IR (ATR): $\tilde{\nu} = 2920$ (w), 1602 (w), 1438 (m), 1379 (m), 1315 (m), 1116 (w), 1032 (m), 944 (w), 754 (s), 729 (s), 451 cm^{-1} (m). MS (EI, 70 eV): *m/z* (%) = 261 (M^+, 100), 246 (18), 230 (6), 215 (6), 202 (6), 170 (7). HRMS (ESI): calcd for $C_{19}H_{20}N$ ($[M+H]^+$): 262.15903; found: 262.15892. Elemental analysis calcd. for $C_{19}H_{19}N$ (261.36): C, 87.31; H, 7.33; N, 5.36; found: C, 87.43; H, 7.70; N, 5.136.

N-Methyl-2,5-bis(3-(trifluoromethyl)phenyl)pyrrole (**3m**): According to the general procedure, **3m** was isolated as a light yellow oil using Ar–Br (3.0 mmol, 109 mg, 30%) with CsOPiv (3.0 mmol) as the base. ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 3.64$ (s, 3H, CH_3), 6.41 (s, 2H, CH), 7.54–7.63 (m, 4H, CH), 7.66–7.69 (m, 2H, CH), 7.75–7.75 ppm (m, 2H, CH). ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 34.3$ (CH_3), 109.9 (CH), 123.6 (q, $^3J = 3.6$ Hz, CH), 124.1 (q, $^1J = 273.4$ Hz, CF_3), 125.3 (q, $^3J = 3.8$ Hz, CH), 129.0 (CH), 131.0 (q, $^2J = 32.2$ Hz, C), 131.7 (CH), 133.9, 136.1 ppm (C). IR (ATR): $\tilde{\nu} = 2924$ (w), 1588 (w), 1459 (m), 1325 (s), 1238 (m), 1160 (s), 1116 (s), 1047 (s), 902 (m), 801 (m), 766 (s), 699 cm^{-1} (s). MS (EI, 70 eV): *m/z* (%) = 369 (M^+, 100), 350 (8), 285 (3), 259 (3), 202 (2), 185 (5). HRMS (ESI): calcd for $C_{19}H_{14}F_6N$ ($[M+H]^+$): 370.1025; found: 370.10242. EA: calcd. for $C_{19}H_{13}F_6N$ (369.30): C, 61.79; H, 3.55; N, 3.79; found C, 61.48; H, 3.641; N, 3.671.

1,2,5-Triphenyl-1*H*-pyrrole (**6a**): According to the general procedure, **6a** was isolated as a light yellow solid by using Ar–Br (2.4 mmol, 154 mg, 52%) with CsOPiv (2.4 mmol) as the base, m.p. 231–232 °C. ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 6.47$ (s, 2H, CH), 7.00–7.06 (m, 6H, CH), 7.11–7.17 (m, 6H, CH), 7.20–7.23 ppm (m, 3H, CH). ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 109.9$ (CH), 126.2 (CH), 127.2 (CH), 127.8 (CH), 128.7 (2 x CH), 128.8 (CH), 133.2 (C), 135.8 (C), 138.9 ppm (C). IR (ATR): $\tilde{\nu} = 3052$ (w), 2916 (w), 1596 (m), 1494 (m), 1481 (m), 1395 (w), 1334 (w), 774 (s), 692 (s), 595 cm^{-1} (m). MS (EI, 70 eV): *m/z* (%) = 295 (M^+, 100), 217 (10), 191 (25), 165 (11), 139 (7), 115 (8), 77 (19), 51 (13). HRMS (EI, 70 eV): calcd. for $C_{22}H_{17}N$: 295.13555; found: 295.13543.

N-Phenyl-2,5-bis(4-(trifluoromethyl)phenyl)-1*H*-pyrrole (**6b**): According to the general procedure, **6b** as a light yellow solid by using Ar–Br or Ar–Cl (2.4 mmol) with CsOPiv (2.4 mmol) as the base (Ar–Br: 223 mg, 52%; Ar–Cl: 95 mg, 22%). m.p. 187–189 °C. ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 6.56$ (s, 2H, CH), 7.01–7.04 (m, 2H, CH), 7.11–7.14 (m, 4H, CH), 7.29–7.32 (m, 3H, CH), 7.39–7.42 ppm (m, 4H, CH). ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 111.4$ (CH), 124.1 (q, $^1J_{C-F} =$ 271.9 Hz, CF_3), 124.9 (q, $^3J_{C-F} = 3.9$ Hz, CH), 128.0 (CH), 128.2 (q, $^2J_{C-F} = 32.2$ Hz, C), 128.4 (CH), 128.7 (CH), 129.3 (CH), 135.1 (C), 136.3 (C), 138.2 ppm (C). IR (ATR): $\tilde{\nu} = 1610$ (w), 1497 (w), 1421 (m), 1347 (s), 1323 (s), 1162 (s), 1115 (s), 901 (m), 774 (s), 697 cm^{-1} (s). MS (EI, 70 eV): *m/z* (%) = 431 (M^+, 100), 412 (9), 259 (8), 191 (10), 146 (9), 77 (10). HRMS (EI, 70 eV): calcd. for $C_{24}H_{15}F_6N$: 431.11032; found: 431.10984.

N-Phenyl-2,5-di(*p*-tolyl)-1*H*-pyrrole (**6c**): According to the general procedure, **6c** was isolated as a light yellow solid by using Ar–Br (2.4 mmol, 119 mg, 37%) with CsOPiv (2.4 mmol) as a base, m.p. 215–217 °C. ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 2.27$ (s, 6H, CH_3), 6.43 (s, 2H, CH), 6.93–6.98 (m, 8H, CH), 7.02–7.04 (m, 2H, CH), 7.22–7.24 ppm (m, 3H, CH). ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 21.0$ (CH_3), 109.4 (CH), 127.0 (CH), 128.5 (2×CH), 128.6 (CH), 128.9 (CH), 130.4 (C), 135.6 (C), 135.7 (C), 139.1 ppm (C). IR (ATR): $\tilde{\nu} = 2917$ (w), 1494 (s), 1332 (m), 814 (s), 768 (s), 693 (s), 579 (s), 521 (s), 401 cm^{-1} (s). MS (EI, 70 eV): *m/z* (%) = 323 (M^+, 100), 205 (8), 191 (9), 77 (13), 51 (6). HRMS (EI, 70 eV): calcd. for $C_{24}H_{21}N$: 323.16685; found: 323.16660.

N-Phenyl-2,5-bis(4-nitrophenyl)-1*H*-pyrrole (**6d**): According to the general procedure, **6d** was isolated as an orange solid by using Ar–Br or Ar–Cl (2.4 mmol) with CsOPiv (2.4 mmol) as the base (Ar–Br: 180 mg, 47%; Ar–Cl: 135 mg, 35%), m.p. 253–255 °C. ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 6.67$ (s, 2H, CH), 7.04–7.07 (m, 2H, CH), 7.12–7.17 (m, 4H, CH), 7.30–7.40 (m, 3H, CH), 7.99–8.04 ppm (m, 4H, CH). ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 112.9$ (CH), 123.4 (CH), 128.4 (CH), 128.5 (CH), 128.7 (CH), 129.7 (CH), 135.2 (C), 137.7 (C), 138.8 (C), 145.9 ppm (C). IR (ATR): $\tilde{\nu} = 1585$ (s), 1501 (s), 1320 (s), 1105 (s), 850 (s), 772 (s), 747 (s), 697 (s), 521 cm^{-1} (m). MS (EI, 70 eV): *m/z* (%) = 385 (M^+, 100), 339 (7), 291 (24), 278 (8), 265 (6), 189 (7), 146 (10), 30 (6). HRMS (EI, 70 eV): calcd. for $C_{22}H_{15}N_3O_4$: 385.10571; found: 385.10543. EA: calcd. for $C_{22}H_{15}N_3O_4$ (385.37): C, 68.57; H, 3.92; N, 10.90; found: C, 68.37; H, 3.80; N, 11.03.

N-Phenyl-2,5-bis(4-methoxyphenyl)-1*H*-pyrrole (**6e**): According to the general procedure, **6e** was isolated as a yellow solid by using Ar–Br or Ar–Cl (2.4 mmol) with CsOPiv (2.4 mmol) as the base (Ar–Br: 53 mg, 15%; Ar–Cl: 18 mg, 5%), m.p. 149–151 °C. ^{1}H NMR

(300 MHz, $CDCl_3$): $\delta = 3.73$ (s, 6H, OCH_3), 6.37 (s, 2H, CH), 6.67–6.72 (m, 4H, CH), 6.94–7.02 (m, 6H, CH), 7.20–7.23 ppm (m, 3H, CH). ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 55.1$ (OCH_3), 108.9 (CH), 113.3 (CH), 125.9 (C), 127.0 (CH), 128.6 (CH), 128.9 (CH), 129.9 (CH), 135.1 (C), 139.0 (C), 158.0 ppm (C). IR (ATR): $\tilde{\nu} = 2927$ (w), 2831 (w), 1496 (s), 1382 (m), 1281 (m), 1239 (s), 1173 (s), 1025 (s), 824 (s), 751 (s), 695 (s), 583 (s), 523 cm^{-1} (s). MS (EI, 70 eV): m/z (%) = 355 (M^+, 100), 340 (56), 296 (6), 268 (10), 178 (9), 77 (10). HRMS (EI, 70 eV): calcd. for $C_{24}H_{21}NO_2$: 355.15668; found: 355.15638.

N-Phenyl-2,5-bis(4-cyanophenyl)-1*H*-pyrrole (**6 f**): According to the general procedure, **6 f** was isolated as a white solid using Ar–Br (2.4 mmol, 217 mg, 63%) with CsOPiv (2.4 mmol) as the base, m.p. 289–291 °C. ^1H NMR (300 MHz, $CDCl_3$): $\delta = 6.59$ (s, 2H, CH), 7.00–7.03 (m, 2H, CH), 7.06–7.10 (m, 4H, CH), 7.28–7.37 (m, 3H, CH), 7.40–7.44 ppm (m, 4H, CH). ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 109.7$ (C), 112.2 (CH), 118.8 (C), 128.4 (CH), 128.5 (2×CH), 129.5, 131.8 (CH), 135.1, 136.9, 137.8 ppm (C). IR (ATR): $\tilde{\nu} = 2221$ (s), 1598 (s), 1532 (s), 1490 (s), 1428 (m), 1344 (s), 1178 (m), 840 (s), 778 (s), 697 (s), 560 cm^{-1} (s). MS (EI, 70 eV): m/z (%) = 345 (M^+, 100), 242 (6), 216 (13), 190 (8), 77 (16), 51 (12). HRMS (EI, 70 eV): calcd. for $C_{24}H_{15}N_3$: 345.12605; found: 345.12565.

N-Phenyl-2,5-bis(3-(trifluoromethyl)phenyl)-1*H*-pyrrole (**6 g**): According to the general procedure, **6 g** was isolated as a white solid by using Ar–Br (2.4 mmol, 185 mg, 43%) with CsOPiv (2.4 mmol) as the base, m.p. 201–203 °C. ^1H NMR (300 MHz, $CDCl_3$): $\delta = 6.55$ (s, 2H, CH), 7.00–7.03 (m, 2H, CH), 7.18–7.21 (m, 2H, CH), 7.26–7.30 (m, 7H, CH), 7.36–7.39 ppm (m, 2H, CH). ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 110.8$ (CH), 122.9 (q, $^3J_{C-F} = 3.8$ Hz, CH), 123.8 (q, $^1J_{C-F} = 272.3$ Hz, CF_3), 125.2 (q, $^3J_{C-F} = 3.8$ Hz, CH), 128.0 (CH), 128.3 (CH), 128.7 (CH), 129.2 (CH), 130.3 (q, $^2J_{C-F} = 32.2$ Hz, C), 131.5 (CH), 133.5 (C), 134.8 (C), 138.0 ppm (C). IR (ATR): $\tilde{\nu} = 1611$ (m), 1498 (m), 1433 (m), 1318 (s), 1168 (s), 1104 (s), 1061 (s), 1013 (s), 837 (s), 778 (s), 703 (s), 597 (s), 493 cm^{-1} (m). MS (EI, 70 eV): m/z (%) = 431 (M^+, 100), 412 (7), 259 (10), 191 (9), 77 (12), 51 (6). HRMS (EI, 70 eV): calcd. for $C_{24}H_{15}F_6N$: 431.11032; found: 431.10999. Elemental analysis calcd. for $C_{24}H_{15}F_6N$ (431.37): C, 66.82; H, 3.50; N, 3.25; found: C, 67.01; H, 3.46; N, 3.28.

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