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Generation of Aryl Radicals from Aryl Halides: Rongalite-Promoted Transition-Metal-Free Arylation

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Supporting Information Placeholder

ABSTRACT: A new and practical method for the generation of aryl radicals from aryl halides is reported. Rongalite as a novel precursor of super electron donors was used to initiate a series of electron-catalyzed reactions under mild conditions. These transition-metal-free radical chain reactions enable the efficient formation of C-C, C-S and C-P bond through homolytic aromatic substitution or $S_{RN}1$ reactions. Moreover, the synthesis of antipsychotic drug Quetiapine was performed on gram scale through the described method. This protocol demonstrated its potential as a promising arylation method in organic synthesis.

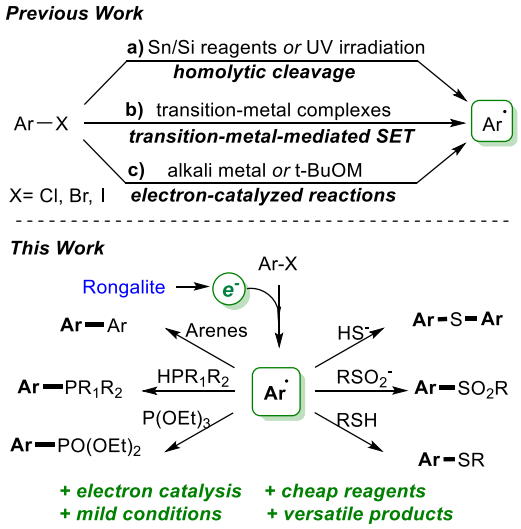
INTRODUCTION

Aryl radicals are important synthetic intermediates in organic chemistry.[1] Generating aryl radicals from aryl halides is the most useful way to access these highly reactive intermediates. Traditionally, halogen abstraction, photo-induced homolytic cleavage of carbon-halogen (C-X) bond and transition-metal-mediated single electron transfer (SET) strategy have been widely used to generate aryl radicals (Scheme 1a, 1b).[2] However, they suffer from a series of limitations, including harsh reaction conditions, limited substrate scopes and the usage of expensive or toxic reagents like silicon or tin reagents.

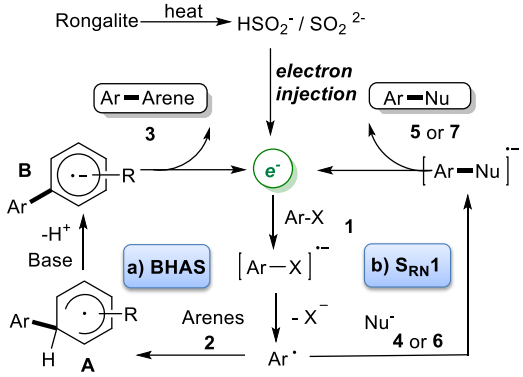
Recently, transition-metal-free coupling between aryl halides and arenes in the presence of *t*-BuOK or *t*-BuONa, referred to as base-promoted homolytic aromatic substitution (BHAS), has been well demonstrated.[3,4] The mechanistic studies indicated that the in situ generated organic electron donors can initiate single electron transfer (SET) process to provide aryl radicals.[5] These transformations were recognized as "electron-catalyzed reactions"[3a,3b,6a], which not only played an important role in modern radical chemistry but also provided a promising way to obtain radical intermediates (Scheme 1c).[3,6] Despite these achievements, the application of this electron-catalysis strategy in the generation of aryl radicals was still limited due to the high redox potentials of aryl halides,[7] which resulted in a dilemma between the efficient generation of aryl radicals and the avoiding of harsh conditions (such as the usage of liquid ammonia, alkali metal and super-strong bases). In this context, we tried to develop novel electron donors as a new but yet practical way to generate aryl radicals from aryl halides with the application of electron-catalysis strategy.

Rongalite ($Na^+HOCH_2SO_2^-\cdot 2H_2O$) is a cheap industrial product that has been used in rubber, textile and dye industry for a long time,[8] and it is also a useful green reagent in synthetic chemistry.[9,10] More importantly, It has been identified as the precursor of highly reductive sulfoxylate anion ($SO_2^{\cdot-}$).[10,11] Inspired by the properties of rongalite, we envisioned that the highly reductive sulfur-contained species ($SO_2^{\cdot-}$/HSO_2^-) could be a new type of super electron donors to generate aryl radicals from aryl halides **1**. As shown in Scheme 2a, the further trapping of aryl radicals with arenes **2** lead to intermediates **A**, which undergo deprotonation and electron transfer with aryl halides **1** can provide the coupling products **3**.[12] This reaction is representative to evaluate the property of novel electron donors. Herein, we describe a simple and practical approach to access aryl radicals from aryl halides in the presence of rongalite under transition-metal-free condition. The arylation of arenes, thiolates, sulfides, sulfinates, phosphines and phosphites have been

Scheme 1. Methods to generate aryl radicals



Scheme 2. Proposed mechanism

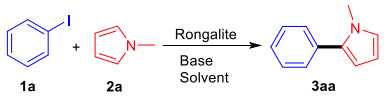


achieved (Scheme 1). Moreover, an efficient and low-cost preparation of antipsychotic drug Quetiapine was achieved on gram scale under mild conditions to further illustrate the synthetic utility of this approach.

RESULTS AND DISCUSSION

Considering the privilege of the biaryl scaffold in pharmaceuticals,[13] we chose the reaction between iodobenzene **1a** with N-methylpyrrole **2a** as model reaction (Table 1) to optimize the reaction conditions. At the very beginning, the reaction was performed at 80 ℃ in DMSO under nitrogen with rongalite as a precursor of super electron donors. Desired biaryl product **3aa** was obtained in only 5% yield (Table 1, entry 1). Therefore, base was introduced into the reaction with the purpose of accelerating the deprotonation step (Table 1, entry 2-5). Pleasingly, the addition of KOH increased the yield to 56%. Further screening of other parameters such as solvents and temperature did not improve the yield (Table 1, entry 6-9). To our delight, decreasing amount of solvent to 0.5 mL led to a 78% of yield (Table 1, entry 10), which indicated a great influence of the concentration on this reaction. Subsequently, it was found that the increased concentration of N-methylpyrrole **2a** could give rise to a 90% yield of the product **3aa** (Table 1, entry 11). Finally, control experiment showed that rongalite is essential in the reaction (Table 1, entry 12).

Table 1. Optimization of reaction conditions [a]



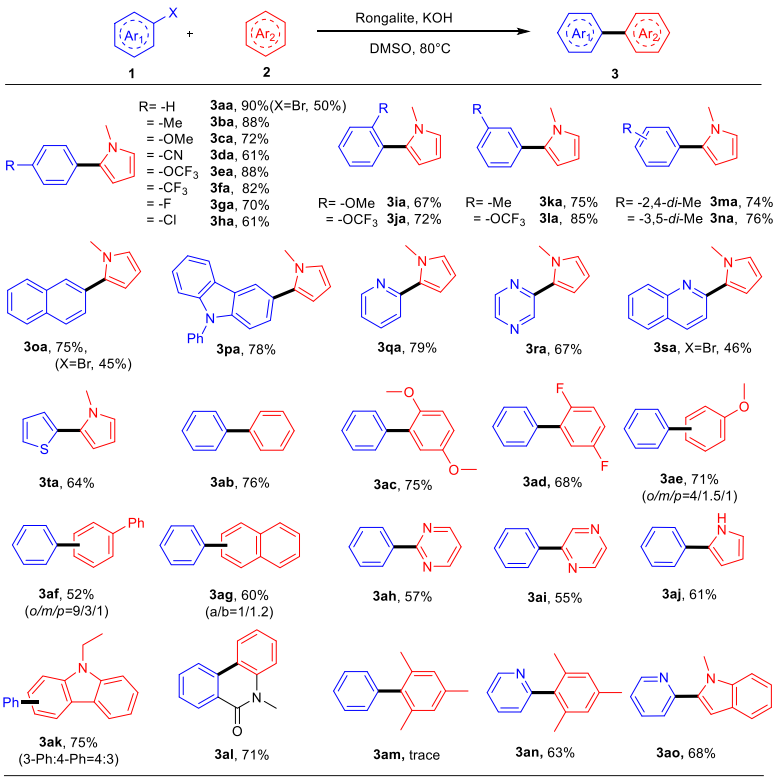
Entry	Temperature	Base	Solvent	Yield[b](%)
1	80	-	DMSO	5
2	80	DBU	DMSO	23
3	80	K_2CO_3	DMSO	9
4	80	K_3PO_4	DMSO	13
5	80	KOH	DMSO	56
6	80	KOH	DMF	8
7	80	KOH	CH_3CN	trace
8	60	KOH	DMSO	trace
9	100	KOH	DMSO	50
10[c]	80	KOH	DMSO	78
11[c,d]	80	KOH	DMSO	90
12[c,d,e]	80	KOH	DMSO	n.d.

[a] Reaction conditions: Iodobenzene **1a** (0.2 mmol), N-methylpyrrole **2a** (1.0 mmol), rongalite (0.4 mmol), base (0.4mmol) in solvent (2.0 ml) at 80 ℃ for 24 h under N_2. [b] Isolated yield based on Iodobenzene **1a**. [c] Solvent (0.5 ml). [d] N-methylpyrrole **2a** (3.0 mmol). [e] Without rongalite.

With the above optimal reaction conditions in hand, we investigated the scope of this homolytic aromatic substitutions (Table 2). Aryl halides that contain electron-withdrawing (halogen, trifluoromethyl, trifluoromethoxy and cyano) and electron-donating (methyl and methoxy) groups reacted with N-methylpyrrole **2a** to give the corresponding biaryls **3aa**-**3ha** in 61-90% yields, indicating that both electron rich and electron deficient aryl halides can be employed in the reaction. The substitution pattern of phenyl ring had no influence on the reaction efficiency as well, with the desired products **3ia**-**3na** obtained in 67–85% yields. 2-iodonaphthalene was also suitable substrate for the synthesis of **3oa** in 75% yield. Notably, a series of heteroaromatic halides were tolerated in this reaction, providing the corresponding products **3pa**-**3ta** in good yields, which are very useful in medicinal chemistry. Gratifyingly, aryl bromide also underwent this coupling with desired products **3aa**, **3oa** and **3sa** formed in moderate yields. Next, we turned our attention to study the scope of arenes **2**. Electron density in the arenes didn't affect the reaction, and the desired products **3ab**-**3ad** were obtained in good yields. Single substituted arenes participated in the reaction to give the coupling products **3ae**-**3ag** as a mixture of regioisomers in 52-71% yields. Heterocycles could also be tolerated, with products **3ah**-**3ak** produced in moderate to good yields. Intramolecular coupling was also achieved giving **3al** in 71% yield. Unfortunately, the reaction between iodobenzene **1a** and mesitylene was unsuccessful, indicating that the sterically hindered biaryls are difficult to be produced. However, electron-deficient 2-iodopyridine exhibited higher reactivity, with sterically hindered product **3an** obtained in yield of 63%. The reaction between iodobenzene and N-methylindole showed no chemoselectivity, but reaction with 2-iodopyridine can give single substituted N-methylindole **3ao** in 68% yield, which also demonstrated the higher reactivity of 2-iodopyridine.

Considering the importance of carbon-heteroatom bond-forming reactions in organic synthesis and drug discovery, we then turned our interest to extend the utility of these rongalite-promoted reactions. Since the $S_{RN}1$ reactions have been classified as the electron-catalyzed process,[3a, 3b] we hypothesized that $S_{RN}1$ reactions could be achieved under the similar conditions, with the efficient construction of C-S and C-P bonds (Scheme 2b). We started our research with the reaction between iodobenzene **1a** and sodium benzenethiolate **4a**. Surprisingly, the presented reaction condition was perfectly suitable to generate a series of thioethers without further optimization (Table 3). The model reaction provided diphenyl sulfide **5a** in 89% yield. Several asymmetric diaryl sulfides **5b**-**5c** and **5g** were obtained in 82-95% yields. The reaction tolerated heterocycles, with the corresponding products **5d**-**5f** produced in moderate to good yields. Alkyl thiol was also employed in the coupling to give the product **5h** in 62% yield.

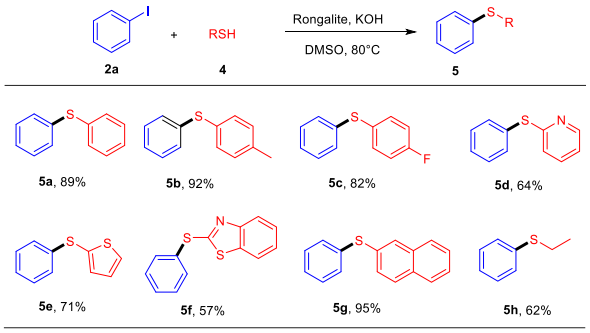
Table 2. Substrate scope of homolytic aromatic substitutions [a]



[a] Standard Reaction conditions: A mixture of aryl halides **1** (0.2 mmol), arenes **2** (15eq, 3 mmol), rongalite (2eq, 0.4 mmol) and KOH (3eq, 0.6 mmol) in DMSO (0.5 ml) was stirred for 24 h at 80 ℃ under N_2. [b] Yields of isolated.

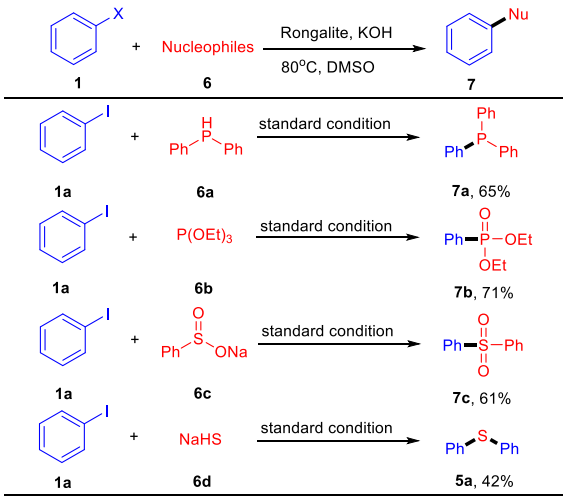
Encouraged by these results, we continued to evaluate the generality of this strategy by using diphenylphosphane **6a**, triethylphosphite **6b**, benzene sulfonate **6c** and sodium hydrosulfide **6d** as substrates to do the $S_{RN}1$ reactions. To our surprise, all these nucleophiles were transformed into the corresponding products **7** in 42-71% yields under the same condition, which exhibited extremely wide substrate scope of this catalytic system (Table 4). To the best of our knowledge, this protocol represents the first application of $S_{RN}1$ strategy in the synthesis of sulfonyl compounds from aryl radicals. These transformations enabled the rapid preparation of different analogues, together with the mild conditions and the availability of all reagents, making it a promising synthetic method in the field of medicinal chemistry.

Table 3. Application in the construction diaryl sulfides [a,b]



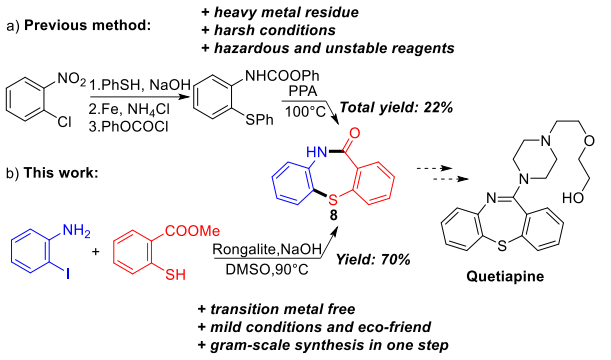
[a] Standard Reaction conditions: A mixture of aryl halides **1** (0.2 mmol), thiophenol **4** (2eq, 0.4 mmol), rongalite (2eq, 0.4 mmol) and KOH (3eq, 0.6 mmol) in DMSO (0.5 ml) was stirred for 24 h at 80 ℃ under N_2. [b] Yields of isolated.

Table 4. Applications in $S_{RN}1$ reactions [a,b]



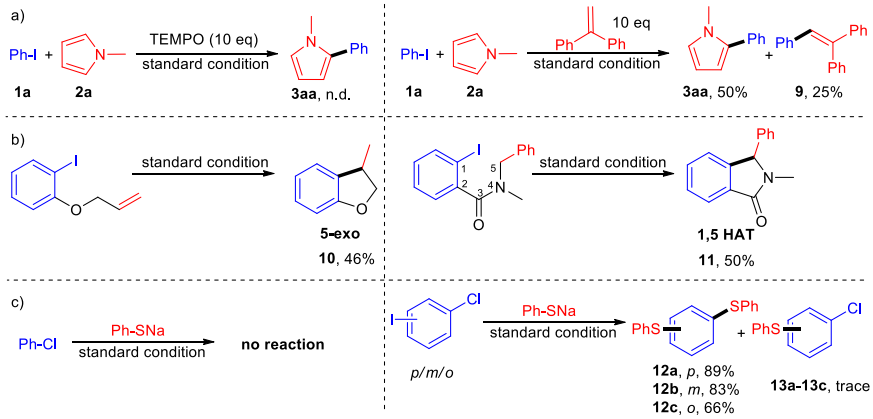
[a] Standard conditions: A mixture of aryl halides **1** (0.2 mmol), nucleophiles **6** (2eq, 0.4 mmol), rongalite (2eq, 0.4 mmol) and KOH (2eq, 0.4 mmol) in DMSO (0.5 ml) was stirred for 24 h at 80 ℃ under N_2. [b] Yields of isolated.

Scheme 3. Application in drug synthesis



To further explore its potential in the synthesis of important pharmaceuticals, we applied this methodology for the synthesis of the Quetiapine, an antipsychotic drug that has been used for more than 20 years.[14] Traditionally, harsh conditions and hazardous reagents are inevitable in the synthesis of Quetiapine. In a typical protocol, key intermediate **8** can be synthesized by four steps in only 22% yield (Scheme 3a).[15] However, based on this radical arylation strategy, the intermediate **8** could be obtained on gram scale with a significantly improved efficiency under transition-metal-free conditions (Scheme 3b). Under a slightly optimized condition, the reaction between 2-iodoaniline and methyl 2-mercaptobenzoate provides compound **8** in 70% yield in one step (Figure S1). Then, the final product Quetiapine was synthesized from **8** through the reported approach.[16] It is worth noting that the unprotected amino group was well tolerated in the reaction, so that C-S and C-N bond can be formed in one step to construct the seven-membered ring. The availability of reagents, mild conditions and broad substrate scope make it possible to be used in the pharmaceutical industry.

Scheme 4. Mechanistic experiments



To validate the proposed mechanism, a few mechanistic studies have been carried out. First, Electron Paramagnetic Resonance (EPR) experiments were performed and the results showed the existence of radicals under the reaction condition (Figure 1, see supporting information for detail), though we did not know what exact radicals were generated. Notably, no signal was observed in the absence of either rongalite or iodobenzene **1a** (Figure S3, S4), which suggested the occurrence of single electron transfer (SET) between rongalite and iodobenzene **1a**. These data clearly support the proposed initiation steps. (Scheme 2). Additionally, some control reactions have been conducted as well. The model reaction was completely inhibited after the introduction of 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO). In the meanwhile, radical trapping experiment using 1,1-diphenylethylene under the standard reaction conditions was performed, with the products **3aa** and **9** obtained in 50% and 25% yields respectively (Scheme 4a). Pleasingly, 1,5-hydrogen atom transfer (HAT) and reductive radical cyclization can be applied under the standard conditions as well (Scheme 4b), gave the corresponding products **10** and **11** in moderate yields. All these evidences indicated that radicals are involved in these reactions. Furthermore, a series of dihaloarenes treated with **4a** gave the disubstituted products **12a-12c** in good to excellent yields and trace of single substituted products **13a-13c** was observed (chlorobenzene reacted with **4a** yielded no desired product), which accommodates perfectly with the previously proposed $S_{RN}1$ mechanism (Scheme 4c)[17] and proves the existence of radical anion as SET-reductant to sustain the innate chain cycle. In addition, we have tried to determine the redox potentials of electron donors. Unfortunately, since the generation of sulfur dioxide is irreversible, it's unlikely to measure the redox potential (Figure S7). As a result, it's difficult to learn more mechanistic insights from redox potentials. However, the irreversible loss of halide anion (Br^-/I^-) and SO_2 followed by SET could be the driving force for the reduction of aryl halides,[18] which also fits with the proposed mechanism (Scheme 2).

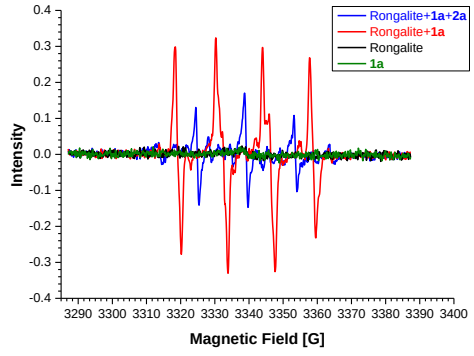


Figure 1. EPR spectroscopy.

CONCLUSION

In summary, we have developed a novel method to generate aryl radicals from aryl halides based on the electron catalysis theory. Rongalite was used as a novel precursor of super electron donors to initiate the radical chain reactions. Homolytic aromatic substitution (HAS) and $S_{RN}1$ reactions were achieved to construct a series of carbon (sp^2)- carbon or carbon (sp^2)- heteroatom bond under mild conditions. In addition, gram-scale synthesis of antipsychotic drug Quetiapine under transition-metal-free conditions was demonstrated. The reaction is mild, cheap, and provides a promising arylation method in organic synthesis.

EXPERIMENTAL SECTION

General Information. Unless otherwise noted, materials obtained from commercial suppliers were used as received. Otherwise noted, all reactions were performed with dry solvents under an atmosphere of nitrogen gas in dried glassware using standard Schlenk techniques. All work-up and purification procedures were carried out with reagent-grade solvents in air. Thin-layer chromatography (TLC) analyses were performed on commercial glass plates bearing a 0.25 mm layer of Merck Silica gel 60F254 and visualized with ultraviolet light (λ = 254 nm). Purification was done by column chromatography using silica gel (spherical neutral, 200–300 mesh) and preparative TLC using silica gel (Merck 60PF254). Liquid Chromatograph Mass Spectra (LC-MS) was conducted on Agilent 1260 Infinity and Agilent 6120 quadrupole MS. Nuclear magnetic resonance (NMR) spectra was recorded on BRUKER ASCENDTM 400 to give 1H NMR (400 MHz) spectra and 19F NMR (400 MHz) spectra, and BRUKER ASCENDTM 600 for 13C NMR (150 MHz) spectra. Chemical shifts for 1H NMR are expressed in parts per million (ppm) relative to tetramethylsilane (δ 0.00 ppm) or residual peak of CDCl3 (δ 7.26 ppm). Chemical shifts for 13C NMR are expressed in ppm relative to CDCl3 (δ 77.16 ppm). Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, dd = doublet of doublets, t = triplet, m = multiplet), coupling constant (Hz), and integration. High resolution mass spectra (HRMS) were obtained from AB SCIEX Triple TOFTM 5600+ LC/MS with electrospray ionization (ESI) and atmospheric pressure chemical ionization (APCI). Cyclic Voltammograms (CV) were recorded with a CHI660E potentiostat. Electron Paramagnetic Resonance (EPR) spectra was recorded on BRUKER E500-10/12. 2-iodo-N-methyl-N-phenylbenzamide[19], N-benzyl-2-iodo-N-methylbenzamide[20] and 1-(allyloxy)-2-iodobenzene[21] were prepared according to a published procedure.

General procedure for preparation of products 3aa-3ao. The starting aryl halide (-I/-Br) **1** (0.2 mmol), corresponding (hetero-)arene **2** (3.0 mmol, 15 eq), rongalite (0.4 mmol, 2 eq), KOH (0.4 mmol, 2 eq) were charged in a 10 ml Schlenk tube under N_2. After addition of DMSO (0.5 ml), the tube was sealed and the resulting solution was heated in an oil bath at 80℃ for 24~36 h. After cooling the tube to room temperature, H_2O (4 ml) was added and the resulting mixture was extracted with EtOAc (4 ml * 3). The combined organic layer was dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by chromatography to provide the product **3aa-3ao**.

*1-Methyl-2-phenyl-1H-pyrrole (**3aa**)*.[22] White solid (28.3 mg, 90%; using bromobenzene as the substrate, yield=50%); R_f = 0.4 (PE/EA=200/1); LC-MS (ESI) [M+1]+ 158.0; ^{1}H NMR (400 MHz, Chloroform-d) δ 7.48 – 7.41 (m, 4H), 7.35 – 7.33 (dd, *J* = 6.1, 3.1 Hz, 1H), 6.77 – 6.76 (m, 1H), 6.29 – 6.25 (m, 2H), 3.70 (s, 3H); ^{13}C{^{1}H} NMR (150 MHz, Chloroform-d) δ 133.6, 132.3, 127.6, 127.3, 125.7, 122.6, 107.6, 106.7, 33.9.

*1-Methyl-2-(p-tolyl)-1H-pyrrole (**3ba**)*.[22] White solid (30.1 mg, 88%); R_f = 0.4 (PE/EA=200/1); LC-MS (ESI) $[M+1]^+$ 172.1; ^{1}H NMR (400 MHz, Chloroform-d) δ 7.34 – 7.32 (d, 2H), 7.26 – 7.23 (d, 2H), 6.73 (m, 1H), 6.23 (m, 2H), 3.68 (s, 3H), 2.42 (s, 3H); ^{13}C{^{1}H} NMR (150 MHz, Chloroform-d) δ 136.5, 134.6, 130.5, 129.0, 128.6, 123.3, 108.3, 107.6, 34.9, 21.2.

*2-(4-Methoxyphenyl)-1-methyl-1H-pyrrole (**3ca**)*.[22] White solid (26.9 mg, 72%); R_f = 0.4 (PE/EA=200/1); LC-MS (ESI) $[M+1]^+$ 188.1; ^{1}H NMR (400 MHz, Chloroform-d) δ 7.39 – 7.37 (m, 2H), 7.01 – 6.99 (m, 2H), 6.75 – 6.74 (m, 1H), 6.26 – 6.22 (m, 2H), 3.89 (s, 3H), 3.68 (s, 3H); ^{13}C{^{1}H} NMR (150 MHz, Chloroform-d) δ 157.6, 133.3, 128.9, 124.9, 121.9, 112.8, 106.9, 106.5, 54.2, 33.8.

*4-(1-Methyl-1H-pyrrol-2-yl)benzonitrile (**3da**)*.[22] White solid (22.2 mg, 61%); R_f = 0.4 (PE/EA=200/1); LC-MS (ESI) $[M+1]^+$ 183.0; ^{1}H NMR (400 MHz, Chloroform-d) δ 7.69 – 7.66 (m, 2H), 7.52 – 7.49 (m, 2H), 6.80 – 6.79 (m, 1H), 6.36 – 6.35 (m, 1H), 6.25 – 6.23 (m, 1H), 3.72 (s, 3H); ^{13}C{^{1}H} NMR (150 MHz, Chloroform-d) δ 137.7, 132.6, 132.3, 128.3, 125.9, 119.0, 110.8, 109.7, 108.6, 35.5.

*1-Methyl-2-(4-(trifluoromethoxy)phenyl)-1H-pyrrole (**3ea**)*.[22] Light yellow oil (42.5 mg, 88%); R_f = 0.4 (PE/EA=200/1); LC-MS (ESI) $[M+1]^+$ 242.0; ^{1}H NMR (400 MHz, Chloroform-d) δ 7.42 – 7.39 (m, 2H), 7.25 – 7.22 (m, 2H), 6.72 (m, 1H), 6.23 – 6.20 (m, 2H), 3.65 (s, 3H); ^{13}C{^{1}H} NMR (150 MHz, Chloroform-d) δ 147.4, 132.5, 131.5, 129.2, 123.5, 120.3, 119.9 (q, *J* = 256.9 Hz), 108.6, 107.3, 34.4.

*1-Methyl-2-(4-(trifluoromethyl)phenyl)-1H-pyrrole (**3fa**)*.[23] White solid (36.9 mg, 82%); R_f = 0.4 (PE/EA=200/1); LC-MS (ESI) $[M+1]^+$ 226.0; ^{1}H NMR (400 MHz, Chloroform-d) δ 7.69 – 7.67 (m, 2H), 7.56 – 7.54 (m, 2H), 6.80 – 6.79 (m, 1H), 6.36 – 6.34 (m, 1H), 6.27 – 6.26 (m, 1H), 3.72 (s, 3H); ^{13}C{^{1}H} NMR (150 MHz, Chloroform-d) δ 136.9, 133.1, 128.6 (q, *J* = 65.1 Hz), 128.4, 125.4 (q, *J* = 273.3 Hz), 124.9, 124.3 (q, *J* = 273.3 Hz), 109.9, 108.3, 35.2.

*2-(4-Fluorophenyl)-1-methyl-1H-pyrrole (**3ga**)*.[22] White solid (24.5 mg, 70%); R_f = 0.4 (PE/EA=200/1); LC-MS (ESI) $[M+1]^+$ 176.0; ^{1}H NMR (400 MHz, Chloroform-d) δ 7.39 – 7.35 (m, 2H), 7.13 – 7.08 (m, 2H), 6.73 – 6.72 (m, 1H), 6.21 – 6.20 (m, 2H), 3.64 (s, 3H); ^{13}C{^{1}H} NMR (150 MHz, Chloroform-d) δ 161.3 (d, *J* = 246.4 Hz), 132.9, 129.7 (d, *J* = 7.9 Hz), 128.9 (d, *J* = 3.3 Hz), 122.9, 114.7 (d, *J* = 21.7 Hz), 108.0, 107.1, 34.3.

*2-(4-Chlorophenyl)-1-methyl-1H-pyrrole (**3ha**)*.[22] White solid (23.4 mg, 61%); R_f = 0.4 (PE/EA=200/1); LC-MS (ESI) $[M+1]^+$ 192.0; ^{1}H NMR (400 MHz, Chloroform-d) δ 7.41 – 7.35 (m, 4H), 6.76 (t, *J*=2.2, 1H), 6.27 – 6.24 (m, 2H), 3.68 (s, 3H); ^{13}C{^{1}H} NMR (150 MHz, Chloroform-d) δ 133.6, 132.9, 132.1, 130.1, 128.9, 124.4, 109.3, 108.3, 35.3.

*2-(2-Methoxyphenyl)-1-methyl-1H-pyrrole (**3ia**)*.[22] Yellow oil (25.1 mg, 67%); R_f = 0.4 (PE/EA=200/1); LC-MS (ESI) $[M+1]^+$ 188.1; ^{1}H NMR (400 MHz, Chloroform-d) δ 7.41 – 7.32 (m, 2H), 7.06 – 6.99 (m, 2H), 6.78 – 6.77 (m, 1H), 6.28 – 6.26 (m, 1H), 6.20 – 6.18 (m, 1H), 3.83 (s, 3H), 3.53 (s, 3H); ^{13}C{^{1}H} NMR (150 MHz, Chloroform-d) δ 156.4, 131.3, 130.1, 128.1, 121.5, 121.4, 119.5, 109.7, 107.9, 106.5, 54.3, 33.5.

*1-Methyl-2-(2-(trifluoromethoxy)phenyl)-1H-pyrrole (**3ja**)*. Yellow oil (34.7 mg, 72%); R_f = 0.4 (PE/EA=200/1); LC-MS (ESI) $[M+1]^+$ 242.1; ^{1}H NMR (400 MHz, Chloroform-d) δ 7.42

– 7.33 (m, 4H), 6.77 – 6.76 (m, 1H), 6.25 – 6.20 (m, 2H), 3.52 (s, 3H); $^{13}C\{^{1}H\}$ NMR (150 MHz, Chloroform-d) δ 146.6, 132.2, 128.3, 128.0, 126.5, 126.0, 122.6, 120.2, 119.80 (q, *J* = 257.8 Hz), 109.6, 107.2, 33.9; ^{19}F NMR (400 MHz, Chloroform-d) δ 107.6; HRMS (ESI) m/z calcd for C12H10F3NO $[M+H]^+$: 242.0787, found 242.0778.

*1-Methyl-2-(m-tolyl)-1H-pyrrole (**3ka**)*.[22] White solid (25.7 mg, 75%); R_f = 0.4 (PE/EA=200/1); LC-MS (ESI) $[M+1]^+$ 172.1; ^{1}H NMR (400 MHz, Chloroform-d) δ 7.35 – 7.31 (m, 1H), 7.27 – 7.24 (m, 2H), 7.17 – 7.15 (m, 1H), 6.75 (m, 1H), 6.26 – 6.24 (m, 2H), 3.70 (s, 3H), 2.43 (s, 3H); $^{13}C\{^{1}H\}$ NMR (150 MHz, Chloroform-d) δ 137.9, 134.7, 133.3, 129.4, 128.2, 127.5, 125.7, 123.5, 108.5, 107.7, 35.0, 21.5.

*1-Methyl-2-(3-(trifluoromethoxy)phenyl)-1H-pyrrole (**3la**)*. Yellow oil (41.0 mg, 85%); R_f = 0.4 (PE/EA=100/1); LC-MS (ESI) $[M+1]^+$ 242.1; ^{1}H NMR (400 MHz, Chloroform-d) δ 7.44 – 7.39 (m, 1H), 7.35 – 7.33 (m, 1H), 7.26 (s, 1H), 7.16 – 7.14 (m, 1H), 6.75 – 6.74 (m, 1H), 6.28 (d, *J* = 1.9 Hz, 1H), 6.22 (d, *J* = 2.6 Hz, 1H), 3.68 (s, 3H); $^{13}C\{^{1}H\}$ NMR (150 MHz, Chloroform-d) δ 149.3, 135.3, 133.0, 129.7, 126.7, 124.5, 120.9, 120.5 (q, *J* = 256.8 Hz), 118.9, 109.5, 108.1, 35.1; ^{19}F NMR (400 MHz, Chloroform-d) δ 107.1; HRMS (ESI) m/z calcd for C12H10F3NO $[M+H]^+$: 242.0787, found 242.0777.

*2-(2,4-Dimethylphenyl)-1-methyl-1H-pyrrole (**3ma**)*. Yellow oil (27.4 mg, 74%); R_f = 0.4 (PE/EA=100/1); LC-MS (ESI) $[M+1]^+$ 186.1; ^{1}H NMR (400 MHz, Chloroform-d) δ 7.19 – 7.15 (m, 2H), 7.08 (m, 1H), 6.75 – 6.74 (m, 1H), 6.25 (dd, *J* = 3.6, 1.9 Hz, 1H), 6.10 (d, *J* = 3.5 Hz, 1H), 3.44 (s, 3H), 2.41 (s, 3H), 2.21 (s, 3H); $^{13}C\{^{1}H\}$ NMR (150 MHz, Chloroform-d) δ 137.0, 136.6, 132.3, 130.1, 129.7, 129.2, 125.1, 120.5, 107.4, 106.2, 33.0, 20.1, 18.9; HRMS (ESI) m/z calcd for C13H15N $[M+H]^+$: 186.1277, found 186.1278.

*2-(3,5-Dimethylphenyl)-1-methyl-1H-pyrrole (**3na**)*.[23] Colorless oil (28.2 mg, 76%); R_f = 0.4 (PE/EA=200/1); LC-MS (ESI) $[M+1]^+$ 186.1; ^{1}H NMR (400 MHz, Chloroform-d) δ 7.05 (s, 2H), 6.98 (s, 1H), 6.72 (m, 1H), 6.22 (m, 2H), 3.68 (s, 3H), 2.38 (s, 6H); $^{13}C\{^{1}H\}$ NMR (150 MHz, Chloroform-d) δ 137.2, 134.2, 132.7, 127.9, 125.9, 122.8, 107.8, 107.0, 34.4, 20.8.

*1-Methyl-2-(naphthalen-2-yl)-1H-pyrrole (**3oa**)*.[24] White solid (31.1 mg, 75%; using 2-bromonaphthalene as the substrate, yield=45%); R_f = 0.4 (PE/EA=200/1); LC-MS (ESI) $[M+1]^+$ 208.1; ^{1}H NMR (400 MHz, Chloroform-d) δ 7.89 – 7.85 (m, 4H), 7.59 – 7.57 (m, 1H), 7.52 – 7.49 (m, 2H), 6.79 (m, 1H), 6.37 – 6.36 (m, 1H), 6.28 – 6.27 (m, 1H), 3.76 (s, 3H); $^{13}C\{^{1}H\}$ NMR (150 MHz, Chloroform-d) δ 134.6, 133.4, 132.2, 130.8, 127.9, 127.9, 127.7, 127.1, 126.9, 126.3, 125.8, 123.9, 109.2, 108.0, 35.2.

*3-(1-Methyl-1H-pyrrol-2-yl)-9-phenyl-9H-carbazole (**3pa**)*. White solid (50.3 mg, 78%); R_f = 0.4 (PE/EA=50/1); LC-MS (ESI) $[M+1]^+$ 323.0; ^{1}H NMR (400 MHz, Chloroform-d) δ 8.22 – 8.20 (m, 2H), 7.66 – 7.64 (m, 4H), 7.51 – 7.47 (m, 5H), 7.36 – 7.34 (m, 1H), 6.81 (d, *J* = 2.7 Hz, 1H), 6.36 – 6.32 (m, 2H), 3.75 (s, 3H); $^{13}C\{^{1}H\}$ NMR (150 MHz, Chloroform-d) δ 140.2, 138.9, 136.5, 134.3, 128.9, 126.5, 126.2, 126.0, 125.1, 124.3, 122.3, 122.2, 121.8, 119.6, 119.3, 119.0, 108.9, 108.5, 107.3, 106.6, 33.9; HRMS (ESI) m/z calcd for C23H18N2 $[M+H]^+$: 323.1543, found 323.1540.

*2-(1-Methyl-1H-pyrrol-2-yl)pyridine (**3qa**)*.[25] Yellow oil (25.0 mg, 79%); R_f = 0.4 (PE/EA=50/1); LC-MS (ESI) $[M+1]^+$ 159.0; ^{1}H NMR (400 MHz, Chloroform-d) δ 8.58 – 8.56 (m, 1H), 7.66 – 7.61 (m, 1H), 7.55 – 7.53 (m, 1H), 7.09 – 7.06 (m, 1H), 6.75 (m, 1H), 6.60 – 6.58 (m, 1H), 6.20 – 6.19 (m, 1H), 4.01 (s, 3H); $^{13}C\{^{1}H\}$ NMR (150 MHz, Chloroform-d) δ 152.8, 148.6, 136.3, 132.4, 126.5, 121.6, 120.3, 110.8, 107.8, 36.9.

*2-(1-Methyl-1H-pyrrol-2-yl)pyrazine (**3ra**)*.[26] Yellow oil (21.3 mg, 67%); R_f = 0.4 (PE/EA=50/1); LC-MS (ESI) $[M+1]^+$ 160.0; ^{1}H NMR (400 MHz, Chloroform-d) δ 8.83 (m, 1H), 8.44 (m, 1H), 8.28 – 8.27 (m, 1H), 6.80 – 6.79 (m, 1H), 6.73 – 6.71 (m, 1H), 6.22 – 6.20 (m, 1H), 3.99 (s, 3H); $^{13}C\{^{1}H\}$ NMR (150 MHz, Chloroform-d) δ 148.6, 142.9, 142.8, 140.2, 128.9, 127.9, 111.9, 108.3, 37.2.

*2-(1-Methyl-1H-pyrrol-2-yl)quinolone (**3sa**)*.[27] Yellow solid (19.2 mg, 46%); R_f = 0.4 (PE/EA=50/1); LC-MS (ESI) $[M+1]^+$ 209.1; ^{1}H NMR (400 MHz, Chloroform-d) δ 8.08 – 8.06 (m, 2H), 7.77 – 7.66 (m, 3H), 7.49 – 7.45 (m, 1H), 6.83 – 6.81 (m, 2H), 6.26 – 6.25 (m, 1H), 4.22 (s, 3H); $^{13}C\{^{1}H\}$ NMR (150 MHz, Chloroform-d) δ 151.1, 146.5, 134.9, 131.1, 128.4, 127.9, 126.7, 126.4, 125.0, 124.5, 119.1, 111.4, 106.8, 36.6.

*1-Methyl-2-(thiophen-2-yl)-1H-pyrrole (**3ta**)*.[28] Yellow oil (20.9 mg, 64%); R_f = 0.4 (PE/EA=200/1); LC-MS (ESI) $[M+1]^+$ 164.0; ^{1}H NMR (400 MHz, Chloroform-d) δ 7.25 (m, 1H), 7.07 – 7.05 (m, 1H), 7.03 – 7.01 (m, 1H), 6.71 – 6.70 (m, 1H), 6.33 – 6.32 (m, 1H), 6.17 – 6.15 (m, 1H), 3.72 (s, 3H); $^{13}C\{^{1}H\}$ NMR (150 MHz, Chloroform-d) δ 135.0, 127.3, 127.1, 124.9, 124.5, 123.9, 110.0, 107.9, 35.2.

*1,1'-Biphenyl (**3ab**)*.[29] White solid (23.4 mg, 76%); R_f = 0.5 (PE/EA=200/1); ^{1}H NMR (400 MHz, Chloroform-d) δ 7.65 – 7.62 (m, 4H), 7.50 – 7.46 (m, 4H), 7.40 – 7.36 (m, 2H); $^{13}C\{^{1}H\}$ NMR (150 MHz, Chloroform-d) δ 141.3, 128.8, 127.3, 127.12.

*2,5-Dimethoxy-1,1'-biphenyl (**3ac**)*.[30] White solid (32.1 mg, 75%); R_f = 0.4 (PE/EA=100/1); ^{1}H NMR (400 MHz, Chloroform-d) δ 7.55 – 7.52 (m, 2H), 7.44 – 7.40 (m, 2H), 7.36 – 7.33 (m, 1H), 6.94 – 6.91 (m, 2H), 6.88 – 6.84 (m, 1H), 3.81 (s, 3H), 3.76 (s, 3H); $^{13}C\{^{1}H\}$ NMR (150 MHz, Chloroform-d) δ 153.8, 150.8, 138.4, 131.8, 129.5, 128.0, 127.1, 116.8, 113.2, 112.8, 56.4, 55.8.

*2,5-Difluoro-1,1'-biphenyl (**3ad**)*.[31] Colorless oil (25.8 mg, 68%); R_f = 0.4 (PE/EA=200/1); ^{1}H NMR (400 MHz, Chloroform-d) δ 7.57 – 7.54 (m, 2H), 7.49 – 7.41 (m, 3H), 7.17 – 7.12 (m, 2H), 7.02 – 7.00 (m, 1H); $^{13}C\{^{1}H\}$ NMR (150 MHz, Chloroform-d) δ 158.8 (d, *J* = 242.3 Hz), 155.8 (d, *J* = 243.6 Hz), 134.8, 130.4 (dd, *J* = 16.1, 8.1 Hz), 128.9 (d, *J*=3.1 Hz), 128.6, 128.2, 117.3 (dd, *J*=26.0, 8.8 Hz), 116.9 (dd, *J* = 25.2, 4.5 Hz), 115.15 (dd, *J* = 23.8, 8.5 Hz).

*The mixture of 2-methoxy-1,1'-biphenyl, 3-methoxy-1,1'-biphenyl and 4-methoxy-1,1'-biphenyl (**3ae**)*.[29] Colorless oil (26.2 mg, 71%, *o*/*m*/*p*=4/1.5/1); R_f = 0.4 (PE/EA=200/1); ^{1}H NMR (400 MHz, Chloroform-d) δ 7.59 – 7.17 (m, 7H), 7.12 – 6.75 (m, 2H), 3.80 – 3.62 (m, 3H).

*The mixture of 1,1':2',1''-terphenyl, 1,1':3',1''-terphenyl and 1,1':4',1''-terphenyl (**3af**)*.[32] Yellow oil (23.9 mg, 52%, *o*/*m*/*p*=9/3/1); R_f = 0.4 (PE/EA=100/1).

*The mixture of 1-phenylnaphthalene and 2-phenylnaphthalene (**3ag**)*.[29] R_f = 0.4 (PE/EA=100/1). Yellow oil (24.5 mg, 60%, α/β=1/1.2).

*2-Phenylpyrimidine (**3ah**)*.[33] Colorless oil (17.8 mg, 57%); R_f = 0.4 (PE/EA=50/1); LC-MS (ESI) $[M+1]^+$ 157.0; ^{1}H NMR (400 MHz, Chloroform-d) δ 8.81 (d, *J* = 4.8 Hz, 2H), 8.45 – 8.43 (m, 2H), 7.51 – 7.49 (m, 3H), 7.19 (t, *J* = 4.8 Hz, 1H); $^{13}C\{^{1}H\}$ NMR (150 MHz, Chloroform-d) δ 164.9, 157.4, 137.7, 130.9, 128.7, 128.3, 119.2.

*2-Phenylpyrazine (**3ai**)*.[34] Yellow solid (17.2 mg, 55%); R_f = 0.4 (PE/EA=50/1); LC-MS (ESI) $[M+1]^+$ 157.0; ^{1}H NMR (400 MHz, Chloroform-d) δ 9.04 (s, 1H), 8.65 (s, 1H), 8.52 (s, 1H), 8.02 (d, *J* = 8.2 Hz, 2H), 7.55 – 7.48 (m, 3H); $^{13}C\{^1H\}$ NMR (150 MHz, Chloroform-d) δ 152.9, 144.2, 142.8, 142.2, 136.3, 129.9, 129.1, 127.0.

*2-Phenyl-1H-pyrrole (**3aj**)*.[34] White solid (17.5 mg, 61%); R_f = 0.4 (PE/EA=50/1); LC-MS (ESI) $[M+1]^+$ 144.0; ^{1}H NMR (400 MHz, Chloroform-d) δ 8.46 (s, 1H), 7.51 – 7.49 (m, 2H), 7.41 – 7.37 (m, 2H), 7.26 – 7.22 (m, 1H), 6.88 (m, 1H), 6.57 – 6.56 (m, 1H), 6.34 – 6.33 (m, 1H); $^{13}C\{^1H\}$ NMR (150 MHz, Chloroform-d) δ 131.8, 131.1, 127.9, 125.2, 122.8, 117.8, 109.1, 104.9.

*9-Ethyl-3-phenyl-9H-carbazole (**3ak-3-Ph**)*.[35] White solid (23.3 mg, 42.8%); R_f = 0.4 (PE/EA=100/1); LC-MS (ESI) $[M+1]^+$ 272.1; ^{1}H NMR (400 MHz, Chloroform-d) δ 8.33 (s, 1H), 8.16 (d, *J* = 7.5 Hz, 1H), 7.75 – 7.72 (m, 3H), 7.55 – 7.40 (m, 5H), 7.37 – 7.33 (m, 1H), 7.28 – 7.24 (m, 1H), 4.41 (q, *J*=7.2 Hz, 2H), 1.47 (t, *J* = 6.4 Hz, 3H); $^{13}C\{^1H\}$ NMR (150 MHz, Chloroform-d) δ 141.2, 139.4, 138.4, 131.3, 127.7, 126.3, 125.4, 124.8, 124.2, 122.4, 122.1, 119.5, 117.9, 117.9, 107.6, 107.6, 36.6, 12.8.

*9-Ethyl-4-phenyl-9H-carbazole (**3ak-4-Ph**)*.[36] White solid (17.4 mg, 32.1%); R_f = 0.4 (PE/EA=200/1); LC-MS (ESI) $[M+1]^+$ 272.1; ^{1}H NMR (400 MHz, Chloroform-d) δ 7.71 – 7.68 (m, 2H), 7.60 – 7.53 (m, 5H), 7.48 – 7.45 (m, 3H), 7.18 – 7.15 (m, 1H), 7.05 – 7.01 (m, 1H), 4.45 (q, *J* = 7.2 Hz, 2H), 1.50 (t, *J* = 7.2 Hz, 3H); $^{13}C\{^1H\}$ NMR (150 MHz, Chloroform-d) δ 140.4, 139.2, 139.1, 136.9, 128.2, 127.3, 126.4, 124.4, 124.3, 121.5, 121.5, 119.5, 119.3, 117.4, 107.2, 106.3, 36.5, 12.7.

*5-Methylphenanthridin-6(5H)-one (**3al**)*.[37] White solid (29.7 mg, 71%); R_f = 0.4 (PE/EA=10/1); LC-MS (ESI) $[M+1]^+$ 210.0; ^{1}H NMR (400 MHz, Chloroform-d) δ 8.53 (dd, *J* = 8.0, 1.5 Hz, 1H), 8.29 – 8.19 (m, 2H), 7.73 (ddd, *J* = 8.4, 7.1, 1.5 Hz, 1H), 7.61 – 7.48 (m, 2H), 7.38 (d, *J* = 8.8 Hz, 1H), 7.30 (td, *J* = 7.6, 1.1 Hz, 1H), 3.79 (s, 3H); $^{13}C\{^1H\}$ NMR (150 MHz, Chloroform-d) δ 160.6, 137.0, 132.5, 131.3, 128.5, 127.9, 126.9, 124.6, 122.2, 121.4, 120.6, 118.2, 114.0, 28.9.

*2-Mesitylpyridine (**3an**)*.[30] Colorless oil (24.8 mg, 63%); R_f = 0.4 (PE/EA=100/1); LC-MS (ESI) $[M+1]^+$ 198.1; ^{1}H NMR (400 MHz, Chloroform-d) δ 8.72 – 8.71 (m, 1H), 7.76 – 7.72 (m, 1H), 7.25 – 7.22 (m, 2H), 6.94 (brs, 2H), 2.33 (s, 3H), 2.02 (s, 6H); $^{13}C\{^1H\}$ NMR (150 MHz, Chloroform-d) δ 159.4, 149.0, 137.1, 136.8, 135.6, 135.0, 127.7, 124.1, 120.9, 20.5, 19.5.

*1-Methyl-4-(pyridin-2-yl)-1H-indole (**3ao**)*.[38] Yellow solid (28.3 mg, 68%); R_f = 0.4 (PE/EA=50/1); LC-MS (ESI) $[M+1]^+$ 209.1; ^{1}H NMR (400 MHz, Chloroform-d) δ 8.70 (d, *J* = 5.0 Hz, 1H), 7.78 – 7.70 (m, 2H), 7.66 (d, *J* = 8.1 Hz, 1H), 7.41 (d, *J* = 8.3 Hz, 1H), 7.30 – 7.21 (m, 2H), 7.16 – 7.12 (m, 1H), 6.87 (s, 1H), 4.07 (s, 3H); $^{13}C\{^1H\}$ NMR (150 MHz, Chloroform-d) δ 152.2, 148.7, 139.4, 138.6, 136.9, 127.5, 123.7, 122.7, 121.8, 121.0, 120.0, 109.9, 103.9, 32.0.

General procedure for preparation of products 5a-5h or 7a-7c. The starting material **1a** (0.2 mmol), nucleophiles **4** or **6** (0.4 mmol, 2 eq), rongalite (0.4 mmol, 2 eq), KOH (0.4 mmol, 2 eq) were charged in a 10 ml Schlenk tube under N_2. After addition of DMSO (0.5 ml), the tube was sealed and the resulting solution was heated in an oil bath set at 80℃ for 24 h. After cooling the tube to room temperature, H_2O (4 ml) was added and the resulting mixture was extracted with EA (4 ml * 3). The combined organic layer was dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by chromatography to provide the product **5a**-**5h** or **7a**-**7c**.

*Diphenylsulfane (**5a**)*.[39] Light yellow oil (33.2 mg, 89%; using NaSH as the substrate, yield=42%); R_f = 0.4 (PE/EA=200/1); LC-MS (ESI) $[M+1]^+$ 187.0; ^{1}H NMR (400 MHz, Chloroform-d) δ 7.41 – 7.26 (m, 10H); $^{13}C\{^1H\}$ NMR (150 MHz, Chloroform-d) δ 135.8, 131.0, 129.2, 127.0.

*Phenyl(p-tolyl)sulfane (**5b**)*.[39] Yellow oil (36.8 mg, 92%); R_f = 0.4 (PE/EA=200/1); LC-MS (ESI) $[M+1]^+$ 201.0; ^{1}H NMR (400 MHz, Chloroform-d) δ 7.34 – 7.32 (m, 2H), 7.30 – 7.29 (m, 4H), 7.24 – 7.20 (m, 1H), 7.18 – 7.16 (m, 2H), 2.37 (s, 3H); $^{13}C\{^1H\}$ NMR (150 MHz, Chloroform-d) δ 137.6, 137.1, 132.3, 131.3, 130.1, 129.8, 129.0, 126.4, 21.1.

*(4-Fluorophenyl)(phenyl)sulfane (**5c**)*.[39] Colorless oil (33.5 mg, 82%); R_f = 0.4 (PE/EA=200/1); LC-MS (ESI) $[M+1]^+$ 205.0; ^{1}H NMR (400 MHz, Chloroform-d) δ 7.41 – 7.38 (m, 2H), 7.31 – 7.23 (m, 5H), 7.07 – 7.02 (m, 2H); $^{13}C\{^1H\}$ NMR (150 MHz, Chloroform-d) δ 162.4 (d, *J* = 247.7 Hz), 136.6, 134.1 (d, *J* = 8.1 Hz), 130.2 (d, *J*=3.4 Hz), 130.0, 129.2, 126.8, 116.4 (d, *J* = 21.6 Hz).

*2-(Phenylthio)pyridine (**5d**)*.[40] Colorless oil (23.9 mg, 64%); R_f = 0.4 (PE/EA=50/1); LC-MS (ESI) $[M+1]^+$ 188.0; ^{1}H NMR (400 MHz, Chloroform-d) δ 8.42 (d, *J* = 4.8 Hz, 1H), 7.59 (dd, *J* = 6.6, 3.0 Hz, 2H), 7.45 – 7.41 (m, 4H), 7.01 – 6.98 (m, 1H), 6.87 (d, *J* = 8.1 Hz, 1H); $^{13}C\{^1H\}$ NMR (150 MHz, Chloroform-d) δ 161.5, 149.5, 136.8, 134.9, 131.0, 129.6, 129.1, 121.4, 119.9.

*2-(Phenylthio)thiophene (**5e**)*.[39] Yellow oil (27.3 mg, 71%); R_f = 0.4 (PE/EA=100/1); LC-MS (ESI) $[M+1]^+$ 193.0; ^{1}H NMR (400 MHz, Chloroform-d) δ 7.49 (d, *J* = 5.4 Hz, 1H), 7.34 – 7.30 (m, 1H), 7.29 – 7.22 (m, 2H), 7.24 – 7.14 (m, 3H), 7.13 – 7.05 (m, 1H); $^{13}C\{^1H\}$ NMR (150 MHz, Chloroform-d) δ 138.7, 136.0, 131.3, 131.2, 129.0, 127.9, 127.2, 126.1.

*2-(Phenylthio)benzo[d]thiazole (**5f**)*.[41] White solid (27.7 mg, 57%); R_f = 0.4 (PE/EA=100/1); LC-MS (ESI) $[M+1]^+$ 244.0; ^{1}H NMR (400 MHz, Chloroform-d) δ 7.81 (d, *J* = 8.2 Hz, 1H), 7.67 (d, *J* = 6.7 Hz, 2H), 7.58 (d, *J* = 8.1 Hz, 1H), 7.45 – 7.39 (m, 3H), 7.37 – 7.30 (m, 1H), 7.22 – 7.18 (m, 1H); $^{13}C\{^1H\}$ NMR (150 MHz, Chloroform-d) δ 168.9, 152.7, 134.4, 134.3, 129.5, 128.9, 128.9, 125.2, 123.4, 120.9, 119.8.

*Naphthalen-2-yl(phenyl)sulfane (**5g**)*.[42] White solid (44.9 mg, 95%); R_f = 0.4 (PE/EA=100/1); LC-MS (ESI) $[M+1]^+$ 237.0; ^{1}H NMR (400 MHz, Chloroform-d) δ 7.88 (s, 1H), 7.79 (td, *J* = 14.2, 13.5, 9.3 Hz, 3H), 7.51 – 7.41 (m, 5H), 7.36 – 7.28 (m, 3H); $^{13}C\{^1H\}$ NMR (150 MHz, Chloroform-d) δ 135.8, 133.8, 133.0, 132.3, 131.0, 129.9, 129.2, 128.8, 128.7, 127.7, 127.4, 127.0, 126.6, 126.2.

*Ethyl(phenyl)sulfane (**5h**)*.[43] Colorless oil (17.1 mg, 62%); R_f = 0.4 (PE/EA=200/1); LC-MS (ESI) $[M+1]^+$ 139.0; ^{1}H NMR (400 MHz, Chloroform-d) δ 7.37 – 7.21 (m, 4H), 7.16 (t, *J* = 7.3 Hz, 1H), 2.94 (q, *J* = 7.4 Hz, 2H), 1.31 (t, *J* = 7.4 Hz, 3H); $^{13}C\{^1H\}$ NMR (150 MHz, Chloroform-d) δ 136.6, 129.1, 128.8, 125.8, 27.7, 14.4.

*Triphenylphosphane (**7a**)*.[44] White solid (34.1 mg, 65%); R_f = 0.4 (PE/EA=200/1); LC-MS (ESI) $[M+1]^+$ 263.1; ^{1}H NMR (400 MHz, Chloroform-d) δ 7.34 (m, 15H); $^{13}C\{^1H\}$ NMR (150 MHz, Chloroform-d) δ 136.94 , 133.90 (d, *J* = 19.1 Hz), 128.96 , 128.67 (d, *J* = 7.1 Hz).

*Diethyl phenylphosphonate (**7b**)*.[45] Colorless oil. (30.0 mg, 70%); R_f = 0.4 (PE/EA=200/1); LC-MS (ESI) $[M+1]^+$ 215.0; ^{1}H NMR (400 MHz, Chloroform-d) δ 7.81 (dd, *J* = 13.5, 7.8 Hz, 2H), 7.55 (t, *J* = 7.5 Hz, 1H), 7.49 – 7.46 (m, 2H), 4.12 (ddd, *J* = 19.3, 16.5, 7.8 Hz, 4H), 1.32 (t, *J* = 7.1 Hz, 6H); ^{13}C{^{1}H} NMR (150 MHz, Chloroform-d) δ 132.5, 131.9 (d, *J* = 9.9 Hz), 128.6, 128.5, 62.2 (d, *J* = 5.5 Hz), 16.4 (d, *J* = 6.5 Hz).

*Sulfonyldibenzene (**7c**)*.[46] White solid (26.6 mg, 61%); R_f = 0.4 (PE/EA=10/1); LC-MS (ESI) $[M+1]^+$ 219.0; ^{1}H NMR (400 MHz, Chloroform-d) δ 7.95 (d, *J* = 7.4 Hz, 4H), 7.57 (t, *J* = 7.1 Hz, 2H), 7.50 (t, *J* = 7.4 Hz, 4H); ^{13}C{^{1}H} NMR (150 MHz, Chloroform-d) δ 141.7, 133.2, 129.3, 127.7.

Procedure for the Gram-Scale Syntheses of Quetiapine. The starting material 2-iodoaniline (8 mmol), methyl 2-mercaptobenzoate (12 mmol, 1.5 eq), rongalite (16 mmol, 2 eq), NaOH (32 mmol, 4 eq) were charged in a 50 ml flask under N_2. After addition of DMSO (20 ml), the flask was sealed and the resulting solution was heated in an oil bath at 90℃ for 48 h. After cooling the tube to room temperature, the mixture was filtered through celite, washed with ethyl acetate and concentrated under reduced pressure. The residue was purified by chromatography to provide the compound **8** as faint yellow solid. (Strict anhydrous and anaerobic conditions were needed, otherwise the generation of major byproduct 2-((2-aminophenyl)thio)benzoic acid will be unavoidable.) Phosphorous oxychloride (1.1 mmol) was added into a stirred solution of compound **8** (1.0 mmol), and N,N-Dimethylaniline (0.5 mmol) in Toluene (5 ml), the mixture heated in an oil bath at 110℃ for 8 h. After cooled to 25℃, the mixture was diluted with EA (12 ml) and washed with water and 4% $NaHCO_3$ solution. The organic layer is dried under vacuum and taken for next step. A mixture of the intermediate (obtained from the above), 1-Hydroxyethylethoxypiperazine (2.0 mmol) and trimethyl-amine (2.0 mmol) in DMF (3 ml) was stirred in an oil bath at 110℃ for 8 h. After cooled to 25℃, the mixture was purified by chromatography to provide **Quetiapine** as thick oil.

*Dibenzo[b,f][1,4]thiazepin-11(10H)-one (**8**)*.[47a] Faint yellow solid (1.27 g, 70%); R_f = 0.4 (PE/EA=4/1); LC-MS (ESI) $[M+1]^+$ 228.0; ^{1}H NMR (400 MHz, DMSO-d6) δ 10.73 (s, 1H), 7.70 – 7.64 (m, 1H), 7.60 – 7.41 (m, 4H), 7.36 (t, *J* = 7.7 Hz, 1H), 7.22 (d, *J* = 8.0 Hz, 1H), 7.14 (t, *J* = 7.5 Hz, 1H); ^{13}C{^{1}H} NMR (150 MHz, DMSO-d6) δ 168.4, 139.9, 137.9, 136.3, 132.6, 132.1, 131.4, 131.3, 129.9, 129.0, 128.9, 125.4, 123.2.

Quetiapine.[47b] Colorless thick oil (249.3 mg, 65% by two steps); R_f = 0.4 (DCM/MeOH=10/1); LC-MS (ESI) $[M+1]^+$ 384.1; ^{1}H NMR (400 MHz, Chloroform-d) δ 7.50 (d, *J* = 7.0 Hz, 1H), 7.38 (d, *J* = 7.9 Hz, 1H), 7.34 – 7.28 (m, 3H), 7.17 (t, *J* = 7.7 Hz, 1H), 7.07 (d, *J* = 8.2 Hz, 1H), 6.88 (t, *J* = 7.4 Hz, 1H), 3.93 – 3.38 (m, 11H), 2.95 – 2.11 (m, 6H); ^{13}C{^{1}H} NMR (150 MHz, Chloroform-d) δ 160.7, 149.0, 140.1, 134.2, 132.3, 132.3, 130.9, 129.2, 129.1, 128.4, 128.1, 125.4, 122.9, 72.5, 67.8, 62.1, 58.1, 53.3, 46.3.

Control experiments. The starting material **1a** (0.2 mmol) and **2a** (3.0 mmol, 15 eq), rongalite (0.4 mmol, 2 eq), KOH (0.4 mmol, 2 eq) together with additive 1,1-Diphenylethylene (2.0 mmol, 10 eq) were charged in a 10 ml Schlenk tube under N_2. After addition of DMSO (0.5 ml), the tube was sealed and the resulting solution was heated in an oil bath at 80℃ for 24 h. After completion, H_2O (4 ml) was added and the resulting mixture was extracted with EtOAc (4 ml * 3). The combined organic layer was dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by chromatography to provide the product both **3aa** and **9**. *Ethene-1,1,2-triyltribenzene (**9**)*.[48] Colorless oil (17.9 mg, 25%); R_f = 0.4 (PE/EA=200/1); ^{1}H NMR (400 MHz, Chloroform-d) δ 7.39 – 7.30 (m, 8H), 7.25 (m, 2H), 7.20 – 7.10 (m, 3H), 7.08 – 7.05 (m, 2H), 7.00 (s, 1H); ^{13}C{^{1}H} NMR (150 MHz, Chloroform-d) δ 143.4, 142.6, 140.4, 137.4, 130.4, 129.6, 128.6, 128.2, 128.2, 128.0, 127.6, 127.5, 127.4, 126.7.

The starting material N-benzyl-2-iodo-N-methylbenzamide or 1-(allyloxy)-2-iodobenzene (0.2 mmol), rongalite (0.4 mmol, 2 eq) and KOH (0.4 mmol, 2 eq) were charged in a 10 ml Schlenk tube under N_2. After addition of DMSO (0.5 ml), the tube was sealed and the resulting solution was heated in an oil bath at 80℃ for 24 h. After completion, H_2O (4 ml) was added and the resulting mixture was extracted with EtOAc (4 ml * 3). The combined organic layer was dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by chromatography to provide the product **10** or **11**.

*2-Methyl-3-phenylisoindolin-1-one (**10**)*.[49] White solid (22.3 mg, 50%); R_f = 0.4 (PE/EA=10/1); LC-MS (ESI) $[M+1]^+$ 224.1; ^{1}H NMR (400 MHz, Chloroform-d) δ 7.97 – 7.80 (m, 1H), 7.47 – 7.45 (m, 2H), 7.37 – 7.35 (m, 3H), 7.21 – 7.10 (m, 3H), 5.34 (s, 1H), 2.98 (s, 3H); ^{13}C{^{1}H} NMR (150 MHz, Chloroform-d) δ 167.8, 145.0, 136.0, 130.7, 130.6, 128.1, 127.67, 127.3, 126.4, 122.5, 121.9, 65.6, 26.5.

*3-Methyl-2,3-dihydrobenzofuran (**11**)*.[50] Colorless oil (12.3 mg, 46%); R_f = 0.4 (PE/EA=200/1); ^{1}H NMR (400 MHz, Chloroform-d) δ 7.17 – 7.11 (m, 2H), 6.90 – 6.86 (m, 1H), 6.80 (d, *J* = 7.9 Hz, 1H), 4.71 – 4.67 (m, 1H), 4.10 – 4.06 (m, 1H), 3.55 (m, 1H), 1.34 (d, *J* = 6.9 Hz, 3H); ^{13}C{^{1}H} NMR (150 MHz, Chloroform-d) δ 159.9, 132.4 128.1, 123.9, 120.6, 109.6, 78.6, 36.6, 19.4.

The corresponding chlroiodobenzene (*o*/*m*/*p*; 0.2 mmol), sodium benzenethiolate **4a** (0.8 mmol, 4 eq), rongalite (0.4 mmol, 2 eq) and KOH (0.4 mmol, 2 eq) were charged in a 10 ml Schlenk tube under N_2. After addition of DMSO (0.5 ml), the tube was sealed and the resulting solution was heated in an oil bath at 80℃ for 24 h. After completion, H_2O (4 ml) was added and the resulting mixture was extracted with EtOAc (4 ml * 3). The combined organic layer was dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by silica chromatography to provide the corresponding disubstituted products **12**, along with traces of the monosubstituted products **13**.

*1,4-Bis(phenylthio)benzene (**12a**)*.[51] White solid (52.4 mg, 89%); R_f = 0.4 (PE/EA=100/1); LC-MS (ESI) $[M+1]^+$ 295.0; ^{1}H NMR (400 MHz, Chloroform-d) δ 7.38 – 7.30 (m, 10H), 7.23 – .22 (m, 4H); ^{13}C{^{1}H} NMR (150 MHz, Chloroform-d) δ 135.1, 134.9, 131.5, 131.2, 129.3, 127.4.

*1,3-Bis(phenylthio)benzene (**12b**)*.[51] Yellow oil (48.9 mg, 83%); R_f = 0.4 (PE/EA=100/1); LC-MS (ESI) $[M+1]^+$ 295.0; ^{1}H NMR (400 MHz, Chloroform-d) δ 7.37 – 7.26 (m, 10H), 7.22 (s, 1H), 7.20 – 7.18 (m, 1H), 7.14 – 7.12 (m, 2H); ^{13}C{^{1}H} NMR (150 MHz, Chloroform-d) δ 137.7, 134.5, 131.8, 131.3, 129.6, 129.3, 128.3, 127.6.

*1,2-Bis(phenylthio)benzene (**12c**)*.[51] White solid (38.9 mg, 66%); R_f = 0.4 (PE/EA=100/1); LC-MS (ESI) $[M+1]^+$ 295.0; ^{1}H NMR (400 MHz, Chloroform-d) δ 7.40 – 7.30 (m, 10H), 7.15 – 7.14 (m, 4H); ^{13}C{^{1}H} NMR (150 MHz, Chloroform-d) δ 136.4, 133.5, 130.8, 130.4, 128.3, 126.5.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

^{1}H and ^{13}C NMR spectra of compounds **3**, **5**, **7**, **8**, **9**, **10**, **11** and **12** (PDF) / EPR Spectrum (PDF) / Cyclic Voltammetry Experiments (PDF)

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Notes

The authors declare no competing financial interest.

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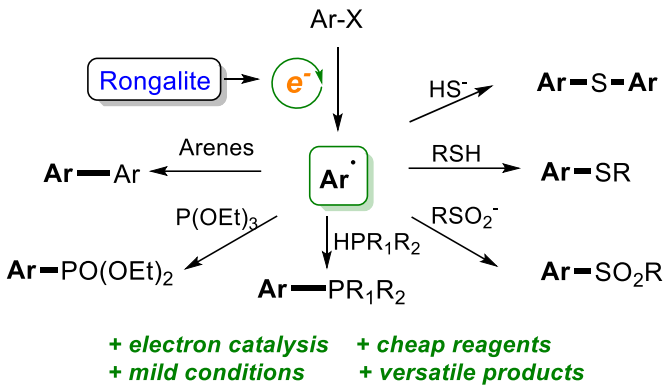

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