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Polyfunctionalized biaryls accessed by a one-pot nucleophilic aromatic substitution and sigmatropic rearrangement reaction cascade under mild conditions

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ABSTRACT

A practical synthetic method has been developed for polyfunctionalized biaryls based on a facile one-pot nucleophilic aromatic substitution (S_NAr) reaction and [5,5]- or [3,3]-sigmatropic rearrangement reaction cascade. Under mild basic conditions, *N*-arylhydroxylamines reacted with *o*-activated fluoro (het)arenes to form *N*,*O*-diarylhydroxylamine intermediates which underwent spontaneously selective [5,5]-sigmatropic rearrangement reaction to produce diverse functionalized 4-amino-4′-hydroxy-1,1′-biaryls. A sequential S_NAr reaction and [3,3]-sigmatropic rearrangement took place between *N*-arylhydroxylamines and 2-fluoropyridine derivatives or 4-fluorobenzonitrile to afford functionalized 2-amino-2′-hydroxy-1,1′-biaryls. As invaluable and unique building blocks, the resulting biaryls were applied in the straightforward synthesis of N_2,O_2-coronarene, carbazole, aza- and diaza carbazole derivatives.

1. Introduction

Polyfunctionalized biaryls such as 4-amino-4′-hydroxy-1,1′-biaryls are useful structural scaffolds in synthetic organic chemistry, drug design and discovery [1–3], and functional materials [4]. 4-Amino-4′-hydroxy-1,1′-biphenyl, for example, constitutes the core of novel necroptosis inducers [1] while 5-(4-aminophenyl) pyridin-2-ol derivatives are potent carboxylic acid diacyglycerol acyltransferase 1 inhibitors [3]. 4-Amino-4′-hydroxy-1,1′-biphenyl has also been used as a building block in the fabrication of liquid crystalline materials [4]. Among the methods [1–3,5–8] reported for the synthesis of 4-amino-4′-hydroxy-1,1′-biaryl compounds, the most frequently used one is the palladium-catalyzed cross coupling reaction between pre-functionalized aryl halides and arylboronic acids or esters (Suzuki reaction) [1–3,5,6]. Functional group transformations such as reduction of the nitro group of 4′-nitro-[1,1′-biphenyl]-4-ol derivatives also provide a synthetic route to 4-amino-4′-hydroxy-1,1′-biaryl compounds [4]. In this regard, 4′-nitro-[1,1′-biphenyl]-4-ol derivatives are obtained either from the Suzuki reaction of 1-bromo-4-nitrobenzene [5,6] or from the nitration of [1,1′-biphenyl]-4-ol derivatives [4]. Diels-Alder reaction of 1-ethynyl-4-nitrobenzene with (cyclohexa-1,5-dien-1-yloxy) trimethylsilane followed by aromatization at 140 °C has also been reported to afford 4′-nitro-[1,1′-biphenyl]-4-ol in 40% yield [7].

Heteracalixaromatics [9–11] and coronarenes [12–16] are composed of *meta*- and *para*-(het)arylenes, respectively, with heteroatom linkages alternatively in a macrocyclic manner. Both types of macrocycles are versatile synthetic host molecules to recognize various cations, anions and charge-neutral guest species [9–16]. To enrich the structure diversity and to exploit application of heteracalixaromatics and coronarenes, we became interested in 4-amino-4′-hydroxy-1,1′-biaryl derivatives which are invaluable building blocks for the fabrication of functional and giant cavities. To obtain primary materials used in the construction of macrocycles for supramolecular applications, a synthetic method featuring (a) the avoidance of transition metal catalysts, (b) the use of cheap and easily available reactants, (c) the tolerance to various functional groups, and (d) simple operation procedures such as a reaction cascade in one-pot is highly desired. We report herein the synthesis of polyfunctionalized biaryls from the nucleophilic aromatic substitution reaction (S_NAr) of *N*-arylhydroxylamines and halo (het)arenes via the sigmatropic rearrangements of *N*,*O*-diarylhydroxylamine intermediates. Synthetic applications of the

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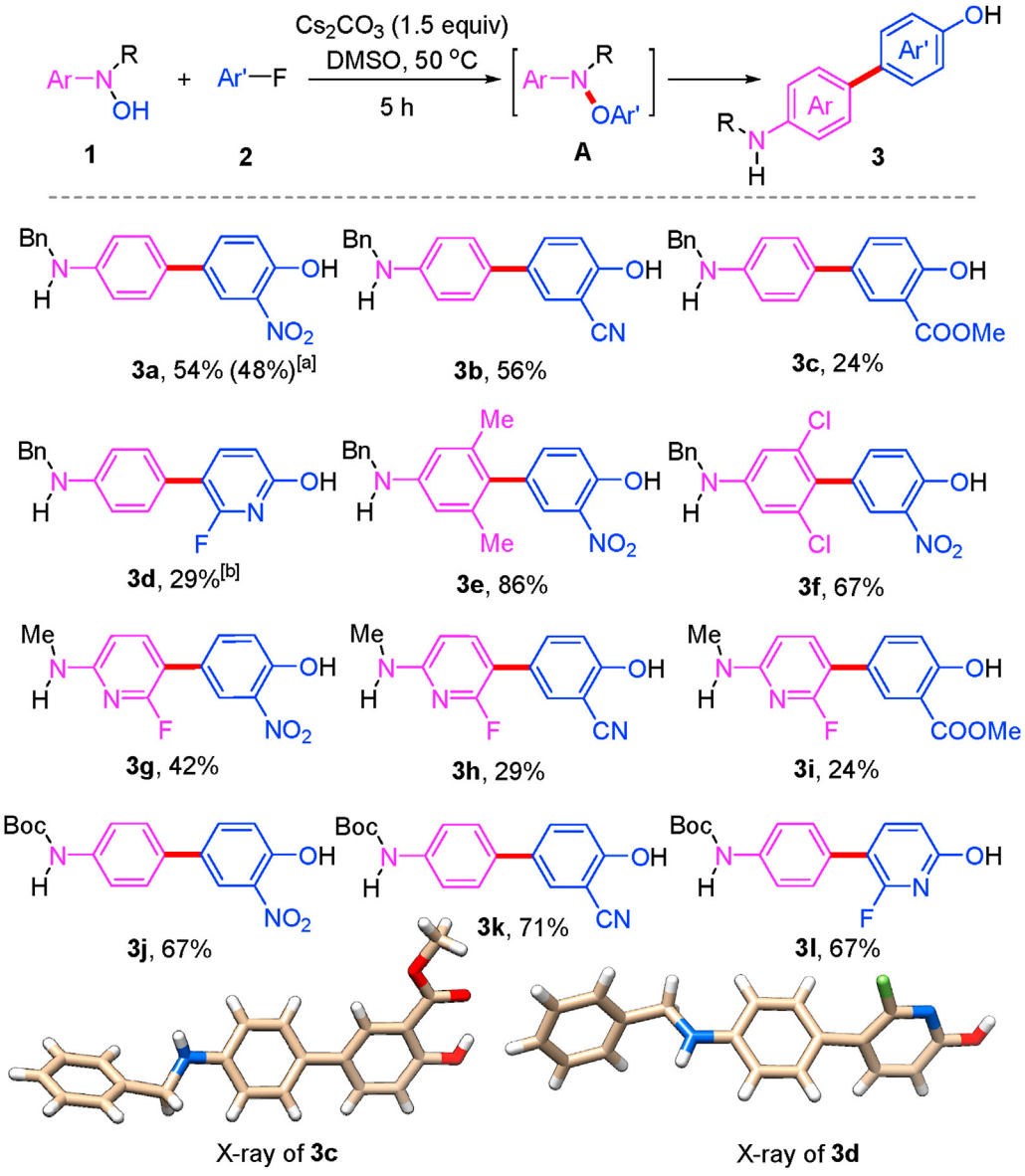
resulting products will also be demonstrated.

A literature survey shows, in comparison with benzidine rearrangement [17], examples of rearrangement reactions of *N*,*O*-diarylhydroxylamines are limited and the mechanism remains largely unexplored although the first report of [5,5]-sigmatropic rearrangement may date back to early 1960s [18]. When reacting *N*-acetyl-*N*-phenylhydroxylamine or *N*-hydroxy-*N*-phenylacetamide with a diphenyliodonium salt to prepare *N*-acetyl-*N*,*O*-diphenylhydroxylamine, Cox and Dunn [18] reported in 1963 the isolation of *N*-(4′-hydroxy-[1,1′-biphenyl]-4-yl)acetamide in 33% yield. Later in 1970s, Sheradsky [19–21] studied the reaction of benzyl *N*-hydroxy-*N*-phenylcarbamate with several nitrated halo (het)arenes in ethanolic potassium hydroxide demonstrating the synthesis of 4-amino-4′-hydroxy-biaryl products. It should be addressed that, in addition to Refs. [5,5]-sigmatropic rearrangement, *N*,*O*-diarylhydroxylamines are able to undergo other reactions [18,20,22–25]. One overlooked but synthetically useful reaction is [3,3]-sigmatropic rearrangement [22–24]. Very recently, Kürti and co-workers [23] reported the addition of ArMgX to *o*-halonitrobenzenes at low temperature. The resulting transient *N*,*O*-diarylhydroxylamines undergoes rapid [3,3]-sigmatropic rearrangement to afford mainly 2-amino-2′-hydroxy-1,1′-biaryls in moderate yields. Intriguingly, the reaction does not take place when the *o*-halo substituent was replaced by other groups [23].

2. Results and discussion

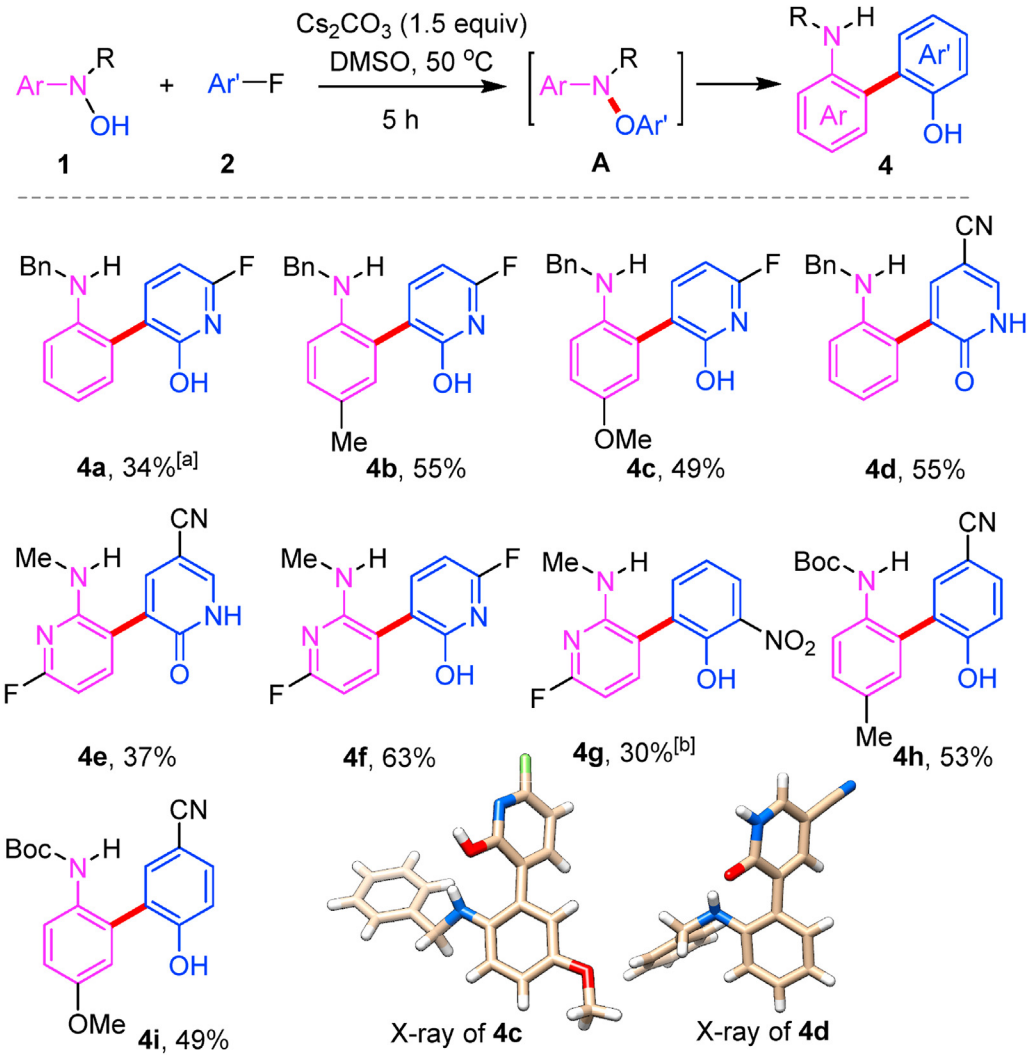
We embarked our study with the examination of S_NAr reaction between *N*-benzyl-*N*-phenylhydroxylamine **1a** and 1-fluoro-2-nitrobenzene **2a** with the initial attempt to synthesize *N*,*O*-diarylhydroxylamine, a potential building unit for the construction of all heteroatom-linked homo calixaromatics [26,27] and coronarenes [28]. In the presence of Cs_2CO_3 as a base, the reaction proceeded smoothly at 50 °C in DMSO. Instead of *N*,*O*-diarylhydroxylamine A, the reaction afforded straightforwardly nitro-bearing 4-benzylamino-4′-hydroxy-1,1′-biphenyl **3a**, a [5,5]-sigmatropic rearrangement product of A, as the major product in 54% yield in 5 h (Scheme 1). 1-Chloro-2-nitrobenzene **2a**′ reacted similarly as **2a**



Scheme 1. Synthesis of polyfunctionalized biaryls **3** from the reaction of **1** with **2**. [a] Yield from the reaction using 1-chloro-2-nitrobenzene **2a'**. [b] **4a** was also isolated in 34%.

to give the same product **3a** in a slightly decreased yield (48%) because of the diminished reactivity of **2a′** in comparison to **2a**. Upon further optimization of reaction conditions, we found that polar aprotic solvent DMSO afforded highest yield compared with other less polar solvents such as CH_3CN and THF. Only trace amount of **3a** were obtained by using CH_3CN or THF as solvent. Temperature also plays an important role. Yields dropped a little bit when the reaction was carried out at r. t. - 40 °C (5–10% falling range) while too high temperature gave a messy mixture. Besides Cs_2CO_3, K_2CO_3 could also serve as a base in spite of lower yields. The reaction gave an inseparable mixture when other bases such as NaOAc and NaO^{t}Bu were used. The reaction was extended readily to other fluorobenzene substrates which contain other electron-withdrawing functional groups. Cyano-bearing biaryl analog **3b** was obtained for example from the same reaction using 2-fluorobenzonitrile **2b**. Methyl 2-fluorobenzoate **2c** underwent similar reaction with **1a** to form the corresponding product **3c** albeit in a lower yield due to the saponification of the methyl ester group under the reaction conditions. In order to introduce pyridine nucleus into the biaryl scaffolds, 2,6-difluoropyridine **2d** was employed. The reaction of **1a** with **2d** went to completion with 5 h, resulting in the desired biaryl compound, namely, 5-(4-(benzylamino)phenyl)-6-fluoropyridin-2-ol **3d** in 29% yield. Notably, from the same reaction mixture, 3-(2-(benzylamino)phenyl)-6-fluoropyridin-2-ol **4a**, which is derived from Refs. [3,3]-sigmatropic rearrangement of *N*,*O*-diarylhydroxylamine intermediate A, was also isolated in 34% yield (Scheme 2). We will discuss this issue later.

The substituent effect on the reactivity of arylhydroxylamine was then examined. To our delight, results illustrated in Scheme 1 show that *N*-arylhydroxylamines substituted with either electron-donation (**1b**) or electron-withdrawing (**1c**) groups on phenyl acted as excellent substrates. They reacted efficiently with 1-fluoro-2-nitrobenzene **2a** to produce 4-amino-4′-hydroxy-1,1′-biphenyl derivatives **3e** and **3f** in the yield of 86% and 67%, respectively. Heterocyclic hydroxylamine such as *N*-(6-fluoropyridin-2-yl)-*N*-methylhydroxylamine **1d**, which was quantitatively prepared from the reaction of 2,6-difluoropyridine **2d** with *N*-methylhydroxylamine (3 equiv.) within in 1 h, was also capable of reacting with fluorobenzenes **2a-c**. The chemical yields of the 4-amino-4′-hydroxy-1,1′-biaryl products **3g-i** were only moderate owing to the decreased nucleophilicity of hydroxylamine **1d**. In the synthesis of **3g**, its isomer, **4g**, which is derived from Refs. [3,3]-sigmatropic rearrangement of *N*,*O*-diarylhydroxylamine intermediate A, was also isolated in 30% yield (Scheme 2). In these cases, there were also side-reactions forming quite a few polar and inseparable



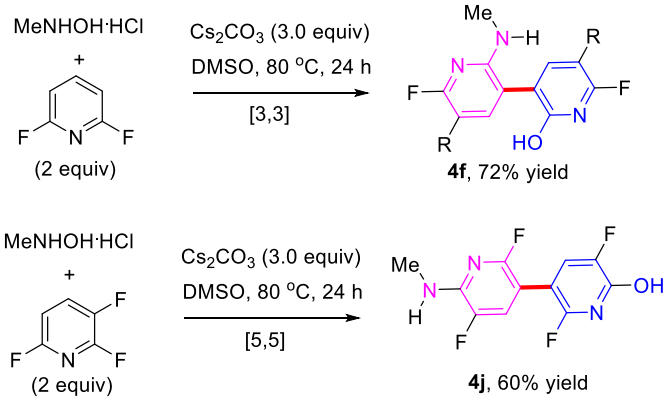
Scheme 2. Synthesis of polyfunctionalized biaryls **4** from the reaction of **1** with **2**. [a] **3d** was also isolated in 29%. [b] **3g** was also isolated in 42%.

compounds based on thin layer chromatography (TLC) analysis of the reaction mixture. From the reaction of **1d** with **2a**, for instance, we managed to isolate a small amount of 2-((6-fluoropyridin-2-yl)(methyl)amino)-6-nitrophenol (8%) (see Supporting Information). Finally, *N*-Boc-*N*-phenylhydroxylamine **1e** was found to be a good substrate. The reaction of **1e** with activated fluorobenzenes **2a**-**b**, **2d** proceeded efficiently to furnish products **3j**-**l** in 67–71% yields.

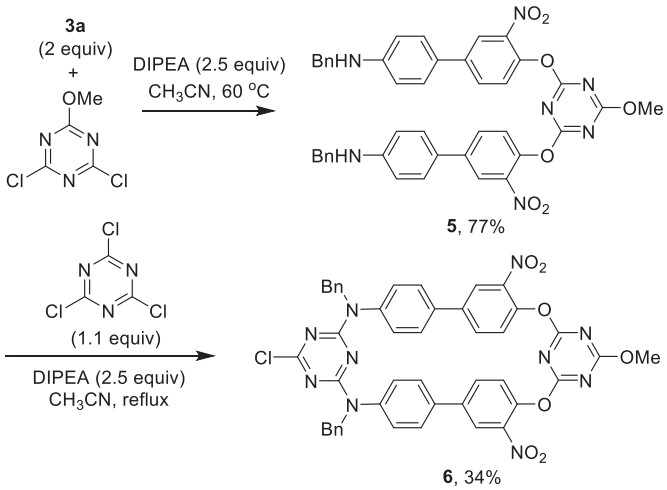
The outcomes summarized in Scheme 1 show clearly that *N*-arylhydroxylamines **1a**-**e** acted as *O*-nucleophiles to react with halo (het)arenes **2a**-**d** to form *N*,*O*-diarylhydroxylamine intermediates A which are highly reactive to undergo spontaneously and predominantly [5,5]-sigmatropic rearrangement producing functionalized 4-amino-4′-hydroxy-1,1′-biaryls **3a**-**l**. However, in the case of the reaction between 2,6-difluoropyridine **2d** and **1a** or **1g**, formation of both [5,5]- and [3,3]-sigmatropic rearrangement products **3a**,**g** and **4a**,**g** were observed. This promoted us to further investigate the reaction of *N*-arylhydroxylamines that bear an *N*-(*para*-substituted phenyl) moiety as the presence of a *para*-substituent would block the pathway of [5,5]-sigmatropic rearrangement, enabling [3,3]-sigmatropic rearrangement and therefore the selective synthesis of 2-amino-2′-hydroxy-1,1′-biaryl compounds (Scheme 2). In accordance to our expectation, reaction of *N*-(*p*-methylphenyl)- and *N*-(*p*-methoxyphenyl)-hydroxylamines **1f** and **1g** with 2,6-difluoropyridine **2d** yielded indeed 2-amino-2′-hydroxy-1,1′-biaryls **4b** and **4c**, respectively. When 5-cyano-2-fluoropyridine **2e** was utilized to react with **1a** or **1d**, a sequential S_NAr and [3,3]-sigmatropic rearrangement reactions took place similarly. Evidenced by spectroscopic data and X-ray diffraction analysis, products **4d** and **4e** adopt pyridin-2(1*H*)-one tautomeric structure. It is worth noting that the reaction between **1d** and **2d** resulted in the formation of [3,3]-sigmatropic rearrangement product 6,6′-difluoro-2'-(methylamino)-[3,3′-bipyridin]-2-ol **4f** in 63%. 6-Fluoro-3-((6-fluoropyridin-2-yl) (methyl)amino)pyridin-2-ol (10%) was also isolated as a by-product (see Supporting Information). Intriguingly, no formation of 2,2′-difluoro-6'-(methylamino)-[3,3′-bipyridin]-6-ol product, which is derived from Refs. [5,5]-sigmatropic rearrangement of *N*,*O*-dipyridylhydroxylamine intermediate A, was observed. Finally, the reaction between 4-fluorobenzonitrile **2f** and *N*-Boc-*N*-(*p*-methylphenyl)-hydroxylamine **1h** or *N*-Boc-*N*-(*p*-methoxyphenyl)-hydroxylamine **1i** afforded the corresponding biphenyl **4h** or **4i** in the yield of 53% or 49%, respectively [29] (Scheme 2).

Since *N*-(6-fluoropyridin-2-yl)-*N*-methylhydroxylamine **1d** was prepared nearly quantitatively from the reaction of *N*-methylhydroxylamine hydrochloride with equimolar 2,6-difluoropyridine **2d** under mild conditions, the synthesis of 3,3′-bipyridine **4f** was then attempted from the reaction of **2d** and *N*-methylhydroxylamine hydrochloride in 2:1 stoichiometry. Gratifyingly, a tandem one-pot reaction comprising two directional *N*- and *O*-nucleophilic reactions of hydroxylamine with **2d** followed by Refs. [3,3]-sigmatropic rearrangement resulted in the production of **4f** in 72% yield (Scheme 3). An overall yield of 72% for a three-step cascade echoes the efficiency of every bond forming reaction is as high as to 90%. Moreover, the one-pot tandem method was readily extended to the synthesis of tetrafluorinated 6'-(methylamino)-[3,3′-bipyridin]-6-ol **4j** from the [5,5]-rearrangement reaction of *N*-methylhydroxylamine with 2,3,6-trifluoropyridine (Scheme 3).

Condensed functionalities confer the resulting biaryl products **3** and **4** invaluable platforms in organic synthesis because of conceivable diverse functional group transformations. To demonstrate the synthetic utility of the method, 4-amino-4′-hydroxy-1,1′-biphenyl **3a** was employed as a building block to construct N_2,O_2-corona [2]biphenyl [2]triazine analog **6** by means of a fragment coupling protocol. As depicted in Scheme 4, S_NAr reaction between



Scheme 3. One-pot synthesis of 3,3′-bipyridine derivatives 4f and 4j.

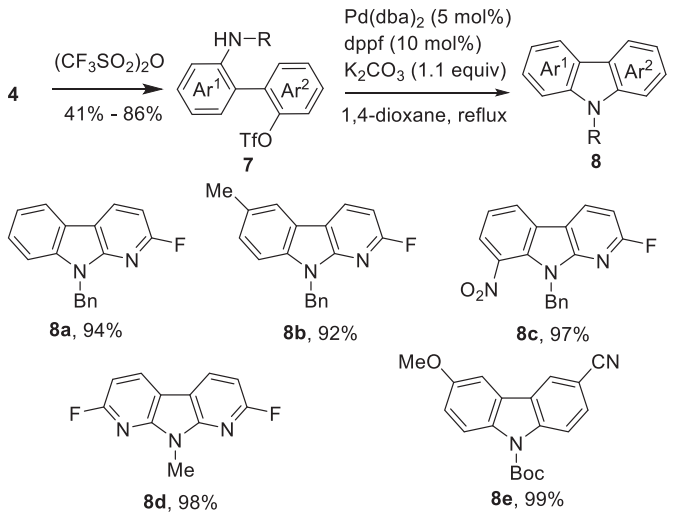


Scheme 4. Synthesis of macrocycle 6.

2,4-dichloro-6-methoxy-1,3,5-triazine and **3a** (2 equiv) afforded intermediate **5** which underwent macrocyclic condensation with cyanuric acid chloride to produce macrocyclic compound **6**. The enlarged cavity and functional groups would render the macrocycle **6** useful in supramolecular applications [10,11,16]. 2-Amino-2′-hydorxy-1,1′-biaryls, on the other hand, were easily and efficiently converted, through a consecutive process of *O*-triflation and intramolecular palladium-catalyzed C–N bond forming reaction, into functionalized 9*H*-carbazole, aza-9*H*-carbazole and diaza-9*H*-carbazole compounds **8** which are the privileged scaffolds for the discovery of drugs [30] and functional materials [31] (Scheme 5).

3. Conclusion

In conclusion, we have developed a practical cascade nucleophilic aromatic substitution and sigmatropic rearrangement method for the synthesis of polyfunctionalized biaryls which are hardly accessible by other means. We have revealed that *N*,*O*-diarylhydroxylamines generated in situ underwent [5,5]-sigmatropic rearrangement reaction predominantly, yielding 4-amino-4′-hydroxy-1,1′-biaryls. The reaction was steered away by the presence of a *para*-substituent on the aryl moiety to Refs. [3,3]-sigmatropic rearrangement to produce 2-amino-2′-hydroxy-1,1′-biaryls. The easy availability of starting materials, transition metal-free and mild one-pot reaction conditions, incorporation of multiple functionalities and tunable reaction pathways would render this



Scheme 5. Synthesis of 9*H*-carbazole, aza-9*H*-carbazole and diaza-9*H*-carbazole compounds 8.

method highly attractive and useful in organic synthesis.

4. Experimental section

General. Reagents and solvents were purchased from commercial sources and preserved under argon. More sensitive compounds were stored in a desiccator or glove-box if required. Reagents were used without further purification unless otherwise noted. All reactions were performed under argon (or nitrogen) and stirring unless otherwise noted. When needed oven dried glassware was used (T°>100 °C) or under vacuum with a heat gun (T°>200 °C). Anhydrous solvents were purified and dried following standard procedures. Flash column chromatography was performed using Silicycle SiliaFlash® P60 230–400 mesh. TLC analysis was performed on pre-coated, glass-backed silica gel plates. TLC's were revealed by UV fluorescence (254 nm) then one of the following: $KMnO_4$, phosphomolybdic acid, ninhydrin, pancaldi, *p*-anisaldehyde, vanillin. Melting points were uncorrected. The ^1H NMR, ^{13}C NMR and ^{19}F NMR spectra were recorded on a JEOL ECX-400 400 MHz spectrometers, ^1H frequency is at 400.13 MHz, ^{13}C frequency is at 100.62 MHz, ^{19}F frequency is at 376.31 MHz. Chemical shifts (δ) were reported in parts per million (ppm) relative to residual solvent peaks rounded to the nearest 0.01 for proton and 0.1 for carbon (ref: DMSO [$\delta_H = 2.50$; $\delta_C = 39.52$] and $CHCl_3$ [$\delta_H = 7.26$, $\delta_C = 77.16$]). Coupling constants (J) were reported in Hz to the nearest 0.1 Hz. Peak multiplicity was indicated as follows s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet) and br (broad). Attribution of peaks was done using the multiplicities and integrals of the peaks. The high resolution mass spectra (HRMS) were recorded on a GCT-MS Micromass UK spectrometer or a microTOF-Q spectrometer. Infrared spectra were recorded using a PerkinElmer Spectrum 100 FT-IR spectrometer with KBr pellets in the 4000-400 cm^{-1} region.

General procedure for the synthesis of [5,5]-rearrangement product 3. To a 25 mL Schlenk tube were charged with *N*-arylhydroxylamines **1** (1 mmol), aryl fluoride **2** (1 mmol), and Cs_2CO_3 (489 mg, 1.5 mmol, 1.5 equiv). The reaction mixture was purged three times with Ar. DMSO (2 mL) was injected to the Schlenk tube and the resulting mixture was stirring at 50 °C for 5 h. The reaction mixture was quenched with water, neutralized with 1 N HCl to pH = 7. The resulting mixture was extracted with ethyl acetate (3 × 10 mL) and dried over anhydrous Na_2SO_4. After removal of solvents, the residue was purified by column chromatography on silica gel to give **3**.

4.1. 4'-(Benzylamino)-3-nitro-[1,1'-biphenyl]-4-ol (**3a**)

Purification: Flash column chromatographed on a silica gel column (petroleum ether and ethyl acetate = 10/1) (173 mg, 54% yield): yellow solid, m. p. 107–108 °C; ^1H NMR (400 MHz, DMSO-d_6) δ 10.80 (s, 1H), 7.95 (d, J = 2.7 Hz, 1H), 7.73 (dd, J = 8.7, 2.3 Hz, 1H), 7.45–7.28 (m, 6H), 7.22 (t, J = 7.1 Hz, 1H), 7.13 (d, J = 8.7 Hz, 1H), 6.65 (d, J = 8.7 Hz, 2H), 6.47 (t, J = 6.2 Hz, 1H), 4.31 (d, J = 6.4 Hz, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 150.6, 148.7, 140.6, 137.3, 133.1, 132.9, 128.9, 127.6, 127.4, 127.3, 125.8, 121.3, 120.0, 113.4, 46.7; IR (KBr, cm^{-1}) ν 3218, 3030, 1612, 1519, 1488. HRMS (ESI-ion trap) calcd. for $C_{19}H_{15}N_2O_3^-$ $[M - H]^-$ 319.1088. Found: 319.1087.

4.2. 4'-(Benzylamino)-4-hydroxy-[1,1'-biphenyl]-3-carbonitrile (**3b**)

Purification: Flash column chromatographed on a silica gel column (petroleum ether and ethyl acetate = 15/1) (169 mg, 56% yield): white solid, m. p. 196–197 °C; ^1H NMR (400 MHz, DMSO-d_6) δ 10.91 (s, 1H), 7.71 (d, J = 2.3 Hz, 1H), 7.66 (d, J = 8.7 Hz, 1H), 7.44–7.27 (m, 6H), 7.22 (t, J = 7.2 Hz, 1H), 7.01 (d, J = 8.7 Hz, 1H), 6.62 (d, J = 8.7 Hz, 2H), 6.42 (t, J = 6.0 Hz, 1H), 4.30 (d, J = 6.0 Hz, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 158.4, 148.1, 140.2, 132.4, 131.8, 129.3, 128.3, 127.2, 126.74, 126.66, 125.7, 117.2, 116.6, 112.7, 99.2, 46.3; IR (KBr, cm^{-1}) ν 3219, 2243, 1611, 1500. HRMS (ESI-ion trap) calcd. for $C_{20}H_{15}N_2O^-$ $[M - H]^-$ 299.1190. Found: 299.1190.

4.3. Methyl 4'-(benzylamino)-4-hydroxy-[1,1'-biphenyl]-3-carboxylate (**3c**)

Purification: Flash column chromatographed on a silica gel column (petroleum ether and ethyl acetate = 10/1) (81 mg, 24% yield): white solid, m. p. 107–108 °C; ^1H NMR (400 MHz, DMSO-d_6) δ 10.38 (s, 1H), 7.87 (d, J = 2.3 Hz, 1H), 7.69 (dd, J = 8.7, 2.3 Hz, 1H), 7.45–7.27 (m, 6H), 7.22 (t, J = 7.1 Hz, 1H), 6.99 (d, J = 8.2 Hz, 1H), 6.65 (d, J = 8.7 Hz, 2H), 6.41 (t, J = 6.0 Hz, 1H), 4.30 (d, J = 6.0 Hz, 2H), 3.90 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 169.4, 158.3, 148.1, 140.3, 133.0, 132.3, 128.5, 127.3, 126.85, 126.80, 126.5, 126.3, 117.9, 113.3, 112.9, 52.6, 46.4; IR (KBr, cm^{-1}) ν 3379, 3027, 2679, 1612, 1490. HRMS (ESI-ion trap) calcd. for $C_{21}H_{18}NO_3$- $[M - H]^-$ 332.1292. Found: 332.1292.

4.4. 5-(4-(Benzylamino)phenyl)-6-fluoropyridin-2-ol (**3d**)

Purification: Flash column chromatographed on a silica gel column (petroleum ether and ethyl acetate = 10/1) (86 mg, 29% yield): white solid, m. p. 210–211 °C; ^1H NMR (400 MHz, DMSO-d_6) δ 11.20 (s, 1H), 7.79 (dd, J = 10.8, 8.0 Hz, 1H), 7.45–7.27 (m, 4H), 7.25–7.18 (m, 3H), 6.64 (d, J = 8.7 Hz, 2H), 6.59 (d, J = 7.8 Hz, 1H), 6.48 (t, J = 6.0 Hz, 1H), 4.30 (d, J = 6.0 Hz, 2H); ^{19}F NMR (376 MHz, DMSO-d_6) δ −74.60 (d, J = 11.7); ^{13}C NMR (100 MHz, DMSO-d_6) δ 160.9 (d, J = 15.3 Hz), 158.1 (d, J = 236.4 Hz), 148.4, 143.5, 140.6, 129.4, 128.9, 127.6, 127.2, 121.4, 113.9 (d, J = 26.7 Hz), 112.9, 107.2, 46.6; IR (KBr, cm−1) ν 3392, 3031, 1612, 1489. HRMS (ESI-ion trap) calcd. for $C_{18}H_{14}FN_2O^-$ $[M - H]^-$ 293.1096. Found: 293.1095.

4.5. 4'-(Benzylamino)-2',6'-dimethyl-3-nitro-[1,1'-biphenyl]-4-ol (**3e**)

Purification: Flash column chromatographed on a silica gel column (petroleum ether and ethyl acetate = 15/1) (300 mg, 86%

yield): white solid, m. p. 131–132 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.90 (s, 1H), 7.52 (d, J = 2.3 Hz, 1H), 7.38–7.20 (m, 6H), 7.13 (d, J = 8.2 Hz, 1H), 6.34 (s, 2H), 6.18 (t, J = 6.2 Hz, 1H), 4.26 (d, J = 6.2 Hz 2H), 1.85 (s, 6H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 150.8, 148.1, 140.9, 137.7, 136.7136.5, 132.5128.7, 127.52, 127.47, 127.1, 126.2, 119.3, 111.8, 46.6, 21.3; IR (KBr, cm^{-1}) ν 3402, 3237, 2859, 1610, 1529, 1427. HRMS (ESI-ion trap) calcd. for $C_{21}H_{19}N_2O_3^-$ [M − H]$^-$ 347.1401. Found: 347.1399.

4.6. 4'-(Benzylamino)-2',6'-dichloro-3-nitro-[1,1'-biphenyl]-4-ol (**3f**)

Purification: Flash column chromatographed on a silica gel column (petroleum ether and ethyl acetate = 20/1) (261 mg, 67% yield): yellow solid, m. p. 114–115 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.15 (s, 1H), 7.68 (s, 1H), 7.50–6.80 (m, 8H), 6.73 (br s, 2H), 4.33 (s, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 151.4, 149.6, 139.1, 137.4, 136.5, 134.3, 128.5, 127.7, 127.2, 127.0, 126.8, 122.9, 118.7, 111.3, 45.9; IR (KBr, cm^{-1}) ν 3417, 3203, 1604, 1538. HRMS (ESI-ion trap) calcd. for $C_{19}H_{13}Cl_2N_2O_3$- [M − H]$^-$ 387.0309. Found: 387.0307.

4.7. 4-(2-Fluoro-6-(methylamino)pyridin-3-yl)-2-nitrophenol (**3g**)

Purification: Flash column chromatographed on a silica gel column (petroleum ether and ethyl acetate = 10/1) (110 mg, 42% yield): yellow solid, m. p. 169–170 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.03 (s, 1H), 7.94 (d, J = 2.3 Hz, 1H), 7.80–7.58 (m, 2H), 7.17 (d, J = 8.7 Hz, 1H), 7.08 (d, J = 4.6 Hz, 1H), 6.43 (d, J = 6.4 Hz, 1H), 2.77 (d, J = 5.0 Hz, 3H); ^{19}F NMR (376 MHz, DMSO-d_6) δ −73.99 (d, J = 9.0 Hz); ^{13}C NMR (100 MHz, DMSO-d_6) δ 159.1 (d, J = 232.6 Hz), 158.2 (d, J = 18.2 Hz), 150.7, 140.7, 136.8, 134.5, 126.0 (d, J = 5.7 Hz), 123.7 (d, J = 3.8 Hz), 119.3, 105.0 (d, J = 36.2 Hz), 104.5 27.9; IR (KBr, cm^{-1}) ν 3283, 3131, 1638, 1539, 1457. HRMS (ESI-ion trap) calcd. for $C_{12}H_9FN_3O_3^-$ [M − H]$^-$ 262.0633. Found: 262.0632.

4.8. 5-(2-Fluoro-6-(methylamino)pyridin-3-yl)-2-hydroxybenzonitrile (**3h**)

Purification: Flash column chromatographed on a silica gel column (petroleum ether and ethyl acetate = 5/1) (71 mg, 29% yield): white solid, m. p. 193–195 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.16 (s, 1H), 7.76–7.63 (m, 2H), 7.60 (d, J = 8.7 Hz, 1H), 7.05 (d, J = 8.7 Hz, 2H), 6.41 (d, J = 6.4 Hz, 1H), 2.76 (d, J = 4.6 Hz, 3H); ^{19}F NMR (376 MHz, DMSO-d_6) δ −74.28 (d, J = 8.6 Hz); ^{13}C NMR (100 MHz, DMSO-d_6) δ 159.1 (d, J = 232.6 Hz), 158.9, 158.1 (d, J = 17.1 Hz), 140.9, 134.4, 134.3, 132.0, 126.4 (d, J = 4.7 Hz), 117.0, 116.5, 105.2 (d, J = 27.7 Hz), 99.2 28.0; IR (KBr, cm^{-1}) ν 3250, 2237, 1627, 1572, 1427. HRMS (ESI-ion trap) calcd. for $C_{13}H_9FN_3O^-$ [M − H]$^-$ 242.0735. Found: 242.0733.

4.9. Methyl 5-(2-fluoro-6-(methylamino)pyridin-3-yl)-2-hydroxybenzoate (**3i**)

Purification: Flash column chromatographed on a silica gel column (petroleum ether and ethyl acetate = 8/1) (67 mg, 24% yield): white solid, m. p. 157–158 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.48 (s, 1H), 7.84 (s, 1H), 7.75–7.54 (m, 2H), 7.12–6.92 (m, 2H), 6.43 (dd, J = 8.2, 1.4 Hz, 1H), 3.90 (s, 3H), 2.77 (d, J = 4.6 Hz, 3H); ^{19}F NMR (376 MHz, DMSO-d_6) δ −74.47 (d, J = 11.7 Hz); ^{13}C NMR (100 MHz, DMSO-d_6) δ 169.0, 159.1 (d, J = 235.5 Hz), 158.6, 158.0 (d, J = 17.2 Hz), 140.8, 135.0, 128.9, 126.1 (d, J = 4.7 Hz), 117.8, 113.2, 105.7, 105.3 (d, J = 39.1 Hz), 52.6, 27.9; IR (KBr, cm^{-1}) ν 3289, 1686, 1637, 1439. HRMS (ESI-ion trap) calcd. for $C_{14}H_{12}FN_2O_3^-$ [M − H]$^-$ 275.0837. Found: 275.0839.

4.10. tert-Butyl (4'-hydroxy-3'-nitro-[1,1'-biphenyl]-4-yl) carbamate (**3j**)

Purification: Flash column chromatographed on a silica gel column (petroleum ether and ethyl acetate = 5/1) (221 mg, 67% yield): orange solid, m. p. 147–149 °C; 1H NMR (400 MHz, DMSO-d_6) δ 10.98 (br s, 1H), 9.46 (br s, 1H), 8.07 (d, J = 2.4 Hz, 1H), 7.82 (dd, J = 8.7, 2.4 Hz, 1H), 7.58–7.53 (m, 4H), 7.19 (d, J = 8.7 Hz, 1H), 1.48 (s, 9H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 152.7, 150.8, 139.1, 137.2, 132.7, 131.4, 131.2, 126.5, 121.9, 119.6, 118.5, 79.1, 28.1; IR (KBr, cm^{-1}) ν 3367, 3181, 2968, 1702, 1511, 1427, 1322, 1231, 1157, 823; HRMS (ESI) Calcd. for $C_{17}H_{17}O_5N_2^-$ [M − H]$^-$ 329.1143. Found: 329.1142.

4.11. tert-Butyl (3'-cyano-4'-hydroxy-[1,1'-biphenyl]-4-yl) carbamate (**3k**)

Purification: Flash column chromatographed on a silica gel column (petroleum ether and ethyl acetate = 5/1) (220 mg, 71% yield): light yellow solid, m. p. 200–202 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.11 (br s, 1H), 9.42 (br s, 1H), 7.85 (d, J = 2.4 Hz, 1H), 7.76 (dd, J = 8.8, 2.4 Hz, 1H), 7.55–7.50 (m, 4H), 7.07 (d, J = 8.7 Hz, 1H), 1.48 (s, 9H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 159.2, 152.7, 138.9, 132.4, 131.8, 131.4, 130.3, 126.4, 118.4, 117.0, 116.7, 99.4, 79.1, 28.1; IR (KBr, cm^{-1}) ν 3292, 2236, 1693, 1531, 1427, 1283, 1248, 1156, 819; HRMS (ESI) Calcd. for $C_{18}H_{17}N_2O_3^-$ [M − H]$^-$ 309.1245. Found: 309.1243.

4.12. tert-Butyl (4-(2-fluoro-6-hydroxypyridin-3-yl)phenyl) carbamate (**3l**)

Purification: Flash column chromatographed on a silica gel column (petroleum ether and ethyl acetate = 5/1) (204 mg, 67% yield): white solid, m. p. 210–211 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.35 (s, 1H), 9.44 (s, 1H), 7.88 (t, J = 9.4 Hz, 1H), 7.53 (d, J = 8.7 Hz, 2H), 7.41 (d, J = 8.2 Hz, 2H), 6.64 (d, J = 8.2 Hz, 1H), 1.48 (s, 9H); ^{19}F NMR (376 MHz, DMSO-d_6) δ −74.29 (d, J = 8.6 Hz); ^{13}C NMR (100 MHz, DMSO-d_6) δ 161.5 (d, J = 16.2 Hz), 157.7 (d, J = 237.4 Hz), 152.7, 143.4 (d, J = 4.8 Hz), 138.9, 128.5, 127.4 (d, J = 4.8 Hz), 118.1, 112.5 (d, J = 26.7 Hz), 106.9, 79.1, 28.1; IR (KBr, cm^{-1}) ν 3391, 2981, 1704, 1589, 1508. HRMS (ESI$^-$ion trap) calcd. for $C_{16}H_{16}FN_2O_3$: [M − H]$^-$ 303.1150. Found: 303.1150.

General procedure for the synthesis of [3,3]-rearrangement product 4. To a 25 mL Schlenk tube were charged with *N*-arylhydroxylamines **1** (1 mmol), aryl fluoride **2** (1 mmol), and Cs_2CO_3 (489 mg, 1.5 mmol, 1.5 equiv). The reaction mixture was purged three times with Ar. DMSO (2 mL) was injected to the Schlenk tube and the resulting mixture was stirring at 50 °C for 5 h. The reaction mixture was quenched with water, neutralized with 1 N HCl to pH = 7. The resulting mixture was extracted with ethyl acetate (3 × 10 mL) and dried over anhydrous Na_2SO_4. After removal of solvents, the residue was purified by column chromatography on silica gel to give **4**.

4.13. 3-(2-(Benzylamino)phenyl)-6-fluoropyridin-2-ol (**4a**)

Purification: Flash column chromatographed on a silica gel column (petroleum ether and ethyl acetate = 10/1) (101 mg, 34% yield): white solid, m. p. 150–151 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.52 (s, 1H), 7.69 (t, J = 8.2 Hz, 1H), 7.34 (d, J = 7.3 Hz, 2H), 7.28 (t, J = 7.6 Hz, 2H), 7.19 (t, J = 7.1 Hz, 1H), 7.06–7.00 (m, 1H), 6.91 (dd, J = 7.6, 1.6 Hz, 1H), 6.67 (dd, J = 7.8, 2.7 Hz, 1H), 6.57 (t, J = 7.1 Hz, 1H), 6.42 (d, J = 8.2 Hz, 1H), 5.29 (br, 1H), 4.28 (s, 2H); ^{19}F NMR (376 MHz, DMSO-d_6) δ −73.08; ^{13}C NMR (100 MHz, DMSO-d_6) δ 161.5 (d, J = 235.5 Hz), 160.3 (d, J = 14.3 Hz), 146.2, 146.1, 140.7,

131.3, 129.3, 129.1, 127.5, 127.3, 122.5, 118.0, 116.8, 111.3, 100.4 (d, J = 35.3 Hz), 46.9; IR (KBr, cm^{-1}) ν 3446, 3026, 1600, 1578, 1442. HRMS (ESI-ion trap) calcd. for $C_{18}H_{14}FN_2O^-$ [M − H]$^-$ 293.1096. Found: 293.1094.

4.14. 3-(2-(Benzylamino)-5-methylphenyl)-6-fluoropyridin-2-ol (**4b**)

Purification: Flash column chromatographed on a silica gel column (petroleum ether and ethyl acetate = 8/1) (170 mg, 55% yield): white solid, m. p. 148−150 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.51 (br, 1H), 7.68 (t, J = 8.2 Hz, 1H), 7.33−7.23 (m, 4H), 7.18 (t, J = 7.0 Hz, 1H), 6.85 (d, J = 8.5 Hz, 1H), 6.75 (s, 1H), 6.66 (dd, J = 7.9, 2.4 Hz, 1H), 6.36 (d, J = 7.9 Hz, 1H), 5.06 (br, 1H), 4.25 (s, 2H), 2.14 (s, 3H); ^{19}F NMR (376 MHz, DMSO-d_6) δ −73.15; ^{13}C NMR (100 MHz, DMSO-d_6) δ 160.8 (d, J = 235.5 Hz), 160.0 (d, J = 16.2 Hz), 145.3 (d, J = 8.6 Hz), 143.4, 140.4, 131.2, 128.9, 128.2, 126.8, 126.4, 124.1, 122.0, 117.6 (d, J = 4.8 Hz), 110.7, 99.3 (d, J = 35.2 Hz), 46.6, 19.9; IR (KBr, cm^{-1}) ν 3419, 3026, 1592, 1519, 1472. HRMS (ESI-ion trap) calcd. for $C_{19}H_{16}FN_2O^-$ [M − H]$^-$ 307.1252. Found: 307.1252.

4.15. 3-(2-(Benzylamino)-5-methoxyphenyl)-6-fluoropyridin-2-ol (**4c**)

Purification: Flash column chromatographed on a silica gel column (petroleum ether and ethyl acetate = 5/1) (159 mg, 49% yield): white solid, m. p. 173−174 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.30 (br, 1H), 7.72 (t, J = 8.2 Hz, 1H), 7.33−7.16 (m, 5H), 6.73−6.58 (m, 3H), 6.44 (d, J = 8.7 Hz, 1H), 5.20 (br, 1H), 4.21 (s, 2H), 3.63 (s, 3H); ^{19}F NMR (376 MHz, DMSO-d_6) δ −72.78; ^{13}C NMR (100 MHz, DMSO-d_6) δ 160.9 (d, J = 234.6 Hz), 159.9 (d, J = 15.2 Hz), 150.6, 145.3 (d, J = 8.5 Hz), 140.4, 139.8, 128.2, 126.9, 126.5, 123.3, 117.4 (d, J = 5.7 Hz), 116.9, 113.8, 112.0, 99.3 (d, J = 36.2 Hz), 55.3, 47.2; IR (KBr, cm^{-1}) ν 3380, 3030, 1620, 1519, 1472. HRMS (ESI-ion trap) calcd. for $C_{19}H_{16}FN_2O_2^-$ [M − H]$^-$ 323.1201. Found: 323.1201.

4.16. 5-(2-(Benzylamino)phenyl)-6-oxo-1,6-dihydropyridine-3-carbonitrile (**4d**)

Purification: Flash column chromatographed on a silica gel column (petroleum ether and ethyl acetate = 5/1) (166 mg, 55% yield): white solid, m. p. 161−162 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.60 (s, 1H), 8.32 (d, J = 2.4 Hz, 1H), 7.64 (d, J = 2.4 Hz, 1H), 7.37 (d, J = 7.3 Hz, 2H), 7.29 (t, J = 7.3 Hz, 2H), 7.19 (t, J = 7.0 Hz, 1H), 7.14−7.00 (m, 1H), 6.96 (dd, J = 7.6, 1.5 Hz, 1H), 6.57 (t, J = 7.3 Hz, 1H), 6.42 (d, J = 7.9 Hz, 1H), 5.60 (s, 1H), 4.28 (d, J = 4.3 Hz, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 160.6, 146.1, 143.4, 140.2, 140.1, 131.9, 130.6, 129.0, 128.2, 126.8, 126.5, 121.8, 117.3, 115.6, 110.5, 89.9, 46.3. IR (KBr, cm^{-1}) ν 3295, 3061, 2229, 1642. HRMS (ESI-ion trap) calcd. for $C_{19}H_{14}N_3O^-$ [M − H]$^-$ 300.1142. Found: 300.1142.

4.17. 6′-Fluoro-2′-(methylamino)-2-oxo-1,2-dihydro-[3,3′-bipyridine]-5-carbonitrile (**4e**)

Purification: Flash column chromatographed on a silica gel column (petroleum ether and ethyl acetate = 5/1) (91 mg, 37% yield): white solid, m. p. 198−199 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.62 (d, J = 5.5 Hz, 1H), 7.60 (t, J = 7.6 Hz, 1H), 7.48 (d, J = 6.0 Hz, 1H), 6.24 (d, J = 7.8 Hz, 1H), 4.55 (d, J = 10.5 Hz, 1H), 4.31 (d, J = 10.5 Hz, 1H), 2.94 (s, 3H); ^{19}F NMR (376 MHz, DMSO-d_6) δ −74.14 (d, J = 8.6 Hz); ^{13}C NMR (100 MHz, DMSO-d_6) δ 167.0, 164.0 (d, J = 233.6 Hz), 160.9 (d, J = 18.1 Hz), 142.6, 137.4 (d, J = 8.6 Hz), 119.5, 115.8 (d, J = 3.8 Hz), 95.3 (d, J = 37.1 Hz), 82.9, 60.8, 41.9, 31.3; IR (KBr, cm^{-1}) ν 3293, 2870, 2218, 1702, 1661. HRMS (ESI-ion trap) calcd. for $C_{12}H_8FN_4O^-$ [M − H]$^-$ 243.0688. Found: 243.0685.

4.18. 6,6′-Difluoro-2′-(methylamino)-[3,3′-bipyridin]-2-ol (**4f**)

Purification: Flash column chromatographed on a silica gel column (petroleum ether and ethyl acetate = 5/1) (151 mg, 63% yield): white solid, m. p. 212 °C, sublimation; ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.47 (s, 1H), 7.64 (t, J = 8.2 Hz, 1H), 7.30 (t, J = 8.2 Hz, 1H), 6.64 (dd, J = 8.0, 2.5 Hz, 1H), 6.15 (dd, J = 7.8, 2.7 Hz, 1H), 6.04 (s, 1H), 2.70 (d, J = 4.1 Hz, 3H); ^{19}F NMR (376 MHz, DMSO-d_6) δ −71.63 (d, J = 8.6 Hz), −72.39; ^{13}C NMR (100 MHz, DMSO-d_6) δ 162.4 (d, J = 230.7 Hz), 161.1 (d, J = 235.5 Hz), 160.3 (d, J = 15.3 Hz), 156.1 (d, J = 18.1 Hz), 145.4 (d, J = 8.6 Hz), 142.4 (d, J = 9.5 Hz), 114.9 (d, J = 4.8 Hz), 113.3 (d, J = 4.8 Hz), 99.8 (d, J = 36.2 Hz), 92.6 (d, J = 37.2 Hz), 28.3; IR (KBr, cm^{-1}) ν 3437, 2942, 1619, 1588. HRMS (ESI-ion trap) calcd. for $C_{11}H_8F_2N_3O^-$ [M − H]$^-$ 236.0641. Found: 236.0637.

4.19. 2-(6-Fluoro-2-(methylamino)pyridin-3-yl)-6-nitrophenol (**4g**)

Purification: Flash column chromatographed on a silica gel column (petroleum ether and ethyl acetate = 5/1) (79 mg, 30% yield): orange solid, m. p. 177−179 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.49 (br s, 1H), 8.07 (dd, J = 8.4, 1.7 Hz, 1H), 7.52 (dd, J = 7.4, 1.7 Hz, 1H), 7.36 (dd, J = 8.4, 7.8 Hz, 1H), 7.10 (dd, J = 8.4, 7.4 Hz, 1H), 6.20 (dd, J = 7.7, 2.8 Hz, 1H), 6.05 (br s, 1H), 2.71 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 162.6 (d, J = 231 Hz), 155.9 (d, J = 18 Hz), 151.4, 142.2 (d, J = 9 Hz), 138.7, 135.9, 128.2, 124.9, 119.9, 113.5 (d, J = 4 Hz), 92.8 (d, J = 37 Hz), 28.2; IR (KBr, cm^{-1}) ν 3457, 3161, 3079, 1619, 1597, 1531, 1444, 1398, 1316, 1266, 1216, 746; HRMS (ESI-ion trap) Calcd. for $C_{12}H_9O_3N_3F^-$ [M − H]$^-$ 262.0633; Found: 262.0631.

4.20. tert-Butyl (5′-cyano-2′-hydroxy-5-methyl-[1,1′-biphenyl]-2-yl)carbamate (**4h**)

Purification: Flash column chromatographed on a silica gel column (petroleum ether and ethyl acetate = 4/1) (172 mg, 53% yield): white solid, m. p. 205−207 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.82 (br s, 1H), 7.91 (br s, 1H), 7.63 (dd, J = 8.5, 2,2 Hz, 1H), 7.50 (d, J = 2.1 Hz, 1H), 7.31 (d, J = 8.1 Hz, 1H), 7.14 (dd, J = 8.2, 1.6 Hz, 1H), 7.08−7.06 (m, 2H), 2.29 (s, 3H), 1.31 (s, 9H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 158.6, 153.3, 135.5, 133.7, 133.4, 133.0, 131.5, 131.3, 128.6, 127.4, 125.2, 119.4, 116.6, 101.2, 78.6, 27.9, 20.4; IR (KBr, cm^{-1}) ν 3377, 3183, 2229, 1682, 1603, 1504, 1280, 1159, 841; HRMS (ESI-ion trap) Calcd. for $C_{19}H_{19}N_2O_3^-$ [M − H]$^-$ 323.1401; Found: 323.1399.

4.21. tert-Butyl (5′-cyano-2′-hydroxy-5-methoxy-[1,1′-biphenyl]-2-yl)carbamate (**4i**)

Purification: Flash column chromatographed on a silica gel column (petroleum ether and ethyl acetate = 4/1) (167 mg, 49% yield): white solid, m. p. 189−191 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.83 (br s, 1H), 7.93 (br s, 1H), 7.63 (dd, J = 8.5, 2.2 Hz, 1H), 7.53 (d, J = 2.1 Hz, 1H), 7.26 (d, J = 8.6 Hz, 1H), 7.07 (d, J = 8.5 Hz, 1H), 6.91 (dd, J = 8.8, 3.0 Hz, 1H), 6.82 (d, J = 2.9 Hz, 1H), 3.75 (s, 3H), 1.29 (s, 9H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 158.7, 156.4, 153.7, 135.4, 133.7, 133.0, 128.9, 127.5, 127.3, 119.5, 116.7, 115.8, 113.6, 101.0, 78.4, 55.3, 28.0; IR (KBr, cm^{-1}) ν 3393, 3147, 2969, 2230, 1675, 1603, 1504, 1285, 1161, 1032, 874, 838; HRMS (ESI-ion trap) Calcd. for $C_{19}H_{19}N_2O_4^-$ [M − H]$^-$ 339.1350; Found: 339.1347.

One-pot synthesis of 3,3′-bipyridine derivatives 4f and 4j. To a 25 mL Schlenk tube were charged with *N*-methylhydroxylamine hydrochloride (83.5 mg, 1 mmol), Cs_2CO_3 (978 mg, 3 mmol). The reaction mixture was purged three times with Ar. DMSO (2 mL) was injected and the resulting mixture was stirring at room

temperature for 30 min. Aryl fluoride **2** (2 mmol) was added and the resulting mixture was stirring at 80 °C for 24 h. The reaction mixture was quenched with water, neutralized with 1 N HCl to pH = 7. The resulting mixture was extracted with ethyl acetate (3 × 10 mL) and dried over anhydrous Na_2SO_4. After removal of solvents, the residue was purified by column chromatography on silica gel to give **4**.

4.22. 5,5′,6,6′-Tetrafluoro-2′-(methylamino)-[3,3′-bipyridin]-2-ol (*4j*)

Purification: Flash column chromatographed on a silica gel column (petroleum ether and ethyl acetate = 3/1) (164 mg, 60% yield): white solid, m. p. 268–270 °C; ^{1}H NMR (400 MHz, DMSO-d_6, 60 °C) δ 12.25 (br s, 1H), 7.82–7.78 (m, 1H), 7.60–7.55 (m, 1H), 7.10 (br s, 1H), 2.85 (d, J = 4.6 Hz, 3H); ^{13}C NMR (100 MHz, DMSO-d_6, 60 °C) δ 154.1 (d, J = 232 Hz), 152.2 (d, J = 237 Hz), 150.5, 147.3, 145.8 (d, J = 247 Hz), 143.3 (d, J = 247 Hz), 128.8–128.7 (m, 1C), 124.8–124.7 (m, 1C), 105.3–105.0 (m, 1C), 97.8–97.5 (m, 1C), 27.2; IR (KBr, cm^{-1}) ν 3278, 3129, 1634, 1573, 1509, 1470, 1429, 1231, 1178, 1073, 910, 789, 738; HRMS (ESI-ion trap) Calcd. for $C_{11}H_6N_3OF_4^-$ [M − H]$^-$ 272.0453; Found: 272.0451.

Synthesis of 5. To a solution of **3a** (128 mg, 0.4 mmol) and DIPEA (65 mg, 0.5 mmol) in dry acetonitrile (2 mL) which was pre-heated to 60 °C, a solution of 2,4-dichloro-6-methoxy-1,3,5-triazine (36 mg, 0.2 mmol) in acetonitrile (1.5 mL) was added dropwise during 4 h. The resulting solution was stirred at 60 °C for 3 h until **3a** was consumed. The mixture was then cooled gradually to room temperature, a saturated ammonium chloride was added to pH = 7 to quench the reaction. The resulting mixture was extracted with dichloromethane (3 × 50 mL). The combined organic layers were washed with brine (50 mL), and dried over anhydrous Na_2SO_4. After removal of solvent, the residue was chromatographed on a silica gel column with a mixture of petroleum ether and acetone as the mobile phase to give pure product **5** (115 mg, 77% yield): yellow solid, m. p. 137–139 °C; ^{1}H NMR (400 MHz, Acetone-d$_6$) δ 8.15 (d, J = 2.4 Hz, 2H), 7.92 (dd, J = 8.4, 2.4 Hz, 2H), 7.46–7.40 (m, 10H), 7.32 (t, J = 7.6 Hz, 4H), 7.23 (t, J = 8.2 Hz, 2H), 6.75 (d, J = 8.7 Hz, 4H), 5.83 (t, J = 5.2 Hz, 1H), 4.42 (s, 4H), 3.93 (s, 3H); ^{13}C NMR (100 MHz, Acetone-d$_6$) δ 174.4, 173.1, 149.47, 142.3, 141.9, 140.8, 140.0, 131.8, 128.5, 127.8, 127.3, 126.9, 125.4, 125.2, 122.0, 113.1, 55.5, 47.1; IR (KBr, cm^{-1}) ν 3512, 3421, 3028, 1609, 1523, 1489, 1364, 1223, 1117, 816. HRMS (ESI-ion trap) calcd. for $C_{42}H_{33}N_7O_7Cl^-$ [M+Cl]$^-$ 782.2136. Found: 782.2142.

Synthesis of 6. To a solution of DIPEA (32 mg, 0.25 mmol) in dry acetonitrile (20 mL), which was pre-heated to reflux, a solution of **5** (75 mg, 0.1 mmol) and cyanuric chloride (20 mg, 0.11 mmol) in acetonitrile (20 mL) was added dropwise during 12 h. The resulting solution was stirred for 12 h until **5** was consumed. The mixture was then cooled gradually to room temperature, a saturated ammonium chloride was added to pH = 7 to quench the reaction. The resulting mixture was extracted with dichloromethane (3 × 50 mL). The combined organic phase was washed with brine (50 mL), and dried over anhydrous Na_2SO_4. After removal of solvent, the residue was chromatographed on a silica gel column with a mixture of petroleum ether and acetone as the mobile phase to give pure product **6** (29 mg, 34% yield): white or pale yellow solid, m. p. > 300 °C; ^{1}H NMR (400 MHz, Acetone-d$_6$) δ 8.09 (d, J = 2.0 Hz, 2H), 7.87 (dd, J = 8.4, 2.4 Hz, 2H), 7.52 (t, J = 2.0 Hz, 2H), 7.50 (t, J = 2.2 Hz, 2H), 7.32–7.20 (m, 16H), 5.26 (s, 4H), 4.14 (s, 3H); ^{13}C NMR (100 MHz, Acetone-d$_6$) δ 175.4, 172.8, 169.9, 165.5, 143.6, 142.6, 141.7, 139.2, 137.8, 135.0, 132.5, 128.5, 128.2, 127.9, 127.4, 125.4, 122.9, 55.9, 52.3; IR (KBr, cm^{-1}) ν 3033, 2953, 1600, 1563, 1541, 1361, 1219, 1115, 824, 733. HRMS (MALDI) calcd. for $C_{45}H_{32}ClN_{10}O^+$ [M+H]$^+$ 859.2139. Found: 859.2134.

Synthesis of 7. To a solution of **4** (2 mmol) in dry pyridine (4 mL) was added Tf_2O (0.42 mL, 2.5 mmol, 1.25 equiv) dropwise at 0 °C. The resulting solution was stirred at room temperature overnight. Dilute hydrochloric acid (1 N) was added to the mixture to pH = 3 to quench the reaction. Than resulting mixture was diluted with water (20 mL) and extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (petroleum ether and ethyl acetate) to give compound **7**.

4.23. 3-(2-(Benzylamino)phenyl)-6-fluoropyridin-2-yl trifluoromethanesulfonate (*7a*)

Purification: Flash column chromatographed on a silica gel column (petroleum ether and ethyl acetate = 10/1) (478 mg, 56% yield): colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 (t, J = 7.8 Hz, 1H), 7.34–7.23 (m, 6H), 7.12 (dd, J = 8.2, 3.0 Hz, 1H), 7.04 (dd, J = 7.5, 1.5 Hz, 1H), 6.82 (td, J = 7.5, 1.0 Hz, 1H), 6.74 (d, J = 8.3 Hz, 1H), 4.33 (s, 2H), 3.71 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.8 (d, J = 249 Hz), 151.0 (d, J = 14 Hz), 147.7 (d, J = 7 Hz), 145.5, 138.9, 130.9 (d, J = 7 Hz), 128.8, 127.5, 127.4, 124.5 (d, J = 6 Hz), 118.9 (q, J = 319 Hz), 117.81, 117.76, 111.9, 110.7 (d, J = 34 Hz), 100.1, 48.4; IR (KBr, cm^{-1}) ν 3437, 2921, 2850, 1602, 1576, 1511, 1474, 1422, 1213, 1134, 975, 844; HRMS (ESI-ion trap) Calcd. for $C_{19}H_{13}N_2O_3F_4S^-$ [M − H]$^-$ 425.0589; Found: 425.0589.

4.24. 3-(2-(Benzylamino)-5-methylphenyl)-6-fluoropyridin-2-yl trifluoromethanesulfonate (*7b*)

Purification: Flash column chromatographed on a silica gel column (petroleum ether and ethyl acetate = 10/1) (362 mg, 41% yield): light yellow soild, m. p. 89–91 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.26 (t, J = 8.0 Hz, 1H), 7.55 (dd, J = 8.2, 2.5 Hz, 1H), 7.32–7.24 (m, 4H), 7.20–7.16 (m, 1H), 6.94 (dd, J = 8.4, 1.8 Hz, 1H), 6.79 (d, J = 1.8 Hz, 1H), 6.39 (d, J = 8.4 Hz, 1H), 5.58 (t, J = 6.0 Hz, 1H), 4.24 (d, J = 5.9 Hz, 2H), 2.15 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 159.4 (d, J = 245 Hz), 149.9 (d, J = 13 Hz), 149.2 (d, J = 8 Hz), 143.4, 140.2, 130.8, 130.5, 128.1, 126.6, 126.4, 124.7 (d, J = 5 Hz), 124.1, 117.8 (q, J = 319 Hz), 117.1, 111.3, 111.0, 46.2, 19.7; IR (KBr, cm^{-1}) ν 3427, 3030, 2920, 1606, 1519, 1473, 1413, 1212, 977, 839, 606; HRMS (ESI-ion trap) Calcd. for $C_{20}H_{15}N_2O_3F_4S^-$ [M − H]$^-$ 439.0745; Found: 439.0745.

4.25. 2-(6-Fluoro-2-(methylamino)pyridin-3-yl)-6-nitrophenyl trifluoromethanesulfonate (*7c*)

Purification: Flash column chromatographed on a silica gel column (petroleum ether and ethyl acetate = 10/1) (680 mg, 86% yield): yellow oil; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.33 (dd, J = 8.1, 1.8 Hz, 1H), 7.90 (dd, J = 7.8, 1.8 Hz, 1H), 7.83–7.79 (m, 1H), 7.55 (t, J = 8.1 Hz, 1H), 6.54–6.52 (m, 1H), 6.29 (dd, J = 7.9, 2.8 Hz, 1H), 2.73 (d, J = 4.5 Hz, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 163.3 (d, J = 234 Hz), 155.8 (d, J = 18 Hz), 144.2 (d, J = 9 Hz), 142.3, 138.9, 138.7, 133.0, 130.3, 126.4, 117.5 (q, J = 319 Hz), 110.1 (d, J = 5 Hz), 93.4 (d, J = 38 Hz), 28.1; IR (KBr, cm^{-1}) ν 3425, 2962, 1580, 1541, 1511, 1428, 1395, 1363, 1229, 1218, 1133, 799, 756; HRMS (ESI-ion trap) Calcd. for $C_{13}H_8N_3O_5F_4S^-$ [M − H]$^-$ 394.0126; Found: 394.0124.

4.26. 6,6′-Difluoro-2′-(methylamino)-[3,3′-bipyridin]-2-yl trifluoromethanesulfonate (*7d*)

Purification: Flash column chromatographed on a silica gel column (petroleum ether and ethyl acetate = 5/1) (605 mg, 82% yield): white solid, m. p. 140–141 °C; ^{1}H NMR (400 MHz, DMSO-d_6)

δ 8.27 (t, J = 8.0 Hz, 1H), 7.57 (q, J = 7.6 Hz 2 Hz, 1H), 7.47 (t, J = 8.4 Hz, 1H), 6.47 (d, J = 4.6 Hz, 1H), 6.27 (dd, J = 7.8, 2.7 Hz, 1H), 2.71 (d, J = 4.6 Hz, 3H); ^{19}F NMR (376 MHz, DMSO-d_6) δ −68.97 (d, J = 5.6 Hz), −69.38 (d, J = 5.6 Hz), −73.73; ^{13}C NMR (100 MHz, DMSO-d_6) δ 163.3 (d, J = 233.6 Hz), 160.5 (d, J = 245.0 Hz), 155.9 (d, J = 18.1 Hz), 149.9 (d, J = 14.3 Hz), 149.4 (d, J = 8.6 Hz), 143.2 (d, J = 8.6 Hz), 122.2 (d, J = 4.8 Hz), 117.8 (q, J = 318.5 Hz), 111.4 (d, J = 34.3 Hz), 108.9 (d, J = 3.8 Hz), 93.3 (d, J = 38.1 Hz), 28.0; IR (KBr, cm^{-1}) ν 3444, 2946, 1621, 1587. HRMS (ESI-ion trap) calcd. for $C_{12}H_9F_5N_3O_3S^+$ $[M+H]^+$ 370.0279. Found: 370.0277.

4.27. 2'-((tert-Butoxycarbonyl)amino)-5-cyano-5'-methoxy-[1,1'-biphenyl]-2-yl trifluoromethanesulfonate (**7e**)

Purification: Flash column chromatographed on a silica gel column (petroleum ether and ethyl acetate = 8/1) (728 mg, 77% yield): colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79–7.76 (m, 2H), 7.54–7.49 (m, 2H), 7.00 (dd, J = 8.9, 2.9 Hz, 1H), 6.75 (d, J = 2.9 Hz, 1H), 5.87 (br s, 1H), 3.80 (s, 3H), 1.30 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.4, 153.8, 149.6, 136.8, 134.8, 133.6, 129.3, 128.5, 127.5, 123.3, 118.4 (q, J = 319 Hz), 117.0, 116.1, 115.7, 113.2, 80.8, 55.8, 28.3; IR (KBr, cm^{-1}) ν 3346, 2980, 2235, 1715, 1515, 1485, 1426, 1218, 1160, 870, 616; HRMS (ESI-ion trap) Calcd. for $C_{20}H_{18}N_2O_6F_3S^-$ $[M-H]^-$ 471.0838; Found: 471.0839.

Synthesis of 8. To a Schlenk tube were charged with **7** (1 mmol), Pd $(dba)_2$ (29 mg, 0.05 mmol), dppf (55 mg, 0.1 mmol), K_2CO_3 (152 mg, 1.1 mmol) at room temperature. The reaction mixture was purged three times with Ar. To the reaction mixture was injected anhydrous 1,4-dioxane (2 mL) and heated to reflux. After 2 h, The resulting mixture was cooled to room temperature and filtered with Celite. The filtrate was concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (petroleum ether and ethyl acetate) to give compound **8**.

4.28. 9-Benzyl-2-fluoro-9H-pyrido[2,3-b]indole (**8a**)

Purification: Flash column chromatographed on a silica gel column (petroleum ether and ethyl acetate = 5/1) (260 mg, 94% yield): colorless oil; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.69 (t, J = 8.0 Hz, 1H), 8.18 (d, J = 7.4 Hz, 1H), 7.62 (d, J = 8.2 Hz, 1H), 7.45 (ddd, J = 8.3, 7.2, 1.2 Hz, 1H), 7.30–7.19 (m, 6H), 6.98 (dd, J = 8.2, 1.0 Hz, 1H), 5.62 (s, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 161.6 (d, J = 236 Hz), 148.7 (d, J = 18 Hz), 138.9, 137.1, 133.8 (d, J = 10 Hz), 128.5, 127.3, 127.0, 126.2, 120.8, 120.5, 119.8, 112.8 (d, J = 3 Hz), 110.3, 100.0 (d, J = 38 Hz), 44.3; IR (KBr, cm^{-1}) ν 1599, 1573, 1485, 1354, 1199, 803, 701; HRMS (ESI-ion trap) Calcd. for $C_{18}H_{14}N_2F^+$ $[M+H]^+$ 277.1136; Found: 277.1138.

4.29. 9-Benzyl-2-fluoro-6-methyl-9H-carbazole (**8b**)

Purification: Flash column chromatographed on a silica gel column (petroleum ether and ethyl acetate = 5/1) (267 mg, 92% yield): white solid, m. p. 115–117 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.87 (t, J = 8.0 Hz, 1H), 8.60 (d, J = 7.4 Hz, 1H), 8.11 (d, J = 8.7 Hz, 1H), 7.47 (t, J = 7.9 Hz, 1H), 7.15 (d, J = 8.0 Hz, 1H), 3.83 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 161.5 (d, J = 235 Hz), 148.8 (d, J = 17 Hz), 137.2, 133.7 (d, J = 9 Hz), 129.5, 128.5, 127.5, 127.3, 127.0, 120.7, 119.9, 112.7 (d, J = 3 Hz), 110.1, 99.7 (d, J = 38 Hz), 44.3, 20.9; IR (KBr, cm^{-1}) ν 2938, 1598, 1572, 1484, 1412, 1353, 1198, 936, 802, 700; HRMS (ESI-ion trap) Calcd. for $C_{19}H_{16}N_2F^+$ $[M+H]^+$ 291.1292; Found: 291.1290.

4.30. 2-Fluoro-9-methyl-8-nitro-9H-pyrido[2,3-b]indole (**8c**)

Purification: Flash column chromatographed on a silica gel column (petroleum ether and ethyl acetate = 5/1) (237 mg, 97% yield): yellow solid, m. p. 203–205 °C; ^{1}H NMR (400 MHz, DMSO-d_6, 60 °C) δ 8.83–8.79 (m, 1H), 8.56–8.54 (m, 1H), 8.07 (d, J = 7.9 Hz, 1H), 7.44 (t, J = 7.5 Hz, 1H), 7.10 (d, J = 8.3 Hz, 1H), 3.81 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6, 60 °C) δ 162.0 (d, J = 238 Hz), 150.1 (d, J = 18 Hz), 135.7, 134.5 (d, J = 10 Hz), 130.8, 126.0, 123.8, 122.5, 119.7, 111.7, 101.7 (d, J = 38 Hz), 30.7; IR (KBr, cm^{-1}) ν 3083, 1600, 1586, 1516, 1477, 1423, 1351, 1289, 1221, 1146, 974, 805, 736; HRMS (ESI-ion trap) Calcd. for $C_{12}H_9N_3O_2F^+$ $[M+H]^+$ 246.0673; Found: 246.0673.

4.31. 2,7-Difluoro-9-methyl-9H-pyrrolo[2,3-b:5,4-b']dipyridine (**8d**)

Purification: Flash column chromatographed on a silica gel column (petroleum ether and ethyl acetate = 20/1) (215 mg, 98% yield): white solid, m. p. 234–236 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.65 (t, J = 7.8 Hz, 2H), 7.01 (d, J = 8.2 Hz, 2H), 3.83 (s, 3H); ^{19}F NMR (376 MHz, DMSO-d_6) δ −70.35; ^{13}C NMR (100 MHz, DMSO-d_6) δ 161.1 (d, J = 237.4 Hz), 148.3 (d, J = 18.1 Hz), 133.6 (d, J = 9.6 Hz), 110.4, 100.6 (d, J = 38.1 Hz), 26.0; IR (KBr, cm^{-1}) ν 1581, 1498, 1409. HRMS (ESI-ion trap) calcd. for $C_{11}H_8F_2N_3^+$ $[M+H]^+$ 220.0681. Found: 220.0677.

4.32. tert-Butyl 3-cyano-6-methoxy-9H-carbazole-9-carboxylate (**8e**)

Purification: Flash column chromatographed on a silica gel column (petroleum ether and ethyl acetate = 5/1) (319 mg, 99% yield): white solid, m. p. 162–163 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.69 (d, J = 1.4 Hz, 1H), 8.27 (d, J = 8.7 Hz, 1H), 8.06 (d, J = 9.1 Hz, 1H), 7.86 (dd, J = 8.7, 1.7 Hz, 1H), 7.82 (d, J = 2.6 Hz, 1H), 7.15 (dd, J = 9.1, 2.7 Hz, 1H), 3.86 (s, 3H), 1.70 (s, 9H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 156.1, 149.7, 140.2, 132.4, 130.4, 125.6, 125.0, 124.6, 119.3, 116.7, 116.6, 116.5, 105.1, 103.9, 84.9, 55.6, 27.7; IR (KBr, cm^{-1}) ν 2981, 2228, 1734, 1493, 1359, 1220, 1158, 1139, 816; HRMS (ESI-ion trap) Calcd. for $C_{19}H_{19}N_2O_3^+$ $[M+H]^+$ 323.1390; Found: 323.1391.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

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