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Highly Efficient Suzuki–Miyaura Coupling of Heterocyclic Substrates through Rational Reaction Design

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Abstract: A dicyclohexyl(2-sulfo-9-(3-(4-sulfophenyl)propyl)-9*H*-fluoren-9-yl)phosphonium salt was synthesized in 64% overall yield in three steps from simple commercially available starting materials. The highly water-soluble catalyst obtained from the corresponding phosphine and [Na_2PdCl_4] enabled the Suzuki coupling of a broad variety of *N*- and *S*-heterocyclic substrates. Chloropyridines (-quinolines) and aryl chlorides were coupled with aryl-, pyridine- or indoleboronic acids in quantitative yields in water/*n*-butanol solvent mixtures in the presence of 0.005–0.05 mol% of Pd catalyst at 100°C, chloropurines were quantitatively Suzuki coupled in the presence of 0.5 mol% of catalyst, and *S*-heterocyclic aryl chlorides and aryl- or 3-pyridylboronic acids required 0.01–0.05 mol% Pd catalyst for full conversion. The key to the high activity of the Pd-phosphine catalyst is the rational design of the reaction parameters (i.e., the presence of water in the reaction mixture, good solubility of reactants and catalyst in *n*-butanol/water (3:1), and the electron-rich and sterically demanding nature of the phosphine ligand).

Keywords: cross-coupling · indoles · palladium · purines · thiophenes

Introduction

The biological activity associated with numerous nitrogen- and sulfur-containing heterocycles explains their wide use as active pharmaceutical ingredients.[1–6] Consequently, a sizable portion of recent US patents reports on organic process development of aromatic heterocycles.[7,8] A useful synthetic tool for the modification of such compounds is the Suzuki–Miyaura coupling,[9,10] which has been applied for the preparation of arylpyridines,[11,12] bipyridines,[11–15] arylpyrimidines,[16–18] pyridopyridines[11,12,19–21] and aryltriazines,[22,23] the synthesis of nucleosides[24,25] or the introduction of thiophene,[26,27] benzothiazole[28] or indolyl[29–32] moieties.

Nonetheless, the cross-coupling chemistry of heterocyclic substrates suffers from limitations. In particular, *N*-heterocycles or compounds bearing free amino moieties are regarded as challenging substrates.[11,33–37] Problems include the inhibition of the catalytically active centre by *N*-coordination, the trimerization of boronic acids[38] and the poor reactivities of electron-deficient boronic acids. In some cases primary or secondary amino groups have been masked by protective groups to allow the coupling of such substrates, while without *N*-protection the Suzuki coupling was less efficient.[39] Lacking general and efficient cross-coupling protocols, synthetic chemists resort to heteroaryl bromides as coupling substrates[40,41] instead of the cheaper and more easily available aryl chlorides, which require at least 1 mol% of catalyst for quantitative conversion.[42–44] Recently, significant improvements in the coupling of heteroaryl chlorides have been reported by Guram et al.,[45,46] Buchwald et al.[35] and Fu et al.[33] Interestingly, some of the more efficient coupling reactions involving heterocyclic substrates were performed in water[25,47–60] or in water-containing solvent mixtures (with toluene, dioxane, CH_3CN or *n*-butanol).

We have recently demonstrated that water in combination with water-soluble, sulfonated fluorenylphosphine Pd complexes is a very useful solvent for Suzuki coupling reactions of *N*-heterocycles.[61] Our working hypothesis is that basic nitrogen atoms in pyridines, indoles or primary amines prefer to engage in hydrogen-bonding interactions with water rather than to inhibit the catalytically active metal centre. Apart from being a cheap, safe and benign solvent,[62–64] water has the additional advantage that the organic products of the coupling reactions are often poorly soluble and can thus easily be separated from the reaction mixture. This advantage, though, also turns out to be a drawback, as the aryl halide reactants tend to be poorly soluble in water, leading

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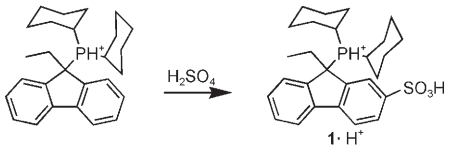
to a decrease in the overall rate of the coupling reaction due to mass transfer limitations. In order to improve the efficiency of Suzuki reactions further, we reasoned that increasing the solubility of the reactants in water by addition of a co-solvent should lead to even faster Suzuki coupling reactions. However, this must be achieved without compromising the previously mentioned advantages. The cosolvent should be benign: it should form a biphasic mixture with water at room temperature and a single solvent phase at elevated temperatures to avoid mass transfer limitations.[65] *n*-Butanol fulfils the criteria defined above: it has a large phase separation region with water at room temperature,[66] but forms monophasic mixtures at elevated temperatures, does not interfere with the Suzuki reaction, has a satisfactory boiling point and proves to represent a good trade-off between economical, safety and ecological aspects.[67,68]

We wish to report here on highly efficient Suzuki coupling reactions of various *N*- and *S*-heterocyclic substrates in the presence of a highly water-soluble catalyst, based on a disulfonated phosphine, in an optimized water/*n*-butanol mixture.

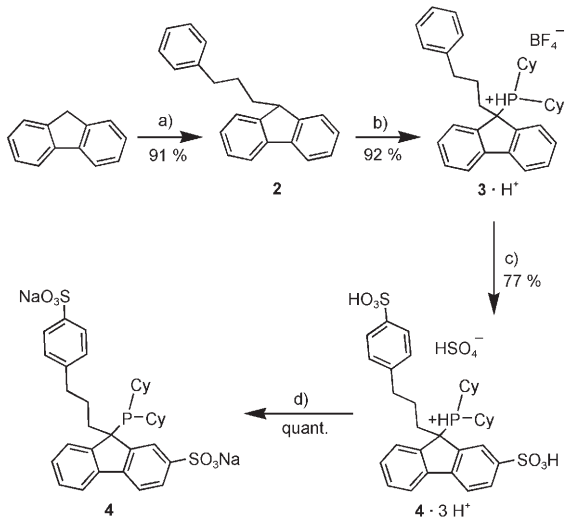
Results and Discussion

Synthesis of a highly water-soluble disulfonated fluorenyldialkylphosphine: We have recently reported the synthesis of fluorenylphosphines whose Pd complexes are excellent catalysts for various cross-coupling reactions.[61,69,70] Some of these phosphines are easily monosulfonated by treating their respective phosphonium salts with sulfuric acid (Scheme 1).[61] Nonetheless, the water solubilities of the corresponding Pd–phosphine complexes remain modest.



Scheme 1. Monosulfonation of a 9-ethylfluorenyldicyclohexylphosphonium salt.

Disulfonation of 9-ethylfluoren-9-yldicyclohexylphosphonium salt **1**·H$^+$ was not successful. The use of more reactive sulfonating reagents (oleum, $ClSO_3H$) on phosphine **1** led to the quantitative oxidation of P^{III} during aqueous workup, while less forcing reaction conditions afforded only the monosulfonated product. Consequently, we introduced another phenyl ring at the periphery of the ligand to serve as an anchor for a second sulfonato group (Scheme 2). The corresponding dicyclohexylfluorenylphosphonium salt **3** is readily sulfonated on treatment with sulfuric acid, affording the disulfonated fluorenylphosphonium salt **4**·3H$^+$. Treatment of this reaction mixture with dilute NaOH and subsequent methanolic workup afforded the free phosphine **4** as the corresponding sodium salt in 65% overall yield from fluorene,



Scheme 2. Synthesis of the disulfonated fluorenyldialkylphosphine **4**. a) 3-phenylpropan-1-ol, 3-phenylpropanal, KOH, 150°C; b) *n*BuLi, Cy_2PCl, MTBE, −30°C, aq. HBF_4; c) CH_2Cl_2, H_2SO_4, 50°C; d) NaOH.

through the use of simple commercially available starting materials.[71] Following our report on the large-scale synthesis of various fluorenylphosphines (including **3**·H$^+$),[70] we now routinely perform the double sulfonation of **3**·H$^+$ on a 50 g scale using sulfuric acid, completely avoiding the formation of undesired phosphine oxides—even when the reaction is carried out in the presence of oxygen.

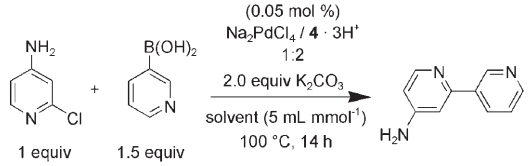
Optimizing the water/*n*-butanol system: As pointed out before, the poor solubility of aryl halides in pure water appears to be a drawback for coupling reactions in this solvent. We first wanted to test whether the addition of *n*-butanol as a co-solvent would enhance the catalytic activity of the [Pd/**4**] complex in Suzuki cross-coupling reactions. The catalyst was formed in situ by treatment of two equivalents of phosphonium salt **4**·3H$^+$ with $[Na_2PdCl_4]$ in the presence of six equivalents of base and the reactants. We chose the coupling of 4-amino-2-chloropyridine and 3-pyridylboronic acid as the test reaction, and obtained quantitative conversion (93%) in water/*n*-butanol (1:1) solvent with the [Pd/**4**] complex as formed in situ as catalyst.

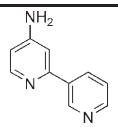
In pure water significantly lower conversion (44%) was observed under the same conditions (Table 1), while in *n*-butanol no coupling (<1%) occurred. This result confirms our initial idea that the reaction rate can be enhanced by providing better substrate solubility, while on the other hand a significant amount of water in the *n*-butanol is required to allow highly effective cross-coupling reactions.

We next studied the impact of the *n*-butanol/water ratio in Suzuki reactions of heterocycles to optimize the solvent composition in a more systematic manner. With the same catalyst as before, 2-chloro-4-picoline was coupled with *p*-tolylboronic acid in pure water, pure *n*-butanol or various mixtures of the two solvents (Figure 1).

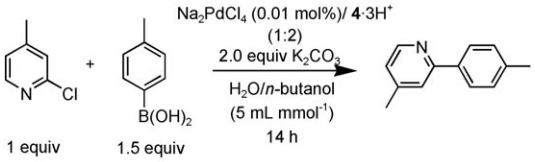
At 80°C and 0.01 mol% [Pd] loading in pure water 59% conversion was observed, increasing on addition of *n*-buta-

Table 1. Influence of solvent on catalytic activity: water versus water/*n*-butanol.



Entry	Aryl chloride	Boronic acid	Product	Conv. [%][a]
1				44[b] 93[c] <1[d]

[a] Average of two runs, determined by GC with heptadecane as internal standard. [b] In pure water as solvent. [c] In H_2O/*n*-butanol 1:1 as solvent. [d] In *n*-butanol.



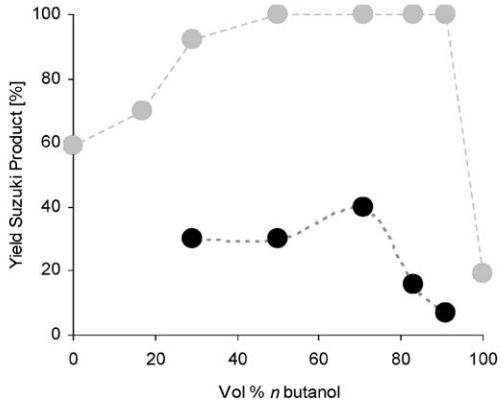


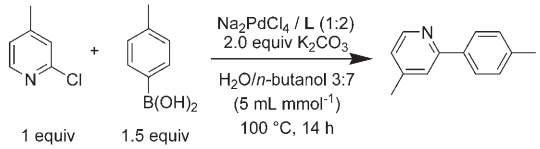
Figure 1. Effect of water/*n*-butanol ratio on catalytic activity. Reaction temperature: ●: 80 °C. ●: 60 °C.

nol to reach 100% conversion over a wide range of water/*n*-butanol compositions of 1:1 to 1:9. With a further increase in the alcohol content, the conversion drops drastically to only 19% conversion in pure *n*-butanol (technical grade). To identify the best solvent composition the screen was repeated at a lower reaction temperature (60 °C). Under these conditions a catalytic optimum was found at approximately 75% (*v*/*v*) *n*-butanol. Almost the same water/*n*-butanol composition was used by Billingsley and Buchwald for the Suzuki coupling of 2-bromothiophene and pyrrole boronate esters.[72]

From the water/*n*-butanol phase diagram,[66] we believe that a water/*n*-butanol 1:3 solvent mixture provides the highest possible water content in a homogeneous solution at 100 °C. At higher water contents the water/*n*-butanol mixture turns biphasic, leading to significantly diminished yields in cross-coupling reactions. Further increasing the amount of *n*-butanol results in drastically lowered yields—obviously a certain amount of water is very important. Consequently, the 1:3 water/*n*-butanol ratio represents a good trade-off between good substrate solubility, a monophasic reaction at elevated temperatures and biphasic behavior at ambient conditions, combined with maximum water content.

We next compared the catalytic activities of Pd complexes formed in situ with the doubly sulfonated phosphine **4**, the monosulfonated phosphine **1** and the phosphine **3**. Those three ligands are electron-rich and sterically demanding phosphines, which is essential for the formation of high-activity Pd complexes.[73,74] This was done to demonstrate the superiority of highly polar Pd complexes over their medium-polar and lipophilic counterparts. On treatment of 2-chloro-4-picoline with *p*-tolylboronic acid at 100 °C in the water/*n*-butanol (1:3) mixture, Pd complexes with the doubly sulfonated phosphine **4**·3 H^+ showed significantly higher catalytic activity than their mono- and non-sulfonated relatives (Table 2). Under the same set of conditions, the palladium salt alone (i.e., in the absence of phosphine) does not afford any detectable cross-coupling product (Table 2, entry 3).

Table 2. Catalytic activity of water-soluble and water-insoluble catalysts.



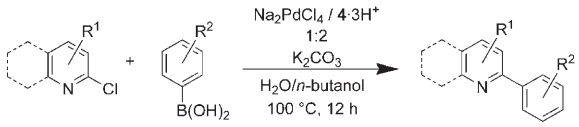
Entry	Ligand **L**	Cat. loading [mol%]	Yield [%][a]
1	**4**	0.01	>99
2	**4**	0.005	>99
3	–	0.01[b]	0
4	**1**	0.01	>99
5	**1**	0.005	73
6	**3**	0.01	79
7	**3**	0.005	59

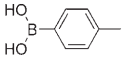
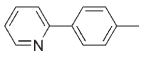
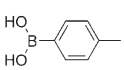
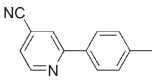
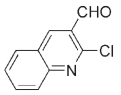
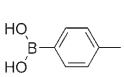
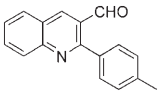
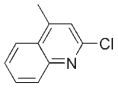
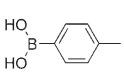
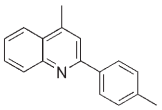
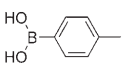
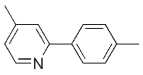
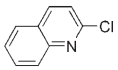
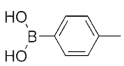
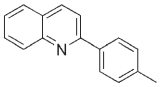
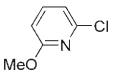
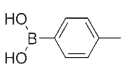
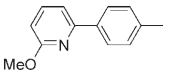
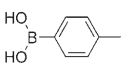
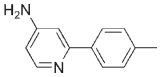
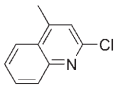
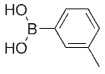
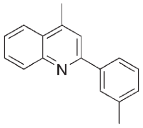
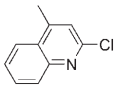
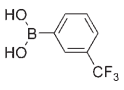
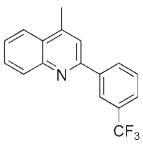
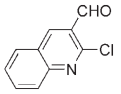
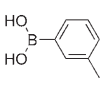
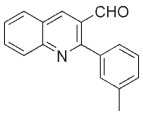
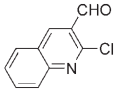
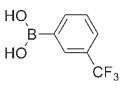
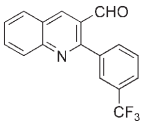
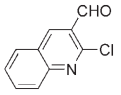
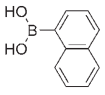
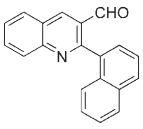
[a] Average of two runs, determined by GC with heptadecane as internal standard. [b] Control experiment: 0.01 mol% [Na_2PdCl_4], no phosphine ligand.

Suzuki cross-coupling of *N*-heterocycles: We next wanted to demonstrate the generality of the optimized reaction conditions for Suzuki reactions of *N*-heterocyclic substrates by coupling a number of different 2-chloropyridines and 2-chloroquinolines in Suzuki reactions with various boronic acids (mainly tolyl- and naphthylboronic acid) (Table 3).

Coupling reactions of 2-chloropyridines with sterically unhindered boronic acids (*p*-tolyl-, *m*-tolyl-) or electron-deficient *m*-(trifluoromethyl)phenylboronic acid were carried out at 100 °C in *n*-butanol/water (3:1) over 12 h with K_2CO_3 as the base and in the presence of 0.005 mol% of Pd catalyst[75] (Table 1, entries 1–12). Even with the sterically hindered 1-naphthylboronic acid, quantitative conversion was achieved in the presence of 0.01 mol% of Pd catalyst (Table 3, entries 13–19). Difficult substrates such as the highly basic 4-amino-2-chloropyridine reacted with *p*-tolyl-

Table 3. Suzuki reactions with 2-chloropyridines and 2-chloroquinolines with arylboronic acids in water/*n*-butanol (1:3)[a]



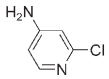
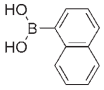
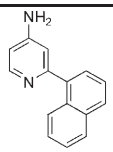
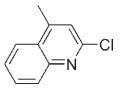
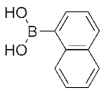
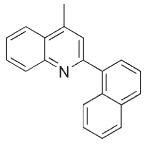
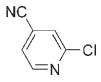
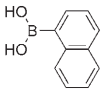
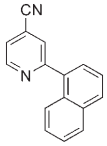
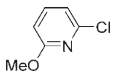
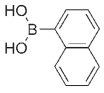
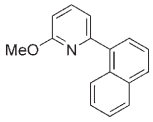
Entry	Aryl chloride	Boronic acid	Product	Pd [mol%]	Conv. [%][b]	Yield[c]
1				0.005	≥99	95
2				0.005	≥99	92
3				0.005	≥99	91
4				0.005	≥99	95
5				0.005	≥99	94
6				0.005	≥99	96
7				0.005	≥99	94
8				0.01 0.005	≥99 78	92
9				0.005	≥99	96
10				0.005	≥99	96
11				0.005	≥99	94
12				0.005	≥99	95
13				0.01	≥99	92
14				0.01	≥99	96
15				0.01	≥99	95

boronic acid or 1-naphthylboronic acid to afford quantitative conversions at 0.01 mol% catalyst loading (Table 3, entries 8, 16). For these substrates the Pd-phosphine complex **4** is about four times more active in water/*n*-butanol than in pure water and 10 to 100 times more active than other recently reported catalysts.[33,35,76]

Suzuki coupling of *N*-heterocyclic boronic acids: More challenging Suzuki substrate combinations are those in which both coupling partners contain a pyridyl or an amino moiety. In order to probe the activity of our catalytic system we screened reactions of various 2-chloropyridines and 2-chloroquinolines with 3-pyridylboronic acid. With 0.01 mol% catalyst loading, 2-chloropyridines and 2-chloroquinolines reacted smoothly with 3-pyridylboronic acid to afford near quantitative conversion (Table 4, entries 1–5). The highly basic 4-amino-2-chloropyridine was coupled in near quantitative yield with 3-pyridylboronic acid (Table 4, entry 7) or with 2,4-dimethoxy-3-pyridylboronic acid (Table 4, entry 9) when 0.05 mol% catalyst were applied.

Our optimized reaction protocol is not limited to 2-chloropyridines as coupling partners. Both 4-chloropyridine and the less activated 3-chloropyridine coupled quantitatively with *p*-tolylboronic acid (Table 5, entries 1 and 2) in the presence of as little as 0.05 mol% of catalyst. Sterically hindered boronic acids such as 2,6-dimethylboronic acid (Table 5, entry 3) reacted smoothly in the same manner with 4-chloropyridine. 3-Pyridylboronic acid—an electron-deficient metalloid—gave quantitative conversion with either 3-chloropyridine or 4-chloropyridine (Table 5, entries 4 and 5).

Table 3. (Continued)

Entry	Aryl chloride	Boronic acid	Product	Pd [mol%]	Conv. [%][b]	Yield[c]
16				0.01	≥99	91
17				0.01	≥99	94
18				0.01	≥99	91
19				0.01	≥99	95

[a] Reaction conditions: 1.0 equiv aryl halide, 1.2 equiv boronic acid, 3.2 equiv K_2CO_3, degassed water (1.5 mL mmol^{-1}), degassed *n*-butanol (4.5 mL mmol^{-1}), 100 °C, cat.: the corresponding volume of aqueous catalyst stock solution (c_{Pd} = 0.001 mol L^{-1}, Na_2PdCl_4/ligand (**4**·3H$^+$) L/Pd 2:1. Reaction times and temperature were not optimized. [b] Average of two runs, determined by GC with heptadecane as internal standard. [c] Average of two runs; products were isolated by column chromatography (silica gel), cyclohexene/EtOAc/NEt_3 10:1:1.

Application of the standard coupling protocol to deactivated 4-chloroanisole with the sterically hindered and electron-deficient 2,4-dimethoxy-3-pyridylboronic acid led to quantitative product formation (Table 4, entry 8). The same outcome was observed when the deactivated 1-(4-chlorophenyl)-1*H*-pyrrole was coupled with 3-anisylboronic acid (Table 5, entry 6) or *N*-heterocyclic boronic acids (3-pyridylboronic acid; Table 5, entry 7).

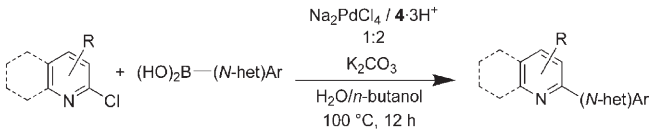
Because of its ubiquitous appearance in natural products, compounds bearing an indole ring are of importance for pharmaceutical chemistry[77] as, for example, antitumor agents.[78,79] Suzuki couplings of aryl halides with the corresponding indoleboronic acids should thus represent a convenient approach for the introduction of this heterocycle. In a comprehensive study of the reactivity of haloindoles and indoleboronic acids in Suzuki cross-couplings, Giralt et al.[30] noted that unprotected indoleboronic acid is not well suited for Suzuki reactions. It is thus not surprising that most of the known cross-coupling protocols either utilize *N*-protected indoleboronic acids,[80] accepting the need for a protection/deprotection sequence, or otherwise are restricted to the use of the more active aryl bromides as coupling partners.[29,34,41,81,82] Recently, the use of improved catalysts and modified reaction protocols has allowed the coupling of aryl chlorides with unprotected indoleboronic acids—unfortunately, though, this requires catalyst loadings of 2–5 mol%.[33,35,72]

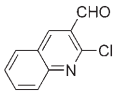
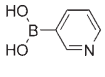
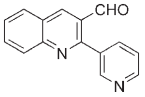
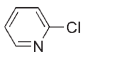
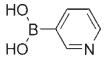
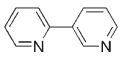
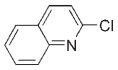
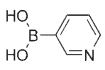
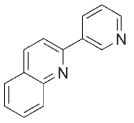
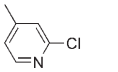
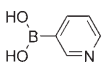
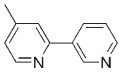
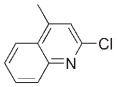
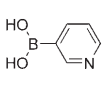
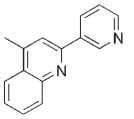
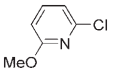
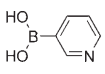
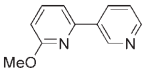
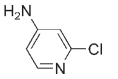
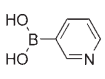
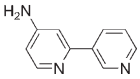
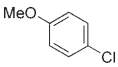
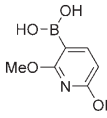
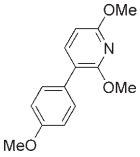
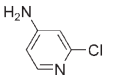
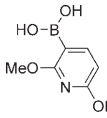
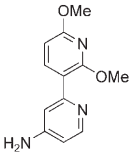
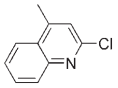
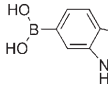
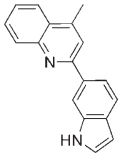
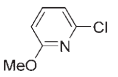
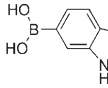
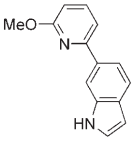
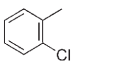
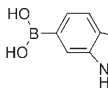
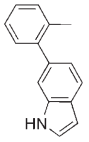
With our newly developed reaction protocol (Table 4), catalyst loadings of only 0.05 mol% [Pd/**4**] are sufficient to couple indole-6-boronic acid with *N*-heterocyclic aryl chlorides such as 2-chloro-6-methoxypyridine (Table 4, entry 11) in 95% yield. Even deactivated and sterically hindered aryl chlorides such as 2-chlorotoluene were coupled under the same conditions in 91% yield (Table 4, entry 12). In the absence of *N*-protecting groups, the Suzuki pathway is the preferred one.

Suzuki coupling of purines: Purines, the core bases of the DNA and RNA nucleotide building blocks adenine and guanine, represent an important class of biologically active compounds and are used as antiviral[83–87] or anticancer agents.[85,88–93] Suzuki couplings have been used to introduce various substituted aryl groups into purine systems.[89,94] However, unprotected halo-9*H*-purine bases proved to be unreactive in common cross-coupling protocols, due to removal of the *N*9 proton.[44,95] Cross-coupling proceeded only when *N*9 was decorated with a protective group, although high Pd catalyst loadings (at least 5 mol%) combined with elevated reaction temperatures were still required.[88,89,94,96–98] Recently, Shaughnessy and co-workers reported improved Suzuki arylations of unprotected bromonucleosides in the presence of water-soluble arylphosphine Pd complexes in aqueous media, eliminating the need for protection/deprotection steps.[25,60] An extension of this method for cross-coupling of free chloropurine bases offering high-yielding cross-couplings was reported by Hocek, but again excessive amounts of catalyst (5–10 mol%) combined with microwave irradiation were required.[59] Interestingly, the use of highly water-soluble ligands is essential for the reported protocols. Shaughnessy and Hocek independently demonstrated that highly water-soluble ligands—such as triphenylphosphine-trissulfonate (TPPTS)—have a significant higher catalytic activity in Suzuki couplings of halopurines than poorly soluble phosphine ligands.[25,60,99] Hence, excellent water solubility of the catalyst seems to be essential for coupling of halopurines in aqueous media.

In contrast to previous work, the Pd complex of our doubly sulfonated phosphine **4**·3H$^+$ allows Suzuki couplings of unprotected chloropurines in the presence of only 0.5 mol% catalyst. 6-Chloro-9*H*-purine was successfully Suzuki-coupled with *p*-tolylboronic acid and *m*-anisylboronic acid in 91 and 86% yields, respectively, in water/*n*-butanol as solvent (Table 6).

Table 4. Suzuki reactions with 2-chloropyridines, 2-chloroquinolines and deactivated aryl chlorides with *N*-heterocyclic boronic acids in water/*n*-butanol 1:3.[a]



Entry	Aryl chloride	Boronic acid	Product	Pd [mol %]	Conv.[b] [%]	Yield[c] [%]
1				0.01	≥99	91
2				0.01	≥99	93
3				0.01	≥99	93
4				0.01	≥99	89
5				0.01	≥99	92
6				0.05	≥99	93
7				0.05 0.02	≥99 63	90
8				0.05	≥99	92
9				0.05	97	90
10				0.05	≥99	92
11				0.05	≥99	95
12				0.05	≥99	91

[a]–[c] Same conditions as reported in Table 3.

Suzuki couplings of *S*-heterocyclic aryl chlorides: Thiophenes and *N*,*S*-heterocyclic thiazoles are abundant in natural products, and many compounds bearing thiophene moieties are of interest in pharmaceutical and fine chemistry, due to their biological activities.[20,100,101,102–110] Aryl derivatives of benzothiazole have attracted interest due to their biological activities as glutamate receptor antagonists.[28] There are a few reports on Suzuki couplings of chlorothiophenes in the presence of catalyst loadings of 1–2 mol %.[72,111,112]

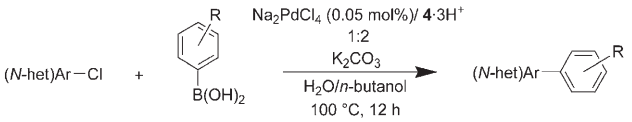
We were interested to know whether the catalyst formulation successfully applied in the synthesis of *N*-heterocycles would also be useful in the synthesis of *S*-heterocyclic biaryls. 3-Chlorothiophene was quantitatively coupled with *p*-tolylboronic acid (Table 7, entry 1) in water/*n*-butanol at 100 °C in the presence of 0.05 mol % of [Pd/**4**] complex generated in situ as catalyst. Quantitative conversion was achieved in the reactions of 2-chlorothiophene with the electron-deficient 3-pyridylboronic acid (Table 7, entry 2) and of 5-chloro-2-methylbenzothiazole with *p*-tolylboronic acid (Table 7, entry 3). When 3-pyridylboronic acid was used as an electron-deficient metalloid a catalyst loading of 0.05 mol % gave 95 % yield.

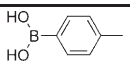
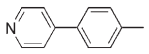
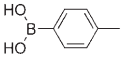
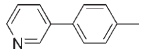
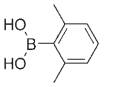
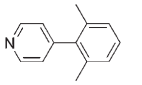
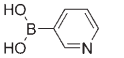
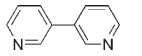
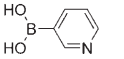
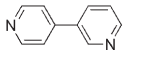
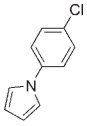
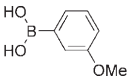
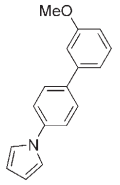
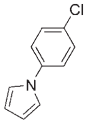
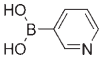
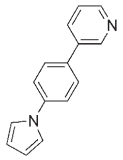
The reaction protocol used for the *N*-heterocycles can thus also be applied to the *S*-heterocycles with use of between 0.01–0.05 mol % of catalyst with quantitative conversion of the substrates.

Summary and Conclusions

A disulfonated sterically demanding and electron-rich flu-

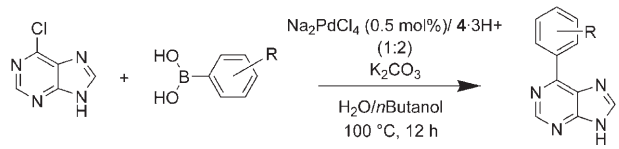
Table 5. Suzuki reactions with several activated and deactivated *N*-heterocyclic aryl chlorides in water/*n*-butanol 1:3.[a]

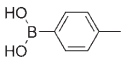
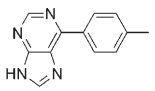
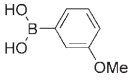
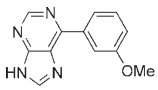


Entry	Aryl chloride	Boronic acid	Product	Conv. [%][b]	Yield [%][c]
1				≥99	95
2				≥99	93
3				≥99	93
4				≥99	94
5				≥99	95
6				≥99	94
7				≥99	90

[a]–[c] Same conditions as reported in Table 3.

Table 6. Suzuki reactions with 6-chloropurine in water/*n*-butanol 1:3.[a]



Entry	Aryl chloride	Boronic acid	Product	Conv. [%][b]	Yield [%][c]
1				97	91
2				94	86

[a], [b] Same conditions as reported in Table 3. [c] Average of two runs; products were isolated by column chromatography (silica gel), CH_2Cl_2/MeOH/NEt_3 5:1:1.

orenylphosphine (**4**) was synthesized in three steps from simple commercially available starting materials in 64% overall yield on a 50 g scale. The corresponding air-stable phosphonium salt (**4**·3H$^+$) is readily deprotonated under cross-coupling conditions and forms a highly water-soluble Pd complex with [Na_2PdCl_4]. We have demonstrated for various substrate combinations that chloropyridines (-quinolines) and aryl chlorides can be Suzuki-coupled with aryl-, pyridine- or indoleboronic acids in quantitative yields in water/*n*-butanol solvent, in the presence of between 0.005–0.05 mol% of this Pd catalyst at 100°C. Chloropurines are quantitatively Suzuki-coupled in the presence of 0.5 mol% of catalyst. *S*-Heterocyclic aryl chlorides and aryl- or 3-pyridylboronic acids require 0.01–0.05 mol% Pd catalyst for full conversion.

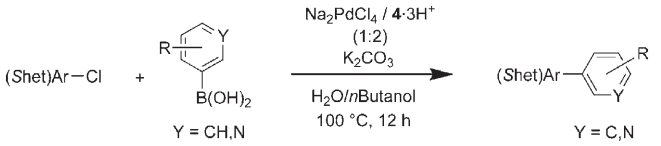
Essential for the superior performance of the disulfonated fluorenylphosphine in the Suzuki coupling of heterocyclic substrates is the rational reaction design, based on the excellent water solubility of the Pd catalyst, the electron-rich and sterically demanding nature of the phosphine ligand, the good solubility of all reactants in the *n*-butanol/water (3:1) solvent mixture, the presence of a significant amount of water in the reaction solvent and the monophasic nature of the reaction mixture at the reaction temperatures.

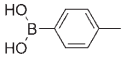
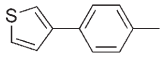
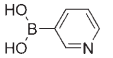
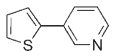
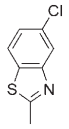
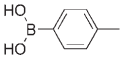
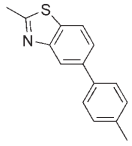
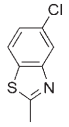
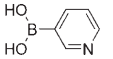
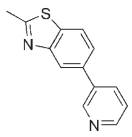
All of these properties combined furnish a catalyst of unprecedented activity for Suzuki couplings of a broad range of *N*- and *S*-heterocyclic substrates.

Experimental Section

All chemicals were purchased as reagent grade from commercial suppliers and were used without further purification, unless otherwise noted. Solvents used (water, *n*-butanol, all technical grade) were deaerated by the freeze and thaw technique (2×). Potassium carbonate used in cross-coupling reactions was technical grade. The phosphine ligands PhenPropFluPCy$_2$·HBF$_4$ (**3**) and PropPhenFluPCy$_2$DS (**4**·3H$^+$) are also commercially available under the trade name *cataCXium F* and *cataCXium F sulf* from Evonik–Degussa GmbH. All experiments were carried out under argon unless otherwise noted. Proton (^{1}H NMR), carbon (^{13}C NMR), phosphorus (^{31}P NMR) and nitrogen (^{15}N NMR) nuclear magnetic resonance spectra were recorded on a Bruker DRX 500 instrument at 500 MHz, 125.75 MHz, 202.46 MHz and 50.69 MHz, respectively at 293 K. The chemical shifts are given in parts per million (ppm) on the delta scale (δ) and are referenced to tetramethylsilane ($\delta = 0$ ppm,

Table 7. Suzuki reactions of *S*-heterocyclic chlorides in *n*-butanol/water 1:3.[a]



Entry	Aryl chloride	Boronic acid	Product	Pd [mol %]	Conv. [%][b]	Yield %[c]
1				0.05	≥99	93
2				0.05	≥99	90
3				0.01	≥99	89
4				0.05	≥99	95

[a]–[c] Same conditions as reported in Table 3.

^{1}H NMR), 65% aq. H_3PO_4 ($\delta = 0$ ppm, ^{31}P NMR) and nitromethane ($\delta = 0$ ppm, ^{15}N NMR). Abbreviations for NMR data: s = singlet, d = doublet, t = triplet, q = quartet, qi = quintet, dd = doublet of doublets, dt = doublet of triplets, dq = doublet of quartets, tt = triplet of triplets, m = multiplet, br = broad. Selected NMR spectra are given in the Supporting Information. Mass spectra were recorded on a Finnegan MAT 95 magnetic sector spectrometer. Thin layer chromatography (TLC) was performed on Fluka silica gel 60 F 254 (0.2 mm) on aluminum plates. Silica gel columns for chromatography were prepared with E. Merck silica gel 60 (0.063–0.20 mesh ASTM). Quantitative elemental analyses were performed on a Vavio Micro instrument (Elementar Analysensysteme, GmbH, Germany). GC experiments were run on a Clarus 500 GC with autosampler and FID detector. Column: Varian CP-Sil 8 CB (l = 15 m, di = 0.25 mm, dF = 1.0 μm), N_2 (flow: 17 cm sec^{-1}; split 1:50). Injector temperature: 270 °C, detector temperature: 350 °C. Temperature program: isotherm 150 °C for 5 min, heating to 300 °C at 25 °C min^{-1}, isotherm for 15 min. 9-(3-Phenylpropyl)-9*H*-fluorene (**2**) was prepared by a published procedure.[70]

9-(3-Phenylpropyl)FluPCy$_2$·HBF$_4$ (3·H$^+$): 9-(3-Phenylpropyl)-9*H*-fluorene (**2**, 117 g, 0.410 mol) was suspended in dry methyl *tert*-butyl ether (MTBE, 2.7 L) under argon in a 6 L three-necked round-bottomed flask. *n*BuLi (2.5 M in hexane, 162 mL, 0.406 mol) was added at 0 °C over 10 min. The reaction mixture was warmed to 20 °C, forming a deep red, clear solution that was stirred for an additional 2 h at ambient temperature. The mixture was then cooled to −30 °C, and Cy_2PCl (92.75 g, 0.399 mol) was added over 10 min. The red color disappeared to form a yellow clear solution, which was stirred for an additional 1 h at 20 °C (precipitation of LiCl started after about 20 min). The suspension was extracted with degassed water (1 × 750 mL) to remove the LiCl. The clear, slightly yellowish organic layer was treated with aqueous HBF_4 (48%, 59 mL, 0.451 mol) with vigorous stirring over 2 min to precipitate the title compound as white crystals. More HBF_4 (25 mL, 2 M in water) was added, the suspension was stirred for another 10 min, and the precipitate was then separated by suction filtration (glass frit G3) and washed with MTBE (2 × 100 mL). Drying of the product at 60 °C in vacuo afforded **3**·H$^+$ (208 g, 92%) as white crystals. ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 7.85$ (d, $^3J = 7.5$ Hz, 2H; *CH*, ar), 7.69 (d, $^3J = 7.5$ Hz, 2H; *CH*, ar), 7.56 (t, $^3J = 7.0$ Hz, 2H; C*H*, ar), 7.48 (t, $^3J = 7.5$ Hz, 2H; *CH*, ar), 7.20–7.14 (m, 2H; C*H*, ar), 7.14–7.01 (m, 1H; C*H*, ar), 6.92 (d, $^3J = 7.5$ Hz, 2H; C*H*, ar), 6.47 (d, $^1J = 479.5$ Hz, 1H; P*H*), 2.75–2.67 (m, 2H; Flu-CH_2), 2.47 (t, $^3J = 7.5$ Hz, 2H; Ph-CH_2), 2.23–2.11 (m, 2H; C*H*), 1.87–1.01 (m, 20H; Cy-CH_2), 0.93–0.84 ppm (m, 2H; CH_2-CH_2-CH_2); ^{13}C{^{1}H} NMR (125.8 MHz, $CDCl_3$): $\delta = 141.4$ (d, $J_{P,C} = 4.3$ Hz), 141.1, 139.9 (d, $J_{P,C} = 1.8$ Hz), 130.3, 129.2, 128.4, 128.3, 126.0, 125.0, (d, $J_{P,C} = 1.8$ Hz), 121.1, 52.3 (d, $J_{P,C} = 34.2$ Hz), 34.9, 32.9, 31.2 (d, $J_{P,C} = 34.1$ Hz), 29.4 (d, $J_{P,C} = 3.6$ Hz), 28.0 (d, $J_{P,C} = 3.5$ Hz), 26.8, 26.7, 26.6, 26.5, 24.9, 24.3, 24.2 ppm; ^{31}P{^{1}H} NMR (202.5 MHz, $CDCl_3$): $\delta = 35.6$ ppm; ^{31}P NMR (202.5 MHz, $CDCl_3$): $\delta = 35.6$ ppm (d, $J_{P,H} = 477.5$ Hz); elemental analysis calcd (%) for $C_{34}H_{42}BF_4P$: C 71.83, H 7.45; found: C 71.54, H 7.40.

PropPhenFluPCy$_2$DS disodium salt (4): 9-(3-Phenylpropyl)FluCy$_2$·HBF_4 (**3**·H$^+$, 400 mg, 0.70 mmol) was dissolved in CH_2Cl_2 (2 mL) in a 25 mL Schlenk tube. After addition of conc. H_2SO_4 (1 mL, 18.8 mmol) the solution was stirred overnight at 50 °C. The solution was added dropwise to ice; in the end a clear colorless solution was obtained. After degassing of this solution, it was neutralised with NaOH (20% solution in degassed water), in the presence of degassed phenolphthaleine solution as an indicator. The water was removed in vacuo until Na_2SO_4 started to precipitate. Degassed MeOH (10 mL) was then added to precipitate most of the Na_2SO_4, which was removed by filtration to give a clear filtrate. Removal of the volatiles in vacuo afforded **4** (412 mg, 86%) as a white solid. ^{1}H NMR (500 MHz, CD_3OD): $\delta = 7.97$ (s, 1H; C*H*, ar), 7.89–7.85 (m, 3H; C*H*, ar), 7.66–7.61 (m, 2H; C*H*, ar), 7.43–7.30 (m, 3H; C*H*, ar), 7.97 (d, $^3J = 8.0$ Hz, 2H; C*H*, ar), 2.53–2.29 (m, 4H; CH_2), 2.00–0.73 ppm (m, 24H; C*H*+CH_2); ^{13}C{^{1}H} NMR (125.77 MHz, CD_3OD): $\delta = 151.2$, 150.2, 146.3, 145.3, 144.4, 144.0, 141.5, 129.6, 129.3, 128.6, 127.3, 126.4, 125.5 (d, $J_{P,C} = 5.1$ Hz), 123.2 (d, $J_{P,C} = 3.3$ Hz), 121.8, 121.0, 57.1 (d, $J_{P,C} = 28.5$ Hz), 38.8 (d, $J_{P,C} = 22.7$ Hz), 36.8, 35.2, 35.0, 34.9, 34.7, 34.7, 34.6, 34.5, 31.6 (d, $J_{P,C} = 10.4$ Hz), 31.1 (d, $J_{P,C} = 7.5$ Hz), 29.2 (d, $J_{P,C} = 13.1$ Hz), 28.9, 28.8, 28.8, 28.5 (d, $J_{P,C} = 7.03$ Hz), 27.8, 27.6, 27.4, 27.2, 26.9 (d, $J_{P,C} = 10.4$ Hz), 26.2 ppm; ^{31}P{^{1}H} NMR (202.46 MHz, CD_3OD): $\delta = 33.6$ ppm; MS (70 eV): *m*/*z*: 700 [*M*+O]$^+$, 684 [*M*]$^+$, 601 [*M*−Cy]$^+$.

PropPhenFluPCy$_2$DS·H_2SO_4 (4b·3H$^+$): Concentrated sulfuric acid (270 mL, 5 mol) was added at 0 °C under argon to a solution of 9-(3-phenylpropyl)FluPCy$_2$·HBF_4 (**3**·H$^+$, 50 g, 0.88 mol) in CH_2Cl_2 (100 mL, technical grade). The reaction mixture was warmed up to 50 °C with stirring. After removal of the $CHCl_2$, the reaction mixture was stirred at 50 °C overnight. The clear, slightly yellow solution was poured onto ice (1500 g). The white precipitate was separated by suction filtration and washed with ice water (2 × 100 mL). The precipitate was dissolved in MeOH (300 mL) and filtered, and the clear, colorless filtrate was added dropwise to MTBE (1600 mL, vigorously stirred) to precipitate the product. Decantation of the solvent and removal of the volatiles in vacuo afforded the pure product (**4**·3H$^+$) (50.3 g, 77%) as a white solid. ^{1}H NMR (500 MHz, CD_3OD): $\delta = 8.26$ (s, 1H; C*H*, ar), 8.13–8.08 (m, 3H; C*H*, ar), 7.73 (d, $^3J = 8.0$ Hz, 1H; C*H*, ar), 7.69–7.64 (m, 1H; C*H*, ar), 7.67 (d, $^3J = 8.5$ Hz, 2H; C*H*, ar), 7.57 (dt, $^5J = 0.5$, 7.0 Hz, 1H; C*H*, ar), 7.04 (d, $^3J = 8.5$ Hz, 2H; C*H*, ar), 2.89–2.80 (m, 1H; C*H*), 2.74–2.62 (m, 2H; C*H* and CH_2), 2.59–2.45 (m, 2H; CH_2), 2.44–2.33 (m, 1H; CH_2), 1.92–1.83 (m, 1H; CH_2), 1.80–0.93 (m, 20H; CH_2), 0.87–0.76 ppm (m, 1H; CH_2); ^{13}C NMR (125.77 MHz, CD_3OD): $\delta = 147.6$, 145.6, 145.1 (d, $J_{P,C} = 4.4$ Hz), 144.2, 142.5 (d, $J_{P,C} = 4.8$ Hz), 142.4 (d, $J_{P,C} = 2.8$ Hz), 141.7 (d, $J_{P,C} = 4.2$ Hz), 132.2, 131.2, 129.8, 129.7, 127.6, 126.8 (d, $J_{P,C} = 3.9$ Hz), 124.4 (d, $J_{P,C} = 3.9$ Hz), 123.6, 122.9, 53.7 (d, $J_{P,C} = 33.5$ Hz), 35.8, 34.5, 32.7 (d, $J_{P,C} = 3.8$ Hz), 32.5 (d, $J_{P,C} = 4.0$ Hz), 31.2 (d, $J_{P,C} = 3.9$ Hz), 30.6 (d, $J_{P,C} = 3.5$ Hz), 30.0 (d, $J_{P,C} = 3.3$ Hz), 29.8 (d, $J_{P,C} = 3.3$ Hz), 28.1, 28.0, 28.0, 27.9, 27.9, 27.8, 27.8, 27.7, 26.4 (d, $J_{P,C} = 1.5$ Hz), 25.4, 25.3 ppm; ^{31}P {^{1}H} NMR

(202.46 MHz, CD_3OD): $\delta = 34.2$ ppm; MS (70 eV): m/z: 641 $[M-HSO_4^-]^+$, 639 $[M-H_2SO_4-H]^-$, 442 $[M-H_2SO_4-PCy_2-H]^-$.

General procedure for Suzuki cross-coupling reactions in aqueous *n*-butanol

Preparation of catalyst stock solution: $[Na_2PdCl_4]$ (5.9 mg, 0.02 mmol), PropPhenFluPCy$_2$DS·H_2SO_4 (**4**·3H$^+$, 30 mg, 0.04 mmol) and K_2CO_3 (33 mg, 0.24 mmol) were placed in a 25 mL Schlenk tube and evacuated and backfilled with Ar thrice. Degassed water (20 mL) was added, and the mixture was stirred at 55 °C for 3 h to provide a clear, nearly colorless solution. The $c_{[Pd]}$ of this catalyst stock solution is 0.001 mmol mL^{-1}.

Cross-coupling reaction: The boronic acid (1.2 mmol) and K_2CO_3 (440 mg, 3.2 mmol) were placed in a 25 mL Schlenk tube and evacuated and backfilled with Ar thrice. Degassed water (1 mL) and degassed *n*-butanol (3 mL) were then added together with the aryl halide (1 mmol) and the appropriate volume of catalyst stock solution (e.g., 1 mL of the solution prepared above was added to obtain a catalyst loading of 0.1 mol %). The reaction mixture was stirred for 12 h at 100 °C and then cooled to room temperature. Water (5 mL) was added and the product was extracted with methyl *tert*-butyl ether (2×5 mL). The organic layer was concentrated in vacuo, and the residue was purified by column chromatography (silica (20×3 cm), cyclohexene/EtOAc/NEt_3 (10:1:1) as eluent) to afford the pure corresponding cross-coupling product in 86–96 % yield.

Analytical data for the Suzuki products

2-*p*-Tolylpyridine (Table 3, entry 1): The NMR spectra were identical to those in the literature.[113]

2-*p*-Tolylisonicotinonitrile (Table 3, entry 2): ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 8.75$ (dd, $^5J = 0.5$, $^3J = 5.0$ Hz, 1H; C*H*, ar), 7.84–7.80 (m, 3H; C*H*, ar), 7.32 (dd, $^4J = 1.0$, $^3J = 5.0$ Hz, 1H; C*H*, ar), 7.24 (d, $^3J = 8.0$ Hz, 2H; C*H*, ar), 2.35 ppm (s, 3H; CH_3); ^{13}C{^{1}H} NMR (125.77 MHz, $CDCl_3$): $\delta = 157.7$, 149.5, 139.5, 133.5, 128.8, 125.8, 121.8, 120.7, 120.1, 115.8, 20.3 ppm; HRMS: m/z: calcd for $C_{13}H_{10}N_2$: 194.0844; found: 194.08414.

2-*p*-Tolylquinoline-3-carbaldehyde (Table 3, entry 3): ^{1}H NMR (500 MHz, CD_3CN): $\delta = 10.12$ (s, 1H; C*H*O), 8.85 (s, 1H; C*H*, ar), 8.14–8.09 (m, 3H; C*H*, ar), 7.91 (ddd, $^5J = 1.5$, $^3J = 7.0$, 8.5 Hz, 1H; C*H*, ar), 7.76 (ddd, $^5J = 1.5$, $^3J = 7.0$, 8.5 Hz, 1H; C*H*, ar), 7.59 (td, $^4J = 2.0$, $^3J = 8.0$ Hz, 2H; C*H*, ar), 7.41–7.38 (m, 2H; C*H*, ar), 2.45 ppm (s, 3H; CH_3); ^{13}C{^{1}H} NMR (125.77 MHz, CD_3CN): $\delta = 191.1$, 159.6, 149.1, 139.2, 137.9, 135.1, 132.3, 130.0, 129.3, 128.8, 128.8, 127.7, 127.1, 126.0, 20.1 ppm; HRMS: m/z: calcd for $C_{17}H_{13}NO$: 247.0997; found: 247.09700.

4-Methyl-2-*p*-tolylquinoline (Table 3, entry 4): The NMR spectra were identical to those in the literature.[114]

4-Methyl-2-*p*-tolylpyridine (Table 3, entry 5): The NMR spectra were identical to those in the literature.[115]

2-*p*-Tolylquinoline (Table 3, entry 6): The NMR spectra were identical to those in the literature.[115]

2-Methoxy-6-*p*-tolylpyridine (Table 3, entry 7): ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 7.93$ (d, $^3J = 8.5$ Hz, 2H; C*H*, ar), 7.58 (dd, $^3J = 7.5$, 8.0 Hz, 1H; C*H*, ar), 7.29 (dd, $^5J = 0.5$, $^3J = 7.5$ Hz, 1H; C*H*, ar), 7.24 (dd, $^5J = 0.5$, $^3J = 8.5$ Hz, 2H; C*H*, ar), 6.64 (d, $^3J = 8.0$ Hz, 1H; C*H*, ar), 4.02 (s, 3H; OCH_3), 2.39 ppm (s, 3H; CH_3); ^{13}C{^{1}H} NMR (125.77 MHz, $CDCl_3$): $\delta = 164.1$, 155.2, 139.5, 139.2, 136.8, 129.7, 127.0, 112.8, 109.2, 53.5, 21.7 ppm; HRMS: m/z: calcd for $C_{13}H_{13}NO$: 199.0997; found: 199.09999.

2-*p*-Tolylpyridin-4-ylamine (Table 3, entry 8): ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 8.25$ (d, $^3J = 5.5$ Hz, 1H; ar), 7.78 (d, $^3J = 8.0$ Hz, 2H; ar), 7.21 (d, $^3J = 8.0$ Hz, 2H; ar), 6.85 (s, 1H; ar), 6.39 (dd, $^3J = 5.5$, $^4J = 2.5$ Hz, 1H; ar), 4.35 (brs, 2H; NH_2), 2.36 ppm (s, 3H; CH_3); ^{13}C{^{1}H} NMR (125.77 MHz, $CDCl_3$): $\delta = 157.2$, 152.6, 159.0, 137.6, 136.0, 128.2, 125.7, 107.2, 105.1, 20.2 ppm; HRMS: m/z: calcd for $C_{12}H_{12}N_2$: 184.1001; found: 184.09808.

4-Methyl-2-*m*-tolylquinoline (Table 3, entry 9): ^{1}H NMR (500 MHz, CD_3CN): $\delta = 8.06$–8.01 (m, 3H; C*H*, ar), 7.99–7.96 (m, 1H; C*H*, ar), 7.82 (d, $^5J = 0.5$ Hz, 1H; C*H*, ar), 7.71 (ddd, $^5J = 1.5$, $^3J = 6.5$, 8.5 Hz, 1H; C*H*, ar), 7.55 (ddd, $^5J = 1.0$, $^3J = 6.5$, 8.5 Hz, 1H; C*H*, ar), 7.40 (t, $^3J = 8.0$ Hz, 1H; C*H*, ar), 7.30–7.27 (m, 1H; C*H*, ar), 2.71 (d, $^5J = 0.5$ Hz, 3H; CH_3), 2.44 ppm (s, 3H; CH_3); ^{13}C{^{1}H} NMR (125.77 MHz, CD_3CN): $\delta = 156.2$, 147.6, 144.9, 139.1, 138.1, 129.7, 129.5, 129.0, 128.3, 127.6, 126.9, 125.7, 124.1, 123.6, 119.0, 20.3, 17.7 ppm; HRMS: m/z: calcd for $C_{17}H_{15}N$: 233.1205; found: 233.12109.

4-Methyl-2-(3-trifluoromethyl-phenyl)-quinoline (Table 3, entry 10): ^{1}H NMR (500 MHz, CD_3CN): $\delta = 8.54$ (s, 1H; C*H*, ar), 8.41 (d, $^3J = 7.0$ Hz, 1H; C*H*, ar), 8.08–8.02 (m, 2H; C*H*, ar), 7.87–7.85 (m, 1H; C*H*, ar), 7.78–7.71 (m, 2H; C*H*, ar), 7.68 (t, $^3J = 7.5$ Hz, 1H; C*H*, ar), 7.60–7.56 (m, 1H; C*H*, ar), 2.73–2.72 ppm (m, 3H; CH_3); ^{13}C{^{1}H} NMR (125.77 MHz, CD_3CN): $\delta = 154.2$, 147.5, 145.6, 140.0, 130.5, 130.1 (q, $^2J = 31.8$ Hz, *C*CF_3), 129.6, 129.3, 129.3, 127.1, 126.2, 125.4 (q, $^3J = 4.4$ Hz, *C*H*C*CF_3), 123.7, 124.2 (q, $^1J = 271.8$ Hz, *C*F_3), 123.5 (q, $^3J = 2.9$ Hz, *C*H*C*CF_3), 118.7, 17.7 ppm; HRMS: m/z: calcd for $C_{17}H_{12}NF_3$: 287.0922; found: 287.09206.

2-*m*-Tolylquinoline-3-carbaldehyde (Table 3, entry 11): ^{1}H NMR (500 MHz, CD_3CN): $\delta = 10.10$ (s, 1H; C*H*O), 8.83 (s, 1H; C*H*, ar), 8.12–8.08 (m, 2H; C*H*, ar), 7.90 (ddd, $^5J = 1.5$, $^3J = 7.0$, 9.0 Hz, 1H; C*H*, ar), 7.67 (ddd, $^5J = 1.0$, $^3J = 7.0$, 8.0 Hz, 1H; C*H*, ar), 7.53–7.50 (m, 1H; C*H*, ar), 7.46–7.43 (m, 2H; C*H*, ar), 7.40–7.35 (m, 1H; C*H*, ar), 2.45 ppm (s, 3H; CH_3); ^{13}C{^{1}H} NMR (125.77 MHz, CD_3CN): $\delta = 191.0$, 159.8, 149.0, 138.1, 137.9, 137.8, 132.3, 130.4, 129.5, 129.3, 128.8, 128.0, 127.6, 127.2, 127.1, 126.0, 20.2 ppm; HRMS: m/z: calcd for $C_{17}H_{13}NO$: 247.0997; found: 247.09813.

2-(3-Trifluoromethyl-phenyl)-quinoline-3-carbaldehyde (Table 3, entry 12): ^{1}H NMR (500 MHz, CD_3CN): $\delta = 10.10$ (s, 1H; C*H*O), 8.87 (s, 1H; C*H*, ar), 8.15–8.10 (m, 2H; C*H*, ar), 8.03 (s, 1H; C*H*, ar), 7.93 (ddd, $^5J = 1.5$, $^3J = 7.0$, 8.5 Hz, 1H; C*H*, ar), 7.91–7.84 (m, 2H; C*H*, ar), 7.76–7.68 ppm (m, 2H; C*H*, ar); ^{13}C{^{1}H} NMR (125.77 MHz, CD_3CN): $\delta = 190.6$, 157.7, 148.9, 139.3, 139.2, 133.6, 132.6, 129. (q, $^2J = 32.3$ Hz, *C*CF_3), 129.2, 128.9, 128.9, 127.6, 127.5, 126.3 (q, $^3J = 3.9$ Hz, *C*HCCF_3), 126.2, 125.3 (q, $^3J = 3.8$ Hz, *C*HCCF_3), 124.0 ppm (q, $^1J = 272.4$ Hz, *C*F_3); HRMS: m/z: calcd for $C_{17}H_{10}NOF_3$: 301.0714; found: 301.06928.

2-Naphthalen-1-yl-quinoline-3-carbaldehyde (Table 3, entry 13): ^{1}H NMR (500 MHz, CD_3CN): $\delta = 9.74$ (s, 1H; C*H*O), 8.96 (s, 1H; C*H*, ar), 8.22 (d, $^3J = 8.0$ Hz, 1H; C*H*, ar), 8.13 (dd, $^5J = 0.5$, $^3J = 8.5$ Hz, 1H; C*H*, ar), 8.09 (d, $^3J = 8.0$ Hz, 1H; C*H*, ar), 8.04 (d, $^3J = 8.0$ Hz, 1H; C*H*, ar), 7.96 (ddd, $^5J = 1.0$, $^3J = 6.5$, 8.5 Hz, 1H; C*H*, ar), 7.75 (ddd, $^5J = 1.5$, $^3J = 7.0$, 8.5 Hz, 1H; C*H*, ar), 7.67 (dd, $^3J = 7.0$, 8.0 Hz, 1H; C*H*, ar), 7.62–7.52 (m, 3H; C*H*, ar), 7.44 ppm (ddd, $^5J = 1.5$, $^3J = 7.0$, 8.5 Hz, 1H; C*H*, ar); ^{13}C{^{1}H} NMR (125.77 MHz, CD_3CN): $\delta = 190.6$, 159.2, 149.3, 137.8, 135.6, 133.2, 132.5, 131.8, 129.5, 128.9, 128.8, 128.8, 128.1, 127.9, 127.5, 126.6, 126.4, 126.0, 125.0, 125.0 ppm; HRMS: m/z: calcd for $C_{20}H_{13}NO$: 283.0997; found: 283.09811.

2-Naphthalen-1-ylpyridine (Table 3, entry 14): The NMR spectra were identical to those in the literature.[116]

2-Naphthalen-1-ylquinoline (Table 3, entry 15): The NMR spectra were identical to those in the literature.[117]

2-Naphthalen-1-ylpyridin-4-ylamine (Table 3, entry 16): ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 8.20$ (d, $^3J = 5.5$ Hz, 1H; ar), 8.01 (d, $^3J = 8.0$ Hz, 1H; ar), 7.76 (t, $^3J = 9.5$ Hz, 2H; ar), 7.43–7.33 (m, 4H; ar), 6.47 (d, $^4J = 2.0$ Hz, 1H; ar), 6.27 (dd, $^3J = 5.5$, $^4J = 2.5$ Hz, 1H; ar), 4.37 ppm (brs, 2H; NH_2); ^{13}C{^{1}H} NMR (125.77 MHz, $CDCl_3$): $\delta = 158.5$, 152.4, 148.5, 138.0, 132.7, 130.2, 127.4, 127.1, 125.8, 125.1, 124.9, 124.7, 124.1, 109.6, 107.1 ppm; HRMS: m/z: calcd for $C_{15}H_{12}N_2$: 220.1001; found: 220.09869.

4-Methyl-2-naphthalen-1-ylquinoline (Table 3, entry 17): The NMR spectra were identical to those in the literature.[118]

1-Naphthylisonicotinonitrile (Table 3, entry 18): ^{1}H NMR (500 MHz, CD_3CN): $\delta = 8.75$ (dd, $^5J = 0.5$ Hz, $^3J = 5.0$ Hz, 1H; C*H*, ar), 8.75 (dd, $^4J = 2.5$ Hz, $^3J = 6.5$ Hz, 1H; C*H*, ar), 7.82–7.81 (m, 1H; C*H*, ar), 7.81–7.79 (m, 2H; C*H*, ar), 7.58 (dd, $^5J = 1.5$ Hz, $^3J = 5.5$ Hz, 1H; C*H*, ar), 7.45–7.42 (m, 2H; C*H*, ar), 7.38 (ddd, $^5J = 1.0$ Hz, $^3J = 7.0$ Hz, $^3J = 7.5$ Hz, 1H; C*H*, ar), 7.34 ppm (ddd, $^5J = 1.0$ Hz, $^3J = 6.5$ Hz, $^3J = 8.0$ Hz, 1H; C*H*, ar); ^{13}C{^{1}H} NMR (125.77 MHz, CD_3CN): $\delta = 159.2$, 149.6, 135.6, 133.5, 130.3, 129.6, 128.2, 127.8, 127.0, 126.7, 126.1, 125.1, 124.7, 124.0, 121.2, 116.3 ppm; HRMS: m/z: calcd for $C_{16}H_{10}N_2$: 230.0844; found: 230.08168.

2-Methoxy-6-naphthalen-1-ylpyridine (Table 3, entry 19): The NMR spectra were identical to those in the literature.[119]

2-Pyridin-3-ylquinoline-3-carbaldehyde (Table 4, entry 1): ^{1}H NMR (500 MHz, CD_3CN): $\delta = 10.15$ (s, 1H; C*H*O), 8.93 (s, 1H; C*H*, ar), 8.87 (d, $^5J = 1.5$ Hz, 1H; C*H*, ar), 8.73 (dd, $^5J = 1.5$ Hz, $^3J = 4.5$ Hz, 1H; C*H*, ar), 8.19–8.14 (m, 2H; C*H*, ar), 8.07–8.04 (m, 1H; C*H*, ar), 7.96 (ddd, $^5J = 1.0$ Hz, $^3J = 6.5$ Hz, $^3J = 8.5$ Hz, 1H; C*H*, ar), 7.73 (ddd, $^5J = 1.0$ Hz, $^3J = 7.0$ Hz, $^3J = 8.0$ Hz, 1H; C*H*, ar), 7.54 ppm (ddd, $^5J = 0.5$ Hz, $^3J = 4.5$ Hz, $^3J = 8.0$ Hz, 1H; C*H*, ar); ^{13}C{^{1}H} NMR (125.77 MHz, CD_3CN): $\delta = 190.7$, 156.5, 150.1, 149.6, 149.0, 139.6, 137.1, 132.7, 129.3, 128.9, 127.7, 127.7, 126.2, 123.9, 122.9 ppm; HRMS: *m*/*z*: calcd for $C_{15}H_{10}N_2O$: 234.0793; found: 234.07699.

[2,3′]Bipyridinyl (Table 4, entry 2): The NMR spectra were identical to those in the literature.[120]

2-Pyridin-3-ylquinoline (Table 4, entry 3): The NMR spectra were identical to those in the literature.[121,122]

4-Methyl-[2,3′]bipyridinyl (Table 4, entry 4): The NMR spectra were identical to those in the literature.[20]

4-Methyl-2-pyridin-3-ylquinoline (Table 4, entry 5): The NMR spectra were identical to those in the literature.[123]

6-Methoxy-[2,3′]bipyridinyl (Table 4, entry 6): The NMR spectra were identical to those in the literature.[124]

[2,3′]Bipyridinyl-4-ylamine (Table 4, entry 7): ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 9.01$ (d, $^4J = 1.5$ Hz, 1H; ar), 8.53 (dd, $^3J = 5.0$ Hz, $^4J = 1.5$ Hz, 1H; ar), 8.22 (d, $^3J = 6.0$ Hz, 1H; ar), 8.16 (dt, $^3J = 8.0$ Hz, $^4J = 2.0$ Hz, 1H; ar), 6.29–6.26 (m, 1H; ar), 6.87 (d, $^4J = 2.0$ Hz, 1H; ar), 6.44 (dd, $^3J = 6.0$ Hz, $^4J = 2.5$ Hz, 1H; ar), 4.53 ppm (s, 2H; NH_2); ^{13}C{^{1}H} NMR (125.77 MHz, $CDCl_3$): $\delta = 154.5$, 152.8, 149.5, 148.6, 147.1, 134.4, 133.4, 122.5, 107.9, 105.5 ppm; HRMS: *m*/*z*: calcd for $C_{10}H_9N_3$: 171.0797; found: 171.07820.

2,6-Dimethoxy-3-(4-methoxyphenyl)pyridine (Table 4, entry 8): ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 7.52$ (d, $^3J = 8.0$ Hz, 1H; C*H*, ar), 7.45 (d, $^3J = 9.0$ Hz, 2H; C*H*, ar), 6.93 (d, $^3J = 9.0$ Hz, 2H; C*H*, ar), 6.36 (d, $^3J = 8.0$ Hz, 1H; C*H*, ar), 3.96 (s, 3H; OC$H_{3\ \mathrm{Pyr}}$), 3.95 (s, 3H; OC$H_{3\ \mathrm{Pyr}}$), 3.82 ppm (s, 3H; OC$H_{3\ \mathrm{(Anis)}}$); ^{13}C{^{1}H} NMR (125.77 MHz, $CDCl_3$): $\delta =$ 162.3, 159.6, 159.0, 141.6, 130.4, 129.7, 115.9, 114.1, 101.3, 55.7, 54.0, 53.8 ppm; HRMS: *m*/*z*: calcd for $C_{14}H_{15}NO_3$: 245.1052; found: 245.10379.

2′,6′-Dimethoxy-[2,3′]bipyridinyl-4-ylamine (Table 4, entry 9): ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 8.27$ (dd, $^3J = 5.7$, $J = 0.6$ Hz, 1H; C*H*, ar), 8.20 (d, $^3J = 8.2$ Hz, 1H; C*H*, ar), 7.21 (dd, $J = 2.5$, 0.6 Hz, 1H; C*H*, ar), 6.43–6.40 (m, 2H; C*H*, ar), 4.18 (br s, 2H; NH_2), 4.02 (s, 3H; OCH_3), 3.96 ppm (s, 3H; OCH_3); ^{13}C{^{1}H} NMR (125.77 MHz, $CDCl_3$): $\delta = 161.8$, 158.7, 153.8, 151.3, 148.7, 141.3, 113.5, 108.9, 106.8, 100.5, 52.6, 52.4 ppm; HRMS: *m*/*z*: calcd for $C_{12}H_{13}N_3O_2$: 231.1008; found: 231.10084.

2-(1*H*-Indol-6-yl)-4-methylquinoline (Table 4, entry 10): ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 9.54$ (br s, 1H; N*H*), 8.49–8.48 (m, 1H; C*H*, ar), 8.21 (dq, $^3J = 8.5$, $J = 0.6$ Hz, 1H; C*H*, ar), 7.99 (dd, $^3J = 8.5$, $J = 1.3$ Hz, 1H; C*H*, ar), 7.84 (dd, $^3J = 8.2$, $J = 1.6$ Hz, 1H; C*H*, ar), 7.80–7.79 (m, 1H; C*H*, ar), 7.73 (d, $^3J = 8.2$ Hz, 1H; C*H*, ar), 7.68 (ddd, $^3J = 8.2$ Hz, $^3J = 7.0$, $J = 1.5$ Hz, 1H; C*H*, ar), 7.51 (ddd, $^3J = 8.2$ Hz, $^3J = 7.0$, $J = 1.3$ Hz, 1H; C*H*, ar), 7.16 (t, $J = 2.8$ Hz, 1H; C*H*, ar), 6.54–6.52 (m, 1H; C*H*, ar), 2.76 ppm (s, 3H; CH_3); ^{13}C{^{1}H} NMR (125.77 MHz, $CDCl_3$): $\delta = 158.3$, 148.2, 144.7, 136.5, 133.4, 129.6, 129.4, 129.1, 127.2, 126.2, 125.6, 123.7, 120.7, 120.3, 119.3, 110.9, 102.2, 19.0 ppm; ^{15}N{^{1}H} NMR (50.69 MHz, $CDCl_3$) $\delta = -250.3$, -90.3 ppm; HRMS: *m*/*z*: calcd for $C_{18}H_{14}N_2$: 258.1157; found: 258.11354.

6-(6-Methoxypyridin-2-yl)-1*H*-indole (Table 4, entry 11): ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 8.25$ (br s, 1H; N*H*), 8.12–8.11 (m, 1H; C*H*, ar), 7.80 (dd, $^3J = 8.5$, $J = 1.6$ Hz, 1H; C*H*, ar), 7.68 (dt, $^3J = 8.5$, $J = 0.7$ Hz, 1H; C*H*, ar), 7.59 (dd, $^3J = 8.2$, 7.6 Hz, 1H; C*H*, ar), 7.35 (dd, $^3J = 7.6$, $J = 0.6$ Hz, 1H; C*H*, ar), 7.20 (dd, $J = 3.1$, $J = 2.2$ Hz, 1H; C*H*, ar), 6.64 (dd, $^3J = 8.2$, $J = 0.6$ Hz, 1H; C*H*, ar), 6.56–6.54 (m, 1H; C*H*, ar), 4.06 ppm (s, 3H; OC$H_{3\ \mathrm{Pyr}}$); ^{13}C{^{1}H} NMR (125.77 MHz, $CDCl_3$): $\delta = 163.7$, 155.8, 139.2, 136.3, 133.3, 128.6, 125.6, 120.6, 118.9, 112.7, 109.6, 108.2, 102.6, 53.2 ppm; HRMS: *m*/*z*: calcd for $C_{14}H_{12}N_2O$: 224.095; found: 224.09509.

6-*o*-Tolyl-1*H*-indole (Table 4, entry 12): ^{1}H NMR (500 MHz, $CDCl_3$): $\delta =$ 8.01 (br s, 1H; N*H*), 7.63 (d, $^3J = 8.2$ Hz, 1H; C*H*, ar), 7.29–7.19 (m, 5H; C*H*, ar), 7.10–7.06 (m, 2H; C*H*, ar), 6.55–6.52 (m, 1H; C*H*, ar), 2.28 ppm (s, 3H; CH_3); ^{13}C{^{1}H} NMR (125.77 MHz, $CDCl_3$): $\delta = 141.9$, 134.9, 134.7, 134.6, 129.2 (2×), 125.8, 125.5, 124.6, 123.5, 120.7, 119.0, 110.5, 101.3, 19.6 ppm; HRMS: *m*/*z*: calcd for $C_{15}H_{13}N$: 207.1048; found: 207.10515.

4-*p*-Tolylpyridine (Table 5, entry 1): ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 8.62$ (dd, $^3J = 4.8$, $J = 1.7$ Hz, 2H; C*H*, ar), 7.53 (d, $^3J = 8.0$ Hz, 2H; C*H*, ar), 7.45 (dd, $^3J = 4.5$, $J = 1.7$ Hz, 2H; C*H*, ar), 7.28 (d, $^3J = 8.0$ Hz, 2H; C*H*, ar), 2.40 ppm (s, 3H; CH_3); ^{13}C{^{1}H} NMR (125.8 MHz, $CDCl_3$): $\delta = 150.6$, 148.6, 139.6, 135.6, 130.2, 127.2, 121.8, 21.6 ppm; ^{15}N NMR (50.7 MHz, $CDCl_3$): $\delta = -74.2$ ppm; HRMS: *m*/*z*: calcd for $C_{12}H_{11}N$: 169.0892; found: 169.08774.

3-*p*-Tolylpyridine (Table 5, entry 2): ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 8.83$ (dd, $^3J = 2.4$, $J = 0.6$ Hz, 1H; C*H*, ar), 8.56 (dd, $^3J = 4.9$, $J = 1.6$ Hz, 1H; C*H*, ar), 7.83 (ddd, $^3J = 7.9$, $J = 2.4$, 1.6 Hz, 1H; C*H*, ar), 7.47 (d, $^3J = 8.2$ Hz, 2H; C*H*, ar), 7.32 (ddd, $^3J = 7.9$, $J = 4.9$, 0.7 Hz, 1H; C*H*, ar), 7.27 (d, $^3J = 7.9$ Hz, 2H; C*H*, ar), 2.40 ppm (s, 3H; CH_3); ^{13}C{^{1}H} NMR (125.8 MHz, $CDCl_3$): $\delta = 147.2$ (2 x), 137.0, 135.5, 133.9, 133.1, 128.8, 125.9, 122.4, 20.1 ppm; ^{15}N NMR (50.7 MHz, $CDCl_3$): $\delta = -68.1$ ppm; HRMS: *m*/*z*: calcd for $C_{12}H_{11}N_1$: 169. 0892; found: 169.08751.

4-(2,6-Dimethylphenyl)pyridine (Table 5, entry 3): ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 8.67$ (dd, $^3J = 4.4$, $J = 1.7$ Hz, 2H; C*H*, ar), 7.20 (dd, $^3J = 8.2$, 7.0 Hz, 1H; C*H*, ar), 7.12 (d, $^3J = 7.0$ Hz, 2H; C*H*, ar), 7.11 (dd, $^3J = 4.4$, $J = 1.7$ Hz, 2H; C*H*, ar), 2.02 ppm (s, 6H; CH_3); ^{13}C{^{1}H} NMR (125.8 MHz, $CDCl_3$): $\delta = 149.1$, 148.4, 138.0, 134.1, 126.8, 126.6, 123.4, 19.6 ppm; ^{15}N NMR (50.7 MHz, $CDCl_3$): $\delta = -72.8$ ppm; HRMS: *m*/*z*: calcd for $C_{13}H_{13}N_1$: 183.1048; found: 183.10352.

[3,3′]-Bipyridyl (Table 5, entry 4): ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 8.85$ (dd, $^3J = 2.5$, $J = 1.0$ Hz, 2H; C*H*, ar), 8.66 (dd, $^3J = 4.8$, $J = 1.5$ Hz, 2H; C*H*, ar), 7.89 (ddd, $^3J = 8.0$, $J = 2.5$, 1.8 Hz, 2H; C*H*, ar), 7.42 ppm (ddd, $^3J = 8.0$, $J = 4.8$, $J = 1.0$ Hz, 2H; C*H*, ar); ^{13}C{^{1}H} NMR (125.8 MHz, $CDCl_3$): $\delta = 149.4$, 148.2, 134.4, 133.5, 123.8 ppm; ^{15}N NMR (50.7 MHz, $CDCl_3$) $\delta = -66.4$ ppm; HRMS: *m*/*z*: calcd for $C_{10}H_8N_2$: 156.0688; found: 156.06957.

[3,4′]-Bipyridyl (Table 5, entry 5): ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 8.90$ (d, $^3J = 2.0$ Hz, 1H; C*H*, ar), 8.72 (dd, $^3J = 4.5$, $J = 1.7$ Hz, 2H; C*H*, ar), 8.69 (dd, $^3J = 4.9$, $J = 1.5$ Hz, 1H; C*H*, ar), 7.93 (ddd, $^3J = 8.0$, $J = 2.4$, 1.7 Hz, 1H; C*H*, ar), 7.51 (dd, $^3J = 4.5$, $J = 1.7$ Hz, 2H; C*H*, ar), 7.43 ppm (ddd, $^3J = 8.0$, 4.9, $J = 0.7$ Hz, 1H; C*H*, ar); ^{13}C{^{1}H} NMR (125.8 MHz, $CDCl_3$): $\delta = 150.6$, 150.2, 148.2, 145.2, 134.3, 133.8, 123.8, 121.6 ppm; ^{15}N NMR (50.7 MHz, $CDCl_3$): $\delta = -66.5$, -69.8 ppm; HRMS: *m*/*z*: calcd for $C_{10}H_8N_2$: 156.0688; found: 156.0679.

1-(3′-Methoxybiphenyl-4-yl)-1*H*-pyrrole (Table 5, entry 6): ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 7.62$ (d, $^3J = 8.6$ Hz, 2H; C*H*, ar), 7.43 (d, $^3J = 8.6$ Hz, 2H; C*H*, ar), 7.35 (t, $^3J = 7.9$ Hz, 1H; C*H*, ar), 7.17 (ddd, $^3J = 7.6$, $J = 1.6$, 0.9 Hz, 1H; C*H*, ar), 7.13–7.10 (m, 3H; C*H*, ar), 6.90 (ddd, $^3J = 8.2$, $J = 2.6$, 0.9 Hz, 1H; C*H*, ar), 6.36 (t, $^3J = 2.2$ Hz, 2H; C*H*, ar), 3.85 ppm (s, 3H; OCH_3); ^{13}C{^{1}H} NMR (125.8 MHz, $CDCl_3$): $\delta = 160.1$, 141.7, 140.0, 138.4, 129.9, 128.2, 120.6, 119.4, 119.3, 112.8, 112.7, 110.6, 55.3 ppm; ^{15}N NMR (50.7 MHz, $CDCl_3$): $\delta = -$ 206.7 ppm; HRMS: *m*/*z*: calcd for $C_{17}H_{15}N_1O_1$: 249.1154; found: 249.11369.

3-(4-Pyrrol-1-ylphenyl)pyridine (Table 5, entry 7): ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 8.86$ (dd, $^3J = 2.5$, $J = 0.6$ Hz, 1H; C*H*, ar), 8.60 (dd, $^3J = 4.8$, $J = 1.6$ Hz, 1H; C*H*, ar), 7.86 (ddd, $^3J = 7.9$, $J = 2.5$, 1.6 Hz, 1H; C*H*, ar), 7.62 (d, $^3J = 8.6$ Hz, 2H; C*H*, ar), 7.49 (d, $^3J = 8.6$ Hz, 2H; C*H*, ar), 7.36 (ddd, $^3J = 7.9$, $J = 4.9$, $J = 0.7$ Hz, 1H; C*H*, ar), 7.13 (t, $^3J = 2.2$ Hz, 2H; C*H*, ar), 6.38 ppm (t, $^3J = 2.2$ Hz, 2H; C*H*, ar); ^{13}C{^{1}H} NMR (125.8 MHz, $CDCl_3$): $\delta = 147.6$, 147.1, 139.6, 134.6, 134.0, 133.0, 127.2, 122.6, 119.8, 118.2, 109.8 ppm; ^{15}N NMR (50.7 MHz, $CDCl_3$): $\delta = -$ 66.8, -206.9 ppm; HRMS *m*/*z* calcd for $C_{15}H_{11}N_2$: 220.1001; found: 220.10105.

6-*p*-Tolyl-9*H*-purine (Table 6, entry 1): ^{1}H NMR (500 MHz, [D_6]DMSO): $\delta = 13.59$ (br s, 1H; NH), 8.92 (s, 1H; ar (pos. 2)), 8.83–8.70 (br m, 2H; ar (*o*-tol)), 8.61 (s, 1H; ar (pos. 8)), 7.39 (d, $^3J = 8.0$ Hz, 2H; ar (*m*-tol)), 2.40 ppm (s, 3H; CH_3); ^{13}C{^{1}H} NMR (125.75 MHz, [D_6]DMSO): $\delta =$ 153.7 (br), 152.5 (br), 152.2, 144.9 (br), 141.1, 133.3, 129.9 (br), 129.6 (4×), 21.4 ppm; ^{15}N NMR (50.69 MHz, [D_6]DMSO): $\delta = -223.1$, -137.9, -130.3, -112.3 ppm; HRMS: *m*/*z*: calcd for $C_{12}H_{10}N_4$: 210.0906; found: 210.08788.

6-(3-Methoxyphenyl)-9*H*-purine (Table 6, entry 2): ^{1}H NMR (500 MHz, [D_6]DMSO): $\delta = 13.40$ (br s, 1H; NH), 8.96 (s, 1H; ar (pos. 2)), 8.65 (s,

1H; ar (pos. 8)), 8.52–8.35 (br m, 2H; (*o*-anis), 7.50 (t, $^3J=8.2$ Hz, 1H; ar (*m*-anis)), 7.14 (ddd, $^3J=8.2$, $J=2.5$, 0.9 Hz, 1H; ar (*p*-anis)), 3.87 ppm (s, 3H; OCH_3); $^{13}C\{^1H\}$ NMR (125.75 MHz, [D$_6$]DMSO): $\delta=159.8$, 154.1 (br), 152.1, 152.0 (br), 145.4 (br), 137.4, 130.2 (br), 130.0, 122.1, 117.0, 114.5, 55.5 ppm; ^{15}N NMR (50.69 MHz, [D$_6$]DMSO): $\delta=-222.8$, -138.0, -128.3, -111.1 ppm; HRMS: *m*/*z*: calcd for $C_{12}H_{10}N_4O$: 226.0855; found: 226.08501.

3-Thiophen-2-ylpyridine (Table 7, entry 2): ^1H NMR (500 MHz, $CDCl_3$): $\delta=8.89$ (s, 1H; C*H*, ar), 8.52 (d, $J=3.5$ Hz, 1H; C*H*, ar), 7.86 (dt, $^3J=8.0$, $J=1.6$ Hz, 1H; C*H*, ar), 7.36 (s, 1H; C*H*, ar), 7.35 (q, $J=1.3$ Hz, 1H; C*H*, ar), 7.30 (dd, $^3J=7.6$, $J=4.8$ Hz, 1H; C*H*, ar), 7.12 ppm (dd, $^3J=5.0$, $J=3.8$ Hz, 1H; C*H*, ar); $^{13}C\{^1H\}$ NMR (125.77 MHz, $CDCl_3$): $\delta=147.4$, 146.0, 139.3, 132.1, 129.5, 127.3, 125.1, 123.2, 122.6 ppm; HRMS: *m*/*z*: calcd for C_9H_7NS: 161.03; found: 161.02992.

2-Methyl-5-*p*-tolylbenzothiazole (Table 7, entry 3): ^1H NMR (500 MHz, $CDCl_3$): $\delta=8.15$ (d, $J=1.6$ Hz, 1H; C*H*, ar), 7.84 (dd, $^3J=8.2$, $J=0.6$ Hz, 1H; C*H*, ar), 7.56 (ddd, $^3J=10.0$, 8.2, $J=1.7$ Hz, 1H; C*H*, ar), 7.55 (d, $^3J=8.0$ Hz, 2H; C*H*, ar), 7.28 (dt, $^3J=7.9$, $J=0.6$ Hz, 2H; C*H*, ar), 2.85 (s, 3H; $SCCH_3$), 2.41 ppm (s, 3H; CH_3-tolyl); $^{13}C\{^1H\}$ NMR (125.77 MHz, $CDCl_3$) $\delta=166.5$, 153.1, 138.5, 136.9, 136.2, 133.3, 128.6, 126.2, 123.0, 120.4, 119.5, 20.1, 19.2 ppm; $^{15}N\{^1H\}$ NMR (50.69 MHz, $CDCl_3$): $\delta=-73.5$ ppm; HRMS: *m*/*z*: calcd for $C_{15}H_{13}NS$: 239.0769; found: 239.07605.

2-Methyl-5-pyridin-3-ylbenzothiazole (Table 7, entry 4): ^1H NMR (500 MHz, $CDCl_3$): $\delta=8.93$ (d, $J=2.2$ Hz, 1H; C*H*, ar), 8.62 (dd, $^3J=4.8$, $J=1.6$ Hz, 1H; C*H*, ar), 8.16 (d, $J=1.6$ Hz, 1H; C*H*, ar), 7.94 (ddd, $^3J=7.9$, $J=2.2$, $J=1.6$ Hz, 1H; C*H*, ar), 7.92 (d, $^3J=8.4$ Hz, 1H; C*H*, ar), 7.57 (dd, $^3J=8.4$, $J=1.9$ Hz, 1H; C*H*, ar), 7.40 (ddd, $^3J=7.9$, $J=4.8$, $J=0.8$ Hz, 1H; C*H*, ar), 2.87 ppm (s, 3H; $SCCH_3$); $^{13}C\{^1H\}$ NMR (125.77 MHz, $CDCl_3$): $\delta=167.1$, 153.2, 147.6, 147.5, 135.3, 135.0, 134.5, 133.5, 122.9, 122.6, 121.0, 119.8, 19.2 ppm; $^{15}N\{^1H\}$ NMR (50.69 MHz, $CDCl_3$): $\delta=-73.6$, -67.2 ppm; HRMS: *m*/*z*: calcd for $C_{13}H_{10}N_2S$: 226.0566; found: 226.05647.

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