

Electron-Rich Silicon Containing Phosphanes for Rapid Pd-Catalyzed C–X Coupling Reactions**

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Palladium-catalyzed cross-coupling reactions are among the most useful and efficient methods for direct access to complex structures in organic synthesis. However, heteroatom-containing compounds can complicate such coupling reactions due to their competitive coordination with the palladium catalyst and electronic effects. As a result, good yields are often only obtained under harsher reaction conditions, such as high temperatures and long reaction times. Here the design of a highly active phosphine ligand is reported that provides excellent yields for C–N coupling reactions at ambient temper-

ature. Incorporation of the phosphorus atom into a cyclohexane ring maintains the pyramidal structure of the phosphorus while reducing steric hindrance. This, and a silicon atom in the cyclohexane moiety, results in an electron-rich phosphinane ligand. This novel silicon containing SabPhos ligand can be obtained in excellent yields in a straightforward synthesis. In palladium catalyzed reactions, this ligand facilitates the coupling of a broad range of heteroaryl chlorides via C–C bonds with boronic acids and C–N bonds with secondary amines in excellent yields under mild conditions.

Introduction

The synthesis of heterocyclic compounds has attracted much attention due to their dominant occurrence in numerous pharmaceuticals, agrochemicals and natural products.^[1,2] For instance, 84% of unique small molecule drugs among FDA-approved U.S. drugs contain at least one nitrogen atom.^[3] Two representative examples are shown in Figure 1. Compound I is known as an antidepressant drug;^[4] II is used as a paradrug in artemisinin combination therapies for the treatment of malaria.^[5]

Due to the importance and prevalence of heteroatom-containing drugs, efforts have been made to synthesize such structures via C–N and C–C cross-coupling reactions.^[6] The most widely used synthetic method is the palladium-catalyzed coupling reaction.^[7] The discovery of effective biaryl phosphane (Phos) ligands by Buchwald and other groups has been pivotal to its success.^[8,9] A variety of structurally diverse Phos ligands are available on the market that proved suitable for these transformations.^[10] Although significant progress has already been made, the development of new Phos ligands to optimize reaction conditions and enable the synthesis of a wide range of

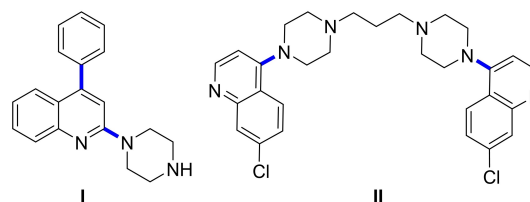


Figure 1. Examples of drugs including one or more N-containing heterocycles. (I) Antidepressant, (II) Piperazine.

compounds is an ongoing challenge.^[11,12] However, heteroatoms, e.g., in pyridine are capable of coordinating palladium and consequently displacing the Phos ligand.^[13] This can cause catalyst deactivation. Therefore, high temperatures (usually 90–200 °C) and long reaction times (12–24 h) are generally required to counteract the coordination of the heteroatom.^[14,15] As a result, the applied ligands mostly lack the property to rapidly form C–X bonds with heteroaryl halides under mild conditions despite their high catalytic potential. Efforts have been made to optimize ligand structures to overcome this issue. Biaryl phosphorinane structures were recently reported to catalyze heteroatom-containing substrates for sulfonamidation reactions, C–O and C–N coupling reactions of primary amines in the presence of palladium.^[16] However, in the field of Buchwald-Hartwig amination of secondary amines, this issue has rarely been addressed in recent years.

In this work, we report the design of the new Phos ligand SabPhos comprising a phosphacycle on the successful biaryl backbone.

Results and Discussion

The aim to incorporate the coordinating phosphorus atom into a cyclohexane ring was to overcome the destabilization of the

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pyramidal structure of the phosphorous by cyclohexyl moieties, i.e. P(Cy)₂. The cyclohexane ring maintains the pyramidal structure of the phosphorus while reducing steric hindrance. A similar strategy was successfully used to stabilize stereogenic nitrogen compounds.^[17,18]

The additional silicon in the phosphacycle bears a high potential to increase the electron donating ability and thus balance the catalytic activity to form C–X bonds while sterically hindering the adverse coordination of heteroatoms. Because improvements are still needed in both fields of C–N and C–C coupling of heteroaryls the ligand is investigated in Pd-catalyzed Suzuki-Miyaura reactions of boronic acids and Buchwald-Hartwig aminations of secondary amines (Figure 2).

The potential of phosphasilinane structures has so far not been explored further, as they have only been used as tripodal structures in hydrosilylation reactions of ketones since their development in 1989.^[19,20] Therefore, we established a new synthetic route for our ligand structure. Three isopropyl groups in meta and para positions on the lower aryl ring were chosen because they are present in ligands such as tBuXPhos, BrettPhos, and XPhos that catalyze C–C and C–N coupling reactions.^[16,21] To avoid steric overload of the ligand, methyl groups on the silicon were selected. The biaryl phosphasilinane structure was synthesized starting from the phosphine **1** prepared according to a literature procedure (see Supporting Information).^[22] Addition of *n*-BuLi generated the phosphide which subsequently underwent ring closure with

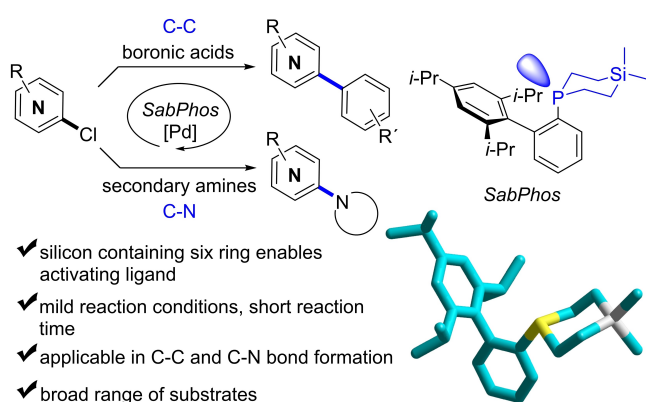
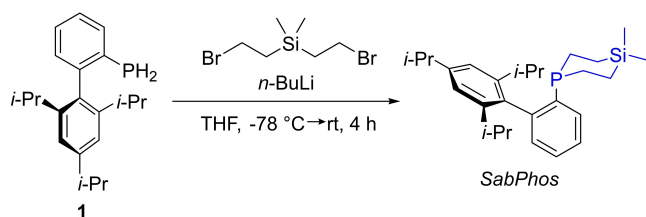


Figure 2. SabPhos ligand structure for palladium-catalyzed C–C and C–N reactions. DFT optimized ligand structure at the B3LYP/DZVP level of theory. Hydrogen atoms have been omitted for clarity. Carbon (cyan), phosphorus (yellow), and silicon (grey).



Scheme 1. One-step synthesis to prepare the SabPhos ligand.

bis(bromoethyl)dimethylsilane producing the SabPhos ligand in an excellent yield of 95% (Scheme 1).

With this new ligand structure in hand, its catalytic potential in Suzuki-Miyaura cross-coupling reactions was investigated. As the model substrates 2-chloroquinoline and phenylboronic acid were chosen to generate coupling product **2**. The investigation of the coupling of quinoline seems appealing, as it is less studied than pyridine but appears as frequently in drugs.^[3] Aryl chlorides are harder to activate than bromides and iodides but have the advantage of being shelf-stable and less expensive.^[23] The reaction was performed in the presence of 1.4 equivalents of base. First, the reaction conditions were optimized by varying different solvents, bases, Pd sources and reaction temperatures (Table 1). The yields were determined by ¹H NMR spectroscopy and mesitylene as internal standard after 4 hours. Coupling with the phenylboronic acid in THF and NaOtBu or K₃PO₄ as base only produced low yields (entries 2 and 3). Enhancing the solubility of the boronic acid by adding H₂O in a ratio of 1/5 (H₂O/THF) resulted in a sevenfold increase of the yield with NaOtBu as base (entries 1 and 2). With KOtBu similar results were achieved (entry 4). The utility of CsOH monohydrate further increased the yield to 54%. Similar yields were also obtained with Pd(OAc)₂ as Pd source (entries 5 and 6). This suggests that the ligand is capable of reducing palladium(II) without any additional reducing agent. An excellent yield of 91% was observed by increasing the temperature to 60 °C after 4 hours (entry 7).

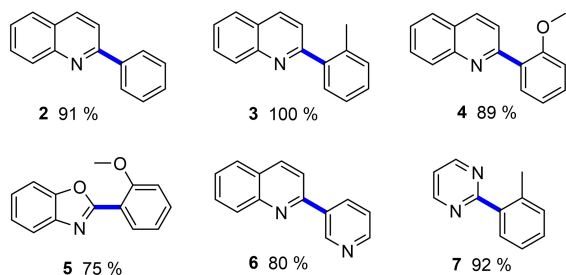
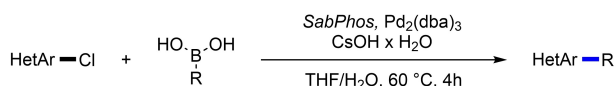
Applying the efficient optimized conditions, various substrates were screened in the Suzuki-Miyaura reaction (Table 1). Substituted aromatic boronic acids were coupled with different heteroaryl chlorides (Scheme 2).

Challenging boronic acids, such as phenyl esters with the methoxy group in meta position, were coupled rapidly with yields of 89 and 75%, respectively (**4** and **5**). Electron donating groups at the phenylboronic acid were reacted with 2-chloroquinoline and 2-chloropyrimidine giving excellent yields (**3** and **7**). For comparison, we performed the Suzuki-Miyaura

Table 1. Optimization of the reaction conditions for C–C coupling.

entry	catalyst	base	solvent	temp [°C]	yield [%]
1	Pd ₂ (dba) ₃	NaOtBu	THF/H ₂ O ^[a]	rt	35
2	Pd ₂ (dba) ₃	NaOtBu	THF	rt	5
3	Pd ₂ (dba) ₃	K ₃ PO ₄	THF	rt	3
4	Pd ₂ (dba) ₃	KOtBu	THF/H ₂ O ^[a]	rt	29
5	Pd ₂ (dba) ₃	CsOH × H ₂ O	THF/H ₂ O ^[a]	rt	54
6	Pd(OAc) ₂	CsOH × H ₂ O	THF/H ₂ O ^[a]	rt	46
7	Pd ₂ (dba) ₃	CsOH × H ₂ O	THF/H ₂ O ^[a]	60	91

Reactant ratios: phenyl boronic acid (1.2 eq.), base (1.4 eq.), SabPhos (4 mol%), Pd source (2 mol%). [a] Ratio of H₂O/THF is 1/5. Yields were determined by ¹H NMR with mesitylene as internal standard.



Scheme 2. Substrate scope – a broadly applicable coupling of heteroaryl chlorides with boronic acids. Reaction conditions: SabPhos (4 mol%), Pd₂(dba)₃ (2 mol%), CsOH × H₂O (1.4 eq.), boronic acid (1.2 eq.), H₂O/THF (1/5). Isolated yields.

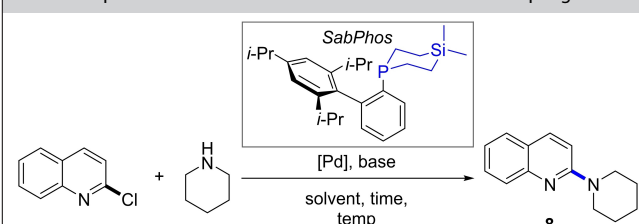
reaction of 2-chloroquinoline and *o*-tolylboronic acid using XPhos and Pd₂(dba)₃ as catalyst under the same reaction conditions. XPhos/ Pd₂(dba)₃ yielded similarly excellent results of 98% compared to complete conversion with SabPhos/ Pd₂(dba)₃ in 4 hours.

The additional coordinating nitrogen atom in the 3-pyridinylboronic acid can complicate the reaction, nevertheless a high yield of 80% was obtained with the SabPhos-based system (6).

C–N bonds of heterocycles are often of high pharmaceutical interest and coupling of heteroaryl structures seem to be only possible under harsh conditions. Furthermore, especially the coupling of secondary amines is challenging and less studied. Therefore, we extended the application of the ligand to Buchwald-Hartwig aminations of secondary amines.^[24] At first, the reaction conditions were optimized to adjust them to the amination reaction (Table 2). Again, 2-chloroquinoline was used as heteroaryl halide and was coupled with the secondary amine piperidine to give the amination product **8**.

Excellent results were obtained with NaOtBu as base in toluene at 60 °C with Pd₂(dba)₃. With 4 mol% SabPhos an outstanding yield of 88% after only 2 hours was achieved (Table 2, entry 2). Using 2-bromoquinoline a comparable yield of 53% after 1 hour at 60 °C was detected (see Supporting Information). Increasing the temperature to 110 °C caused a noticeable decrease in the catalytic activity, probably due to ligand decompositions. At room temperature only a moderate yield was obtained due to the challenging coordinative nature of the heteroaryl halide.^[25] Toluene was found to be the solvent of choice with other solvents including 1,4-dioxane and DME generating low to moderate yields (entries 6 and 7). The reduction of the catalyst concentration had a deteriorating impact on the catalytic activity. In contrast, doubling the concentration did not result in higher yields either (entry 9). It was also observed that exchanging the Pd source Pd₂(dba)₃ with Pd(OAc)₂ resulted in a lower catalytic activity. Only a slight improvement was shown by the addition of NEt₃ as reducing

Table 2. Optimization of the reaction conditions for C–N coupling.

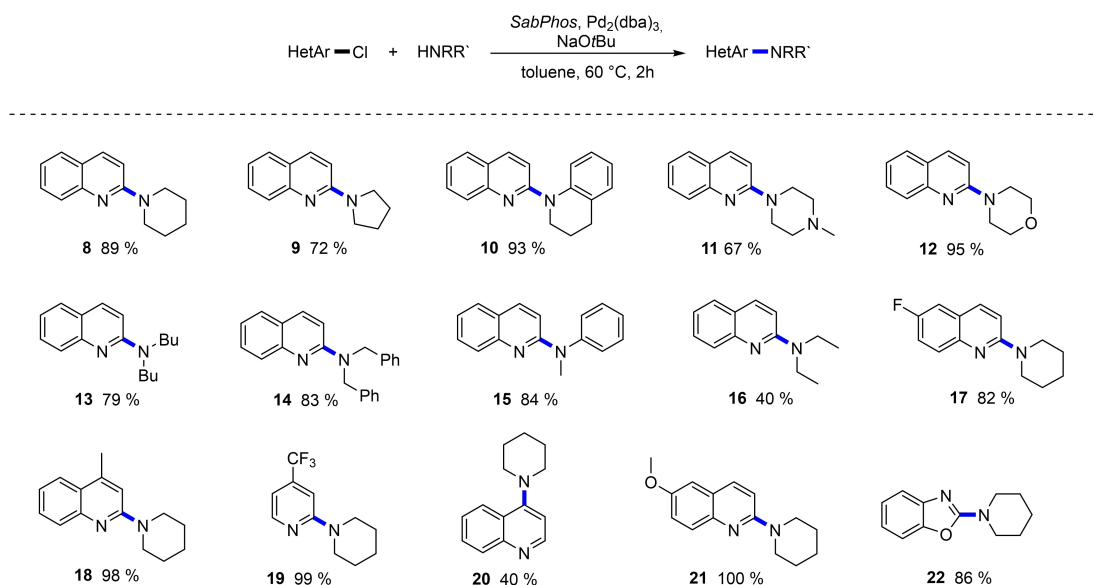


entry	catalyst	base	time	temp [°C]	yield [%]
1	Pd ₂ (dba) ₃	NaOtBu	3 h (1 h)	rt	19 (9)
2	Pd ₂ (dba) ₃	NaOtBu	2 h (1 h)	60	88 (75)
3	Pd ₂ (dba) ₃	NaOtBu	2 h (1 h)	110	58 (56)
4	Pd ₂ (dba) ₃	KOtBu	24 h	90	60
5	Pd ₂ (dba) ₃	KHMDS	24 h	90	48
6 ^[a]	Pd ₂ (dba) ₃	NaOtBu	1 h	60	36
7 ^[b]	Pd ₂ (dba) ₃	NaOtBu	1 h	60	6
8 ^[c]	Pd ₂ (dba) ₃	NaOtBu	1 h	60	14
9 ^[d]	Pd ₂ (dba) ₃	NaOtBu	1 h	60	70
11	Pd(OAc) ₂	NaOtBu	1 h	60	17
12	Pd(OAc) ₂ + NEt ₃	NaOtBu	1 h	60	24
13 ^[e]	Pd ₂ (dba) ₃	NaOtBu	24 h	60	5

Reactant ratios: piperidine (1.2 eq.), base (1.4 eq.) in toluene, SabPhos (4 mol%), Pd source (2 mol%). [a] DME as solvent. [b] 1,4-Dioxane as solvent. [c] SabPhos (1 mol%), Pd source (1 mol%). [d] SabPhos (8 mol%), Pd source (4 mol%). [e] XPhos. Yields were determined by ¹H NMR with mesitylene as internal standard.

agent (Table 2, entries 11 and 12). For comparison, we performed the C–N coupling reaction of 2-chloroquinoline and piperidine using XPhos and Pd₂(dba)₃ as catalyst with NaOtBu as base in toluene at 60 °C (Table 2, entry 13). XPhos/ Pd₂(dba)₃ yielded only 5% of the reaction product after 24 hours while SabPhos/ Pd₂(dba)₃ gave 88% in only 2 hours (Table 2, entry 2). Impressively, with SabPhos a conversion of 75% was already achieved after 1 hour (Table 2, entry 2).

Depending on their structure, amines have very different nucleophilic properties, which increases the importance of developing a catalytic system that operates for a wide range of amines.^[26] Therefore, the substrate scope was extended with the optimized reaction conditions. First, the secondary amine was exchanged with other cyclic medicinally privileged amines such as pyrrolidine, 1,2,3,4-tetrahydroquinoline, N-methylpiperazine and morpholine. All of them prove to be viable substrates, thus affording compounds 9–12 in excellent yields (Scheme 3). Acyclic amines, such as di-*n*-butylamine (13), diphenylamine (14) and *N*-methylaniline (15) were found to couple without difficulty giving 79–84% yields. Coupling of diethylamine (16) only resulted in a moderate yield, which can be attributed to its volatile nature. Next, the scope of heteroaryl chlorides was investigated using piperidine as the amine coupling partner as it is one of the most frequently used nitrogen-containing heterocycles.^[3] Electron poor aryl chlorides reacted readily to form the amination products in high yields (17–19). Using 4-chloroquinoline (20) only a moderate yield could be achieved. The amination of aryl structures containing two heteroatoms such as benzoxazole (21) were successful as well. Electrophilic functional groups such as esters (22) were



Scheme 3. Substrate scope – a broadly applicable coupling of heteroaryl chlorides with secondary amines. Reaction conditions: SabPhos (4 mol %), Pd₂(dba)₃ (2 mol %), NaOtBu (1.4 eq.), secondary amine (1.2 eq.). Isolated yields.

coupled using the SabPhos-based catalyst system demonstrating the high functional group tolerance of this method.

As briefly mentioned above, the conformation of the ligand structure seems to be crucial to the success of the catalyst system. The sp³ hybridization enhances the electron density at the phosphorous atom resulting in a strong overlap and directionality of the coordination to the metal center. The steric bulk and strong electron donor ability of SabPhos presumably promotes the emergence of the oxidative addition complex even under mild conditions.^[21] The silicon in the six-membered ring with two methyl groups provides a steric hindrance and therefore, we assume a prevention of the coordination of the heteroatom to the palladium metal. All these structural features are presumably responsible for the excellent reactivity even under mild conditions.

Conclusion

In summary, a highly activating ligand was designed that opens up an innovative class of ligand structures. Until now, phosphorsilanes have only been used as tripodal systems in catalytic reactions. SabPhos is easily synthesized from the biaryl phosphane with *n*-BuLi and bis(bromoethyl)dimethylsilane. The advantageous steric and electronic properties provide new perspectives for C–C and C–N cross-coupling reactions. Suzuki–Miyaura coupling reactions are one of the most widely used C–C coupling reactions and are commonly applied for the synthesis of pharmaceuticals.^[27] Using the SabPhos ligand in Suzuki–Miyaura cross-coupling reactions with heteroaryl chlorides consistently produced high yields in only 4 hours at 60 °C. Furthermore, a special focus was devoted to making amination reactions more efficient since they are mostly carried out under

harsh conditions at high temperatures and long reactions times. Significant advances were made in the field of Buchwald–Hartwig amination of secondary amines with the SabPhos-based system. A wide range of different substrates were coupled with the catalyst system consisting of SabPhos and Pd₂(dba)₃ in the presence of NaOtBu as base, revealing high functional group tolerance. Due to the special structural properties, which prevent the coordination of the heteroatoms of the substrates and at the same time allow the ligand to work highly effectively, excellent yields were achieved at low temperatures in only 2 hours. The described progress in C–N coupling reactions of secondary amines is of great relevance especially in view of our global responsibility to render industrial processes more energy efficient and sustainable.

Experimental Section

Materials and Methods

All reactions were carried out under an atmosphere of argon gas (Ar 5.0). The argon was further dried by molecular sieve (4 Å). All glassware was flame-dried prior to use and standard Schlenk techniques were applied. The anhydrous solvents (toluene, EtOAc, THF, CDCl₃, THF-d₈, toluene-d₈) were purchased from *Sigma-Aldrich Co. LLC* and stored under exclusion of air and moisture. Degassing was accomplished by at least three *Freeze-Pump-Thaw* cycles. The anhydrous and degassed solvents were stored under argon over molecular sieve (4 Å). Isolated compounds were stored, if needed, at 5 or –20 °C and under argon. All other solvents and chemicals were purchased from manufacturing and trading companies (*Sigma-Aldrich, Inc., USA* and *TCI Europe N.V., Belgium*) and stored according to the respective instructions.

¹H NMR, ¹³C NMR and ³¹P NMR spectra were recorded at room temperature on a *Joel ECP 270* (400 MHz), *Joel ECX 400* (400 MHz),

Bruker Avance III HD (400 MHz, 800 MHz) and a *Varian NMR System* (600 MHz). Chemical shifts were calibrated, using the NMR solvent signal.^[28] The following abbreviations were used for multiplicity: s = singlet, d = doublet, t = triplet, hept = heptet, m = multiplet. Coupling constants through *n* bonds (*J*) are provided in Hertz [Hz]. The software used for data processing was MNova Version 11.0.4. The assignment of all signals was realized by two-dimensional NMR spectroscopy (¹H-¹H-COSY, ¹H-¹³C-HSQC, ¹H-¹³C-HMBC) and supported by ³¹P decoupling experiments. NMR spectra of air and moisture sensitive compounds were measured using *J. Young* NMR tubes.

ESI and EI spectra were recorded with a *Thermo Finnigan LTQ FT Ultra Fourier Transform Ion Cyclotron Resonance* mass spectrometer or a *Thermo ScientificQ Exactive Plus mass spectrometer* (Thermo Fisher Scientific Inc., USA). Electrospray ionization (ESI) or atmospheric pressure chemical ionization (APCI) was used as the ionization technique. If isotopic patterns are pronounced, the most intensive peak is indicated. Regarding ESI analyses, the most abundant peak or the peak referring to the molecular ion is given in comparison with the exactly calculated *m/z* value. In order to lucidly present the results, molecular ions are abbreviated as M. For data processing, the Qual Browser of the *Thermo Scientific Xcalibur 4.1* software suite (Thermo Fisher Scientific Inc., USA) was used.

Elemental analyses were performed using an *Elementar vario MICRO* cube instrument (Elementar Analysensysteme GmbH, Germany).

4,4-Dimethyl-1-(2',4',6'-triisopropyl-[1,1'-biphenyl]-2-yl)-1,4-phosphasilane (SabPhos)

To a solution of (2',4',6'-triisopropyl-[1,1'-biphenyl]-2-yl) phosphane **1** (200 mg, 640 μmol, 1.00 eq.) in THF (6 mL), *n*-BuLi (512 μL, 1.28 mmol, 2.00 eq.) was added slowly at -78 °C. The reaction mixture was stirred for 10 min at this temperature followed by further stirring at room temperature for another 30 min. Bis(2-bromoethyl)dimethylsilane **SI-3** (119 μL, 640 μmol, 1.00 eq.) was added at -78 °C. The reaction mixture was stirred at room temperature overnight. An aqueous saturated NH₄Cl solution (6 mL) was added. The aqueous layer was extracted with EtOAc (3 × 10 mL). The combined organic layers were dried over Na₂SO₄ and concentrated *in vacuo*. SabPhos (252 mg, 594 μL, 93%) was obtained as a slightly yellow oil.

¹H NMR (400 MHz, THF-*d*₈): δ [ppm] = 7.47–7.43 (m, 1H), 7.31–7.23 (m, 2H), 7.10–7.00 (m, 3H), 2.94–2.87 (m, 1H), 2.50–2.39 (m, 2H), 1.65–1.30 (m, 4H), 1.28 (dd, *J* = 7.0, 2.7 Hz, 6H), 1.20–1.12 (m, 6H), 1.02–0.94 (m, 6H), 0.93–0.40 (m, 4H), 0.13–0.10 (m, 6H).

¹³C {¹H} NMR (101 MHz, THF-*d*₈): δ [ppm] = 149.1, 147.4, 146.7, 132.2, 131.2, 127.8, 121.4, 73.9, 45.9, 35.3, 31.3, 25.5, 24.5, 23.6, -3.9.

³¹P{¹H} NMR (162 MHz, CDCl₃): δ [ppm] = -51.74 (s, 1P).

HR-MS (APCI⁺, MeCN): [M]⁺: C₂₇H₄₂PSi⁺ *m/z*: calculated 425.2788, found 425.2797.

General procedure for Pd-catalyzed C–C coupling

150 mg of heteroaryl chloride was dissolved in THF (5 mL) and water (1 mL). Pd₂(dba)₃ (2 mol%), CsOH × H₂O (1.4 eq.) and SabPhos (0.5 M in toluene, 4 mol%) was added. The mixture was warmed to 60 °C and 1.20 equiv. of boronic acid was added. The reaction mixture was stirred for 4 h at 60 °C. Saturated aqueous solution of NH₄Cl (10 mL) was added and the aqueous phase was extracted with EtOAc (2 × 15 mL). The combined organic phases were dried

over Na₂SO₄ and the solvent was removed *in vacuo*. The product was isolated by column chromatography (silica gel, 10:1 EtOAc/cyclohexane).

2-Phenylquinoline (2)

The general procedure was used to couple 2-chloroquinoline (150 mg, 0.92 mmol, 1.00 eq.) and phenylboronic acid (134 mg, 1.10 mmol, 1.20 eq.). The product (172 mg, 0.84 mmol, 91%) was isolated as colorless solid.

¹H NMR (400 MHz, CDCl₃): δ [ppm] = 8.23 (d, *J* = 8.6 Hz, 1H), 8.22–8.14 (m, 2H), 7.89 (d, *J* = 8.6 Hz, 1H), 7.84 (d, *J* = 8.1 Hz, 0H), 7.80–7.69 (m, 1H), 7.58–7.50 (m, 2H), 7.54–7.43 (m, 1H).

¹³C NMR (101 MHz, CDCl₃): δ [ppm] = 157.5, 148.4, 139.8, 136.9, 129.9, 129.8, 129.5, 129.0, 127.7, 127.6, 127.3, 126.4, 119.2.

HR-MS (ESI⁺, CHCl₃): [M]⁺: C₁₅H₁₁N⁺ *m/z*: calc. 206.0964, found 206.0966.

EA: C₁₃H₁₁N [%]: calc. N 6.82; C 87.77; H 5.40, found N 6.65; C 88.17; H 5.41.

2-(*o*-Tolyl)quinoline (3)

The general procedure was used to couple 2-chloroquinoline (150 mg, 0.92 mmol, 1.00 eq.) and *o*-tolylboronic acid (150 mg, 1.10 mmol, 1.20 eq.). The product (200 mg, 0.91 mmol, 100%) was isolated as colorless solid.

¹H NMR (800 MHz, CDCl₃): δ [ppm] = 8.23 (d, *J* = 8.4 Hz, 1H), 8.18 (d, *J* = 7.7 Hz, 1H), 7.87 (d, *J* = 8.1 Hz, 1H), 7.75 (t, *J* = 7.6 Hz, 1H), 7.57 (t, *J* = 7.5 Hz, 1H), 7.55 (d, *J* = 8.4 Hz, 1H), 7.51 (d, *J* = 6.8 Hz, 1H), 7.37–7.30 (m, 3H), 2.42 (s, 3H).

¹³C NMR (201 MHz, CDCl₃): δ [ppm] = 160.6, 160.6, 160.5, 136.5, 136.4, 136.3, 131.2, 130.0, 128.9, 127.8, 127.4, 127.0, 126.8, 126.3, 122.7, 20.7.

MS (EI, CHCl₃): [M]: C₁₆H₁₃N *m/z*: calc. 219.1048, found 219.1016.

EA: C₁₃H₁₄N₂ [%]: calc. N 6.39; C 87.64; H 5.98, found N 6.12; C 87.81; H 6.07.

2-(2-Methoxyphenyl)quinoline (4)

The general procedure was used to couple 2-chloroquinoline (150 mg, 0.92 mmol, 1.00 eq.) and (2-methoxyphenyl)boronic acid (167 mg, 1.10 mmol, 1.20 eq.). The product (192 mg, 0.82 mmol, 89%) was isolated as off-white solid.

¹H NMR (800 MHz, CDCl₃): δ [ppm] = 8.22 (d, *J* = 5.1 Hz, 1H), 8.13 (d, *J* = 8.7 Hz, 1H), 7.91 (d, *J* = 8.5 Hz, 2H), 7.82 (d, *J* = 8.4 Hz, 1H), 7.74–7.69 (m, 1H), 7.53 (t, *J* = 6.3 Hz, 1H), 7.43 (t, *J* = 8.1 Hz, 1H), 7.16 (t, *J* = 7.7 Hz, 1H), 7.04 (d, *J* = 8.5 Hz, 1H), 3.85 (s, 3H).

¹³C NMR (201 MHz, CDCl₃): δ [ppm] = 157.2, 157.2, 148.3, 135.1, 131.5, 130.4, 129.7, 129.6, 129.3, 127.4, 127.1, 126.2, 123.5, 121.3, 111.5, 77.3, 77.2, 77.0, 55.6.

MS (EI, CHCl₃): [M]: C₁₆H₁₃NO *m/z*: calc. 235.0997, found 235.0991.

2-(2-Methoxyphenyl)benzo[d]oxazole (5)

The general procedure was used to couple 2-chloroquinoline (150 mg, 0.98 mmol, 1.00 eq.) and (2-methoxyphenyl)boronic acid (178 mg, 1.17 mmol, 1.20 eq.). The product (165 mg, 0.73 mmol, 75%) was isolated as colorless solid.

¹H NMR (800 MHz, CDCl₃): δ [ppm]=7.85 (dd, *J*=7.3, 1.9 Hz, 1H), 7.52–7.39 (m, 2H), 7.22–7.07 (m, 3H), 7.07–7.00 (m, 1H), 6.92 (d, *J*=9.2 Hz, 1H), 3.92 (s, 3H).

¹³C NMR (201 MHz, CDCl₃): δ [ppm]=164.6, 144.0, 143.5, 137.0, 133.0, 131.1, 125.5, 124.2, 122.8, 121.4, 119.5, 112.5, 110.1, 55.6.

2-(Pyridin-3-yl)quinoline (6)

The general procedure was used to couple 2-chloroquinoline (150 mg, 0.92 mmol, 1.00 eq.) and pyridin-3-ylboronic acid (135 mg, 1.10 mmol, 1.20 eq.). The product (152 mg, 0.74 mmol, 80%) was isolated as colorless solid.

¹H NMR (800 MHz, CDCl₃): δ [ppm]=9.37 (d, *J*=2.3 Hz, 1H), 8.71 (dd, *J*=4.8, 1.7 Hz, 1H), 8.54 (dt, *J*=8.0, 2.0 Hz, 1H), 8.28 (d, *J*=8.6 Hz, 1H), 8.18 (d, *J*=9.0 Hz, 1H), 7.90 (d, *J*=8.6 Hz, 1H), 7.86 (d, *J*=8.2 Hz, 1H), 7.81–7.72 (m, 1H), 7.61–7.53 (m, 1H), 7.48 (dd, *J*=8.0, 4.8 Hz, 1H).

¹³C NMR (201 MHz, CDCl₃): δ [ppm]=154.7, 150.2, 148.8, 148.5, 143.5, 137.38, 135.4, 135.3, 130.2, 129.9, 127.7, 127.0, 123.92, 118.7.

2-(*o*-Tolyl)pyrimidine (7)

The general procedure was used to couple 2-chloropyrimidine (150 mg, 1.31 mmol, 1.00 eq.) and *o*-tolylboronic acid (214 mg, 1.57 mmol, 1.20 eq.). The product (206 mg, 1.21 mmol, 92%) was isolated as yellow oil.

¹H NMR (800 MHz, CDCl₃): δ [ppm]=8.86 (d, *J*=4.9 Hz, 2H), 7.79 (dd, *J*=7.5, 1.5 Hz, 1H), 7.37–7.26 (m, 3H), 7.26–7.22 (m, 1H), 2.54 (s, 3H).

¹³C NMR (101 MHz, CDCl₃): δ [ppm]=167.7, 157.0, 137.9, 137.4, 131.5, 130.6, 129.8, 126.1, 118.7, 21.1.

General procedure for Pd-catalyzed C–N coupling

150 mg of heteroaryl chloride was dissolved in toluene (5 mL). Pd₂(dba)₃ (2 mol%), NaOtBu (1.4 eq.) and SabPhos (0.5 M in toluene, 4 mol%) was added. The mixture was warmed to 60 °C and 1.2 equiv. of secondary amine was added. The reaction mixture was stirred for 2 h at 60 °C. Saturated aqueous solution of NH₄Cl (10 mL) was added and the aqueous phase was extracted with EtOAc (2 × 15 mL). The combined organic phases were dried over Na₂SO₄ and the solvent was removed *in vacuo*. The product was isolated by column chromatography (silica gel, 20:1 EtOAc/cyclohexane).

2-(Piperidin-1-yl)quinoline (8)

The general procedure was used to couple 2-chloroquinoline (150 mg, 0.92 mmol, 1.00 eq.) and piperidine (93.8 mg, 1.10 mmol, 1.20 eq.). The product (173 mg, 0.81 mmol, 89%) was isolated as yellow oil.

¹H NMR (400 MHz, toluene-*d*₆): δ [ppm]=7.92 (d, *J*=8.3 Hz, 1H), 7.47 (d, *J*=9.1 Hz, 1H), 7.40–7.32 (m, 2H), 7.04 (t, *J*=7.4 Hz, 1H), 6.55 (d, *J*=9.1 Hz, 1H), 3.54–3.45 (m, 4H), 1.42–1.33 (m, 6H).

¹³C{¹H} NMR (101 MHz, toluene-*d*₆): δ [ppm]=157.6, 149.0, 137.5, 137.1, 129.5, 127.5, 127.3, 123.4, 122.1, 109.8, 46.4, 26.0, 25.3.

HR-MS (ESI⁺, CHCl₃): [M]⁺: C₁₄H₁₇N₂⁺ *m/z*: calc. 213.1386, found 213.1387.

EA: C₁₄H₁₆N₂ [%]: calc. N 13.20; C 79.21; H 7.60, found N 14.82; C 78.28; H 9.66.

2-(Pyrrolidin-1-yl)quinoline (9)

2-Chloroquinoline (150 mg, 0.92 mmol, 1.00 eq.) and pyrrolidine (0.09 mL, 1.10 mmol, 1.20 eq.) were coupled according to the general procedure. The product (132 mg, 0.66 mmol, 72%) was isolated as colorless solid.

¹H NMR (400 MHz, CDCl₃): δ [ppm]=7.85 (d, *J*=9.1 Hz, 1H), 7.82–7.67 (m, 1H), 7.58 (dd, *J*=8.0, 1.5 Hz, 1H), 7.52 (ddd, *J*=8.5, 6.9, 1.5 Hz, 1), 7.21–7.13 (m, 1H), 6.73 (d, *J*=9.1 Hz, 1H), 3.65 (m, 4H), 2.08–2.01 (m, 4H).

¹³C NMR (101 MHz, CDCl₃): δ [ppm]=155.6, 148.4, 137.3, 129.8, 127.6, 125.8, 122.6, 121.6, 110.5, 47.2, 25.7.

HR-MS (ESI⁺, CHCl₃): [M + H]⁺: C₁₃H₁₅N₂⁺ *m/z*: calc. 199.1230, found 199.1230.

EA: C₁₃H₁₄N₂ [%]: calc. N 14.13; C 78.75; H 7.12, found N 13.51; C 77.25; H 6.67.

3,4-Dihydro-2H-1,2'-biquinoline (10)

The general procedure was used to couple 2-chloroquinoline (150 mg, 0.92 mmol, 1.00 eq.) and 1,2,3,4-tetrahydroquinoline (138 μL, 1.10 mmol, 1.20 eq.). The product (221 mg, 0.85 mmol, 93%) was isolated as colorless solid.

¹H NMR (400 MHz, CDCl₃): δ [ppm]=7.91 (d, *J*=8.4 Hz, 1H), 7.82 (d, *J*=9.1 Hz, 1H), 7.69–7.59 (m, 2H), 7.43 (d, *J*=9.0 Hz, 1H), 7.40–7.30 (m, 2H), 7.22 (d, *J*=7.4 Hz, 1H), 7.16 (t, *J*=7.7 Hz, 1H), 7.07–7.00 (m, 1H), 4.19 (t, *J*=6.3 Hz, 2H), 2.83 (t, *J*=6.5 Hz, 2H), 2.06 (p, *J*=6.4 Hz, 2H).

¹³C NMR (101 MHz, CDCl₃): δ [ppm]=156.5, 148.0, 141.0, 136.4, 130.9, 129.5, 129.1, 127.3, 127.0, 126.1, 124.3, 123.3, 122.6, 120.5, 113.9, 45.9, 27.5, 24.2.

HR-MS (ESI⁺, CHCl₃): [M]⁺: C₁₈H₁₇N₂⁺ *m/z*: calc. 261.1386, found 261.1387.

EA: C₁₈H₁₆N₂ [%]: calc. N 10.76; C 83.04; H 6.19, found N 8.70; C 72.38; H 8.84.

2-(4-Methylpiperazin-1-yl)quinoline (11)

The general procedure was used to couple 2-chloroquinoline (150 mg, 0.92 mmol, 1.00 eq.) and 1-methylpiperazine (122 μL, 1.10 mmol, 1.20 eq.). The product (140 mg, 0.62 mmol, 67%) was isolated as colorless solid.

¹H NMR (400 MHz, CDCl₃): δ [ppm]=7.82 (d, *J*=9.2 Hz, 1H), 7.63 (d, *J*=9.4 Hz, 1H), 7.52 (dd, *J*=8.0, 1.5 Hz, 1H), 7.51–7.41 (m, 1H), 7.20–7.11 (m, 1H), 6.91 (d, *J*=9.2 Hz, 1H), 3.74–3.67 (m, 4H), 2.50 (t, *J*=5.1 Hz, 4H), 2.30 (s, 3H).

¹³C NMR (101 MHz, CDCl₃): δ [ppm]=157.5, 148.0, 137.6, 129.7, 127.3, 126.8, 123.2, 122.6, 109.7, 55.1, 46.3, 45.2.

4-(Quinolin-2-yl)morpholine (12)

The general procedure was used to couple 2-chloroquinoline (150 mg, 0.92 mmol, 1.00 eq.) and morpholine (95 μL, 1.1 mmol, 1.2 eq.). The product (187 mg, 0.87 mmol, 95%) was isolated as colorless solid.

¹H NMR (400 MHz, CDCl₃): δ [ppm]=7.91 (d, *J*=9.1 Hz, 1H), 7.73–7.71 (m, 1H), 7.62 (d, *J*=8.0 Hz, 1H), 7.55 (t, *J*=6.9 Hz, 1H), 6.96 (d, *J*=9.1 Hz, 1H), 3.90–3.83 (m, 4H), 3.72 (m, 4H).

¹³C NMR (101 MHz, CDCl₃): δ [ppm] = 157.7, 147.9, 137.7, 129.8, 127.4, 126.9, 123.4, 122.8, 109.4, 67.0, 1.2,

HR-MS (ESI⁺, CHCl₃): [M]⁺: C₁₃H₁₅ON₂⁺ *m/z*: calc. 215.1179, found 261.1180.

N,N-Dibutylquinolin-2-amine (13)

2-Chloroquinoline (150 mg, 0.92 mmol, 1.00 eq.) and *N,N*-dibutylamine (185 μL, 1.10 mmol, 1.20 eq.) were coupled according to the general procedure. The product (185 mg, 0.72 mmol, 79%) was isolated as colorless solid.

¹H NMR (400 MHz, CDCl₃): δ [ppm] = 7.91 (d, *J* = 9.1 Hz, 1H), 7.80 (d, *J* = 8.4 Hz, 1H), 7.67 (d, *J* = 7.9 Hz, 1H), 7.51–7.46 (m, 1H), 7.35–7.31 (m, 1H), 6.79 (d, *J* = 6.0 Hz, 1H), 3.61–3.55 (m, 4H), 1.68–1.59 (m, 4H), 0.98 (t, *J* = 7.4 Hz, 6H).

¹³C NMR (151 MHz, CDCl₃): δ [ppm] = 156.4, 148.6, 137.0, 129.2, 127.3, 126.4, 122.4, 121.3, 109.3, 48.4, 20.5, 14.2.

N,N-Dibenzylquinolin-2-amine (14)

The general procedure was applied to couple 2-chloroquinoline (150 mg, 0.92 mmol, 1.00 eq.) and dibenzylamine (212 μL, 1.10 mmol, 1.20 eq.). The product (246 mg, 0.76 mmol, 83%) was isolated as yellow solid.

¹H NMR (400 MHz, CDCl₃): δ [ppm] = 7.78 (d, *J* = 9.1 Hz, 1H), 7.69 (d, *J* = 8.4 Hz, 1H), 7.58–7.45 (m, 2H), 7.31–7.26 (d, *J* = 14.1 Hz, 7H), 7.24–7.13 (d, *J* = 20.3 Hz, 4H), 6.78 (d, *J* = 9.1 Hz, 1H), 4.90 (s, 4H).

N-Methyl-N-phenylquinolin-2-amine (15)

The general procedure was used to couple 2-chloroquinoline (150 mg, 0.92 mmol, 1.00 eq.) and *N*-methylaniline (120 μL, 1.10 mmol, 1.20 eq.). The product (181 mg, 0.77 mmol, 84%) was isolated as yellow solid.

¹H NMR (400 MHz, CD₂Cl₂): δ [ppm] = 7.72 (d, *J* = 8.9 Hz, 2H), 7.60 (dd, *J* = 8.0, 1.6 Hz, 1H), 7.57–7.51 (m, 1H), 7.48–7.41 (m, 1H), 7.34–7.20 (m, 2H), 6.75 (d, *J* = 9.2 Hz, 1H), 3.60 (s, 3H).

N,N-Diethylquinolin-2-amine (16)

The general procedure was used to couple 2-chloroquinoline (150 mg, 0.92 mmol, 1.00 eq.) and diethylamine (114 μL, 1.10 mmol, 1.20 eq.). The product (73.7 mg, 0.37 μmol, 40%) was isolated as slightly yellow oil.

¹H NMR (400 MHz, CDCl₃): δ [ppm] = 7.84 (d, *J* = 9.1 Hz, 1H), 7.74–7.61 (m, 1H), 7.56 (d, *J* = 8.1 Hz, 1H), 7.53–7.45 (m, 1H), 7.21–7.10 (m, 1H), 6.83 (d, *J* = 9.2 Hz, 1H), 3.79–3.58 (m, 4H), 1.26 (t, *J* = 7.1 Hz, 6H).

¹³C NMR (101 MHz, CDCl₃): δ [ppm] = 156.0, 148.7, 137.2, 129.5, 127.3, 126.4, 122.3, 121.5, 109.3, 42.6, 13.4.

HR-MS (ESI⁺, CHCl₃): [M]⁺: C₁₃H₁₇N₂⁺ *m/z*: calc. 201.1386, found 201.1386.

EA: C₁₃H₁₆N₂ [%]: calc. N 13.99; C 77.96; H 8.05, found N 13.24; C 75.81; H 8.88.

6-Fluoro-2-(piperidin-1-yl)quinoline (17)

The general procedure was used to couple 2-chloro-6-fluoroquinoline (150 mg, 0.83 mmol, 1.00 eq.) and piperidine (98 μL, 1.0 mmol,

1.2 eq.). The product (157 mg, 0.68 mmol, 82%) was isolated as beige solid.

¹H NMR (400 MHz, CDCl₃): δ [ppm] = 7.79 (d, *J* = 9.2 Hz, 1H), 7.72 (s, 1H), 7.28 (td, *J* = 8.8, 2.7 Hz, 1H), 7.20 (dd, *J* = 8.9, 2.9 Hz, 1H), 7.01 (d, *J* = 9.2 Hz, 1H), 3.71 (s, 4H), 1.69 (s, 6H).

¹³C NMR (101 MHz, CDCl₃): δ [ppm] = 159.4, 157.0, 137.0, 128.2, 122.8, 122.7, 119.1, 118.9, 111.0, 110.7, 110.5, 46.7, 25.9, 24.9.

HR-MS (ESI⁺, CHCl₃): [M]⁺: C₁₄H₁₆FN₂⁺ *m/z*: calc. 231.1292, found 231.1292.

4-Methyl-2-(piperidin-1-yl)quinoline (18)

The general procedure was used to couple 2-chloro-4-methylquinoline (150 mg, 0.84 mmol, 1.00 eq.) and piperidine (0.1 mL, 1.0 mmol, 1.2 eq.). The product (188 mg, 0.83 mmol, 98%) was isolated as yellow solid.

¹H NMR (600 MHz, CDCl₃): δ [ppm] = 7.75 (d, *J* = 8.2 Hz, 1H), 7.54–7.48 (m, 1H), 7.22 (t, *J* = 6.9 Hz, 1H), 6.85 (s, 1H), 3.72 (s, 4H), 2.58 (s, 3H), 1.68 (s, 6H).

¹³C NMR (151 MHz, CDCl₃): δ [ppm] = 157.6, 150.7, 147.8, 129.3, 126.8, 123.5, 123.3, 122.0, 110.3, 46.5, 26.0, 25.0, 19.4.

MS (EI, CHCl₃): [M]: C₁₅H₁₈N₂ *m/z*: calc. 226.1470, found 226.1462.

2-(Piperidin-1-yl)-4-(trifluoromethyl)pyridine (19)

The general procedure was used to couple 2-chloro-4-(trifluoromethyl)pyridine (150 mg, 0.83 mmol, 1.00 eq.) and piperidine (98 μL, 1.0 mmol, 1.2 eq.). The product (189 mg, 0.82 mmol, 99%) was isolated as yellow solid.

¹H NMR (600 MHz, CDCl₃): δ [ppm] = 8.27 (d, *J* = 5.2 Hz, 1H), 6.79 (s, 1H), 6.70 (d, *J* = 6.5 Hz, 1H), 3.60 (t, *J* = 5.2 Hz, 4H), 1.66 (d, *J* = 15.8 Hz, 6H).

¹³C NMR (151 MHz, CDCl₃): δ [ppm] = 149.0, 124.3, 122.5, 107.3, 46.34, 25.58, 24.7.

MS (EI, CHCl₃): [M]: C₁₁H₁₁F₃N₂ *m/z*: calc. 230.1031, found 230.1024.

EA: C₁₁H₁₁F₃N₂ [%]: calc. N 12.17; C 57.39; H 5.69, found N 11.66; C 57.02; H 5.72.

4-(Piperidin-1-yl)quinoline (20)

The general procedure was used to couple 4-chloroquinoline (150 mg, 0.92 mmol, 1.00 eq.) and piperidine (110 μL, 1.10 mmol, 1.20 eq.). The product (78.6 mg, 0.37 mmol, 40%) was isolated as yellow solid.

¹H NMR (600 MHz, CDCl₃): δ [ppm] = 8.69 (d, *J* = 5.0 Hz, 1H), 8.03 (dd, *J* = 21.8, 8.4 Hz, 1H), 7.68–7.61 (m, 1H), 7.50–7.44 (m, 1H), 6.82 (d, *J* = 5.0 Hz, 1H), 3.22–3.17 (m, 5H), 1.89–1.82 (m, 4H), 1.74–1.67 (m, 1H).

¹³C NMR (151 MHz, CDCl₃): δ [ppm] = 158.3, 150.7, 149.5, 129.8, 129.1, 125.2, 124.1, 123.8, 108.7, 53.8, 26.2, 24.6.

HR-MS (ESI⁺, CHCl₃): [M]⁺: C₁₄H₁₆ON₂⁺ *m/z*: calc. 213.1386, found 213.1388.

6-Methoxy-2-(piperidin-1-yl)quinoline (21)

The general procedure was applied to couple 2-chloro-6-methoxyquinoline (150 mg, 0.77 mmol, 1.00 eq.) and piperidine (92 μL,

0.93 mmol, 1.20 eq.). The product (188 mg, 0.78 mmol, 100%) was isolated as beige solid.

¹H NMR (600 MHz, CDCl₃): δ [ppm]=7.80 (d, *J*=9.1 Hz, 1H), 7.21 (dd, *J*=9.1, 2.9 Hz, 1H), 6.98 (d, *J*=9.1 Hz, 1H), 6.94 (d, *J*=2.9 Hz, 1H), 3.87 (s, 3H), 3.68 (s, 4H), 1.68 (s, 6H).

¹³C NMR (151 MHz, CDCl₃): δ [ppm]=157.0, 155.1, 143.7, 136.5, 128.1, 123.2, 121.1, 110.6, 106.2, 55.6, 46.8, 25.9, 24.9.

HR-MS (ESI⁺, CHCl₃): [M]⁺: C₁₅H₁₉ON₂⁺ *m/z*: calc. 243.1492, found 243.1493.

2-(Piperidin-1-yl)benzooxazole (22)

The general procedure was used to couple 2-chlorobenzooxazole (150 mg, 0.98 mmol, 1.00 eq.) and piperidine (0.12 mL, 1.17 mmol, 1.20 eq.). The product (170 mg, 0.84 mmol, 86%) was isolated as bright yellow solid.

¹H NMR (600 MHz, CDCl₃): δ [ppm]=7.35 (d, *J*=7.8 Hz, 1H), 7.23 (d, *J*=7.9 Hz, 1H), 7.15 (td, *J*=7.7, 1.1 Hz, 1H), 7.00 (td, *J*=7.7, 1.2 Hz, 1H), 3.67 (t, *J*=4.4 Hz, 4H), 1.69 (d, *J*=3.7 Hz, 6H).

¹³C NMR (151 MHz, CDCl₃): δ [ppm]=162.4, 148.7, 143.1, 124.1, 120.5, 116.1, 108.7, 46.8, 25.4, 24.2.

MS (EI⁺, CHCl₃): [M]: C₁₂H₁₄N₂O *m/z*: calc. 202.1106, found 202.1100.

EA: C₁₂H₁₄N₂O [%]: calc. N 13.85; C 71.26; H 6.98, found N 13.38; C 70.88; H 6.98.

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Conflict of Interest

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available in the supplementary material of this article.

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