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Pd-PEPPSI-IPent^{An} Promoted Deactivated Amination of Aryl Chlorides with Amines under Aerobic Conditions

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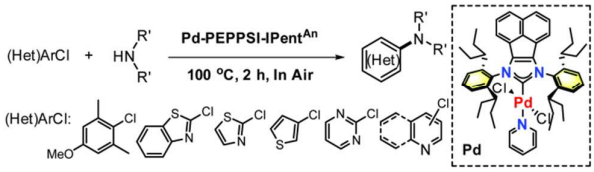
TOC


(Het)ArCl + HN R' R'
Pd-PEPPSI-IPent^An
100 °C, 2 h, In Air
(Het)
R' N R'
(Het)ArCl:
MeO
Cl
S
N
Pd
Pd

ABSTRACT:

We report herein a highly efficient Pd-catalyzed amination by "bulky-yet-flexible" Pd-PEPPSI-IPent^{An} complexes. The relationship between the *N*-heterocyclic carbenes (NHCs) structure and catalytic properties was discussed. Sterically hindered (hetero)aryl chlorides and a variety of aliphatic and aromatic amines can be applied in this cross-coupling, which smoothly proceeded to provide desired products. The operationally simple protocol highlights the rapid access to C_{Ar}-N bond formation under mild conditions without the exclusion of air and moisture.

Introduction

(Hetero)aryl amines presented important structural moieties in a large amount of pharmaceuticals (eg. Sprycel, Rilpivirine, Brexpiprazole, Buspar, etc), bioactive molecules (eg. R116010, RAF709, etc) and functional materials (eg. Hole transport for OLED in Figure 1).[1] The metal-catalyzed cross-coupling reactions have provided concise routes for constructing such target molecular scaffolds.[2-4] Among them, the Pd-catalyzed Buchwald-Hartwig amination reaction has been well established as the generally employed process with wide substrate scopes under mild reaction conditions.[4, 5]

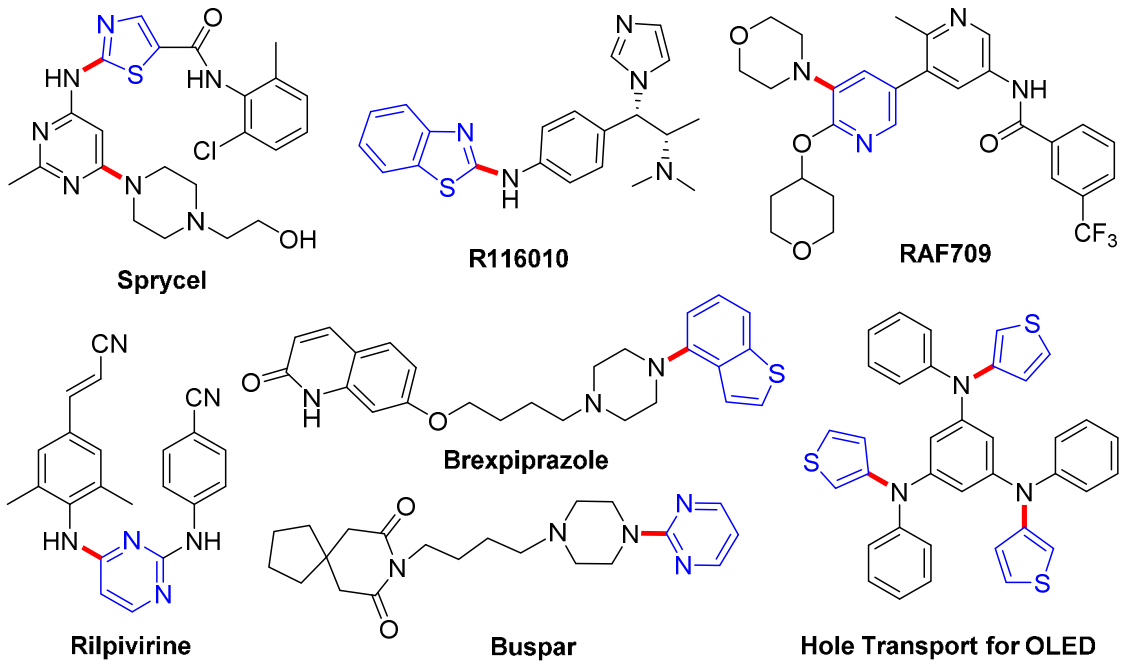


Figure 1. Heteroarylated amines in pharmaceuticals, bioactive compounds and hole transport materials.

In the past two decades, the classes of privileged ligands including sterically demanding and electron-rich phosphines have been well developed and remarkable progress has been achieved in these catalytic systems.[4-6] Nevertheless, the search for phosphine-free ligands is highly desirable

from the environmental and economical viewpoint.[7] Alternatively, *N*-heterocyclic carbenes (NHCs) have emerged as one of the most powerful phosphine-free ligands in the Pd-catalyzed cross-coupling reactions.[8] The group of Nolan firstly demonstrated the well-defined Pd-NHC complexes to generate the aryl amines when aryl chlorides were used as electrophlic substrates.[9] Subsequently, Organ developed a new type of Pd-PEPPSI-NHCs (PEPPSI: pyridine-enhanced precatalyst preparation, stabilization, and initiation), which could mediate C-N bond formation at a low palladium loading, even under room temperature.[10] Afterward, numerous versatile Pd-NHCs have been disclosed to be effective in the arylation of amines with aryl chlorides. [11]

Despite these compelling advances in phosphine-free catalyst design, several drawbacks still limit their utility. First, the transformation is highly challenging when hindered aryl chlorides and sterically demanding anilines or heterocyclic amines were selected as coupling partners in air conditions.[8, 12] The catalytic processes generally need strict oxygen- and moisture-free operation, whereas trace of oxygen would trap the LPd(0) to form the unreactive LPd(O_2).[13] To ensure the stabilization of the low-valent active species in aerobic conditions, the ligand with bulky substituted groups is required.[14] On the contrary, the placement of bulky steirc ligand would retard the oxidative addition and subsequent amine coordination. Second, the five-membered heterocyclic aryl chlorides (especially with sulfide unit), represented the most difficult coupling substrates and there have only been a few examples of catalyst systems that have successfully coupled this type of substrates to date.[15] Presumably, it can be ascribed to the feasible coordination of heteroatoms to the palladium center and also reluctantly undergo reductive elimination of the Pd(II) amido complexes.[16] In order to prevent catalyst poisoning process, the introduction of NHCs with strong σ-donation group is of great interest and importance.[11c, 11e] Very recently, we have reported a series of Pd-PEPPSI complexes

with ancenaphthyl as backbones.[14e, 17] These palladium complexes showed promise for coupling of sterically demanding coupling partners in the Suzuki-Miyaura cross-coupling and Buchwald-Hartwig amination in air. Considering the strong σ-donation and the conformational flexibility of the Pd-PEPPSI complexes, we envisioned that the "bulky-yet-flexible" palladium complexes would act as practical and modular precatalysts to extend the utility in amination reaction.[18, 19] Herein, we report a new strategy for the challenging C_{Ar}-N bond formation by this approach.

RESULTS AND DISCUSSION

Synthesis and Characterization of Pd-PEPPSI complex

The synthesis of the Pd-PEPPSI-IPent^{An} complex of **C1** was followed by the previously reported procedure.[18] An one-pot reaction of imidazolium chloride salt with $PdCl_2$ was heated in the presence of pyridine and K_2CO_3, affording the Pd-PEPPSI-IPent^{An} complex in a high yield of 85%. The palladium complex is moisture- and air-stable either in the solid or in solution state and thus can be stored on benchtop for several months at r.t. The chemical structure of **C1** was characterized by high resolution mass spectrometer (HRMS) and NMR spectroscopy, for which the peak at *m/z*=880.3351 being evidence to the cationic species of $[M+H]^+$. Moreover, the formation of Pd-$C_{carbene}$ bond was confirmed by the disappearance of the imidazolium proton signal in the ^{1}H NMR spectrum and the observed resonance of 159.5 ppm in the ^{13}C NMR spectrum.

X-ray diffraction analysis was conducted on single crystal of **C1** obtained by slow diffusion of hexane into their concentrated solution in CH_2Cl_2. As shown in Figure 2, it revealed a slightly distorted square planar geometry for the palladium complex, in which the carbene ligand was positioned trans to pyridine. The bond length of Pd-C(6) and Pd-N(1) bond lengths are 1.966 (5) and

2.107 (4) Å, respectively, which are comparable to that of the reported Pd-PEPPSI complex (Table 1).[11b, 13, 17b-d, 18] It is noteworthy that the *N*-aryl moieties derived from carbene ligand are oriented nearly perpendicularly to the coordination plane with dihedral angles of 79.41 and 84.15 °, respectively. These results suggest that the bulky alkyl chain would effectively protect the palladium center. In order to further examine the steric property of the synthesized complex, the percent buried volume ($\%V_{bur}$) was then calculated using the application of SambVca.[20, 21] As illustrated in Table 1, the Pd-PEPPSI-IPent^{An} complex of **C1** with pyridine as "throw away" ligand presents a moderate value of 36.1, which is notably higher than that of the Pd-PEPPSI-IPr (34.3) and Pd-PEPPSI-IPr^{An} (34.7). Out of our expectation, the $\%V_{bur}$ value of the Pd-PEPPSI-IPent^{An} complex **C2** with 3-chloropyridine ligand turned out to be 38.2, which is much larger than the value of **C1**. Considering bearing the same carbene ligand, the remarkable difference between the percent buried volume computed for **C1** and **C2** highlights the flexibility of the IPent^{An} ligand, which would play profound effect on the catalytic performance.

Table 1. Comparison of structural parameters in classical Pd–PEPPSI complexes.[a]

Pd–PEPPSI complexes	Pd-C (Å)	Pd-N (Å)	TEP (cm^{-1})	$\%V_{bur}$[b]
IPent^{An} (Py) **C1**	1.966 (5)	2.107 (4)	2041.6	36.1
IPent^{An} (3-ClPy) **C2**	1.965(2)	3.0926(17)	2041.6	38.2
IPent **C3**	1.974 (3)	2.097 (3)	2049.6	37.9
IPr* **C4**	1.974 (6)	2.132 (6)	2052.7	43.1
IPr **C5**	1.969 (3)	2.109 (2)	2050.2	34.3
IPr^{An} **C6**	1.960 (6)	2.113 (6)	2041.8	34.7
(IPr$^{(OMe)}$*IPr)^{An} **C7**	1.963(2)	2.162(2)	NR	35.7
(IPr**)^{An} **C8**	1.953(6)	2.076(6)	2047.4	41.1

[a]All bond distances and $\%V_{Bur}$ have been calculated using cif files obtained from the CCDC. [b]The $\%V_{Bur}$ calculated for Pd-C=2.00 Å. Mesh spacing 0.05 Å. Sphere radius 3.5Å. Bondi radii scaled by 1.17.

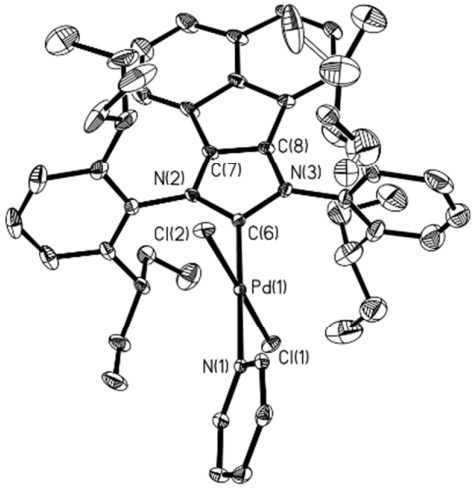


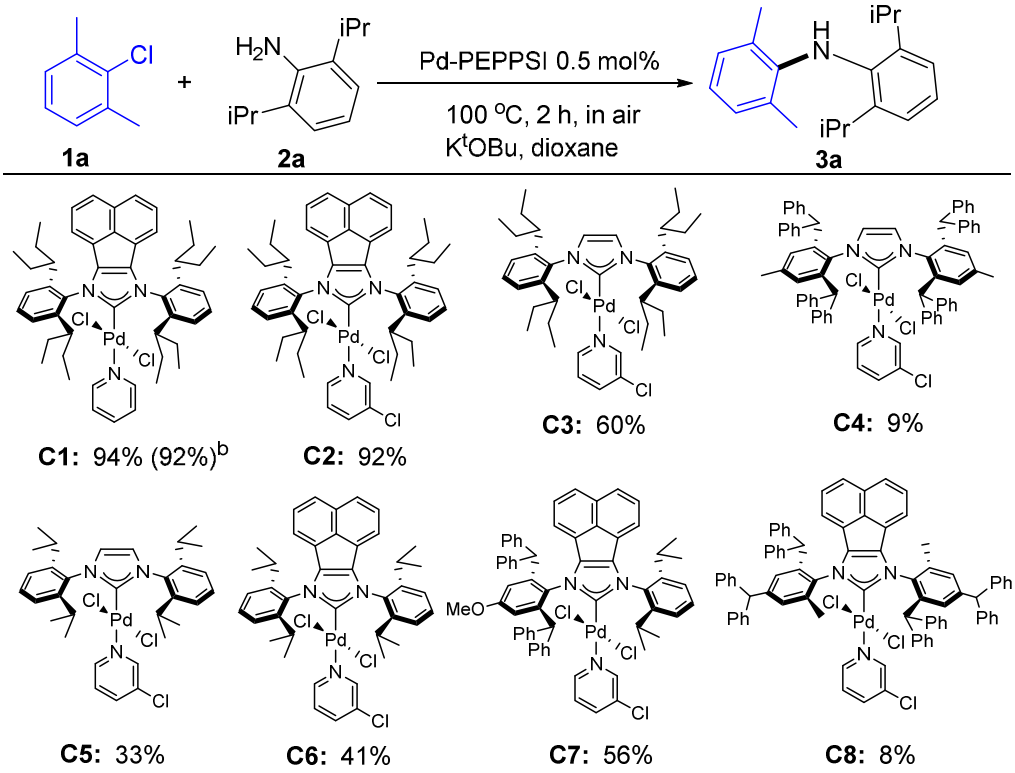
Figure 2. Molecular structure of **C1** depicted in 30% thermal ellipsoids with the hydrogen atoms omitted for clarity. Selected bond distances (Å) and angles (°): Pd(1)-C(6) 1.966(5), Pd(1)-N(1) 2.107(4), Pd(1)-Cl(1) 2.3049(14), Pd(1)-Cl(2) 2.2782(14), N(1)-Pd(1)-C(6) 177.97(19), N(1)-Pd(1)-Cl(1) 91.30(12), C(6)-Pd(1)-Cl(1) 90.70(15), N(1)-Pd(1)-Cl(2) 88.66(12), C(6)-Pd(1)-Cl(2) 89.34(15), Cl(1)-Pd(1)-Cl(2) 178.84(6).

Application in the Pd-catalyzed amination of aryl chlorides

In an effort to demonstrate the catalytic properties of the "bulky-yet-flexible" palladium complexes, the cross-coupling were carried out in air and the solvents were used as received without any further purification. Our investigation began by treating 2-chloro-1,3-dimethylbenzene (**1a**) with 2,6-diisopropylaniline (**2a**). After the reaction condition evaluation (see SI, Table S2 for details), we were delighted to find that the optimized conditions was 0.5 mol% palladium loading, KO^{t}Bu as base and 1,4-dioxane as solvent at 100 °C for 2 h. Under these conditions, the expected *N*-(2,6-diisopropylphenyl)-2,6-dimethylaniline (**3a**) was obtained in a satisfied isolated yield of 92% by Pd-PEPPSI-IPent^{An} (**C1**). Nevertheless, it is deserved to note that the current reaction conditions without anhydrous solvents and the protection of inert gas, requires high temperature and moderate

high palladium loading. Moreover, the effect of the "throw away" ligands was also investigated. In the current study, **C2** bearing 3-chloropyridine was slightly less effective than that of **C1** with pyridine. Presumably, the pyridine might remain attached to the NHC-Pd(0), which could stabilized the Pd(0) active species.

Table 2. Catalyst Screening for the Pd-catalyzed Amination Reaction[a]



[a]Reaction conditions: 2-chloro-1,3-dimethylbenzene (1.0 mmol), 2,6-diisopropylaniline (1.2 mmol), KO^{t}Bu (1.5 mmol), 1,4-dioxane (4.0 mL), in air. GC yields. [b]Isolated yields.

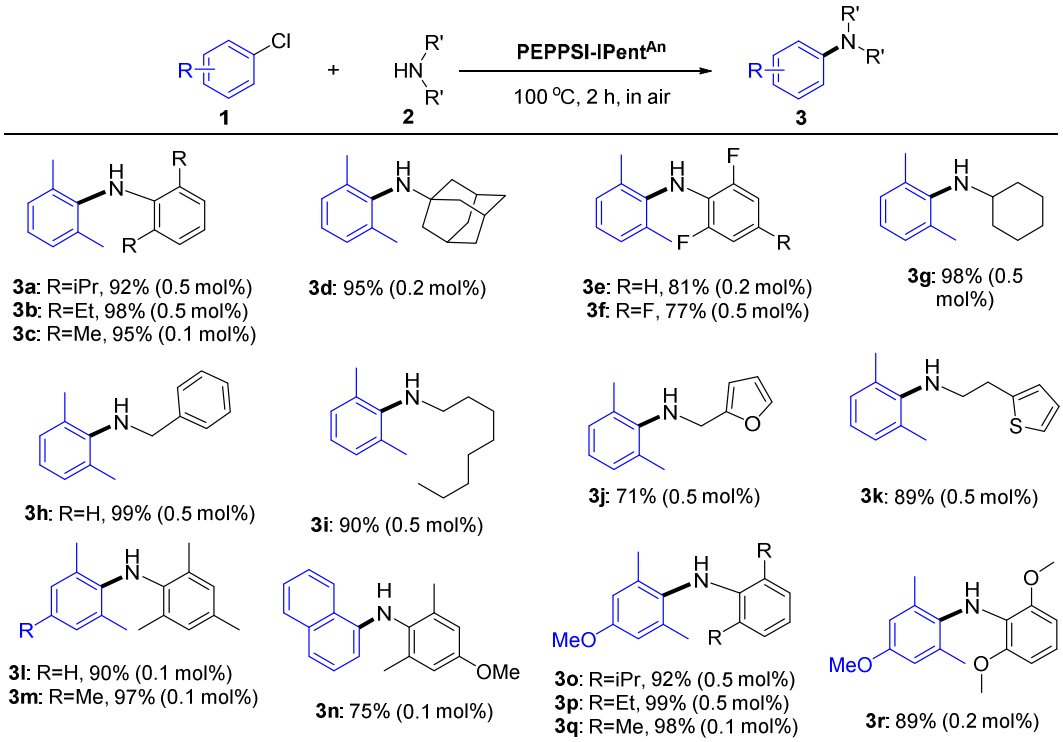
To get further information on the relationship between the catalyst structure and activities, a series of palladium complexes, such as the Pd-PEPPSI-IPent (**C3**),[18b] Pd-PEPPSI-IPr*(**C4**),[13a] Pd-PEPPSI-IPr (**C5**),[18a] Pd-PEPPSI-IPr^{An}(**C6**),[11b] Pd-PEPPSI-(IPr^{OMe}*IPr)^{An} (**C7**),[14e] and Pd-PEPPSI-(IPr**)^{An} (**C8**),[17d] were screened for comparison. As illustrated in Table 2, the precatalysts of Pd-PEPPSI-IPent (**C3**) and Pd-PEPPSI-IPr (**C5**), which were highly efficient under

inert atmosphere (Table S3), however, afforded the desired amination product **3a** in 60% and 33% yield, respectively. Even more, the Pd-PEPPSI-IPr* (**C4**) was much less efficient to give the cross coupling product in 9% yield under the current reaction conditions. Obviously, the steric and the electronic effect of NHCs ligand would play a crucial role. The **C4** bearing 2,6-dibenzhydryl group on *N*-aryl moieties exhibited largest %V_{bur} value of 43.3, implying less flexibility of the ligands around to the palladium center would retard the oxidative addition and subsequent amine coordination. In contrast, the introduction of bulky steric of IPent^{An} in **C1** and **C2** would stabilize the axial site of LPd(0) species to avoid the capture of oxygen. Meanwhile, the maintained configuration flexibility of the alkyl group on *N*-aryl moieties would allow the room adjustment toward the incoming substrates.[17b] Moreover, in our previous report, we found that the Tolman electronic parameter (TEP) for IPent^{An} is 2041.6 cm^{-1}, which indicates higher electron-donating ability than that of other classical Pd-NHCs, such as Pd-PEPPSI-IPent (**C3**) and Pd-PEPPSI-IPr (**C5**).[10b] Therefore, the rate of oxidative addition would be much faster than oxidative addition of O_2 by Pd-PEPPSI-IPent^{An} in this study. Then the palladium complexes of **C6**-**C8** with the same acenaphthyl backbones were evaluated. The palladium complexes **C6** and **C7** showed moderate activity of 41 and 56% yield**,** whereras their V_{bur}% value turned out to be 34.7 and 35.7, respectively. Again, the bulky sterically **C8** (V_{bur}% = 41.1) gave the product of **3a** in a low yield of 8%. These results suggest that the catalytic activity toward deactivated substrates under aerobic conditions is mainly controlled by the supporting backbones as well as *N*-moieties on the NHCs ligand, which demonstrated that the "bulky-yet-flexible" Pd-PEPPSI-IPent^{An} would significantly promote the transformation process.

Having established the promising results of the Pd-PEPPSI-IPent^{An} (**C1**), we then examined the reaction of 2-chloro-1,3-dimethylbenzene (**1a**) with other primary amines. As shown in **Table 3**, a

range of sterically hindered aliphatic and aromatic amines, such as 2,6-diisopropylaniline, 2,6-diethylaniline, 2,6-dimethylaniline and 1-adamantylamine, were exclusively affording the corresponding products (**3a-d**) in high yields by using only 0.1-0.5 mol% palladium. It is significant that the electron-deficient 2,6-difluoroaniline and 2,4,6-trifluoroaniline, which are considered to be the most challenging coupling partners,[10c] can be installed in moderate yields. Other primary alkyl amines containing hexyl, benzylic, octyl, 2-furylmethyl and iophenethyl were all converted to desired products (**3g-3k**) in high to quantitative yields. Moreover, other electron-rich electrophilic reagents, such as 2-chloro-1,3,5-trimethylbenzene and 2-chloro-5-methoxy-1,3-dimethylbenzene, which are sluggish toward oxidative addition, were smoothly coupled with sterically demanding anilines. To our delight, the undesired byproduct of diarylated amines weren't observed in our catalytic systems.[22]

Table 3. C-N Cross-Coupling Reaction of Stercially Hindered Aryl Chlorides with amines.[a]

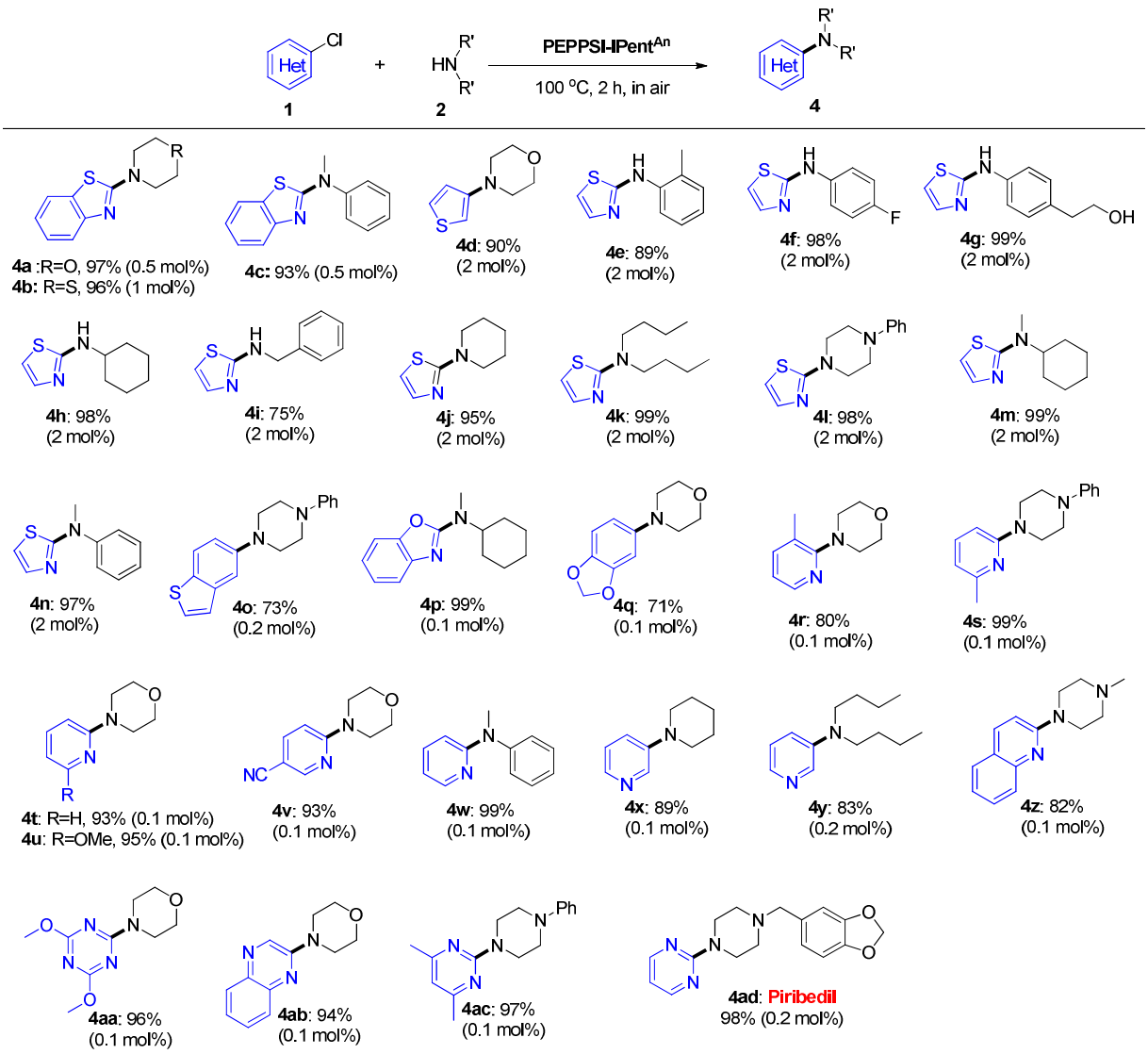


[a]Reaction conditions: aryl chloride (1.0 mmol), amine (1.2 mmol), KO^{t}Bu (1.5 mmol), 1,4-dioxane (4.0 mL), in air. Isolated yields.

Five-membered heteroaryl chlorides, especially with multiple heteroatoms have been recognized as the most challenging substrates in the C-N cross-coupling for a long time.[7a] Inspired by the aforementioned encouraging results, we extended our protocol to the synthesis of sulfide-based arylated amines because of the increased prevalence of such motifs in biologically active molecules and functional materials. As can be seen in **Table 4**, in the presence of relative high palladium loading of 0.2-2 mol%, the sulfide containing aryl chlorides, such as 2-chlorobenzo[d]thiazole and 3-chlorothiophene could be incorporated into the amine substrates to give the corresponding products (such as **4a**-**4d**) in high yields. Importantly, the most deactivated 2-chlorothiazole exhibited excellent reactivity toward a wide range of substituted amines. For example, the aryl anilines with 2-methyl and 4-flroro-substitutents were successfully converted (**4e** and **4f**). It is noteworthy that 2-(4-aminophenyl)ethan-1-ol with protic functional group, was successfully coupled and nearly quantitative yield was afforded in product of **4g**, which would enable the opportunity to be used in further transformations. Moreover, other primary and secondary amines bearing functional groups, such as hexyl, benzylic, piperidinyl, dibutyl, 4-phenylpiperazinyl, *N*-methylcyclohexyl, and *N*-methylphenyl were suitable cross-coupling partners, giving the desired products (**4h**-**4n**) in high yields. Then, we investigated the reactivity of the heteroarylamine (such as 2-aminopyridine) with 2-chlorothiazole, unfortunately, no reaction was performed even in the presence of 5 mol% palladium loading after 24 hours. Probably, 2-aminopyridine would act as a competing ligand and inhibits the catalyst activity.[16b]

To further highlight the robust palladium complex of **C1**, other heteroaryl chlorides, such as 5-chlorobenzo[b]thiophene, 2-chlorobenzo[d]oxazole, 5-chlorobenzo[d][1,3]dioxole, 2-chloropyridine, 3-chloropyridine, 2-chloroquinoline, 2-chloro-1,3,5-triazine, 2-chloroquinoxaline, 2-chloropyrimidine were evaluated (Table 4). To our delight, at a low palladium loading of 0.1-0.2 mol %, the desired products of **4p**-**4ac** were obtained in high to excellent yields. Remarkably, the application of this protocol was further featured by the rapid access to network prescription drug of Piribedil (**4ad**), which is received as an important antiparkinsonian agent and α_2-adrenergic antagonist.

Table 4. C-N Cross-Coupling Reaction of Heteroryl Chlorides with amines.[a]



Reaction conditions: Heterocyclic Chloride (1.0 mmol), amine (1.2 mmol), KO^{t}Bu (1.5 mmol), 1,4-dioxane (4.0 mL). Isolated yields, in air.

CONCLUSION

In summary, we have developed an efficient protocol for versatile C-N cross coupling by bulky-yet-flexible Pd-PEPPSI-IPent^{An} complex. This methodology can circumvent the classic problem emerged limited substrate scopes as well as the requirement of strict oxygen- and moisture-free reaction operation. Under the developed reaction conditions, a wide range of sterically hindered (hetero)aryl chlorides could be coupled with various aliphatic and aromatic amines with

different electronic and steric groups, which enable the reaction to proceed in high yields. Considering the potential toxicology and environmental problem arised from 1,4-dioxane, further studies exploring the environmental, health and safety solvents for C-N cross-couplings are undergoing.

EXPERIMENTAL SECTION

1. Physical Measurements and Materials

The NMR spectra were recorded on a Bruker DMX 400 MHz instrument at room temperature with the decoupled nucleus, employing TMS as an internal standard and $CDCl_3$ as solvent. Elemental analysis was carried out using a Flash EA1112 microanalyzer. High resolution mass spectrometric (HRMS) data were obtained using a LTQ Orbitrap Elite instrument, using a sample concentration of approximately 1 ppm. The X-ray diffraction data of single crystals were obtained with the ω-2θ scan mode on a Bruker SMART 1000 CCD diffractionmeter with graphite-monochromated Mo Kα radiation (λ=0.71073Å) at 100 K for **C1**. Cell parameters were obtained by global refinement of the positions of all collected reflections. Intensities were corrected for Lorentz and polarization effects and empirical absorption. The structures were solved by direct methods and refined by full-matrix least squares on F^2. All hydrogen atoms were placed in calculated positions. Structure solution and refinement were performed by using the SHELXL-97 package. All non-hydrogen atoms were refined anisotropically. Hydrogen atoms were introduced in calculated positions with the displacement factors of the host carbon atoms. Wattecs Parallel Reactor (WP-TEC-1020H) was equipped with 10 tubes × 10 (mL); Power: 650 w; Temperature range: rt-220 ^{o}C; Polytetrafluoroethylene (PTFE) as

sealed material.

2. The Procedures for the Synthesis of Pd-PEPPSI complex of C1.

Imidazolium chloride salt of **L1** and Pd-PEPPSI compound **C2** were reported by our group.[17b, 23] A mixture of imidazolium salt **L1** (1 mmol), palladium dichloride (0.177 g, 1.1 mmol), and K_2CO_3 (1.38 g, 10 mmol) in pyridine (4 mL) was added to a vial under a nitrogen atmosphere. The reaction was refluxed at 90°C for 24 h. When the solution was cooled to room temperature, 20 mL of dichloromethane was added, and then the reaction mixture was passed through a short silica gel column using substantial dichloromethane as elute. Evaporation of the filtrate furnished a yellow-brown solid. The yellow-brown solid was dissolved completely with suitable dichloromethane, and dropped into a large amount of stirring hexane, causing the formation of a yellow precipitate. The suspension was filtered through a sintered funnel. Drying the solid in vacuo produced the desired palladium complex of **C1** as yellow powders in 86% yield (758.8 mg). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.60 – 8.53 (m, 2H), 7.62 (d, *J* = 8.2 Hz, 2 H), 7.50 (dd, *J* = 13.5, 5.8 Hz, 3 H), 7.32 (d, *J* = 7.8 Hz, 4 H), 7.23 (dd, *J* = 11.1, 4.0 Hz, 2 H), 7.06 (dd, *J* = 7.6, 6.5 Hz, 2 H), 6.62 (d, *J* = 7.0 Hz, 2 H), 3.23 (td, *J* = 9.0, 5.5 Hz, 4 H), 2.00 – 1.76 (m, 8 H), 1.33 (ddd, *J* = 14.1, 7.5, 3.6 Hz, 4 H), 1.22 – 1.10 (m, 4 H), 1.06 (d, *J* = 7.2 Hz, 12 H), 0.45 (t, *J* = 7.4 Hz, 12 H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.5, 151.5, 144.6, 140.6, 137.2, 135.5, 129.4, 128.9, 128.8, 127.9, 126.9, 126.8, 126.5, 124.0, 121.6, 40.7, 26.4, 26.2, 12.4, 9.8. Anal.calcd for $C_{50}H_{61}N_3Cl_2Pd$: C, 68.14; H, 6.98; N, 4.77. Found: C, 67.95; H, 7.04; N, 4.72. HRMS calcd for $C_{50}H_{62}N_3Cl_2Pd$ $[M + H]^+$ 880.3350, found 880.3351.

3. General Procedure for Buchwald−Hartwig Amination

Unless otherwise noted, the amination reactions were carried out in air. All solvents were used as received without further purification. A parallel reactor containing a stirred bar was charged with Pd-PEPPSI complexes (0.001−0.02 mmol), amine (1.2 mmol), aryl chloride (1.0 mmol), base (1.5 mmol), and 4 mL of solvent. The reaction mixture was conducted at 100 °C for 2 h. After completion of the reaction, the reaction mixture was cooled to room temperature, and 20 mL of water was added. The mixture was diluted with dichloromethane (5 mL) and extracted three times (3 × 5 mL) with dichloromethane. The organic layer was dried with anhydrous magnesium sulfate, filtered, and evaporated under reduce pressure. The crude cross-coupling products were purified by silica-gel column chromatography using petroleum ether-dichloromethane (20/1) as the eluent

4. NMR data of the cross-coupling products.

N-(2,6-diisopropylphenyl)-2,6-dimethylaniline (3a).[24a] The cross-coupling product was isolated in 92% yield (258.9 mg). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.19 – 7.11 (m, Ar-H, 3 H), 6.96 (d, J = 7.5 Hz, Ar-H, 2 H), 6.75 (t, J = 7.4 Hz, Ar-H, 1 H), 4.82 (s, NH, 1 H), 3.18 (dt, J = 13.7, 6.9 Hz, CH, 2 H), 2.00 (s, CH_3, 6 H), 1.14 (d, J = 6.9 Hz, CH_3, 12 H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 144.1, 143.1, 138.8, 129.5, 125.6, 124.8, 123.2, 119.6, 28.0, 23.4, 19.3.

N-(2,6-diethylphenyl)-2,6-dimethylaniline (3b).[24b] The cross-coupling product was isolated in 98% yield (248.3 mg). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.12 – 6.99 (m, Ar-H, 5H), 6.83 (t, J = 7.4 Hz, Ar-H, 1 H), 4.93 (s, NH, 1 H), 2.48 (q, J = 7.5 Hz, CH_2, 4 H), 2.03 (s, CH_3, 6 H), 1.17 (t, J = 7.5 Hz, CH_3, 6 H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 142.1, 140.4, 136.9, 129.0, 127.6, 126.1, 123.0, 120.6, 24.8, 19.2, 13.8.

Bis(2,6-dimethylphenyl)amine (3c).[17c] The cross-coupling product was isolated in 95% yield (214.1 mg). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.04 – 7.00 (m, Ar-H, 4 H), 6.91 – 6.86 (m, Ar-H, 2 H), 4.84 (s, NH, 1 H), 2.05 (s, CH_3, 12 H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 141.7, 129.5, 128.7, 121.7, 19.1.

(3s,5s,7s)-N-(2,6-dimethylphenyl)adamantan-1-amine (3d).[24c] The cross-coupling product was isolated in 95% yield (242.6 mg). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.02 (d, *J* = 7.4 Hz, Ar-H, 2 H), 6.93 – 6.85 (m, Ar-H, 1 H), 2.37 (s, CH_3, 6 H), 2.05 (s, CH, 3 H), 1.78 (d, *J* = 2.7 Hz, CH_2, 6 H), 1.67 – 1.56 (m, CH_2, 6 H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 143.0, 134.7, 128.3, 122.9, 55.5, 44.3, 36.4, 30.1, 20.6.

N-(2,6-difluorophenyl)-2,6-dimethylaniline (3e). The cross-coupling product was isolated in 81% yield (188.9 mg). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.08 (s, Ar-H, 3 H), 6.87 – 6.79 (m, Ar-H, 2 H), 6.71 – 6.64 (m, Ar-H, 1 H), 5.08 (s, NH, 1 H), 2.26 (s, CH_3, 6 H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 152.8 (dd, *J* = 242.6, 7.0 Hz), 139.0, 135.2, 128.0, 125.55, 124.2 (t, *J* = 12.5 Hz), 117.1 (t, *J* = 9.2 Hz), 112.0 – 110.8(m), 18.5. HRMS calcd for C14 H14 N F2 $[M + H]^+$ 234.1089, found 234.1084 .

N-(2,6-dimethylphenyl)-2,4,6-trifluoroaniline (3f). The cross-coupling product was isolated in 77% yield (193.5 mg). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.10 – 7.00 (m, Ar-H, 3H), 6.71 – 6.57 (m, Ar-H, 2 H), 4.86 (s, NH, 1 H), 2.23 (s, CH_3, 6 H).^{13}C NMR (101 MHz, $CDCl_3$) δ 154.3 (dt, *J* = 240.9, 14.7 Hz), 152.8 (ddd, *J* = 244.8, 14.2, 9.1 Hz), 139.1, 134.5, 128.2, 125.3, 120.8 (td, *J* = 12.9, 4.5 Hz), 100.2 (ddd, *J* = 26.2, 18.7, 9.7 Hz), 18.4. HRMS calcd for C14 H13 N F3 $[M + H]^+$ 252.0995, found 252.0989 .

N-cyclohexyl-2,6-dimethylaniline (3g).[25a] The cross-coupling product was isolated in 98% yield (199.3 mg). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.00 (d, *J* = 7.4 Hz, Ar-H, 2 H), 6.81 (t, *J* = 7.4 Hz, Ar-H, 1 H), 2.98 (t, *J* = 3.7 Hz, CH, 1 H), 2.29 (s, CH_3, 6 H), 1.99 (dd, *J* = 12.3, 2.0 Hz, CH_2, 2 H), 1.76

(dd, J = 9.6, 3.3 Hz, CH_2, 2 H), 1.65 (d, J = 11.0 Hz, CH_2, 1 H), 1.34 – 1.20 (m, CH_2, 3 H), 1.14 (dd, J = 15.5, 6.5 Hz, CH_2, 2 H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 145.1, 128.9, 128.7, 121.1, 56.1, 34.9, 25.9, 25.5, 19.0

N-benzyl-2,6-dimethylaniline (3h).[25b] The cross-coupling product was isolated in 99% yield (209.2 mg). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44 – 7.38 (m, Ar-H, 4 H), 7.37 – 7.32 (m, Ar-H, 1 H), 7.08 (d, J = 7.2 Hz, Ar-H, 2 H), 6.95 – 6.88 (m, Ar-H, 1 H), 4.17 (d, J = 1.8 Hz, CH_2, 2 H), 2.34 (d, J = 1.9 Hz, CH_3, 6 H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 145.8, 140.4, 129.8, 128.8, 128.5, 127.9, 127.2, 122.1, 52.8, 18.4.

2,6-Dimethyl-N-octylaniline (3i).[25c] The cross-coupling product was isolated in 90% yield (210.1 mg). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.01 (d, J = 7.5 Hz, Ar-H, 2 H), 6.83 (t, J = 7.5 Hz, Ar-H, 1 H), 3.01 – 2.97 (m, CH_2, 2 H), 2.31 (s, CH_3, 6 H), 1.59 (dd, J = 14.7, 7.7 Hz, CH_2, 2 H), 1.35 (dd, J = 17.1, 9.5 Hz, CH_2, 10 H), 0.91 (t, J = 6.9 Hz, CH_3, 3 H).^{13}C NMR (101 MHz, $CDCl_3$) δ 146.4, 129.0, 128.7, 121.5, 48.7, 31.8, 31.2, 29.5, 29.3, 27.2, 22.6, 18.5, 14.1.

N-(furan-2-ylmethyl)-2,6-dimethylaniline (3j).[26a] The cross-coupling product was isolated in 71% yield (142.9 mg). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 – 7.37 (m, Ar-H, 1 H), 7.02 (d, J = 7.4 Hz, Ar-H, 2 H), 6.87 (t, J = 7.5 Hz, Ar-H, 1 H), 6.32 (dd, J = 3.1, 1.9 Hz, Ar-H, 1 H), 6.12 (d, J = 3.1 Hz, Ar-H, 1 H), 4.15 (s, CH_2, 2 H), 2.29 (s, CH_3, 6 H).^{13}C NMR (101 MHz, $CDCl_3$) δ 153.7, 145.1, 141.8, 130.0, 128.7, 122.4, 110.3, 106.8, 45.1, 18.2.

2,6-Dimethyl-N-(2-(thiophen-2-yl)ethyl)aniline (3k).[26b] The cross-coupling product was isolated in 89% yield (205.9 mg). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.23 (dd, J = 5.1, 1.2 Hz, Ar-H, 1 H), 7.03 (ddd, J = 7.7, 6.0, 1.8 Hz, Ar-H, 3 H), 6.94 (dd, J = 3.4, 1.0 Hz, Ar-H, 1 H), 6.90 – 6.85 (m, Ar-H, 1

H), 3.35 (t, J = 6.7 Hz, CH_2, 2 H), 3.15 (t, J = 6.7 Hz, CH_2, 2 H), 2.24 (s, CH_3, 6 H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 145.5, 142.0, 129.2, 128.8, 126.9, 125.4, 123.8, 121.8, 49.4, 31.1, 18.3.

N-(2,6-dimethylphenyl)-2,4,6-trimethylaniline (3l).[24a] The cross-coupling product was isolated in 90% yield (215.4 mg). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.01 (d, J = 7.4 Hz, Ar-H, 2 H), 6.87 – 6.82 (m, Ar-H, 3 H), 4.76 (s, NH, 1 H), 2.30 (s, CH_3, 3 H), 2.04 (d, J = 1.7 Hz, CH_3, 12 H).^{13}C NMR (101 MHz, $CDCl_3$) δ 142.2, 139.0, 131.5, 130.5, 129.2, 128.8, 128.4, 120.9, 20.6, 19.1, 19.0.

Dimesitylamine (3m).[26c] The cross-coupling product was isolated in 97% yield (245.8 mg). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.88 – 6.79 (m, Ar-H, 4 H), 4.66 (s, NH, 1 H), 2.29 (s, CH_3, 6 H), 2.02 (s, CH_3, 12 H).^{13}C NMR (101 MHz, $CDCl_3$) δ 139.4, 130.7, 129.4, 129.3, 20.5, 19.0.

N-(4-methoxy-2,6-dimethylphenyl)naphthalen-1-amine (3n). The cross-coupling product was isolated in75% yield (208.0 mg). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07 – 8.04 (m, Ar-H, 1 H), 7.87 – 7.83 (m, Ar-H, 1 H), 7.54 – 7.50 (m, Ar-H, 2 H), 7.28 (d, J = 8.1 Hz, Ar-H, 1 H), 7.23 – 7.19 (m, Ar-H, 1 H), 6.74 (s, Ar-H, 2 H), 6.18 (dd, J = 7.5, 1.1 Hz, Ar-H, 1 H), 5.64 (s, NH, 1 H), 3.84 (s, CH_3, 3 H), 2.20 (s, CH_3, CH_3, 6 H).^{13}C NMR (101 MHz, $CDCl_3$) δ 157.3, 142.0, 137.4, 134.5, 131.3, 128.7, 126.6, 125.7, 124.8, 123.4, 120.1, 118.0, 113.7, 106.1, 55.3, 18.4. HRMS calcd for $C_{19}H_{20}ON$ $[M + H]^+$ 278.1539, found 278.1538.

N-(2,6-diisopropylphenyl)-4-methoxy-2,6-dimethylaniline (3o).[27a] The cross-coupling product was isolated in 92% yield (286.5 mg). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.12-7.09 (m, Ar-H, 2 H), 7.05 (dd, J = 8.9, 5.9 Hz, Ar-H, 1 H), 6.56 (s, Ar-H, 2 H), 5.30 (s, NH, 1 H), 3.77 (s, OCH_3, 3 H), 3.08 (dt, J = 13.7, 6.8 Hz, CH, 2 H), 2.01 (s, CH_3, 6 H), 1.12 (d, J = 6.9 Hz, 12 H). ^{13}C NMR (101 MHz, CDCl3) δ 153.9, 141.5, 139.7, 136.5, 129.9, 123.4, 123.0, 114.4, 55.4, 27.8, 23.5 19.5.

N-(2,6-diethylphenyl)-4-methoxy-2,6-dimethylaniline (3p). The cross-coupling product was isolated in 99% yield (280.6 mg). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.07 (d, *J* = 7.5 Hz, Ar-H, 2 H), 6.98 – 6.93 (m, Ar-H, 1 H), 6.61 (s, Ar-H, 2 H), 4.80 (s, NH, 1 H), 3.81 (s, OCH_3, 3 H), 2.44 (q, *J* = 7.5 Hz, CH_2, 4 H), 2.07 (s, CH_3, 6 H), 1.17 (t, *J* = 7.5 Hz, CH_3, 6 H).^{13}C NMR (101 MHz, $CDCl_3$) δ 154.6, 141.4, 135.2, 133.9, 132.0, 126.3, 121.1, 113.8, 55.3, 24.7, 19.4, 13.7. HRMS calcd for $C_{19}H_{26}ON$ $[M + H]^+$ 284.2009, found 284.2008.

N-(2,6-dimethylphenyl)-4-methoxy-2,6-dimethylaniline (3q). The cross-coupling product was isolated in 98% yield (250.2 mg). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.01 (d, *J* = 7.4 Hz, Ar-H, 2 H), 6.80 (t, *J* = 7.4 Hz, Ar-H, 1 H), 6.64 (s, Ar-H, 2 H), 4.73 (s, NH, 1 H), 3.83 (s, OCH_3, 3 H), 2.11 (s, CH_3, 6 H), 2.04 (s, CH_3, 6 H).^{13}C NMR (101 MHz, $CDCl_3$) δ 155.3, 142.7, 134.7, 133.8, 129.0, 126.6, 119.9, 113.4, 55.2, 19.3, 19.1. HRMS calcd for $C_{17}H_{22}ON$ $[M + H]^+$ 256.1696, found 256.1694.

N-(2,6-dimethoxyphenyl)-4-methoxy-2,6-dimethylaniline (3r). The cross-coupling product was isolated in 89% yield (255.7 mg). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.72 (dd, *J* = 8.7, 7.7 Hz, Ar-H, 1 H), 6.62 – 6.55 (m, Ar-H, 4 H), 5.28 (s, NH, 1 H), 3.80 (s, OCH_3, 3 H), 3.65 (s, OCH_3, 6 H), 2.20 (s, CH_3, 6 H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 156.1, 148.8, 136.8, 134.8, 127.1, 117.3, 112.4, 106.0, 56.5, 55.2, 19.08. HRMS calcd for $C_{17}H_{22}O_3N$ $[M + H]^+$ 288.1594, found 288.1594.

4-(Benzo[d]thiazol-2-yl)morpholine (4a).[27b] The cross-coupling product was isolated in 97% yield (213.7 mg). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64 – 7.55 (m, Ar-H, 2 H), 7.31 (td, *J* = 7.8, 1.2 Hz, Ar-H, 1 H), 7.10 (td, *J* = 7.9, 1.1 Hz, Ar-H, 1 H), 3.86 – 3.82 (m, CH_2, 4 H), 3.65 – 3.60 (m, CH_2, 4 H).^{13}C NMR (101 MHz, $CDCl_3$) δ 169.0, 152.5, 130.5, 126.1, 121.7, 120.8, 119.3, 66.2, 48.5.

2-Thiomorpholinobenzo[d]thiazole (4b).[27c] The cross-coupling product was isolated in 96% yield (226.9 mg). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60 (dd, *J* = 7.9, 0.8 Hz, Ar-H, 1 H), 7.54 (dd, *J* = 8.1, 0.5 Hz, Ar-H, 1 H), 7.30 (td, *J* = 7.8, 1.3 Hz, Ar-H, 1 H), 7.08 (td, *J* = 7.8, 1.1 Hz, Ar-H, 1 H), 4.02 – 3.91 (m, CH_2, 4 H), 2.80 – 2.69 (m, CH_2, 4 H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.1, 152.6, 130.6, 126.0, 121.5, 120.7, 119.1, 51.2, 26.5.

N-methyl-N-phenylbenzo[d]thiazol-2-amine (4c).[27d] The cross-coupling product was isolated in 93% yield (223.5 mg). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64 (d, *J* = 8.1 Hz, Ar-H, 1 H), 7.53 – 7.41 (m, Ar-H, 5 H), 7.37 – 7.28 (m, Ar-H, 2 H), 7.08 (t, *J* = 7.6 Hz, Ar-H, 1 H), 3.65 (s, CH_3, 3 H).^{13}C NMR (101 MHz, $CDCl_3$) δ 168.2, 152.6, 145.7, 131.1, 129.9, 127.4, 125.9, 125.8, 121.7, 120.4, 119.1, 40.4.

4-(Thiophen-3-yl)morpholine (4d).[28a] The cross-coupling product was isolated in 90% yield (152.3 mg). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24 (dd, *J* = 5.2, 3.1 Hz, Ar-H, 1 H), 6.85 (dd, *J* = 5.3, 1.6 Hz, Ar-H, 1 H), 6.19 (dd, *J* = 3.1, 1.6 Hz, Ar-H, 1 H), 3.85 – 3.81 (m, CH_2, 4 H), 3.10 – 3.05 (m, CH_2, 4 H).^{13}C NMR (101 MHz, $CDCl_3$) δ 152.3, 125.5, 119.5, 100.3, 66.6, 50.6.

N-(o-tolyl)thiazol-2-amine (4e).[28b] The cross-coupling product was isolated in 89% yield (169.3 mg). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61 (d, *J* = 8.1 Hz, Ar-H, 1 H), 7.24 (dd, *J* = 7.8, 4.2 Hz, Ar-H, 3 H), 7.08 (t, *J* = 7.4 Hz, Ar-H, 1 H), 6.58 (d, *J* = 3.6 Hz, Ar-H, 1 H), 2.32 (s, CH_3, 3 H).^{13}C NMR (101 MHz, $CDCl_3$) δ 167.5, 139.0, 138.8, 131.1, 129.3, 127.1, 124.5, 120.5, 107.5, 17.8.

N-(4-fluorophenyl)thiazol-2-amine (4f).[28c] The cross-coupling product was isolated in 98% yield (190.3 mg). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.98 (s, Ar-H, 1 H), 7.37 – 7.31 (m, Ar-H, 2 H), 7.27 (d, *J* = 3.5 Hz, Ar-H, 1 H), 7.10 – 7.02 (m, Ar-H, 2 H), 6.60 (d, *J* = 3.7 Hz, Ar-H, 1 H).^{13}C NMR (101

MHz, $CDCl_3$) δ 167.0, 158.8 (d, *J* = 242.7 Hz), 138.5, 136.9 (d, *J* = 2.5 Hz), 120.6 (d, *J* = 7.9 Hz), 116.2 (d, *J* = 22.7 Hz), 107.1.

N-(4-fluorophenyl)thiazol-2-amine (4g). The cross-coupling product was isolated in 99% yield (218.1 mg). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.11 (d, *J* = 3.8 Hz, Ar-H, 1 H), 7.05 (d, *J* = 8.4 Hz, Ar-H, 2 H), 6.64 (dt, *J* = 8.9, 2.2 Hz, Ar-H, 3 H), 4.54 (t, *J* = 7.1 Hz, CH_2, 2 H), 3.00 (t, *J* = 7.1 Hz, CH_2, 2 H).^{13}C NMR (101 MHz, $CDCl_3$) δ 175.0, 144.9, 136.8, 129.8, 127.3, 115.2, 110.9, 72.4, 34.3. HRMS calcd for $C_{11}H_{12}ON_2NaS$ $[M + Na]^+$ 243.0562, found 243.0561.

N-cyclohexylthiazol-2-amine (4h).[28d] The cross-coupling product was isolated in 98% yield (178.6 mg). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.08 (d, *J* = 3.6 Hz, Ar-H, 1 H), 6.45 (d, *J* = 3.6 Hz, Ar-H, 1 H), 5.38 – 5.28 (m, NH, 1 H), 3.41 – 3.29 (m, CH, 1 H), 2.09 (dd, *J* = 12.5, 2.9 Hz, CH_2, 2 H), 1.78 – 1.59 (m, CH_2, 3 H), 1.37 (dd, *J* = 13.1, 11.6 Hz, CH_2, 2 H), 1.25 (dd, *J* = 7.4, 4.0 Hz, CH_2, 3 H).^{13}C NMR (101 MHz, $CDCl_3$) δ 169.5, 138.9, 105.9, 55.0, 33.1, 25.5, 24.7.

N-benzylthiazol-2-amine (4i).[29a] The cross-coupling product was isolated in 75% yield (142.7 mg). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 – 7.28 (m, Ar-H, 5 H), 7.06 (d, *J* = 3.6 Hz, Ar-H, 1 H), 6.48 (d, *J* = 3.6 Hz, Ar-H, 1 H), 5.95 (s, NH, 1 H), 4.47 (s, CH_2, 2 H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.2, 139.0, 137.5, 128.7, 127.7, 127.7, 106.7, 49.9.

2-(Piperidin-1-yl)thiazole (4j).[29b] The cross-coupling product was isolated in 95% yield (159.8 mg). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.15 (d, *J* = 3.6 Hz, Ar-H, 1 H), 6.50 (d, *J* = 3.7 Hz, Ar-H, 1 H), 3.46 – 3.42 (m, CH_2, 4 H), 1.69 – 1.61 (m, CH_2, 6 H).^{13}C NMR (101 MHz, $CDCl_3$) δ 172.5, 139.4, 106.5, 49.7, 25.0, 24.1.

N,N-dibutylthiazol-2-amine (4k).[29c] The cross-coupling product was isolated in 99% yield (210.2 mg). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.12 (d, *J* = 3.7 Hz, Ar-H, 1 H), 6.40 (d, *J* = 3.7 Hz, Ar-H, 1 H),

3.41 – 3.37 (m, CH_2, 4 H), 1.62 (ddd, J = 7.5, 6.0, 3.9 Hz, CH_2, 4 H), 1.34 (dd, J = 15.1, 7.5 Hz, CH_2, 4H), 0.93 (t, J = 7.4 Hz, CH_3, 6 H).^{13}C NMR (101 MHz, $CDCl_3$) δ 170.9, 139.5, 105.1, 51.3, 29.3, 20.1, 13.9.

2-(4-Phenylpiperazin-1-yl)thiazole (4l). The cross-coupling product was isolated in 98% yield (240.4mg). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 – 7.27 (m, Ar-H, 2 H), 7.23 (d, J = 3.6 Hz, Ar-H, 1 H), 7.01 – 6.96 (m, Ar-H, 2 H), 6.92 (t, J = 7.3 Hz, Ar-H, 1 H), 6.61 (d, J = 3.6 Hz, Ar-H, 1 H), 3.65 (dd, J = 6.1, 4.3 Hz, CH_2, 4 H), 3.31 (dd, J = 6.2, 4.2 Hz, CH_2, 4 H).^{13}C NMR (101 MHz, $CDCl_3$) δ 172.1, 151.0, 139.5, 129.2, 120.5, 116.7, 107.7, 48.9, 48.5. HRMS calcd for $C_{13}H_{16}N_3S$ $[M + H]^+$ 246.1059, found 246.1058.

N-cyclohexyl-N-methylthiazol-2-amine (4m). The cross-coupling product was isolated in 99% yield (194.3 mg). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.15 (d, J = 3.7 Hz, Ar-H, 1 H), 6.43 (d, J = 3.7 Hz, Ar-H, 1 H), 3.91 – 3.83 (m, CH, 1 H), 2.93 (s, CH_3, 3 H), 1.86 – 1.80 (m, CH_2, 4 H), 1.70 – 1.64 (m, CH_2, 1 H), 1.49 – 1.35 (m, CH_2, 4 H), 1.11 (dd, J = 12.7, 3.3 Hz, CH_2, 1 H).^{13}C NMR (101 MHz, $CDCl_3$) δ 171.7, 139.4, 105.2, 59.9, 32.3, 29.8, 25.7, 25.5. HRMS calcd for $C_{10}H_{17}N_2S$ $[M + H]^+$ 197.1107, found 197.1105

N-methyl-N-phenylthiazol-2-amine (4n).[29b] The cross-coupling product was isolated in 97% yield (184.6 mg). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 (dd, J = 6.2, 4.3 Hz, Ar-H, 4 H), 7.29 – 7.20 (m, Ar-H, 2 H), 6.47 (d, J = 3.7 Hz, Ar-H, 1 H), 3.53 (s, CH_3, 3 H).^{13}C NMR (101 MHz, $CDCl_3$) δ 170.7, 146.4, 139.3, 129.6, 126.2, 124.8, 107.4, 40.3.

1-(Benzo[b]thiophen-5-yl)-4-phenylpiperazine (4o). The cross-coupling product was isolated in 73% yield (214.9 mg). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69 (d, J = 8.8 Hz, Ar-H, 1 H), 7.34 (d, J = 5.4 Hz, Ar-H, 1 H), 7.28 (d, J = 2.3 Hz, Ar-H, 1 H), 7.26 – 7.21 (m, Ar-H, 2 H), 7.18 (d, J = 5.4 Hz, Ar-H, 1

H), 7.07 (dd, *J* = 8.8, 2.3 Hz, Ar-H, 1 H), 6.94 (dd, *J* = 8.7, 0.9 Hz, Ar-H, 2 H), 6.83 (dd, *J* = 10.5, 4.1 Hz, Ar-H, 1 H), 3.34 – 3.26 (m, CH_2, 8 H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 151.2, 149.1, 140.7, 132.2, 129.2, 127.1, 123.7, 122.8, 120.1, 116.9, 116.4, 110.0, 50.6, 49.5. HRMS calcd for $C_{18}H_{19}N_2S$ $[M + H]^+$ 295.1263, found 295.1262.

N-cyclohexyl-N-methylbenzo[d]oxazol-2-amine (4p).[30a] The cross-coupling product was isolated in 99% yield (228.0 mg). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 (d, *J* = 7.8 Hz, Ar-H, 1 H), 7.23 (d, *J* = 7.9 Hz, Ar-H, 1 H), 7.13 (t, *J* = 7.7 Hz, Ar-H, 1 H), 6.97 (t, *J* = 7.7 Hz, Ar-H, 1 H), 4.17 – 4.08 (m, CH, 1 H), 3.06 (s, CH_3, 3 H), 1.88 – 1.81 (m, CH_2, 4 H), 1.70 (d, *J* = 12.8 Hz, CH_2, 1 H), 1.56 – 1.42 (m, CH_2, 4 H), 1.19 – 1.08 (m, CH_2, 1 H).^{13}C NMR (101 MHz, $CDCl_3$) δ 162.7, 148.6, 143.5, 123.7, 119.9, 115.7, 108.4, 56.7, 29.9, 29.5, 25.6, 25.4.

4-(Benzo[d][1,3]dioxol-5-yl)morpholine (4q).[30b] The cross-coupling product was isolated in 71% yield (147.1 mg). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.72 (d, *J* = 8.4 Hz, Ar-H, 1 H), 6.54 (d, *J* = 2.4 Hz, Ar-H, 1 H), 6.34 (dd, *J* = 8.4, 2.4 Hz, Ar-H, 1 H), 5.89 (s, CH_2, 2 H), 3.85 – 3.81 (m, CH_2, 4 H), 3.04 – 3.00 (m, CH_2, 4 H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 148.2, 147.3, 141.6, 108.5, 108.1, 100.8, 99.5, 66.9, 50.9.

4-(3-Methylpyridin-2-yl)morpholine (4r).[31a] The cross-coupling product was isolated in 80% yield (142.6 mg). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.17 (dd, *J* = 4.8, 1.3 Hz, Ar-H, 1 H), 7.44 – 7.39 (m, Ar-H, 1 H), 6.88 (dd, *J* = 7.3, 4.9 Hz, Ar-H, 1 H), 3.88 – 3.84 (m, CH_2, 4 H), 3.17 – 3.13 (m, CH_2, 4 H), 2.29 (s, CH_3, 3 H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 161.4, 145.4, 139.4, 124.8, 118.1, 67.2, 50.0, 18.3.

1-(6-Methylpyridin-2-yl)-4-phenylpiperazine (4s). The cross-coupling product was isolated in 99% yield (250.8 mg). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46 – 7.40 (m, Ar-H, 1 H), 7.32 (t, *J* = 7.7 Hz,

Ar-H, 2 H), 7.01 (d, *J* = 8.5 Hz, Ar-H, 2 H), 6.92 (td, *J* = 7.3, 0.7 Hz, Ar-H, 1 H), 6.53 (dd, *J* = 14.2, 7.8 Hz, Ar-H, 2 H), 3.74 – 3.69 (m, CH_2, 4 H), 3.35 – 3.30 (m, CH_2, 4 H), 2.45 (s, CH_3, 3 H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.1, 156.8, 151.3, 137.7, 129.1, 119.9, 116.3, 112.9, 103.8, 49.2, 45.3, 24.5. HRMS calcd for $C_{16}H_{20}N_3$ $[M + H]^+$ 254.1652, found 254.1651.

4-(Pyridin-2-yl)morpholine (4t).[31b] The cross-coupling product was isolated in 93% yield (152.7 mg). ^1H NMR (400 MHz, $CDCl_3$) δ 8.19 (dd, *J* = 4.9, 1.2 Hz, Ar-H, 1 H), 7.49 (ddd, *J* = 8.9, 7.2, 2.0 Hz, Ar-H, 1 H), 6.69 – 6.60 (m, Ar-H, 2 H), 3.84 – 3.79 (m, CH_2, 4 H), 3.51 – 3.46 (m, CH_2, 4 H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.6, 147.9, 137.5, 113.8, 106.9, 66.7, 45.6.

4-(6-Methoxypyridin-2-yl)morpholine (4u).[31c] The cross-coupling product was isolated in 95% yield (184.5 mg). ^1H NMR (400 MHz, $CDCl_3$) δ 7.41 (t, *J* = 8.0 Hz, Ar-H, 1 H), 6.12 (dd, *J* = 9.4, 8.0 Hz, Ar-H, 2 H), 3.86 (s, OCH_3, 3 H), 3.83 – 3.79 (m, CH_2, 4 H), 3.49 – 3.45 (m, CH_2, 4 H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.0, 158.3, 140.1, 98.7, 97.9, 66.7, 52.9, 45.5.

6-Morpholinonicotinonitrile (4v).[32a] The cross-coupling product was isolated in 93% yield (176.0 mg). ^1H NMR (400 MHz, $CDCl_3$) δ 8.40 (d, *J* = 1.8 Hz, Ar-H, 1 H), 7.63 (dd, *J* = 9.0, 2.3 Hz, Ar-H, 1 H), 6.58 (d, *J* = 8.8 Hz, Ar-H, 1 H), 3.81 – 3.76 (m, CH_2, 4 H), 3.66 – 3.61 (m, CH_2, 4 H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.5, 152.6, 139.9, 118.4, 105.6, 96.9, 66.4, 44.6.

N-methyl-N-phenylpyridin-2-amine (4w).[32b] The cross-coupling product was isolated in 99% yield (182.4 mg). ^1H NMR (400 MHz, $CDCl_3$) δ 8.27 – 8.21 (m, Ar-H, 1 H), 7.41 (t, *J* = 7.6 Hz, Ar-H, 2 H), 7.33 – 7.20 (m, Ar-H, 4 H), 6.63 – 6.59 (m, Ar-H, 1 H), 6.54 (d, *J* = 8.6 Hz, Ar-H, 1 H), 3.48 (s, CH_3, 3 H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.8, 147.7, 146.8, 136.5, 129.6, 126.3, 125.4, 113.1, 109.1, 38.4.

3-(Piperidin-1-yl)pyridine (4x).[32c] The cross-coupling product was isolated in 89% yield (144.4 mg). ^{1}H NMR (400 MHz, $CDCl_3$) 1H NMR (400 MHz, CDCl3) δ 8.28 (d, J = 2.7 Hz, Ar-H, 1 H), 8.02 (d, J = 3.6 Hz, Ar-H, 1 H), 7.19 – 7.06 (m, Ar-H, 2 H), 3.21 – 3.10 (m, CH_2, 4 H), 1.68 (dt, J = 11.1, 5.6 Hz, CH_2, 4 H), 1.57 (dd, J = 11.0, 5.7 Hz, CH2, 2 H). 13C NMR (101 MHz, CDCl3) δ 147.6, 139.9, 138.8, 123.3, 122.5, 49.8, 25.4, 24.0.

N,N-dibutylpyridin-3-amine (4y).[32d] The cross-coupling product was isolated in 83% yield (171.3 mg). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06 (s, Ar-H, 1 H), 7.87 (d, *J* = 3.7 Hz, Ar-H, 1 H), 7.07 (dd, *J* = 8.5, 4.5 Hz, Ar-H, 1 H), 6.87 (ddd, *J* = 8.6, 3.1, 1.2 Hz, Ar-H, 1 H), 3.28 – 3.24 (m, CH_2, 4 H), 1.59 – 1.52 (m, CH_2, 4 H), 1.35 (dd, *J* = 15.0, 7.5 Hz, CH_2, 4 H), 0.95 (t, *J* = 7.3 Hz, CH_3, 6 H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 143.9, 136.4, 134.5, 123.5, 117.7, 50.4, 29.2, 20.2, 13.9.

2-(4-Methylpiperazin-1-yl)quinolone (4z).[33a] The cross-coupling product was isolated in 82% yield (186.4 mg). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89 (d, *J* = 9.1 Hz, Ar-H, 1 H), 7.70 (d, *J* = 8.4 Hz, Ar-H, 1 H), 7.59 (dd, *J* = 8.0, 1.2 Hz, Ar-H, 1 H), 7.56 – 7.50 (m, Ar-H, 1 H), 7.25 – 7.20 (m, Ar-H, 1 H), 6.99 (d, *J* = 9.1 Hz, Ar-H, 1 H), 3.82 – 3.73 (m, CH_2, 4 H), 2.60 – 2.52 (m, CH_2, 4 H), 2.36 (s, CH_3, 3 H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 157.5, 147.9, 137.5, 129.5, 127.2, 126.6, 123.1, 122.4, 109.6, 55.0, 46.2, 45.1.

4-(4,6-Dimethoxy-1,3,5-triazin-2-yl)morpholine (4aa).[33b] The cross-coupling product was isolated in 96% yield (217.2 mg). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.92 (s, OCH_3, 6 H), 3.84 – 3.79 (m, CH_2, 4 H), 3.71 – 3.67 (m, CH_2, 4 H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.3, 166.7, 66.5, 54.5, 43.9.

4-(Quinoxalin-2-yl)morpholine (4ab).[33c] The cross-coupling product was isolated in 94% yield (202.3 mg). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.56 (s, Ar-H, 1 H), 7.90 (dd, *J* = 8.2, 1.3 Hz, Ar-H, 1 H), 7.70 (dd, *J* = 8.4, 1.0 Hz, Ar-H, 1 H), 7.59 (ddd, *J* = 8.4, 7.0, 1.4 Hz, Ar-H, 1 H), 7.42 (ddd, *J* = 8.3,

6.9, 1.4 Hz, Ar-H, 1 H), 3.90 – 3.85 (m, CH_2, 4 H), 3.79 – 3.74 (m, CH_2, 4 H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 152.3, 141.48, 137.1, 135.4, 130.2, 128.7, 126.6, 125.1, 66.6, 45.0.

4,6-Dimethyl-2-(4-phenylpiperazin-1-yl)pyrimidine (4ac). The cross-coupling product was isolated in 97% yield (260.3 mg). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28 (dd, *J* = 8.7, 7.3 Hz, Ar-H, 2 H), 7.00 – 6.95 (m, Ar-H, 2 H), 6.88 (t, *J* = 7.3 Hz, Ar-H, 1 H), 6.29 (s, Ar-H, 1 H), 4.00 – 3.96 (m, CH_2, 4 H), 3.25 – 3.21 (m, CH_2, 4 H), 2.30 (s, CH_3, 6 H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.1, 161.8, 1515, 129.1, 120.0, 116.5, 109.3, 49.4, 43.7, 24.1. HRMS calcd for $C_{16}H_{21}N_4$ $[M + H]^+$ 269.1761, found 269.1760.

2-(4-(Benzo[d][1,3]dioxol-5-ylmethyl)piperazin-1-yl)pyrimidine (4ad).[33d] The cross-coupling product was isolated in 98% yield (292.4 mg). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.28 (d, *J* = 4.7 Hz, Ar-H, 2 H), 6.88 (s, Ar-H, 1 H), 6.75 (d, *J* = 0.7 Hz, Ar-H, 2 H), 6.45 (t, *J* = 4.7 Hz, Ar-H, 1 H), 5.93 (s, CH_2, 2 H), 3.84 – 3.77 (m, CH_2, 4 H), 3.44 (s, CH_2, 2 H), 2.50 – 2.43 (m, CH_2, 4H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 161.6, 157.6, 147.6, 146.6, 131.8, 122.2, 109.7, 109.4, 107.8, 100.8, 62.8, 52.8, 43.6.

ASSOCIATED CONTENT

Supporting Information

The supporting information including NMR spectra and X-ray crystallographic data is available free of charge on the ACS Publications website http://pubs.acs.org.

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Notes

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