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Buchwald–Hartwig reactions in water using surfactants

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ABSTRACT

Examination of the scope and limitation of the Buchwald–Hartwig cross-coupling reaction in micellar medium is reported. An array of aryl or heteroaryl halides were coupled to diverse nitrogen coupling partners using a combination of $[(allyl)PdCl]_2$ and cBRIDP to afford the corresponding products in moderate to excellent yields. 30 examples are reported, including polar solid and fairly water-soluble organic substrates/reagents.

1. Introduction

Pd-catalyzed Buchwald–Hartwig cross-coupling reaction is one of the most important methodologies in modern organic synthesis,[1] particularly in the synthesis of important intermediates and building blocks for fine chemistry[2] and pharmaceuticals.[3] In the past decade, research efforts led to the discovery of diverse catalysts that are able to couple a wide scope of amines with (hetero)aryl halides under mild reaction conditions. Conventionally, Buchwald–Hartwig cross-coupling reactions are carried out in organic solvents (e.g., THF, dioxane, NMP) and often at above ambient temperatures. Although many attempts have been made to perform these reactions under thermally mild conditions, the use of potentially toxic organic solvents is common, which by definition fails to meet the 12 Principles of Green Chemistry.

Typically, the use of water as the reaction medium often provides beneficial effect in rate enhancement, but, in some cases, organic compounds (reactants) could be insoluble in water and prevent the reactions due to heterogenous purposes (specially with solid compounds).[4] However, the commons apprehension of insolubility of organic substances in aqueous medium often becomes deterrent for the use of water, which however may be circumvented by the use of surfactants.[5] Recently, Lipshutz et al. developed safer surfactants, e.g., polyoxyethanyl α-tocopheryl sebacate (PTS) and polyoxyethanyl-α-tocopheryl succinate (TPGS-750-M), to serve as nanoreactors.[6–9,10a,11] In particular, the second-generation surfactant, TPGS-750-M, forms nanomicelles in water, that are lipophilic on the inside and hydrophilic on the outside, and allowed efficient Pd-catalyzed cross-coupling reactions at 40 °C, e.g., Suzuki–Miyaura,[7] Heck,[8] Buchwald–Hartwig,[9,10a] or Sonogashira reactions.[11] The second-generation surfactant (TPGS-750-M) is often a superior choice than the first-generation surfactant (PTS), with respect to yields, economics of preparation, and levels of purity. Unfortunately, for the interesting Buchwald–Hartwig cross-coupling reactions, only the N-arylation of aniline derivatives has been reported (Scheme 1).[6,9,10a] Moreover, in the reported examples, the reactants used are relatively lipophilic compounds with low molecular weights. Therefore, these reactants generally exist as more or less viscous oils, thereby allowing their incorporations into a micellar system. However, while this article was under review, Lipshutz et al. enlarged the scope of the arylation reaction to urea, carbamate, and sulfonamides derivatives and reported the efficacy of these classes of nitrogen derivatives under micellar conditions.[12]

Herein, we report the scope and limitations of the Buchwald–Hartwig reaction in a micellar medium, as described earlier by Lipshutz's catalyst system, $[(allyl)PdCl]_2$ (1.1%), ^{t}BuONa (1.5 equiv), TPGS-750-M-2% in water (1.0 mL), and cBRIDP (4.4%), 50 °C,[5] by reacting various (hetero)aryl halides with diverse nitrogen coupling partners. In particular, this study utilizes both water-soluble amines, such as dimethylamine, and specific examples of fairly water-soluble polar solid organic substrates/reagents with relatively high melting points.

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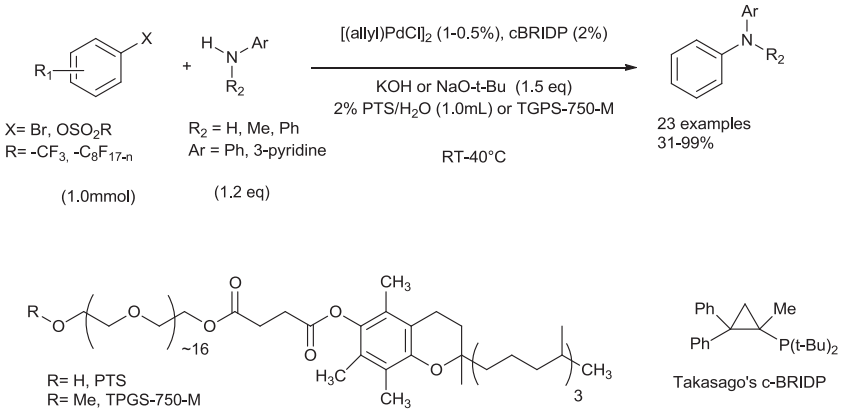
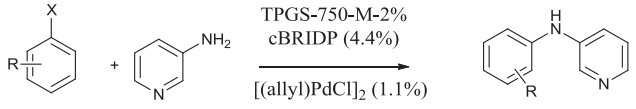


Scheme 1. Pd-catalyzed amination reaction in water in presence of surfactants.

2. Results and discussion

First, the effect of the leaving group on the reaction rate and yield was examined. In fact, Lipshutz et al. reported the reaction with only aryl bromides and TPGS-750-M as the surfactant. In this study, different leaving groups were chosen, e.g., I, Br, Cl, OTf, and OTs. 3-Aminopyridine **2** was chosen as the representative of heteroaryl amines, and the results are summarized in Table 1. Bromotoluene **1b** reacted efficiently in micellar medium, as observed previously by Lipshutz (Table 1, entry 2, 2 h, 88% yield). Aryl iodide **1c** afforded the product in 60% yield (Table 1, entry 3) after 2 h; however, the reaction was quasi-complete (90% yield) after 16 h (Table 1, entry 4). As expected, aryl chloride **1a** was less reactive (16 h, 40% yield, Table 1, entry 1), and 60% of the starting material was recovered. This result is in accordance with the chemoselectivity observed for **1f** (Table 1, entry 7). When a benzene ring bearing both chlorine and bromine atoms was used as the substrate, no reaction was observed on the chlorine position.

Table 1
Study of amination of aryl halides in water in presence of TPGS-750-M



1 **2** **3h, 3n**

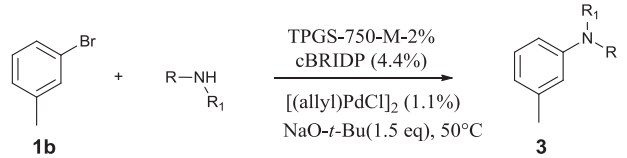
Entry	N°	R	X	Time (h)	N°	**3** (%)
1	**1a**	3-Me	Cl	16	**3h**	40
2	**1b**	3-Me	Br	2	**3h**	88[a,b]
3	**1c**	3-Me	I	2	**3h**	60
4	**1c**	3-Me	I	16	**3h**	90
5	**1d**	3-Me	OTf	2	**3h**	87
6	**1e**	3-Me	OTs	16	**3h**	n.r.[c]
7	**1f**	4-Cl	Br	2	**3n**	72

[a] Without TPGS only 15% of formation of **3h**.
[b] 98% of **3h** (previous work).[9]
[c] n.r. no reaction even in 0.5 M concentration (1 mmol of **1e**/2 mL of TPGS-750-M-2%).

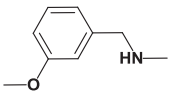
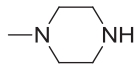
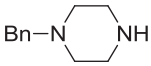
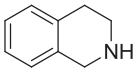
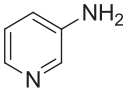
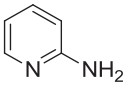
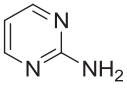
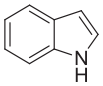
Aryl sulfonates were used owing to their ease of preparation from readily available phenolic precursors. *m*-Tolyl trifluoromethanesulfonate **1d** and *m*-tolyl 4-methylbenzenesulfonate **1e** were synthesized following the reported procedures. The Pd-catalyzed amination of aryl triflates has been previously performed by Lipshutz using the first-generation surfactant (TPS). However, these reactions often resulted in low yields owing to the ^{t}BuONa-catalyzed cleavage of the triflate. The use of NEt_3 as the additive improved the results (76% isolated yield, 0.5 h). Interestingly, in our hands using TPGS-750-M micelles, the N-arylation reaction of OTf derivative **1d** resulted in a high isolated yield (87% yield, Table 1, entry 5) even in the absence of NEt_3. With the *O*-tosyl derivative **1e**, no reaction was observed even at high micellar concentration (Table 1, entry 6). Similar reactivities have been observed in the Buchwald–Hartwig reactions using classical conditions.[1f]

To further investigate the versatility of this method, we carried out a second set of experiments: the cross-coupling reactions of various aliphatic amines (primary amines, acyclic and cyclic secondary amines, anilines, amidines, and heteroaryl amines) with *m*-bromotoluene. The results are summarized in Table 2. The first goal of this study was to investigate the reactivity of the most basic nitrogen derivatives. With the primary amine *n*-$BuNH_2$ (Table 2, entry 1), no trace of the expected product was observed, and the starting material **1b** was recovered unchanged. With the more lipophilic benzylamine, 25% yield of the product was observed by HPLC analysis after 16 h (compare: Table 2, entries 1 and 4). In contrast, the secondary aliphatic amines were found to be more reactive than the primary aliphatic amines (compare: Table 2, entries 1 and 2 and entries 4 and 5). In all these cases, the yields are good. With this in mind, we tried the reactions successfully with water-soluble secondary amines, *N*,*N*-dimethylamine (log *D*=−0.19,[13] Table 2, entry 3) and *N*-methylpiperidine (log *D*=−0.35, Table 2, entry 6). With *N*,*N*-dimethylamine, no reaction was observed under the standard stoichiometric conditions (1.2 equiv of amine, Table 2, entry 3). However, when a large excess of *N*,*N*-dimethylamine (40% in water, 9 equiv) was used, *N*,*N*-dimethylanilino derivative **3b** was obtained in 90% yield (Table 2, entry 3). With 1.2 equiv of *N*-methylpiperidine, only 40% conversion was observed after 16 h (Table 2, entry 6). The use of 5 equiv of *N*-methylpiperidine increased the yield (55% isolated yield, Table 2, entry 6). These results demonstrate that: (i) the N-arylation reactions can be realized with the commercially available aqueous solutions of amines; (ii) the log *D* of the amines does not play a major role in the reaction; and (iii) even water-soluble compounds can be incorporated inside the highly hydrophobic micelles. These results are very interesting because in the classical Buchwald–Hartwig cross-coupling reaction, the aqueous solutions of amines are not tolerated. Instead, highly anhydrous conditions are needed, and highly volatile amines available in aprotic solvents (THF) or ether at low concentrations are used. Two others secondary cyclic amines were examined, *N*-benzylpiperazine (Table 2, entry 7) and tetrahydroisoquinoline (THIQ, Table 2, entry 8). In both the cases, the reactions afforded the corresponding products in satisfactory yields (70–80% isolated yields). This can be explained by the high lipophilicity of these compounds, favoring their rapid concentrations in the micelles. However, the THIQ derivative took

Table 2
Palladium-cross coupling amination with TPGS and amine



1b 3

Entry	Amine	Time (h)	N°	**3** (%)[a]
1	*n*-BuNH$_2$	16	—	n.r.
2	*n*-Bu(Me)NH	16	**3a**	66
3	Me$_2$NH	2	**3b**	n.r. (90)[b]
4	PhCH$_2$NH$_2$	16	**3c**	25
5		16	**3d**	70
6		16	**3e**	40[c] (55)[d]
7		3	**3f**	80
8		16	**3g**	70[e]
9		2	**3h**	87
10		48	**3i**	65[f]
11		16	**3j**	9 (5)[g]
12		2	**3k**	60
13		24	**3l**	86[f]
14		40	**3m**	14

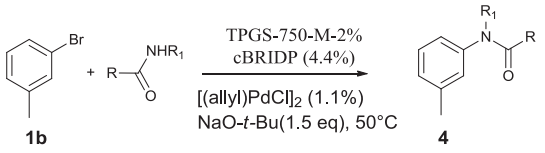
[a] Isolated yields.
[b] (Me)$_2$NH 40% in water was used as solvent.
[c] Estimated by HPLC.
[d] Amine (5 equiv).
[e] Formation of 10% of **8**.
[f] Second addition of 2% of [(allyl)PdCl]$_2$ and 4.4% of cBRIDP after 16 h.
[g] [(Allyl)PdCl]$_2$ (5%) and 4.4% of cBRIDP.

a longer period for the completion of the reaction (16 h). In the case of tetrahydroisoquinoline, the oxidation of the resulting *N*-aryl tetrahydroisoquinoline **3g** afforded the corresponding *N*-aryl 3,4-dihydroisoquinoline-1(2*H*)-one **8**, as the side product (10% yield).

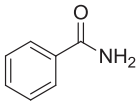
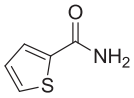
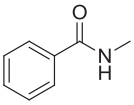
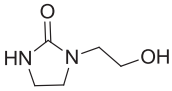
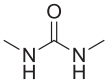
Next, the cross-coupling reactions of 3-bromotoluene with diverse nitrogen-containing heterocycles were carried out (Table 2). With 3-aminopyridine (Table 2, entry 9), the reaction worked pretty well, as described earlier by Lipshutz (88% yield, 2 h).[6] However higher catalyst loadings (2% [(allyl)PdCl]$_2$ and 4.4% cBRIDP) were required for 2-aminopyridine (Table 2, entry 10). This is probably because of the chelating properties of the 2-aminopyridine derivative. In contrast, with 2-aminopyrimidine (Table 2, entry 11), only 9% of the corresponding product was isolated after 1 h or 72 h, even with higher catalyst loadings (5% [(allyl)PdCl]$_2$ and 4.4% cBRIDP). Surprisingly, no trace of aryl bromide **1b** was recovered. This is probably because the guanidine moiety of the 2-aminopyrimidine could coordinate to the Aryl Pd complex and so catalyzes the reductive elimination leading in our case to toluene as observed earlier by Buchwald with monodentate ligands.[14] As shown in Table 2, entries 12–14, the amination process was successfully applied to pyrrole or indole. For example, pyrrole afforded the target N-arylation product in 60% yield after 2 h under the standard conditions (Table 2, entry 12). With indole, the rate for the amination reaction was slightly slower than that for the amination of pyrrole; moreover, this reaction required higher catalyst loadings. However, the expected product was obtained in 86% yield under the standard conditions (Table 2, entry 13). Finally, the reaction yield was very low with indazole (14% yield, Table 2, entry 14) even with higher catalyst loadings.

Finally, we evaluated the efficacy of the amidation reaction of 3-bromotoluene under the micellar conditions. In particular, a set of amides, carbamates, and ureas were selected for this purpose. As expected from the previous results described by Buchwald, our studies,[15] and very recently by Lipshutz[12] the reactions with carbamates (Table 3, entries 1 and 2), ureas (Table 3, entries 7 and 8), and cyclic amide (Table 3, entry 6) in the micellar medium afforded the corresponding products in satisfactory yields, whereas the

Table 3
Palladium-cross coupling N-arylation with TPGS



1b 4

Entry	R–C(O)NHR$_1$	Time (h)	N°	**4** (%)[a]
1	*t*-BOC–NH$_2$	16	**4a**	77
2	*Z*-NH$_2$	16	**4b**	69
3		16	**4c**	28[b]
4		16 16	**4d**	13 21[c]
5		16	**4e**	n.r[d]
6		16	**4f**	80
7		18	**4g**	81
8		24	**4h**	15 65[e]

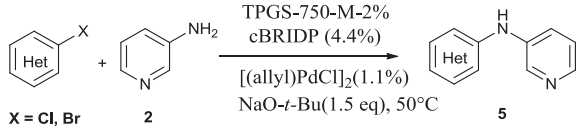
[a] Isolated yields.
[b] Estimated by NMR.
[c] [(Allyl)PdCl]$_2$ (5%) and 4.4% of cBRIDP were used.
[d] n.r. no reaction.
[e] 3-Bromotolyl (2 equiv) was used.

trans-secondary amide did not react (Table 3, entry 5). Interestingly, when other potentially reactive functional groups (e.g., hydroxyl) were present on the amide substrate, chemoselective arylation on the nitrogen was observed (Table 3, entry 7). Surprisingly primary amides afforded the corresponding products in moderate yields (Table 3, entries 3 and 4), even when using higher catalyst loading.

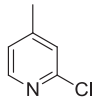
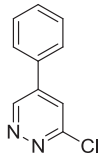
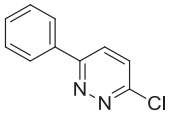
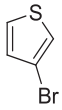
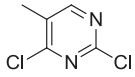
In continuation of our efforts, the N-arylation reaction was studied with several unactivated azaheteroaryl halide coupling partners (Table 4). In this study, we selected 3-aminopyridine as the prototypical partner. Various chloroheterocyclic systems, such as pyridine, pyrazine, pyridazine, pyrimidine (compounds **5a**–**e** and **6**), and thiophene (compound **5f**) were efficiently *N*-substituted with 3-aminopyridine. In particular the reaction conditions were effective for the 2,4-dichloropyrimidine derivative (Table 4, entry 7) because 2,4-pyrimidinediamine **6** was obtained as the major product. In contrast, the very low reactive 3-bromothiophene reacted smoothly; however, it required higher catalyst loadings (5% of $[(allyl)PdCl]_2$). Surprisingly, the reaction of 6-phenyl-3-chloropyridazine failed (Table 4, entry 5). This is probably because of the very low solubility of 6-phenyl-3-chloropyridazine in water (0.067 mg/mL compared to 0.255 mg/mL for the 5-phenyl analog)[16] affording an insoluble precipitate.

Finally, owing to the observed poor reactivities of the primary amines and primary amides, highly electron-deficient 2,6-dichloro-5-methyl pyrimidine **7** was used as the substrate to facilitate the reactions. With the benzamide derivative (Table 5, entry 1), the reaction afforded a 3/1 regioisomeric mixture of **9a** and **10a** in 87% isolated yield. Good results were also observed with benzylamine (Table 5, entry 2). The structure of 2-amino-substituted pyrimidin-4-ol **10b** was established by the heteronuclear NMR experiments (HMBC and HMQC, see the Supplementary data).

Table 4
Palladium-cross coupling N-arylation with TPGS-750-M on heterocyclic systems



X = Cl, Br 2 5

Entry	Heterocycle	Time (h)	N°	**5**[a] (%)
1		2	**5a**	91
2		2	**5b**	71
3		2	**5c**	75
4		16	**5d**	80
5		16	**5e**	0
6		16	**5f**	60[b]
7		16	**5g**	14[c]

[a] Isolated yields.
[b] $[(Allyl)PdCl]_2$ (5%) and 4.4% of cBRIDP were used.
[c] Compound **6** (43%) was isolated.

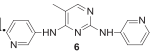
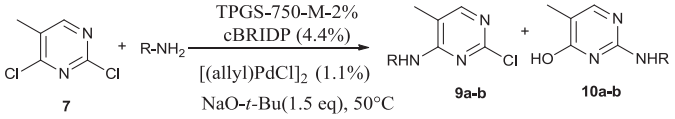


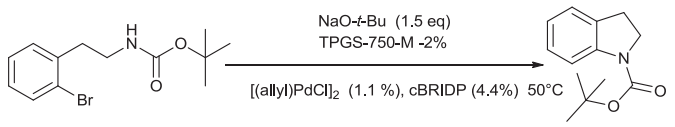
Table 5
Palladium-catalyzed N-heteroarylation of the less reactive amines with **7**



7 9a-b 10a-b

Entry	N°	R	**9** (%)	**10** (%)
1	a	4-MeO–Ph–CO	65	22
2	b	$PhCH_2$	72	14

Our great interest in medicinal heterocyclic chemistry prompted us to evaluate the possible intramolecular cyclization of *N*-protected *o*-bromo-phenethylamine **11**. Under the standard experimental conditions, the expected *N*-Boc-indoline **12** was obtained in excellent isolated yield (84%, Scheme 2). No side product (corresponding indole) was detected by the LC/MS or ^1H NMR analyses.



11 12

Scheme 2. Intramolecular cyclization of *N*-Boc-*o*-bromo-phenethylamine **11** under micellar conditions.

3. Conclusions

We significantly expanded the substrate scope of the Pd-catalyzed amination under micellar conditions (TPGS-750-M). In particular, cyclic amides, anilines, carbamates, ureas, and various nitrogen-containing heterocyclic derivatives were found to be reactive and afforded the corresponding products in excellent yields. We also demonstrated that various iminochlorides (pyridine and pyrazine) and thiophene are largely tolerated in this aqueous micellar media. However, the yields directly depended on their intrinsic aqueous solubilities. In a few reactions, relatively higher levels of catalyst loading (2% Pd) were required. The application of the reaction to various heterocycles makes the method more attractive because of their use in medicinal chemistry. Finally, two chemoselective *N*-arylations (Br vs Cl, urea vs OH) were reported in this study.

The cross-coupling reactions with benzamide derivatives and primary amines pose some challenges; therefore, further studies are currently underway to overcome these problems.

4. Experimental section

4.1. Solubility test using HPLC/UV

In order to determine the solubility concentration of a sample using HPLC/UV, a standard curve for each compound was prepared

from known concentration in DMSO (4.0, 1.5, 0.40, 0.15, and 0.040 μmol/mL). The area under curve (AUC) was measured at the maximum absorbance: λ=203 nm for 5-phenyl-3-chloropyzidazine and λ=200 nm for 6-phenyl-3-chloropyridazine. The equation of the line was then used to calculate the product concentration from the absorbance of the sample. Probe (3.00 mg) was introduced in an Eppendorf tube. 600 μL of a saline solution (9 mg of NaCl dissolved in 1 mL water) was added into the Eppendorf. The solution was then stirred for 24 h at room temperature on an oscillating plate. In order to improve the agitation, a little magnetic stirrer bar was added. The mixture was then centrifuged. Supernatant (3.00 μL) was analyzed by HPLC. The solubility of each sample was then obtained using the equation of the calibration curve: 0.067 mg/mL for the 6-phenyl-3-chloropyridazine and 0.255 mg/mL for the 5-phenyl-3-chloropyridazine.

4.2. Chemistry: general information

All reactions were carried out under a nitrogen atmosphere. Chemicals and solvents were purchased from Sigma–Aldrich and were used without further purification. Analytical TLC was performed using silica gel plates Merck 60F_{254} and plates were visualized by exposure to ultraviolet light. Compounds were purified using Armen spot flash chromatography on silica gel Merck 60 (particle size 0.040–0.063 mm). Yields refer to isolated compounds, estimated to be >97% pure as determined by ^{1}H NMR or HPLC. ^{1}H and ^{13}C NMR spectra were recorded on Bruker Avance Spectrometer operating at 300 MHz/400 MHz and 100 MHz, respectively. All chemical shift values δ and coupling constants J are quoted in parts per million and in hertz, respectively, multiplicity (s=singlet, d=doublet, t=triplet, m=multiplet, br Broad). Analytical RP-HPLC-MS was performed using an LC-MSD 1200SL Agilent with a Thermo Hypersilgold® column (C18, 30 mm×1 mm; 1.9 μm) using the following parameters: (1) the solvent system: A (acetonitrile) and B (0.05% TFA in H_2O); (2) A linear gradient: t=0 min, 98%B; t=5 min, 5% B; t=6 min, 5%B; t=7 min, 98%B; t=9 min, 98%B; (3) Flow rate of 0.3 mL/min; (4) Column temperature: 50 °C; (5) The ratio of products was determined by integration of spectra recorded at 210 nm or 254 nm; (6) Ionization mode: MM-ES+APCI. HPLC were performed using a Dionex UltiMate 300 using the following parameters: flow rate of 0.5 mL/min, column temperature: 30 °C, solvent system: A (MeOH) and B (0.05% TFA in H_2O), t=0–1 min: 50–60% of B then t=1–10 min: 60–100% of B and t=10–15 min: 100% of B. Infra-Red analyses were performed by FT-IR, on a Nicolet 380 ATR from Thermo and wavenumber were expressed in cm^{-1}.

4.3. General procedure

Amine (1.2 equiv) and 3-bromotoluene (1 equiv) were added to an aqueous solution of TPGS-750-M-2% (1 mL/mmol). The mixture was degassed by bubbling Argon in through (5 min). NaO-*t*-Bu (1.5 equiv), of [(allyl)PdCl]$_2$ (1.1%) and cBridp (4.4%) were added together to the previous solution. The mixture was stirred (at 1200 rpm) at 50 °C (2–24 h). Volatiles were evaporated and the crude residue was purified by chromatographic column on silica gel using ethyl acetate and cyclohexane as solvent.

4.4. *N*-Butyl-*N*,3-dimethylaniline (3a)

Following the general procedure, using $Pd_2(allyl)_2Cl_2$ (4.4 mg, 0.011 mmol), cBridp (15.5 mg, 0.044 mmol), 3-bromotoluene (121 μL, 1.0 mmol), *N*-methyl-1-butanamine (148 μL, 1.2 mmol), and NaO-*t*-Bu (144 mg, 1.5 mmol) in aqueous TPGS-750M (2%, 1.0 mL), followed by purification using column chromatography (SiO_2) and *n*-heptane/ethyl acetate (9/1), yielded **3a** as a colorless oil (117 mg, 66% yield). HPLC rt 2.85; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.91–1.00 (3H, t, J=7.2 Hz), 1.31–1.43 (2H, m), 1.53–1.63 (2H, m), 2.34 (3H, s), 2.94 (3H, s), 3.29–3.34 (2H, t, J=7.5 Hz), 6.52–6.56 (3H, m), 7.11–7.16 (1H, m); ^{13}C NMR (101 MHz, $CDCl_3$) δ 14.0, 20.4, 22.0, 29.0, 38.3, 52.6, 109.4, 112.9, 116.8, 129.0, 138.7, 149.6; HRMS (M+H$^+$)(ESI$^+$) 178.1587 [M+H$^+$] (calcd for $C_{12}H_{20}NH^+$ 178.1590).

4.5. *N*,*N*,3-Trimethylaniline (3b)[17]

Following the general procedure, using $Pd_2(allyl)_2Cl_2$ (4.4 mg, 0.011 mmol), cBridp (15.5 mg, 0.044 mmol), 3-bromotoluene (121 μL, 1.0 mmol), TPGS-750M (20 mg), and NaO-*t*-Bu (144 mg, 1.5 mmol) in aqueous dimethylamine (40%, 1.0 mL), followed by purification using column chromatography (SiO_2) and cyclohexane/ethyl acetate (9/1 to 5/5), yielded **3b** as a brown oil (121 mg, 90% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.30 (3H, s), 2.91 (6H, s), 6.51–6.56 (3H, m), 7.09–7.13 (1H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.9, 40.7, 109.9, 113.5, 117.6, 128.9, 138.7, 150.8.

4.6. *N*-Benzyl-3-methylaniline (3c)[18]

Following the general procedure, using $Pd_2(allyl)_2Cl_2$ (4.4 mg, 0.011 mmol), cBridp (15.5 mg, 0.044 mmol), 3-bromotoluene (121 μL, 1.0 mmol), benzylamine (130 μL, 1.2 mmol), and NaO-*t*-Bu (144 mg, 1.5 mmol) in aqueous TPGS-750M (2%, 1.0 mL), followed by purification using column chromatography (SiO_2) and cyclohexane/ethyl acetate (8/2), yielded **3c** as a colorless oil (40 mg, 20% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.30 (3H, s), 3.90–4.06 (1H, br s), 4.34 (2H, s), 6.46–6.59 (3H, m), 7.09 (1H, J=7.5 Hz), 7.27–7.41 (5H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.7, 48.4, 110.0, 113.6, 118.6, 127.2, 127.6, 128.6, 129.2, 139.1, 139.6, 148.3.

4.7. *N*-[(3-Methoxyphenyl)methyl]-*N*,3-dimethylaniline (3d)

Following the general procedure, using $Pd_2(allyl)_2Cl_2$ (4.4 mg, 0.011 mmol), cBridp (15.5 mg, 0.044 mmol), 3-bromotoluene (121 μL, 1.0 mmol), [(3-methoxyphenyl)methyl](methyl)amine (179 μL, 1.2 mmol), and NaO-*t*-Bu (144 mg, 1.5 mmol) in aqueous TPGS-750M (2%, 1.0 mL), followed by purification using column chromatography (SiO_2) and cyclohexane/ethyl acetate (8/2), yielded **3d** as a colorless oil (169 mg, 70% yield). HPLC rt 3.44; ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C) δ 2.32 (3H, s), 3.00 (3H, s), 3.79 (3H, s), 4.50 (2H, s), 6.55–6.60 (3H, m), 6.78–6.86 (3H, m), 7.10–7.15 (1H, t, J=7.5 Hz), 7.22–7.25 (1H, t, J=7.5 Hz); ^{13}C NMR (101 MHz, $CDCl_3$, 25 °C) δ, 22.0, 38.5, 55.2, 56.7, 109.7, 112.1, 112.4, 113.2, 117.6, 119.1, 129.0, 129.6, 138.8, 141.1, 150.0, 159.9; HRMS (M+H$^+$)(ESI$^+$) 242.1540 [M+H$^+$] (calcd for $C_{16}H_{19}NOH^+$ 242.1539).

4.8. 1-Methyl-4-(*m*-tolyl)piperazine (3e)[19]

Following the general procedure, using $Pd_2(allyl)_2Cl_2$ (4.4 mg, 0.011 mmol), cBridp (15.5 mg, 0.044 mmol), 3-bromotoluene (121 μL, 1.0 mmol), *N*-methylpiperazine (133 μL, 1.2 mmol), and NaO-*t*-Bu (144 mg, 1.5 mmol) in aqueous TPGS-750M (2%, 1.0 mL), followed by purification using column chromatography (SiO_2) and ethyl acetate/methanol (10/0 to 8/2), yielded **3e** as an orange oil (71 mg, 40% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.34 (3H, s), 2.49 (3H, s), 2.78 (4H, t, J=4.8 Hz), 3.32 (4H, t, J=4.8 Hz), 6.72–6.77 (3H, m), 7.18 (1H, J=7.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.8, 45.4, 48.6, 54.7, 113.6, 117.2, 121.2, 129.0, 138.9, 139.6.

4.9. 1-Benzyl-4-(*m*-tolyl)piperazine (3f)

Following the general procedure, using $Pd_2(allyl)_2Cl_2$ (4.4 mg, 0.011 mmol), cBridp (15.5 mg, 0.044 mmol), 3-bromotoluene (121 μL, 1.0 mmol), *N*-benzylpiperazine (208 μL, 1.2 mmol), and NaO-*t*-Bu (144 mg, 1.5 mmol) in aqueous TPGS-750M (2%, 1.0 mL),

followed by purification using column chromatography (SiO_2) and ethyl acetate/methanol (10/0 to 8/2), yielded **3f** as an orange oil (212 mg, 80% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.34 (3H, s), 2.63 (4H, t, J=5.0 Hz), 3.22 (4H, t, J=5.0 Hz), 3.60 (2H, s), 6.69–6.77 (3H, m), 7.17 (1H, J=7.8 Hz), 7.28–7.40 (5H, m, H arom); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.8, 49.3, 53.2, 63.1, 113.6, 116.9, 121.2, 127.1, 128.3, 129.0, 129.2, 138.5, 138.7, 151.5. LRMS ($M+H^+$)(ESI^+) 267.1 [$M+H^+$] (calcd for $C_{18}H_{22}N_2H^+$ 267.0).

4.10. *N*-(*m*-Tolyl)tetrahydroisoquinoline (3g)[20]

Following the general procedure, using $Pd_2(allyl)_2Cl_2$ (4.4 mg, 0.011 mmol), cBridp (15.5 mg, 0.044 mmol), 3-bromotoluene (121 μL, 1.0 mmol), tetrahydroisoquinoline (138 μL, 1.2 mmol), and NaO-*t*-Bu (144 mg, 1.5 mmol) in aqueous TPGS-750M (2%, 1.0 mL), followed by purification using column chromatography (SiO_2) and heptane/ethyl acetate (9/1 to 7/3), yielded **3g** (orange oil, 155 mg, 70% yield) and **8** (orange solid, 23.6 mg, 10%).

*4.10.1. Compound **3g**.* ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.36 (3H, s, CH_3), 3.00 (2H, t, J=5.8 Hz, CH_2), 3.56 (2H, t, J=5.8 Hz, CH_2), 4.41 (2H, s), 6.68 (1H, d, J=7.4 Hz), 6.79–6.84 (2H, m), 7.14–7.22 (5H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.0, 29.3, 46.7, 51.0, 112.4, 116.1, 119.7, 126.1, 126.4, 126.7, 128.6, 129.2, 134.7, 135.0, 139.0, 150.8.

*4.10.2. 2-(3-Methylphenyl)-3,4-dihydroisoquinolin-1(2H)-one (**8**).* ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.38 (3H, s, CH_3), 3.14 (2H, t, J=6.4 Hz, CH_2), 3.98 (2H, t, J=6.4 Hz, CH_2), 7.08 (1H, d, J=7.5 Hz, H arom), 7.17 (1H, d, J=7.8 Hz, H arom), 7.20–7.27 (2H, m, H arom), 7.30 (1H, t, J=7.8 Hz, H arom), 7.38 (1H, t, J=7.5 Hz, H arom), 7.47 (1H, td, J=7.5, 1.4 Hz, H arom), 8.16 (1H, dd, J=7.7, 1.4 Hz, H arom). ($M+H^+$)(ESI^+) 238.0 [$M+H^+$] (calcd for $C_{16}H_{16}N_2OH^+$ 238.1).

4.11. *N*-(*m*-Tolyl)pyridin-3-amine (3h)[11]

Following the general procedure, using $Pd_2(allyl)_2Cl_2$ (4.4 mg, 0.011 mmol), cBridp (15.5 mg, 0.044 mmol), 3-bromotoluene (121 μL, 1.0 mmol), 3-aminopyridine (113 mg, 1.2 mmol), and NaO-*t*-Bu (144 mg, 1.5 mmol) in aqueous TPGS-750M (2%, 1.0 mL), followed by purification using column chromatography (SiO_2) and cyclohexane/ethyl acetate (9/1 to 5/5), yielded **3h** as a yellow solid (160 mg, 87% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.30 (3H, s), 5.64–6.70 (1H, br s), 6.80 (1H, d, J=7.7 Hz), 6.84–6.90 (2H, m), 7.12–7.20 (2H, m), 7.38 (1H, ddd, J=1.3, 2.6, 8.3 Hz), 8.13 (1H, dd, J=1.3, 4.8 Hz), 8.35 (1H, d, J=2.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.7, 115.6, 119.2, 123.2, 123.7, 123.9, 129.6, 139.7, 140.1, 140.4, 142.1, one aromatic peak was not detected and is believed to overlap with nearby signals.

4.12. *N*-(*m*-Tolyl)pyridin-2-amine (3i)

2-Aminopyridine (112 mg, 1.2 mmol) and 3-bromotoluene (121 μL, 1.0 mmol) were added to an aqueous solution of TPGS (2%, 1 mL/mmol). The mixture was degassed by bubbling Argon in through (5 min). $Pd_2(allyl)_2Cl_2$ (4.4 mg, 0.011 mmol), cBridp (15.5 mg, 0.044 mmol), and NaO-*t*-Bu (144 mg, 1.5 mmol) were added together to the previous solution. The mixture was stirred at 50 °C (16 h). After 16 h, a second set of $Pd_2(allyl)_2Cl_2$ (4.4 mg, 0.011 mmol) and cBridp (15.5 mg, 0.044 mmol) was added and the mixture was stirred as indicated in Table 2. The residue was purified using column chromatography (SiO_2) and ethyl acetate/cyclohexane (10/0 to 5/5), to obtain **3i** as a brown oil (120 mg, 65% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.27 (3H, s), 6.45–6.55 (1H, br s), 6.64 (1H, t, J=6.2 Hz), 6.62–6.64 (2H, m), 7.04–7.06 (2H, m), 7.13 (1H, d, J=8.0 Hz), 7.38–7.43 (1H, m), 8.12 (1H, J=4.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.5, 108.2, 115.0, 117.5, 121.1, 123.7, 129.1, 137.6, 139.2, 140.4, 148.5, 155.1; ($M+H^+$)(ESI^+) 185.1067 [$M+H^+$] (calcd for $C_{12}H_{12}N_2H^+$ 185.1078).

4.13. *N*-(3-Methylphenyl)pyrimidin-2-amine (3j)

Following the general procedure, using $Pd_2(allyl)_2Cl_2$ (4.4 mg, 0.011 mmol), cBridp (15.5 mg, 0.044 mmol), 3-bromotoluene (121 μL, 1.0 mmol), 2-aminopyrimidine (114 mg, 1.2 mmol), and NaO-*t*-Bu (144 mg, 1.5 mmol) in aqueous TPGS-750M (2%, 1.0 mL), followed by purification using column chromatography (SiO_2) and ethyl acetate/*n*-heptane (1/3), yielded **3j** as a white solid (17 mg, 9% yield). HPLC rt 3.59; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.39 (3H, s), 6.68–6.72 (1H, t, J=4.8 Hz), 6.89–6.92 (1H, d, J=7.5 Hz), 7.23–7.29 (1H, t, J=7.8 Hz), 7.46–7.48 (2H, m), 8.29 (1H, s), 8.43–8.45 (2H, d, J=4.8 Hz); ^{13}C NMR (101 MHz, $CDCl_3$) δ 21.7, 112.3, 117.1, 120.6, 123.7, 128.8, 138.7, 139.5, 158.0, 160.5; HRMS ($M+H^+$)(ESI^+) 186.1027 [$M+H^+$] (calcd for $C_{11}H_{11}N_3H^+$ 186.1026).

4.14. 1-(*m*-Tolyl)-1*H*-pyrrole (3k)[21]

Following the general procedure, using $Pd_2(allyl)_2Cl_2$ (4.4 mg, 0.011 mmol), cBridp (15.5 mg, 0.044 mmol), 3-bromotoluene (121 μL, 1.0 mmol), pyrrole (82 μL, 1.2 mmol), and NaO-*t*-Bu (144 mg, 1.5 mmol) in aqueous TPGS-750M (2%, 1.0 mL), followed by purification using column chromatography (SiO_2) and ethyl acetate/cyclohexane (0/10 to 1/9), yielded **3f** as a red oil (95 mg, 60% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.43 (3H, s), 6.37 (2H, t, J=2.2 Hz), 7.10–7.14 (3H, m), 7.22–7.30 (2H, m), 7.29–7.33 (1H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.4, 110.2, 117.7, 119.3, 121.3, 126.4, 129.3, 139.5, 140.8.

4.15. 1-(*m*-Tolyl)-1*H*-indole (3l)[22]

Indole (135 mg, 1.2 mmol) and 3-bromotoluene (121 μL, 1.0 mmol) were added to an aqueous solution of TPGS (2%, 1 mL/mmol). The mixture was degassed by bubbling Argon in through (5 min). $Pd_2(allyl)_2Cl_2$ (4.4 mg, 0.011 mmol), cBridp (15.5 mg, 0.044 mmol), and NaO-*t*-Bu (144 mg, 1.5 mmol) were added together to the previous solution. The mixture was stirred at 50 °C (16 h). After 16 h, $Pd_2(allyl)_2Cl_2$ (4.4 mg, 0.011 mmol) and cBridp (15.5 mg, 0.044 mmol) were added and the mixture was stirred as indicated in Table 2. The residue was purified using column chromatography (SiO_2) and ethyl acetate/cyclohexane (0/10 to 2/8), to obtain **3l** as colorless oil (180 mg, 86% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.35 (3H, s), 6.58 (1H, t, J=3.6 Hz), 7.07–7.32 (7H, m), 7.46–7.50 (1H, m), 7.58–7.61 (1H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.5, 103.6, 110.6, 120.3, 121.1, 121.5, 122.3, 125.1, 127.3, 128.0, 123.2, 129.5, 135.9, 139.7, 139.8.

4.16. 1-(3-Methylphenyl)-1*H*-indazole (3m)

Following the general procedure, using $Pd_2(allyl)_2Cl_2$ (4.4 mg, 0.011 mmol), cBridp (15.5 mg, 0.044 mmol), 3-bromotoluene (121 μL, 1.0 mmol), indazole (142 mg, 1.2 mmol), and NaO-*t*-Bu (144 mg, 1.5 mmol) in aqueous TPGS-750M (2%, 1.0 mL), followed by purification using column chromatography (SiO_2) and CH_2Cl_2/*n*-heptane (1/1), yielded **3m** as a colorless oil (28 mg, 14% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.48 (3H, s), 7.18–7.27 (2H, m), 7.41–7.47 (2H, m), 7.53–7.57 (2H, m), 7.76–7.78 (1H, d, J=8.6 Hz), 7.80–7.83 (1H, d, J=8.0 Hz), 8.2 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.5, 110.5, 119.7, 121.3, 121.4, 123.6, 125.3, 127.1, 127.5, 129.2, 135.2, 138.8, 139.6, 140.1; HRMS ($M+H^+$)(ESI^+) 209.1077 [$M+H^+$] (calcd for $C_{14}H_{12}N_2H^+$ 209.1073).

4.17. *N*-(4-Chlorophenyl)pyridin-3-amine (3n)[23]

Following the general procedure, using $Pd_2(allyl)_2Cl_2$ (4.4 mg, 0.011 mmol), cBridp (15.5 mg, 0.044 mmol), 1-bromo-4-chlorobenzene (121 μL, 1.0 mmol), 3-aminopyridine (142 mg, 1.2 mmol), and NaO-*t*-Bu (144 mg, 1.5 mmol) in aqueous TPGS-750M (2%, 1.0 mL), followed by purification using column chromatography (SiO_2) and CH_2Cl_2/*n*-heptane (1/1), yielded **3n** as a colorless oil (156 mg, 72% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.80 (1H, s), 7.03 (2H, d, J=8.8 Hz), 7.21–7.28 (3H, m), 7.40 (1H, d, J=8.0 Hz), 8.15–8.25 (1H, br s), 8.36–8.46 (1H, br s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 119.4, 123.8, 126.8, 129.5, 140.3, 140.7, 142.4; two aromatic peaks were not detected and are believed to overlap with nearby signals.

4.18. *tert*-Butyl *N*-(*m*-tolyl)carbamate (4a)[24]

Following the general procedure, using $Pd_2(allyl)_2Cl_2$ (4.4 mg, 0.011 mmol), cBridp (15.5 mg, 0.044 mmol), 3-bromotoluene (121 μL, 1.0 mmol), *tert*-butyl carbamate (129 mg, 1.2 mmol), and NaO-*t*-Bu (144 mg, 1.5 mmol) in aqueous TPGS-750M (2%, 1.0 mL), followed by purification using column chromatography (SiO_2) and heptane/ethyl acetate (95/5 to 8/2), yielded **4a** as a yellow solid (160 mg, 77% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.52 (9H, s), 2.33 (3H, s), 6.42 (1H, s), 6.85 (1H, d, J=7.4 Hz), 7.09 (1H, d, J=8.2 Hz), 7.16 (1H, dd, J=8.2, 7.4 Hz), 7.19 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.7, 28.5, 80.5, 115.8, 119.3, 124.0, 128.9, 138.4, 139.1, 152.9.

4.19. Benzyl *m*-tolylcarbamate (4b)[25]

Following the general procedure, using $Pd_2(allyl)_2Cl_2$ (4.4 mg, 0.011 mmol), cBridp (15.5 mg, 0.044 mmol), 3-bromotoluene (121 μL, 1.0 mmol), benzyl carbamate (181 mg, 1.2 mmol), and NaO-*t*-Bu (144 mg, 1.5 mmol) in aqueous TPGS-750M (2%, 1.0 mL), followed by purification using column chromatography (SiO_2) and ethyl acetate/cyclohexane (2/8), yielded **4b** as an orange oil (165 mg, 69% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.35 (3H, s), 5.22 (2H, s), 6.65–6.70 (1H, br s), 6.91 (1H, d, J=6.4 Hz), 7.17–7.28 (4H, m), 7.36–7.44 (4H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.5, 67.0, 124.4, 128.3, 128.4, 128.6, 128.9, 136.1, 137.7, 139.0, 153.4 two peaks are missing and are believed to overlap nearby; HRMS (M+H$^+$)(ESI$^+$) 242.1181 [M+H$^+$] (calcd for $C_{15}H_{15}NO_2H^+$ 242.1175).

4.20. *N*-(3-Methylphenyl)benzamide (4c)[26]

Following the general procedure, using $Pd_2(allyl)_2Cl_2$ (4.4 mg, 0.011 mmol), cBridp (15.5 mg, 0.044 mmol), 3-bromotoluene (121 μL, 1.0 mmol), benzamide (133 mg, 1.1 mmol), and NaO-*t*-Bu (144 mg, 1.5 mmol) in aqueous TPGS-750M (2%, 1.0 mL), yielded **4c** as a crude product (28% by NMR). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.34 (3H, s), 6.95 (1H, d, J=7.6 Hz), 7.23 (1H, dd, J=7.6, 7.9 Hz), 7.40 (1H, d, J=7.9 Hz), 7.43–7.54 (4H, m), 7.83–7.85 (3H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.5, 117.3, 120.9, 125.4, 127.0, 128.8, 128.9, 131.8, 135.1, 137.9, 139.0, 165.7 (C(O)).

4.21. *N*-(3-Methylphenyl)thiophene-2-carboxamide (4d)[26]

Following the general procedure, using $Pd_2(allyl)_2Cl_2$ (18.3 mg, 0.05 mmol), cBridp (15.5 mg, 0.044 mmol), 3-bromotoluene (121 μL, 1.0 mmol), 2-thienylamide (152 mg, 1.2 mmol), and NaO-*t*-Bu (144 mg, 1.5 mmol) in aqueous TPGS-750M (2%, 1.0 mL), followed by purification using column chromatography (SiO_2) and ethyl acetate/*n*-heptane (1/9), yielded **4d** as a brownish oil (46 mg, 21% yield). HPLC rt 3.97; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.28 (3H, s), 6.90–6.92 (1H, d, J=7.8 Hz), 7.03–7.05 (1H, dd, J=3.7, 5.0 Hz), 7.15–7.19 (1H, t, J=7.8 Hz), 7.37–7.39 (1H, d, J=7.8 Hz), 7.45 (1H, s), 7.47–7.49 (1H, dd, J=1.1, 5.0 Hz), 7.64–7.65 (1H, dd, J=1.1, 3.7 Hz), 8.00 (1H, s); ^{13}C NMR (101 MHz, $CDCl_3$) δ 21.5, 117.6, 121.2, 125.4, 127.8, 128.6, 128.8, 130.8, 137.6, 138.9, 139.5, 160.3; HRMS (M+H$^+$)(ESI$^+$) 218.0630 [M+H$^+$] (calcd for $C_{12}H_{11}NOSH^+$ 218.0634).

4.22. (*m*-Tolyl)pyrrolidin-2-one (4f)[27]

Following the general procedure, using $Pd_2(allyl)_2Cl_2$ (4.4 mg, 0.011 mmol), cBridp (15.5 mg, 0.044 mmol), 3-bromotoluene (121 μL, 1.0 mmol), pyrrolidin-2-one (85 μL, 1.2 mmol), and NaO-*t*-Bu (144 mg, 1.5 mmol) in aqueous TPGS-750M (2%, 1.0 mL), followed by purification using column chromatography (SiO_2) and heptane/ethyl acetate (8/2 to 5/5), yielded **4f** as a yellow solid (140 mg, 80% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.13 (2H, quint., J=7.8 Hz), 2.34 (3H, s), 2.58 (2H, t, J=7.8 Hz), 3.83 (2H, t, J=7.8 Hz), 6.94 (1H, d, J=8.0 Hz), 7.23 (1H, t, J=8.0 Hz), 7.35 (1H, d, J=8.0 Hz), 7.42 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.1, 21.6, 32.8, 49.0, 117.2, 120.8, 125.4, 128.6, 138.7, 139.3, 174.1.

4.23. 1-(2-Hydroxyethyl)-3-(*m*-tolyl)imidazolidin-2-one (4g)

Following the general procedure, using $Pd_2(allyl)_2Cl_2$ (4.4 mg, 0.011 mmol), cBridp (15.5 mg, 0.044 mmol), 3-bromotoluene (121 μL, 1.0 mmol), 1-(2-hydroxyethyl)imidazolidin-2-one (156 mg, 1.2 mmol), and NaO-*t*-Bu (144 mg, 1.5 mmol) in aqueous TPGS-750M (2%, 1.0 mL), followed by purification using column chromatography (SiO_2) and ethyl acetate, yielded **4g** as an orange oil (180 mg, 81% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.36 (3H, s), 3.43 (2H, t, J=5.1 Hz), 3.57 (2H, t, J=8.1 Hz), 3.79–3.83 (4H, m), 6.88 (1H, d, J=7.2 Hz), 7.22 (1H, t, J=7.8 Hz), 7.28–7.31 (1H, m), 7.38 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.7, 43.0, 43.2, 47.5, 61.3, 114.7, 118.4, 123.5, 128.6, 138.6, 140.2, 159.1; HRMS (M+H$^+$)(ESI$^+$) 221.1290 [M+H$^+$] (calcd for $C_{12}H_{16}N_2O_2H^+$ 221.1284).

4.24. 1,3-Dimethyl-1-(3-methylphenyl)urea (4h)

Following the general procedure, using $Pd_2(allyl)_2Cl_2$ (4.4 mg, 0.011 mmol), cBridp (15.5 mg, 0.044 mmol), 3-bromotoluene (242 μL, 2.0 mmol), 1,3-dimethylurea (88 mg, 1.0 mmol), and NaO-*t*-Bu (144 mg, 1.5 mmol) in aqueous TPGS-750M (2%, 1.0 mL), followed by purification using column chromatography (SiO_2) and *n*-heptane/ethyl acetate 3/7 to ethyl acetate, yielded **4h** as a brownish oil (115 mg, 65% yield). HPLC rt 3.15; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.33 (3H, s), 2.68 (3H, d, J=4.8 Hz), 3.20 (3H, s), 4.29 (1H, br), 6.99 (d, 2H, J=7.8 Hz), 7.07 (d, 1H, J=7.8 Hz), 7.25 (t, 1H, J=7.6 Hz); ^{13}C NMR (101 MHz, $CDCl_3$) δ 21.2, 27.4, 37.1, 124.3, 127.9, 128.0, 129.7, 140.0, 143.4, 158.0; HRMS (M+H$^+$)(ESI$^+$) 179.1180 [M+H$^+$] (calcd for $C_{10}H_{14}N_2OH^+$ 179.1179).

4.25. 4-Methyl-*N*-(pyridin-3-yl)pyridin-2-amine (5a)

Following the general procedure, using $Pd_2(allyl)_2Cl_2$ (4.4 mg, 0.011 mmol), cBridp (15.5 mg, 0.044 mmol), 2-chloropicoline (111 μL, 1.0 mmol), 3-aminopyridine (113 mg, 1.2 mmol), and NaO-*t*-Bu (144 mg, 1.5 mmol) in aqueous TPGS-750M (2%, 1.0 mL), followed by purification using column chromatography (SiO_2) and ethyl acetate/methanol(10/0 to 90/10), yielded **5a** as a white solid (180 mg, 92% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.23 (3H, s), 6.57–6.63 (2H, m), 7.03–7.12 (1H, br s), 7.20 (1H, dd, J=4.8, 8.3 Hz), 7.94 (1H, ddd, J=1.2, 2.4, 8.3 Hz), 8.05 (1H, d, J=5.9 Hz), 8.20 (1H, d, J=1.2, 4.6 Hz), 8.55 (1H, d, J=2.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.2, 109.6, 117.3, 123.7, 126.2, 137.7, 141.6, 143.0, 147.8, 149.0, 155.5; HRMS (M+H$^+$)(ESI$^+$) 186.1024 [M+H$^+$] (calcd for $C_{11}H_{11}N_3H^+$ 186.1025).

4.26. Di(pyridin-3-yl)amine (5b)[28]

Following the general procedure, using $Pd_2(allyl)_2Cl_2$ (4.4 mg, 0.011 mmol), cBridp (15.5 mg, 0.044 mmol), 3-chloropyridine (113 mg, 1.0 mmol), 3-pyridinamine (113 mg, 1.2 mmol), and NaO-*t*-Bu (144 mg, 1.5 mmol) in aqueous TPGS-750M (2%, 1.0 mL), followed by purification using column chromatography (SiO_2) and ethyl acetate/methanol(10/0 to 9/1), yielded **5b** as a white solid (120 mg, 92% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.99 (1H, s), 7.20 (2H, dd, J=4.6, 8.1 Hz), 7.41 (2H, d, J=7.3 Hz), 8.20 (2H, d, J=4.4 Hz), 8.39 (2H, d, J=2.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 121.5, 123.7, 137.5, 139.9, 142.6.

4.27. *N*-(Pyridin-3-yl)pyrazin-2-amine (5c)[29]

Following the general procedure, using $Pd_2(allyl)_2Cl_2$ (4.4 mg, 0.011 mmol), cBridp (15.5 mg, 0.044 mmol), 2-chloropyrazine (89 μL, 1.0 mmol), 3-aminopyridine (113 mg, 1.2 mmol), and NaO-*t*-Bu (144 mg, 1.5 mmol) in aqueous TPGS-750M (2%, 1.0 mL), followed by purification using column chromatography (SiO_2) and ethyl acetate/methanol(10/0 to 90/10), yielded **5c** as a white solid (130 mg, 75% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.20 (1H, s), 7.28–7.33 (1H, m), 8.06 (1H, s), 8.17–8.33 (4H, m), 8.72 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 123.7, 126.3, 133.9, 135.6, 136.5, 141.3, 141.6, 143.8, 151.8.

4.28. 5-Phenyl-*N*-(pyridin-3-yl)pyridazin-3-amine (5d)

Following the general procedure, using $Pd_2(allyl)_2Cl_2$ (1.0 mg, 0,0027 mmol), cBridp (3.9 mg, 0.011 mmol), 3-chloro-5-phenylpyridazine (48 mg, 0.25 mmol), 3-pyridinamine (28 mg, 0.3 mmol), and NaO-*t*-Bu (36 mg, 0.38 mmol) in aqueous TPGS-750M (2%, 1.0 mL), followed by purification using column chromatography (SiO_2) and *n*-heptane/ethyl acetate (1/3 to 1/1), yielded **5d** as a pale yellow solid (50 mg, 80% yield). HPLC rt 3.06; ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.51 (1H, d, J=1.9 Hz), 7.56–7.62 (3H, m), 7.89–7.85 (3H, m), 8.45 (1H, d, J=5.3 Hz), 8.54 (1H, dd, J=1.7, 8.7 Hz), 9.27–9.26 (1H, d, J=1.9 Hz), 9.46–9.45 (1H, d, J=1.7 Hz), 10.30–10.35 (1H, br s); ^{13}C NMR (100 MHz, DMSO-d_6) δ 113.9, 126.9, 127.5, 130.0, 130.7, 131.8, 133.8, 134.4, 136.8, 139.6, 140.0, 144.9, 157.3; HRMS (M+H$^+$)(ESI$^+$) 249.1133 [M+H$^+$] (calcd for $C_{15}H_{12}N_4H^+$ 249.1135).

4.29. *N*-(Thiophen-3-yl)pyridine-3-amine (5f)

Following the general procedure, using $Pd_2(allyl)_2Cl_2$ (18.3 mg, 0.05 mmol), cBridp (15.5 mg, 0.044 mmol), 3-bromothiophene (94 μL, 1.0 mmol), 3-pyridinamine (113 mg, 1.2 mmol), and NaO-*t*-Bu (144 mg, 1.5 mmol) in aqueous TPGS-750M (2%, 1.0 mL), followed by purification using column chromatography (*Si-C18*) and water+TFA (0.05%)/methanol(9/1 to 5/5), yielded **5f** as a yellow solid (105 mg, 60% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.10 (1H, dd, J=1.5, 5.1 Hz), 7.28 (1H, dd, J=1.5, 3.0 Hz), 7.64 (1H, dd, J=3.0, 5.1 Hz), 7.82 (1H, dd, J=5.3, 8.5 Hz), 8.00 (1H, dd, J=2.5, 8.7 Hz), 8.25 (1H, d, J=5.3 Hz), 8.44 (1H, d, J=2.6 Hz), 9.49 (1H, s); ^{13}C NMR (100 MHz, DMSO-d_6) δ 109.0, 122.8, 126.5, 127.2, 127.4, 127.7, 131.1, 138.0, 143.9. HRMS (M+H$^+$)(ESI$^+$) 177.0480 [M+H]$^+$ (calcd for $C_9H_8N_2SH^+$ 177.0481).

4.30. 2-Chloro-5-methyl-*N*-(pyridin-3-yl)pyrimidin-4-amine (5g) and 5-ethyl-2-*N*,4-*N*-bis(pyridin-3-yl)pyrimidine-2,4-diamine, 2TFA (6)

Following the general procedure, using $Pd_2(allyl)_2Cl_2$ (18.3 mg, 0.05 mmol), cBridp (15.5 mg, 0.044 mmol), 2,4-dichloro-5-methylpyrimidine (163 mg, 1.0 mmol), 3-pyridinamine (94 mg, 1.0 mmol), and NaO-*t*-Bu (144 mg, 1.5 mmol) in aqueous TPGS-750M (2%, 1.0 mL), followed by purification using two column chromatographies one (SiO_2) and CH_2Cl_2/methanol(95/5 to 9/1), yielded **5g** (white solid, 33 mg, 14%) and (*Si-C18*) and water+TFA (0.05%)/methanol(9/1 to 0/1), **6** (white solid, 169 mg, 43%).

*4.30.1. Compound **5g**.* HPLC rt 2.44; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.11 (3H, s, CH_3), 7.20–7.23 (1H, dd, J=4.8, 8.4 Hz), 7.60–7.66 (1H, br s), 7.90 (1H, s), 8.10–8.13 (1H, ddd, J=1.5, 2.5, 8.4 Hz), 8.21–8.22 (1H, dd, J=1.5, 4.8 Hz), 8.62–8.63 (1H, d, J=2.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C) δ 13.6, 113.7, 123.7, 129.0, 135.3, 142.7, 144.8, 156.6, 158.0, 160.1; HRMS (M+H$^+$)(ESI$^+$) 221.0588 [M+H$^+$] (calcd for $C_{10}H_9ClN_4H^+$ 221.0588);

*4.30.2. Compound **6** (TFA salt).* HPLC rt 2.63; ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.22 (3H, s), 7.76–7.82 (2H, m), 8.15 (1H, s), 8.43 (1H, d, J=5.4 Hz), 8.45 (1H, d, J=8.3 Hz), 8.53 (1H, dd, J=1.3, 5.1 Hz), 8.55 (1H, d, J=8.5 Hz), 9.15 (1H, d, J=2.1 Hz), 9.19 (1H, d, J=2.4 Hz), 9.40–9.46 (1H, br s), 10.35–10.38 (1H, br s), 13.40–13.55 (2H, br s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.8, 109.6, 116.5 (q, J=293 Hz), 126.2, 126.8, 132.7, 133.2, 134.8, 136.0, 138.1, 138.4, 126.8, 139.3, 139.8, 154.1, 155.9, 159.3 (q, J=35 Hz), 159.5; HRMS (M+H$^+$)(ESI$^+$) 279.1348 [M+H$^+$] (calcd for $C_{15}H_{14}N_6H^+$ 279.1353).

4.31. *N*-(2-Chloro-5-methylpyrimidin-4-yl)-4-methoxybenzamide (9a) and *N*-(4-hydroxy-5-methylpyrimidin-2-yl)-4-methoxybenzamide (10a)

Following the general procedure, using $Pd_2(allyl)_2Cl_2$ (4.4 mg, 0.011 mmol), cBridp (15.5 mg, 0.044 mmol), 2,4-dichloro-5-methylpyrimidine (116 μL, 1.0 mmol), 4-methoxybenzamide (181 mg, 1.2 mmol), and NaO-*t*-Bu (144 mg, 1.5 mmol) in aqueous TPGS-750M (2%, 1.0 mL), followed by purification using column chromatography (SiO_2) and ethyl acetate/cyclohexane (80/20 to 10/0), yielded **9a** and **10a** as a mixture (ratio: 66/34) as a white solid (240 mg, 87% yield). ^{1}H NMR (400 MHz, CD_3OD) δ 2.09 (2H, s), 3.83 (2H, s), 3.87 (1H, s), 3.97 (1H, s), 6.89 (0.7H, d, J=8.9 Hz), 6.89 (1.2H, d, J=8.9 Hz), 7.32 (0.3H, s), 7.53 (0.7H, s), 7.87 (1.3H, d, J=8.9 Hz), 7.91 (0.7H, d, J=8.9 Hz), 7.98 (1H, s), 8.55 (0.3H, s), in DMSO-d_6, the δ of the two methyl groups bared by the pyrimidine cycle was 1.83 for **9a** and 1.94 for **10a**; ^{13}C NMR (100 MHz, CD_3OD) δ 13.7, 55.3, 113.3, 117.5, 129.4, 151.4, 158.0, 161.6, 167.5, 173.6, one peak is missing and is believed to relax badly; HRMS (M+H$^+$)(ESI$^+$) of **9a** 166.9981 [M+H$^+$] (calcd for $C_5H_5ClN_2ONa^+$ 166.9988), amide was hydrolyzed during the analysis.

4.32. *N*-Benzyl-2-chloro-5-methylpyrimidin-4-amine (9b) and 2-(benzylamino)-5-methylpyrimidin-4-ol (10b)

Following the general procedure, using $Pd_2(allyl)_2Cl_2$ (4.4 mg, 0.011 mmol), cBridp (15.5 mg, 0.044 mmol), 2,4-dichloro-5-methylpyrimidine (117 μL, 1.0 mmol), benzylamine (109 μL, 1.0 mmol), and NaO-*t*-Bu (144 mg, 1.5 mmol) in aqueous TPGS-750M (2%, 1.0 mL), followed by purification using (*Si-C18*) and water+TFA (0.05%)/methanol(9/1 to 0/1), and, yielded **9b** as a white solid (168 mg, 72% yield) and **10b** as a white solid (33 mg, 14% yield).

*4.32.1. Compound **9b**.* ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.13 (3H, s), 4.79–4.81 (2H, d, J=2.4 Hz), 7.31–7.34 (5H, m), 7.80 (1H, s), 7.90–7.96 (1H, br s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.0, 46.1, 114.1, 128.3, 128.3, 128.9, 135.9, 143.1, 152.0, 162.6; HRMS (M+H$^+$)(ESI$^+$) 234.0791 [M+H$^+$] (calcd for $C_{12}H_{12}ClN_3H^+$ 234.0793).

*4.32.2. Compound **10b**.* ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.27 (3H, s), 4.70–4.74 (2H, br s), 7.33–7.373 (5H, m), 8.06 (1H, s), 9.86–9.92 (1H, br s), 12.57 (1H, br s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 15.5, 45.6,

114.0, 118.6, 128.1, 128.9, 136.1, 146.2, 153.8; HRMS ($M+H^+$)(ESI^+) 216.1127 [$M+H^+$] (calcd for $C_{12}H_{13}N_3OH^+$ 216.1131).

4.33. *tert*-Butyl indoline-1-carboxylate (12)[30]

Following the general procedure, using $Pd_2(allyl)_2Cl_2$ (4.4 mg, 0.011 mmol), cBridp (15.5 mg, 0.044 mmol), *tert*-butyl *N*-[2-(2-bromophenyl)ethyl]carbamate (300 mg, 1.0 mmol), and NaO-*t*-Bu (144 mg, 1.5 mmol) in aqueous TPGS-750M (2%, 1.0 mL), followed by purification using column chromatography (SiO_2) and EtOAc/*n*-heptane (1/9), yielded **12** as a yellow oil (185 mg, 84%); HPLC rt 4.41; ^1H NMR (300 MHz, $CDCl_3$) δ 1.57 (9H, s), 3.09 (2H, t, J=8.7 Hz), 3.94 (2H, t, J=8.7 Hz), 6.92 (2H, t, J=7.6 Hz), 7.10–7.9 (2H, m), 7.75–7.84 (1H, br s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 27.3, 28.5, 47.6, 80.4 (br), 114.7, 122.1, 124.7 (br), 127.4, 130.9 (br), 143.0 (br), 152.6.

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Supplementary data

^1H and ^{13}C NMR charts of the reported compounds, solubility graphs. Supplementary data associated with this article can be found in the online version, at http://dx.doi.org/10.1016/j.tet.2014.03.083.

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