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Synthesis of Biaryl Tertiary Amines through Pd/Norbornene Joint Catalysis in a Remote C−H Amination/Suzuki Coupling Reaction

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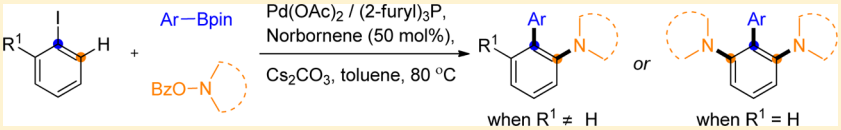
Supporting Information

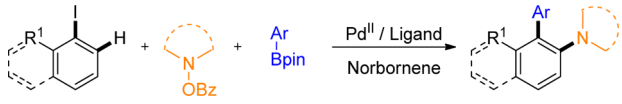


ABSTRACT: Here, we report on an efficient palladium/norbornene-catalyzed domino reaction of aryl halide, *O*-acyl hydroxylamine (R_1R_2N-OBz), and aromatic pinacol boronate (R-Bpin), selectively affording a series of biaryl tertiary amines in good to high yields with excellent functional group tolerance. This catalytic reaction provides a new opportunity for the convergent synthesis of biaryl amines from easily accessible starting materials.

Aromatic amines are of fundamental interest in a number of chemistry related fields, including agrochemicals, pharmaceuticals, electronic materials, organic pigments, photography, and so forth.[1] The importance of arylamines stimulated a rapid increase in modern catalytic methodologies for their synthesis. Currently, remarkable progress has been made in C−N bond formation reactions such as oxidative amidation,[2] hydroamination,[3] or nucleophilic amination,[4] as represented by the well-known Buchwald−Hartwig coupling reactions. Although primary or protected primary and secondary amines are all accessible via such methods, the direct preparation of tertiary amines remains difficult. To meet the demand, a new approach involving an electrophilic amination reaction of organometallic reagents with highly reactive $R^1R^2N^+$ synthons (R^1R^2N-X as an electrophile) has been studied.[5,6] Recently, site-selective amination of heteroaromatic[7] or chelation-assisted ortho-amination of benzamides[8] through catalytic C−H activation was successfully achieved, providing powerful alternatives to previously established carbon−nitrogen bond formation procedures. However, despite significant advances, the installation of amino groups or their surrogates onto unactivated remote C−H bonds, leading directly to aromatic tertiary amines, has received much less attention, presumably due to the fact that achieving a catalytic C−H amination reaction remains a distinct challenge currently.[8]

Not long ago, we[9] and the group of Dong[10] independently reported a novel palladium/norbornene-mediated Catellani-type domino reaction[11,12] of aryl iodide (Ar−I) with a secondary electrophilic amination reagent (R_2N-OBz). With the direction of norbornene, the C−H bond, which was located at the ortho position of C−I, could be selectively activated and reacted with R_2N^+ species to form a new carbon−nitrogen bond,[13] thus representing rather limited examples of palladium/norbornene-mediated Catellani-type ortho-selective C−H amination reactions.[9,10] In the context of this research and because of our continuous interest in domino reactions, we herein report on a Pd/norbornene-catalyzed remote C−H amination reaction of aryl iodide with electrophilic *O*-benzoyl hydroxylamine that was terminated by a Suzuki−Miyaura coupling reaction,[14] with which a series of substituted biaryl tertiary amines was selectively produced in good to high yields (Scheme 1). It is important to note that biaryl amine units

Scheme 1. Pd/Norbornene-Catalyzed Remote C−H Amination/Suzuki−Miyaura Coupling for the Formation of Biaryl Tertiary Amines



widely exist in many biologically active compounds, such as 5-HT_7 receptor agents.[15] Remarkably, suppressing the formation of Suzuki-type byproducts and preventing the coupling reaction of electrophilic R_2N^+ species with organoborates[16] are the keys to the success of this one-pot tandem transformation.

Initial screening of the reaction conditions employed *o*-iodotoluene (**1a**) with morpholino benzoate (**2a**) and phenylboronic acid (**3a**) as a starting point. Treatment of the model substrates with 5 mol % of $Pd(OAc)_2$ and 20 mol % of $(4\text{-}MeOC_6H_4)_3P$ together with 2.0 equiv of norbornene and 3.0 equiv of Cs_2CO_3 in anhydrous toluene at 80 °C yielded only 26% of desired product **4a** (Table 1, entry 1). Further experiments revealed that $(2\text{-furyl})_3P$ might be an optimal choice of ligand, as the yield of **4a** could be improved to 57% (Table 1, entries 2−6). The addition of H_2O (1.0 equiv) did not facilitate the reaction (Table 1, entry 7). Because Suzuki-type byproducts, which are generated from the coupling reaction of **1a** with **3a**, are always predominant in these

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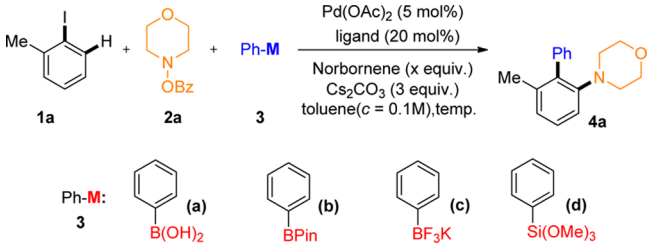
Table 1. Optimization of the Reaction Conditions[a]



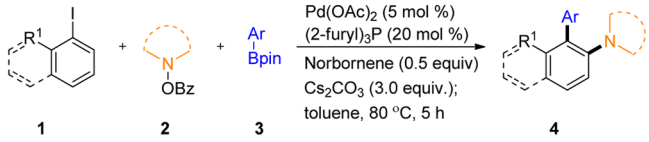
entry	Ph-M	ligand	*x* equiv (norbornene)	temp (°C)	yield (%)
1	3a	$(4\text{-MeOC}_6\text{H}_4)_3\text{P}$	2.0	80	26
2	3a	Ph_3P	2.0	80	30
3	3a	$(4\text{-CF}_3\text{C}_6\text{H}_4)_3\text{P}$	2.0	80	trace
4	3a	$(2\text{-furyl})_3\text{P}$	2.0	80	57
5	3a	Cy_3P	2.0	80	41
6	3a	$t\text{Bu}_3\text{P}\cdot\text{HBF}_4$	2.0	80	n.d.
7	3a	$(2\text{-furyl})_3\text{P}$	2.0	80	49[b]
8	3b	$(2\text{-furyl})_3\text{P}$	2.0	80	92
9	3c	$(2\text{-furyl})_3\text{P}$	2.0	80	trace
10	3d	$(2\text{-furyl})_3\text{P}$	2.0	80	n.d.
11	3b	$(2\text{-furyl})_3\text{P}$	1.0	80	92
12	**3b**	**$(2\text{-furyl})_3\text{P}$**	**0.5**	**80**	**93**
13	3b	$(2\text{-furyl})_3\text{P}$	0.25	80	81
14	3b	$(2\text{-furyl})_3\text{P}$	0.5	100	92
15	3b	$(2\text{-furyl})_3\text{P}$	0.5	60	42

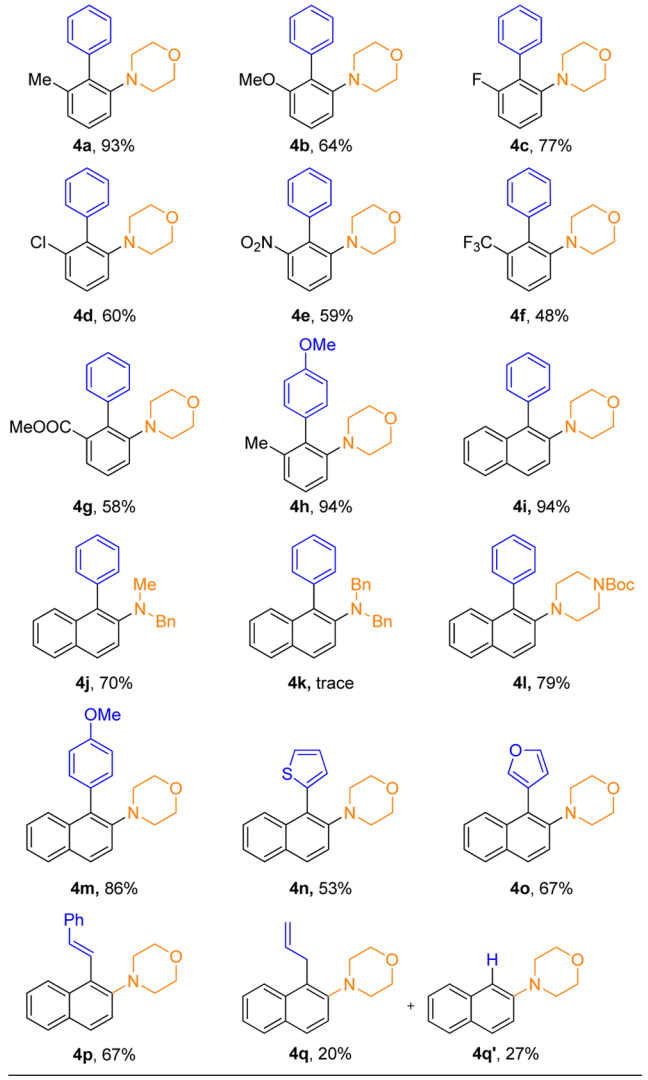
[a]Reaction conditions: **1a** (0.30 mmol), **2a** (0.45 mmol), **3** (0.45 mmol), $Pd(OAc)_2$ (0.015 mmol), ligand (0.06 mmol), norbornene (0.6 mmol), Cs_2CO_3 (0.9 mmol), toluene (3.0 mL, 0.10 M), 80 °C, N_2; isolated yields based on **1a**. [b]With H_2O (1.0 equiv).

reactions, we realized that the reactivity of the organometallic reagent (Ph-M) **3** in the reaction should play a critical role. Therefore, we next screened various organometalated phenyl species, such as phenyl pinacoborate (Ph-Bpin: 4,4,5,5-tetramethyl-2-phenyl-1,3,2-dioxaborolane, **3b**), potassium phenyltrifluoroborate (Ph-BF_3K, **3c**), and trimethoxy(phenyl)silane (Ph-$Si(OMe)_3$, **3d**). To our delight, a dramatically increased yield of 92% was obtained when Ph-Bpin (**3b**) was used (Table 1, entry 8). A complex reaction was observed when **3c** and **3d** were employed (Table 1, entries 9−10). In an attempt to reduce the loading of norbornene, we tested several reactions run at gradually decreasing amounts of this compound. The results revealed that the loading of norbornene could be decreased to 0.5 equiv without any obvious loss of the catalytic efficiency (Table 1, entry 12). Elevating the reaction temperature to 100 °C proved to be less favorable, whereas a rather sluggish result was observed when the temperature was lowered to 60 °C (Table 1, entries 14−15). Therefore, the optimal reaction conditions were highlighted when the reaction was carried out using organo pinacol boronate (Ar-Bpin) as substrate, $Pd(OAc)_2$ (5 mol %) as the catalyst, and $(2\text{-furyl})_3P$ (20 mol %) as the ligand in the presence of 0.5 equiv of norbornene and 3.0 equiv of Cs_2CO_3 in 0.1 mol/L of anhydrous toluene at 80 °C.

With the optimal reaction conditions secured (Table 1, entry 12), we next studied the substrate generality of the reaction, as shown in Table 2. Following the established procedure, a variety of iodoarenes **1**, *N*,*N*-dialkyl-*O*-acyl hydroxylamine **2**, and aromatic pinacol boronate **3** could participate in the reaction smoothly to give the expected biaryl tertiary amines **4**. The reactivity of iodoarenes **1** was first examined by employing

Table 2. Synthesis of Tertiary Amines 4 by a Palladium/Norbornene-Mediated Domino Reaction of Aryl Iodide 1, Secondary R_2N-OBz 2, and Pinacol Boronate 3[a]





[a]Reaction conditions: **1** (0.30 mmol), **2** (0.45 mmol), **3** (0.45 mmol), $Pd(OAc)_2$ (0.015 mmol), $(2\text{-furyl})_3P$ (0.06 mmol), norbornene (0.15 mmol), Cs_2CO_3 (0.9 mmol), toluene (3.0 mL, 0.10 M), 80 °C, N_2; isolated yields based on **1**.

morpholino benzoate **2a** and phenyl pinacol boronate **3b** as starting materials. Results indicated that many important functional groups on the aromatic ring of **1**, such as electron-rich methyl (**1a**) and methoxy (**1b**) groups, electron-deficient fluorine (**1c**), chlorine (**1d**), nitro (**1e**), trifluoromethyl (**1f**), and ester (**1g**) substituents, were compatible in the present catalytic reaction, affording the desired biphenyl tertiary amines **4a**−**4g** in good to excellent yields. Notably, the NO_2 and CF_3 groups were not tolerated in our previously developed C−H amination reaction,[9] and, more importantly, the aromatic molecules that were decorated by these groups are very

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interesting because they frequently display medicinal, biological, or electronic properties.[17] Furthermore, an excellent yield of **4h** was observed in the reaction of *o*-iodotoluene **1a** with morpholino benzoate **2a** and 4-methoxyphenyl pinacol boronate.

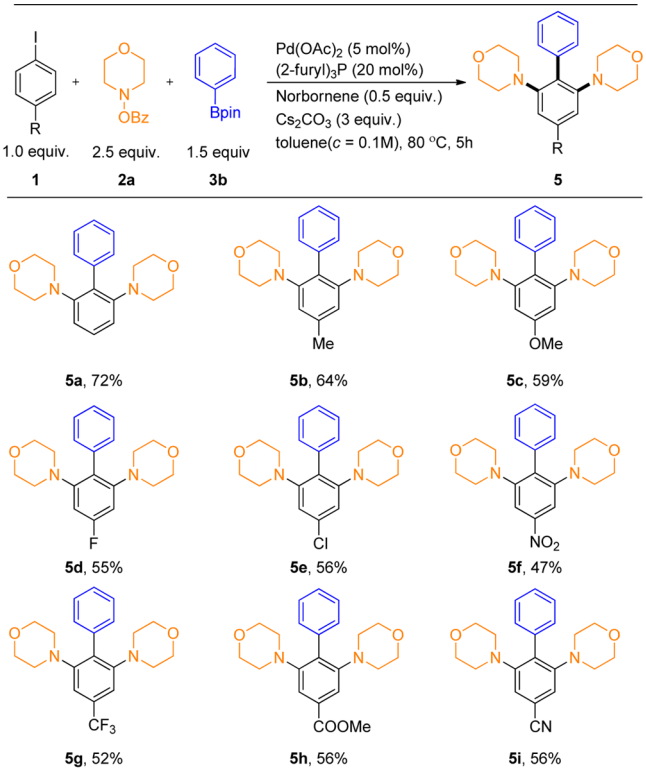
The reactions also worked well in the case of 1-iodonaphthalene (**1i**) with various secondary *O*-benzoyl hydroxylamines **2** and aromatic pinacol boronate **3** (Table 2). For instance, 1-iodonaphthalene (**1i**) reacted with **2a** and **3b** to give the corresponding product (**4i**) in 94% yield. Notably, acyclic *O*-benzoyl-*N*-benzyl-*N*-methylhydroxylamine, a synthetic equivalent of a secondary amine, can participate in the reaction without difficulty, and the expected product (**4j**) was isolated in 70% yield. In contrast, *O*-benzoyl-*N*,*N*-dibenzylhydroxylamine participated in the reaction of **1i** and **3b** sluggishly (**4k**), which presumably is attributed to a steric congestion effect. Besides, a secondary heterocyclic *N*-benzoyloxyamine containing a Boc protecting group was successfully incorporated into the naphthalene substrate in up to 79% yield (**4l**).

Finally, we examined the scope of the aromatic pinacol boronate partners **3** in the cascade reaction (Table 2). With 1-iodonaphthalene **1i** and morpholino benzoate **2a** as starting materials, it was found that the electron-rich aromatic pinacol boronate including heterocyclic 2-thiophenyl (**3n**) and 3-furyl (**3o**) pinacol boronate were compatible in the reaction, delivering the desired aromatic tertiary amines **4m**−**4o** in acceptable yields under the standard conditions. The unactivated styrene cannot participate in our previously developed domino reaction of aryl iodide with *O*-benzoyl hydroxylamines and terminal olefin.[9] Interestingly, we discovered herein that when switching the styrene substrate to 2-styryl pinacol boronate as a coupling partner the corresponding product **4p** was successfully generated in 67% yield. It is also interesting to note that the allyl pinacol boronate can participate in the palladium-catalyzed three-component reaction to afford the desired 4-(1-allylnaphthalen-2-yl)morpholine **4q**, albeit in a relatively low yield.[18] Compound **4q′**, which was formed through the more favored *β*-hydride elimination process, was isolated as the major byproduct in the reaction.[19]

The 2,6-dimorpholino-1,1′-biphenyl derivatives **5** can be generated when aryl iodides **1** bearing no ortho substituent reacted with morpholino benzoate **2a** and phenyl pinacol boronate **3b** (Table 3). Under the standard reactions, a great range of electron-rich (Me, MeO) and electron-poor (F, Cl, NO_2, CF_3, COOMe, and CN) substituents attached at the para position of aryl iodides **1** could participate in the reaction of morpholino benzoate **2a** and phenyl pinacol boronate **3b**, thus affording the corresponding biaryl tertiary diamines **5a**−**5i** in yields ranging from 47 to 72%.

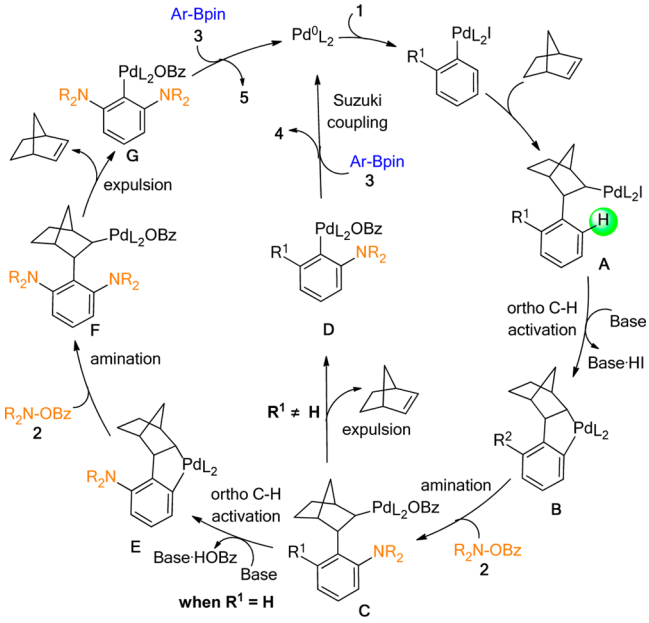
The proposed mechanism for this domino transformation is based on our previous result[9] and the known Catellani reaction (Scheme 2).[11,12] The first step involves oxidative addition of the iodoarene **1** with Pd(0), followed by syn-carbopalladation onto norbornene, forming species **A**. Subsequent ortho C−H activation reaction and elimination of HI with the aid of base give a five-membered palladacycle **B**. The second oxidative addition of *O*-benzoyl-*N*,*N*-dialkylhydroxylamine (R_2N-OBz) **2** to the palladium center in species **B** is proposed to form a Pd(IV) species,[20,21] which undergoes reductive elimination, leading to the ortho-aminated arene **C**. Alternatively, the direct electrophilic amination of R_2N-OBz with palladacycle **B** followed by N−O bond cleavage to form amination complex **C** might take place.[5,8,10] Next, in the case of ortho-blocked

Table 3. Synthesis of 2,6-Dimorpholino-1,1′-biphenyl 5 by a Domino Reaction of Aryl Iodide 1, Morpholino Benzoate 2a, and Phenyl Pinacol Boronate 3b[a]



[a]Reaction conditions: **1** (0.30 mmol), **2a** (0.75 mmol), **3a** (0.45 mmol), $Pd(OAc)_2$ (0.015 mmol), $(2\text{-furyl})_3P$ (0.06 mmol), norbornene (0.15 mmol), Cs_2CO_3 (0.9 mmol), toluene (3.0 mL, 0.10 M), 80 °C, N_2; isolated yields based on **1**.

Scheme 2. Proposed Mechanism



substrates ($R^1 \neq H$), decarbopalladation with concomitant expulsion of norbornene gives an aminated ArPd-OBz intermediate **D**, which undergoes a Suzuki-type cross-coupling reaction with organoboron compound **3** to give the final

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product **4**, along with the regeneration of Pd(0) species to complete the catalytic cycle. When species **C** bears no ortho-substituent (R^1 = H), the C−H activation process can be reiterated in the second ortho position, leading to a new five-membered palladacycle **E** and the amination complex **F**. The subsequent reaction for the expulsion of norbornene followed by suzuki-type cross-coupling with **3** may generate the diaminated product **5**.

In summary, we have developed a palladium/norbornene-mediated highly selective domino reaction of aryl halide, a secondary electrophilic amination agent (R_2N-OBz), and aromatic pinacol boronate (Ar-Bpin), affording a series of biaryl tertiary amines in good to high yields with excellent functional group tolerance. In spite of the considerable studies that were focused on ortho C−C bond formations using a carbon electrophile (R-X) as a coupling partner in traditional Catellani reactions, the present synthesis is unique in its fruitful, expedient synthesis of valuable biaryl tertiary amines.

EXPERIMENTAL SECTION

General Information for the Reagents. Unless otherwise noted, commercial reagents were purchased from commercial suppliers and were used as received. All solvents were dried and distilled according to standard procedures before use. Reactions were conducted in standard Schlenk techniques on vacuum line. Analytical thin-layer chromatography (TLC) was performed using glass plates precoated with 0.25 mm 230−400 mesh silica gel impregnated with a fluorescent indicator (254 nm). Flash column chromatography was performed using silica gel (60 Å pore size, 32−63 μm, standard grade). Organic solutions were concentrated on rotary evaporators at ∼20 Torr (house vacuum) at 25−35 °C. Nuclear magnetic resonance (NMR) spectra were recorded in parts per million (ppm) downstream from internal standard tetramethylsilane (TMS) on the δ scale. High-resolution mass spectrometry (HRMS) analysis was recorded by electron ionization (EI-TOF).

General Procedure for the Preparation of Compound 4. A 25 mL of Schlenk tube equipped with a Teflon-coated magnetic stir bar was charged with aryl iodide **1** (0.30 mmol), *O*-acyl hydroxyamine **2** (0.45 mmol), pinacol boronate **3** (0.45 mmol), $Pd(OAc)_2$ (0.015 mmol), $(2\text{-furyl})_3P$ (0.06 mmol), Cs_2CO_3 (0.9 mmol), norbornene (0.15 mmol), and anhydrous toluene (3.0 mL). The resulting dark brown suspension was stirred at room temperature for 10 min under N_2 and then heated at 80 °C for 5 h. Upon completion, as monitored by TLC, the reaction was allowed to cool to room temperature, diluted with ethyl acetate (5 mL) and water (15 mL), and extracted with ethyl acetate (10 mL × 3). The organic phase was collected and washed with brine, dried over Na_2SO_4, and concentrated. The crude residue was purified by a flash column chromatography on silica gel using petroleum ether/ethyl acetate as eluent to give the corresponding pure product **4**.

4-(6-Methyl-[1,1′-biphenyl]-2-yl)morpholine 4a. 69 mg, 93% yield; white solid; mp 83−84 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.09 (s, 3H), 2.72 (t, *J* = 4.4 Hz, 4H), 3.40 (t, *J* = 4.4 Hz, 4H), 6.90 (d, *J* = 8.4 Hz, 1H), 6.98 (d, *J* = 7.6 Hz,1H), 7.20 (t, *J* = 8.0 Hz,1H), 7.25−7.28 (m, 3H), 7.36−7.39 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.0, 51.9, 66.9, 116.4, 125.0, 126.4, 127.8, 130.3, 136.4, 137.2, 139.3 150.7; HRMS (ESI) calcd for $C_{17}H_{20}NO$ $[M + H]^+$, 254.1545; found, 254.1545.

4-(6-Methoxy-[1,1′-biphenyl]-2-yl)morpholine 4b. 52 mg, 64% yield; white solid; mp 143−144 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.75 (t, *J* = 4.4 Hz, 4H), 3.46 (t, *J* = 4.4 Hz, 4H), 3.70 (s, 3H), 6.69−6.73 (m, 2H), 7.24−7.29 (m, 2H), 7.35−7.44 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 51.7, 55.9, 66.9, 106.5, 111.5, 126.5, 127.6, 128.7, 131.0, 136.0, 151.7, 157.5; HRMS (ESI) calcd for $C_{17}H_{20}NO_2$ $[M + H]^+$, 270.1494; found, 270.1474.

4-(6-Fluoro-[1,1′-biphenyl]-2-yl)morpholine 4c. 58 mg, 77% yield; white solid; mp 71−72 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.77 (t, *J* = 4.4 Hz, 4H), 3.50 (t, *J* = 4.4 Hz, 4H), 6.77−6.84 (m, 2H), 7.19−7.25 (m, 1H), 7.30 (t, *J* = 7.6 Hz, 1H), 7.40 (t, *J* = 7.6 Hz, 2H), 7.50 (d, *J* = 8.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 51.5, 66.8, 110.1 (d, $^2J_{C-F}$ = 23.8 Hz), 113.8, 122.8 (d, $^2J_{C-F}$ = 15.9 Hz), 127.4, 128.2, 129.0, 130.4, 133.7, 152.1 (d, $^3J_{C-F}$ = 5.1 Hz), 160.5 (d, $^1J_{C-F}$ = 242.6 Hz); HRMS (ESI) calcd for $C_{16}H_{16}FNNaO$ $[M + Na]^+$, 280.1114; found, 280.1119.

4-(6-Chloro-[1,1′-biphenyl]-2-yl)morpholine 4d. 49 mg, 60% yield; white solid; mp 99−100 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.66 (t, *J* = 4.4 Hz, 4H), 3.35 (t, *J* = 4.4 Hz, 4H), 6.87 (d, *J* = 7.6 Hz, 1H), 7.09−7.16 (m, 2H), 7.23−7.35 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 51.6, 66.9, 117.3, 124.2, 127.3, 127.4, 127.9, 128.9, 130.6, 134.5, 137.2; 152.4; HRMS (ESI) calcd for $C_{16}H_{17}ClNO$ $[M + H]^+$, 274.0999; found, 274.1004.

4-(6-Nitro-[1,1′-biphenyl]-2-yl)morpholine 4e. 50 mg, 59% yield; yellow solid; mp 117−118 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.74 (t, *J* = 4.4 Hz, 4H), 3.45 (t, *J* = 4.4 Hz, 4H), 7.20 (d, *J* = 7.6 Hz, 1H), 7.33−7.41 (m, 7H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 51.6, 66.7, 117.3, 122.3, 128.1, 128.5, 128.9, 129.2, 134.3, 151.9, 152.1; HRMS (ESI) calcd for $C_{16}H_{17}N_2O_3$ $[M + H]^+$, 285.1239; found, 285.1234.

4-(6-(Trifluoromethyl)-[1,1′-biphenyl]-2-yl)morpholine 4f. 44 mg, 48% yield; white solid; mp 100−101 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.64 (t, *J* = 4.4 Hz, 4H), 3.28 (t, *J* = 4.4 Hz, 4H), 7.15−7.19 (m, 3H), 7.23−7.34 (m, 4H), 7.37 (d, *J* = 8.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 52.1, 66.8, 120.8, 123.3, 124.0 (q, $^1J_{C-F}$ = 272.7 Hz), 127.3, 127.4, 128.4, 130.3 (q, $^2J_{C-F}$ = 29.0 Hz), 130.4, 136.5, 136.6, 152.3; HRMS (ESI) calcd for $C_{17}H_{17}F_3NO$ $[M + H]^+$, 308.1262; found, 308.1271.

Methyl 6-Morpholino-[1,1′-biphenyl]-2-carboxylate 4g. 52 mg, 58% yield; white solid; mp 103−104 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.74 (t, *J* = 4.4 Hz, 4H), 3.47 (t, *J* = 4.4 Hz, 4H), 3.52 (s, 3H), 7.18 (d, *J* = 7.6 Hz, 1H), 7.25−7.41 (m, 7H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 51.6, 51.8, 66.8, 121.9, 123.5, 126.9, 127.7, 128.2, 129.5, 129.6, 134.2, 138.5, 151.0, 169.4; HRMS (ESI) calcd for $C_{18}H_{20}NO_3$ $[M + H]^+$, 298.1443; found, 298.1444.

4-(4′-Methoxy-6-methyl-[1,1′-biphenyl]-2-yl)morpholine 4h. 79 mg, 94% yield; white solid; mp 85−86 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.12 (s, 3H), 2.75 (t, *J* = 4.4 Hz, 4H), 3.46 (t, *J* = 4.4 Hz, 4H), 3.86 (s, 3H), 6.91 (d, *J* = 8.0 Hz, 1H), 6.93−6.96 (m, 2H), 6.99 (d, *J* = 7.6 Hz, 1H), 7.18−7.23 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.2, 51.9, 55.2, 67.1, 113.4, 116.4, 125.1, 127.7, 129.2, 131.5, 137.6, 151.1, 158.2; HRMS (ESI) calcd for $C_{18}H_{21}NNaO_2$ $[M + Na]^+$, 306.1470; found, 306.1480.

4-(1-Phenylnaphthalen-2-yl)morpholine 4i. 81 mg, 94% yield; white solid; mp 135−136 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.83 (t, *J* = 4.0 Hz, 4H), 3.45 (t, *J* = 4.0 Hz, 4H), 7.27−7.43 (m, 6H), 7.47 (t, *J* = 7.6 Hz, 2H), 7.59 (d, *J* = 8.4 Hz, 1H), 7.77−7.83 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 52.0, 67.1, 119.6, 124.3, 125.6, 126.1, 126.8, 127.8, 128.1, 128.8, 130.6, 131.2, 132.2, 133.4, 138.3, 147.4; HRMS (ESI) calcd for $C_{20}H_{20}NO$ $[M + H]^+$, 290.1545; found, 290.1554.

***N*-Benzyl-*N*-methyl-1-phenylnaphthalen-2-amine 4j.** 68 mg, 70% yield; yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.50 (s, 3H), 3.94 (s, 2H), 6.90 (d, *J* = 7.2 Hz, 2H), 7.14−7.16 (m, 2H), 7.28−7.40 (m, 6H), 7.44−7.53 (m, 4H), 7.77−7.84 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 40.8, 61.4, 121.2, 124.3, 125.8, 126.0, 126.8, 126.9, 127.8, 128.1, 128.4, 128.6, 130.5, 131.4, 132.7, 133.8, 139.0, 139.1, 148.7, 152.3; HRMS (ESI) calcd for $C_{24}H_{22}N$ $[M + H]^+$, 324.1752; found, 324.1747.

***tert*-Butyl 4-(1-Phenylnaphthalen-2-yl)piperazine-1-carboxylate 4l.** 92 mg, 79% yield; yellow solid; mp 133−134 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.43 (s, 9H), 2.82 (br, 4H), 3.19 (br, 4H), 7.28−7.39 (m, 6H), 7.46 (t, *J* = 7.6 Hz, 2H), 7.58 (d, *J* = 8.4 Hz, 1H), 7.78−7.83 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 28.4, 43.8, 51.6, 79.5, 119.8, 124.3, 125.6, 126.1, 126.8, 127.8, 128.1, 128.7, 130.6, 131.2, 132.5, 133.3, 138.3, 147.5, 154.8; HRMS (ESI) calcd for $C_{25}H_{29}N_2O_2$ $[M + H]^+$, 389.2229; found, 389.2224.

4-(1-(4-Methoxyphenyl)naphthalen-2-yl)morpholine 4m. 82 mg, 86% yield; white solid; mp 137−138 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.81 (t, *J* = 3.6 Hz, 4H), 3.48 (t, *J* = 3.6 Hz, 4H), 3.82 (s,

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3H), 6.97 (d, J = 8.0 Hz, 2H), 7.27−7.31 (m, 5H), 7.63 (d, J = 7.6 Hz, 1H), 7.76 (t, J = 7.6 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 51.9, 55.3, 67.2, 113.7, 119.6, 124.3, 125.7, 126.1, 128.0, 128.6, 130.3, 130.6, 131.6, 132.4, 133.7, 147.7, 158.6; HRMS (ESI) calcd for $C_{21}H_{22}NO_2$ $[M + H]^+$, 320.1651; found, 320.1645.

4-(1-(Thiophen-2-yl)naphthalen-2-yl)morpholine 4n. 47 mg, 53% yield; white solid; mp 105−106 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.95 (t, J = 4.4 Hz, 4H), 3.62 (t, J = 4.4 Hz, 4H), 7.10 (d, J = 3.6 Hz, 1H), 6.17 (t, J = 4.6 Hz, 1H), 7.34−7.38 (m, 3H), 7.48 (d, J = 5.2 Hz, 1H), 7.78−7.86 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 51.9, 67.1, 119.4, 124.3, 124.4, 125.4, 126.0, 126.4, 126.5, 127.8, 128.8, 129.7, 130.5, 134.2, 138.5, 149.1; HRMS (ESI) calcd for $C_{18}H_{18}NOS$ $[M + H]^+$, 296.1109; found, 296.1127.

4-(1-(Furan-3-yl)naphthalen-2-yl)morpholine 4o. 55 mg, 67% yield; white solid; mp 94−95 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.92 (t, J = 4.4 Hz, 4H), 3.64 (t, J = 4.4 Hz, 4H), 6.64 (s, 1H), 7.31−7.37 (m, 3H) 7.58 (d, J = 5.2 Hz, 2H), 7.76−7.94 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 52.0, 67.2, 113.4, 119.2, 120.8, 122.7, 124.3, 125.3, 126.3, 127.9, 128.9, 130.5, 133.6, 141.7, 142.6, 148.5; HRMS (ESI) calcd for $C_{18}H_{18}NO_2$ $[M + H]^+$, 280.1338; found, 280.1343.

(E)-4-(1-Styrylnaphthalen-2-yl)morpholine 4p. 63 mg, 67% yield; light yellow solid; mp 83−84 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.08 (t, J = 4.4 Hz, 4H), 3.84 (t, J = 4.4 Hz, 4H), 7.04 (d, J = 16.8 Hz, 1H), 7.28−7.47 (m, 6H), 7.57−7.62 (m, 3H), 7.75−7.81 (m, 2H), 8.38 (d, J = 8.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 52.4, 67.6, 118.5, 124.4, 124.8, 125.0, 126.2, 126.4, 127.5, 127.6, 128.3, 128.6, 128.9, 131.0, 132.2, 134.2, 138.0, 148.1; HRMS (ESI) calcd for $C_{22}H_{22}NO$ $[M + H]^+$, 316.1701; found, 316.1693.

4-(1-Allylnaphthalen-2-yl)morpholine 4q. 15 mg, 20% yield; colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.97 (t, J = 4.4 Hz, 4H), 3.88 (t, J = 4.4 Hz, 4H), 4.05 (d, J = 5.6 Hz, 2H), 4.89−5.04 (m, 2H), 6.06−6.15 (m, 1H), 7.36−7.49 (m, 3H), 7.75−7.80 (m, 2H), 7.97 (d, J = 8.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 30.9, 53.3, 67.6, 115.4, 120.2, 124.6, 124.9, 125.9, 127.9, 128.3, 130.1, 131.4, 133.2, 137.7, 148.4; HRMS (ESI) calcd for $C_{17}H_{19}NNaO$ $[M + Na]^+$, 276.1364; found, 276.1346.

General Procedure for the Preparation of Compound 5. A 25 mL of Schlenk tube equipped with a Teflon-coated magnetic stir bar was charged with aryl iodide **1** (0.30 mmol), morpholino benzoate **2a** (0.75 mmol), phenyl pinacol boronate **3b** (0.45 mmol), $Pd(OAc)_2$ (0.015 mmol), $(2\text{-furyl})_3P$ (0.06 mmol), Cs_2CO_3 (0.9 mmol), norbornene (0.15 mmol), and toluene (3.0 mL). The dark brown suspension was stirred at room temperature for 10 min under N_2 and then heated at 80 °C for 5 h. The reaction was monitored by TLC. After being cooled to room temperature, the reaction mixture was diluted with ethyl acetate (5 mL), transferred to a 50 mL of separatory funnel, washed with water (15 mL), and extracted with ethyl acetate (10 mL × 3). The organic phase was collected and washed with brine, dried over Na_2SO_4, and concentrated. The crude residue was purified by a flash column chromatography on silica gel using petroleum ether/ethyl acetate as eluent to give the corresponding pure product **5** as a white solid.

2,6-Dimorpholino-1,1′-biphenyl 5a. 70 mg, 72% yield; white solid; mp 164−165 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.71 (t, J = 4.4 Hz, 8H), 3.46 (t, J = 4.4 Hz, 8H), 6.84 (d, J = 8.0 Hz, 2H), 7.22−7.29 (m, 2H), 7.37 (t, J = 7.6 Hz, 2H), 7.50 (t, J = 8.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 51.9, 67.0, 114.4, 126.4, 127.7, 128.2, 128.7, 131.1, 137.4, 151.5; HRMS (ESI) calcd for $C_{20}H_{25}N_2O_2$ $[M + H]^+$, 325.1916; found, 325.1913.

4,4′-(4-Methyl-[1,1′-biphenyl]-2,6-diyl)dimorpholine 5b. 64 mg, 64% yield; white solid; mp 199−200 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.39 (s, 3H), 2.73 (t, J = 4.4 Hz, 8H), 3.49 (t, J = 4.4 Hz, 8H), 6.68 (s, 2H), 7.24 (t, J = 7.6 Hz, 1H), 7.38 (t, J = 7.6 Hz, 2H), 7.51 (d, J = 7.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.7, 51.9, 67.0, 115.1, 126.3, 126.9, 127.7, 128.2, 131.3, 138.5, 151.4; HRMS (ESI) calcd for $C_{21}H_{27}N_2O_2$ $[M + H]^+$, 339.2073; found, 339.2067.

4,4′-(4-Methoxy-[1,1′-biphenyl]-2,6-diyl)dimorpholine 5c. 58 mg, 59% yield; white solid; mp 165−166 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.68 (t, J = 4.4 Hz, 8H), 3.44 (t, J = 4.4 Hz, 8H), 3.82 (s, 3H), 6.37 (s, 2H), 7.19 (t, J = 7.6 Hz, 1H), 7.31 (t, J = 7.6 Hz, 2H), 7.45 (d, J = 8.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 51.8, 55.2, 66.9, 100.1, 126.2, 127.7, 128.2, 131.4, 137.4, 152.6, 159.9; HRMS (ESI) calcd for $C_{21}H_{27}N_2O_3$ $[M + H]^+$, 335.2022; found, 335.2016.

4,4′-(4-Fluoro-[1,1′-biphenyl]-2,6-diyl)dimorpholine 5d. 56 mg, 55% yield; white solid; mp 170−171 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.67 (t, J = 4.4 Hz, 8H), 3.45 (t, J = 4.4 Hz, 8H), 6.53 (d, J = 10.0, Hz, 2H), 7.24 (t, J = 6.4 Hz,1H), 7.35 (t, J = 7.6 Hz, 2H), 7.45 (d, J = 7.6 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 51.6, 66.8, 101.3, 101.5, 126.6, 127.9, 131.1, 136.8, 153.0 (d, $^3J_{C-F}$ = 10 Hz), 163.0 (d, $^1J_{C-F}$ = 244 Hz); HRMS (ESI) calcd for $C_{20}H_{24}FN_2O_2$ $[M + H]^+$, 343.1822; found, 343.1819.

4,4′-(4-Chloro-[1,1′-biphenyl]-2,6-diyl)dimorpholine 5e. 59 mg, 56% yield; white solid; mp 175−176 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.68 (t, J = 4.4 Hz, 8H), 3.45 (t, J = 4.4 Hz, 8H), 6.78 (s, 2H), 7.24 (t, J = 7.6 Hz,1H), 7.37 (t, J = 7.6 Hz, 2H), 7.46 (d, J = 7.6 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 51.7, 66.8, 114.9, 119.3, 126.8, 128.0, 130.9, 136.6, 138.1, 152.6; HRMS (ESI) calcd for $C_{20}H_{24}ClN_2O_2$ $[M + H]^+$, 359.1526; found, 359.1526.

4,4′-(4-Nitro-[1,1′-biphenyl]-2,6-diyl)dimorpholine 5f. 52 mg, 47% yield; yellow solid; mp 189−190 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.74 (t, J = 4.4 Hz, 8H), 3.48 (t, J = 4.4 Hz, 8H), 7.31 (t, J = 7.2 Hz, 1H), 7.44 (t, J = 7.6 Hz, 2H), 7.51 (d, J = 8.4 Hz, 2H), 7.65 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 51.5, 66.6, 109.6, 127.7, 128.3, 130.3, 135.8, 136.2, 148.3, 152.5; HRMS (ESI) calcd for $C_{20}H_{24}N_3O_4$ $[M + H]^+$, 370.1767; found, 370.1769.

4,4′-(4-(Trifluoromethyl)-[1,1′-biphenyl]-2,6-diyl)-dimorpholine 5g. 61 mg, 52% yield; white solid; mp 172−173 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.72 (t, J = 4.4 Hz, 8H), 3.46 (t, J = 4.4 Hz, 8H), 7.04 (s, 2H), 7.23 (t, J = 7.6 Hz, 1H), 7.40 (t, J = 7.6 Hz, 2H), 7.49 (d, J = 7.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 51.6, 66.8, 111.2, 124.2 (q, $^1J_{C-F}$ = 271 Hz), 127.1, 128.1, 130.7, 133.4, 136.4, 152.1; HRMS (ESI) calcd for $C_{21}H_{24}F_3N_2O_2$ $[M + H]^+$, 393.1790; found, 393.1790.

Methyl 2,6-Dimorpholino-[1,1′-biphenyl]-4-carboxylate 5h. 64 mg, 56% yield; white solid; mp 164−165 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.76 (t, J = 4.4 Hz, 8H), 3.50 (t, J = 4.4 Hz, 8H), 3.96 (s, 3H), 7.30 (t, J = 7.2 Hz, 1H), 7.42 (t, J = 7.6 Hz, 2H), 7.52−7.55 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 51.7, 52.1, 66.8, 115.7, 127.0, 127.9, 130.4, 130.7, 136.6, 151.7, 166.9; HRMS (ESI) calcd for $C_{22}H_{27}N_2O_4$ $[M + H]^+$, 383.1971; found, 383.1980.

2,6-Dimorpholino-[1,1′-biphenyl]-4-carbonitrile 5i. 57 mg, 56% yield; white solid; mp 194−195 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.67 (t, J = 4.4 Hz, 8H), 3.44 (t, J = 4.4 Hz, 8H), 7.04 (s, 2H), 7.28 (t, J = 7.6 Hz, 1H), 7.39 (t, J = 7.6 Hz, 2H), 7.46 (d, J = 7.6 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 51.5, 66.6, 112.3, 118.1, 127.5, 128.2, 128.8, 130.4, 130.9, 135.8, 152.3; HRMS (ESI) calcd for $C_{21}H_{24}N_3O_2$ $[M + H]^+$, 350.1869; found, 350.1855.

■ ASSOCIATED CONTENT

Supporting Information

^{1}H and ^{13}C NMR spectra of all products. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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