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Palladium-Catalyzed Arylation of C(sp^2)−H Bonds with 2-(1-Methylhydrazinyl)pyridine as the Bidentate Directing Group

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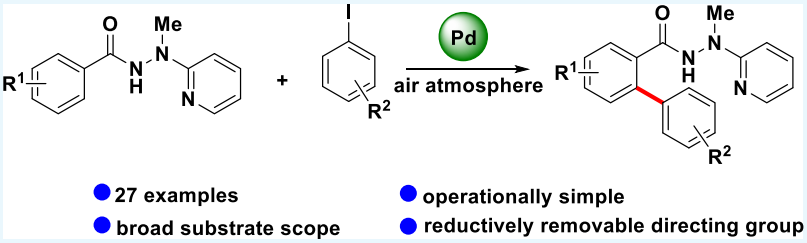

ABSTRACT: Palladium-catalyzed C(sp^2)−H arylation of *ortho* C−H bonds involving 2-(1-methylhydrazinyl)pyridine (MHP) as the directing group has been investigated. The reaction proceeds smoothly under an air atmosphere to generate biaryl derivatives in an environmentally friendly manner while tolerating a wide range of functional groups. Notably, the directing group present in the product could be easily removed under mild reductive conditions.

INTRODUCTION

Transition-metal-catalyzed C−H functionalization is a powerful tool for the transformation of an inert C−H bond into a C−C or C−X (X = N, O, S, F, B, etc.) bond that enables efficient construction of structurally diverse natural products and pharmaceutical compounds.[1,2] In particular, C−H arylation, as an environmentally benign and economically attractive alternative to the traditional cross-coupling reactions that require prefunctionalized substrates and generate stoichiometric metallic wastes, has garnered considerable attention.[3,4] In 2005, Daugulis and co-workers reported their pathbreaking example of 8-aminoquinoline-directed C(sp^2)−H and C(sp^3)−H arylation by utilizing Pd(OAc)$_2$ as the catalyst.[5] It is believed that the bidentate auxiliaries could bind to a metal center and allow direct insertion of a metal catalyst into a proximal C−H bond, followed by functionalization of the resulting organometallic intermediate. Since then, a variety of dual-chelation-assisted C−H arylations have been developed, in which 8-aminoquinoline, picolinic acid, and other related compounds are the most used directing moieties.[6]

The biaryl unit widely occurs in natural products, pharmaceuticals, agrochemicals, and conjugated materials,[7] as exemplified by hippadine,[8] azilsartan,[9] and bifenthrin[10] (Figure 1). By exploiting C(sp^2)−H arylation, the biaryl motifs have been constructed successfully with the aid of metal catalysts such as palladium,[5,11] ruthenium,[12] cobalt,[13] nickel,[14] copper,[15] and iron[16] complexes (Scheme 1).

Recently, we have developed a novel removable bidentate directing group, 2-(1-methylhydrazinyl)pyridine (MHP),[17] which exhibited superior reactivity in the functionalization of aromatic C(sp^2)−H bonds. This directing group can be easily

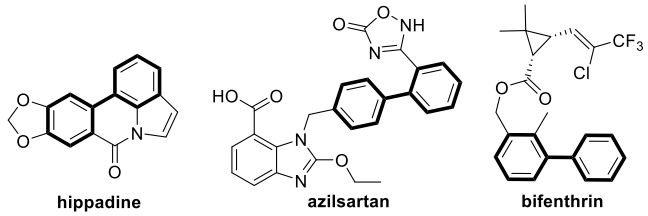

Figure 1. Representative bioactive biaryl derivatives.

synthesized from commercially available materials. So far, we have achieved highly efficient C−H functionalization of benzoyl hydrazides with alkynes,[17a] CO,[17b] allenes,[17c] maleimides,[17d,e] oxabicyclic alkenes,[17f] and isocyanides.[17g] Herein, we report a palladium-catalyzed direct C(sp^2)−H arylation with MHP as the directing group. The current synthetic approach to biaryl derivatives features a broad substrate scope, great functional group tolerance, and operational simplicity. In particular, the directing group present in the products could be easily removed under mild reductive conditions in our case.[17]

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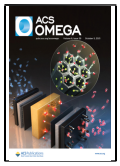
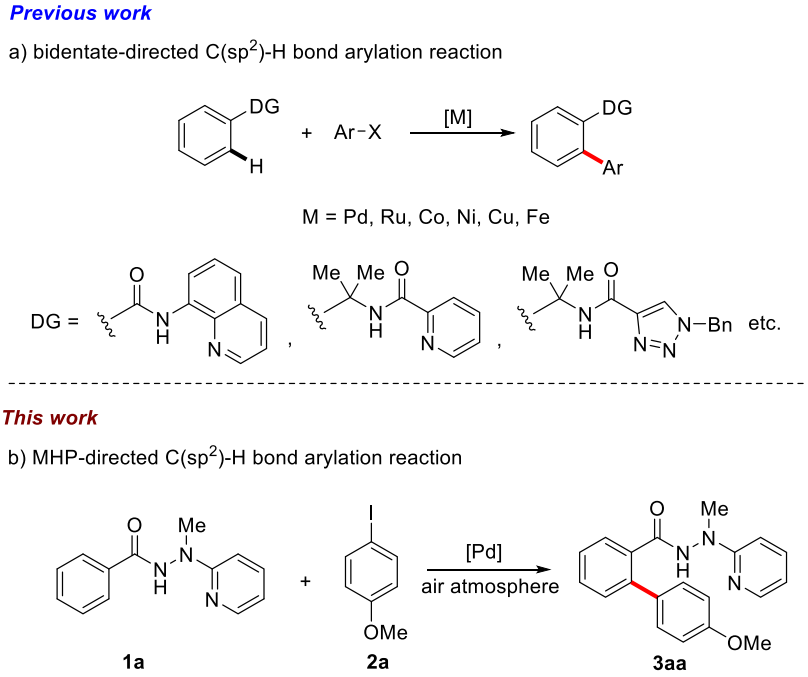


Scheme 1. Transition Metal-Catalyzed C(sp^2)−H Arylation

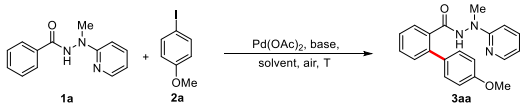


RESULTS AND DISCUSSION

N′-Methyl-*N*′-(pyridin-2-yl)benzohydrazide **1a** and 4-iodoanisole **2a** were chosen as the model substrates to survey the optimal reaction parameters. For the baseline experiment, treatment of **1a** with **2a** in the presence of $Pd(OAc)_2$ (10 mol %), AgOAc (1.5 equiv), and NaOPiv (2.0 equiv) in PhCl at 130 °C for 24 h afforded the desired biphenyl product **3aa** in 10% yield (Table 1, entry 1). Similar results were obtained when AgOAc was replaced with other silver salts such as Ag_2CO_3 and $AgNO_3$ (entries 2 and 3), suggesting that the type of silver salt has little effect on the reaction. A significant enhancement of the reaction efficiency (46%) was realized when the reaction time was extended to 48 h in the absence of any silver salt additives (entry 4). A brief screening of catalysts revealed that $Pd(OAc)_2$ is the optimal catalyst (Table S1). The yield of **3aa** was further improved as the catalyst load was increased to 20 mol % (entry 5). Various bases including NaOAc, Na_2CO_3, $NaHCO_3$, K_2CO_3, and KOAc were evaluated and NaOAc was found to be the best in terms of the reaction outcome (entries 6−10). Comparison of the solvents revealed that *m*-xylene, mesitylene, and dimethylformamide (DMF) were inferior to PhCl (entries 11−13). The yield of **3aa** was increased to 77% when the reaction was conducted at 140 °C, while the yield of **3aa** dropped significantly at 120 °C (entries 14 and 15). The control experiments indicated that the presence of the base was critical to the reaction (entry 16) and that the reaction was completely inhibited in the absence of the $Pd(OAc)_2$ catalyst (entry 17).

Having established the optimized reaction conditions, we next explored the scope of the hydrazide substrates (Scheme 2). Gratifyingly, benzoyl hydrazides bearing either an electron-donating group (e.g., Me, ^{t}Bu, OMe, SMe, OPh, OCF_3, and Ph) or an electron-withdrawing group (e.g., F, Cl, Br, CF_3, and CO_2Me) at the para-position of the aromatic ring were well accommodated, furnishing the expected products in moderate to high yields (**3aa**−**3ma**), which indicated that the reaction might not be sensitive to the electronic effect. Substrates with a meta-substituent (e.g., Me and Cl) on the benzene ring afforded **3na** and **3oa** in 67 and 70% yields, respectively. ortho-Substituted hydrazides were also compatible with this protocol (**3pa**, **3qa**). In addition, the 2-naphthamide derivative was proved to be a suitable substrate, giving the product in 75% yield (**3ra**). However, the hydrazide with a heteroaromatic moiety (such as furan) seemed to be less efficient under the

Table 1. Optimization of Reaction conditions[a]



entry	solvent	additive	base	yield(%)[b]
1[c,d]	PhCl	AgOAc	NaOPiv	10
2[c,d]	PhCl	Ag_2CO_3	NaOPiv	trace
3[c,d]	PhCl	$AgNO_3$	NaOPiv	8
4[d]	PhCl	/	NaOPiv	46
5	PhCl	/	NaOPiv	51
6	PhCl	/	Na_2CO_3	57
7	PhCl	/	NaOAc	69
8	PhCl	/	$NaHCO_3$	53
9	PhCl	/	K_2CO_3	ND
10	PhCl	/	KOAc	26
11	*m*-xylene	/	NaOAc	35
12	mesitylene	/	NaOAc	38
13	DMF	/	NaOAc	ND
14[e]	PhCl	/	NaOAc	54
15[f]	**PhCl**	/	**NaOAc**	**77 (75**[h]**)**
16[f]	PhCl	/	/	30
17[f,g]	PhCl	/	NaOAc	ND

[a]Reaction conditions: **1a** (0.2 mmol), **2a** (0.6 mmol), $Pd(OAc)_2$ (0.04 mmol), base (0.4 mmol), solvent (2.0 mL), 48 h, air, 130 °C. [b]Determined by ^{1}H NMR using 1,3,5-trimethoxybenzene as the internal standard. [c]The reaction time was 24 h, under Ar. [d]$Pd(OAc)_2$ (0.02 mmol) was used. [e]At 120 °C. [f]At 140 °C. [g]In the absence of $Pd(OAc)_2$. [h]Isolated yield. ND = not detectable.

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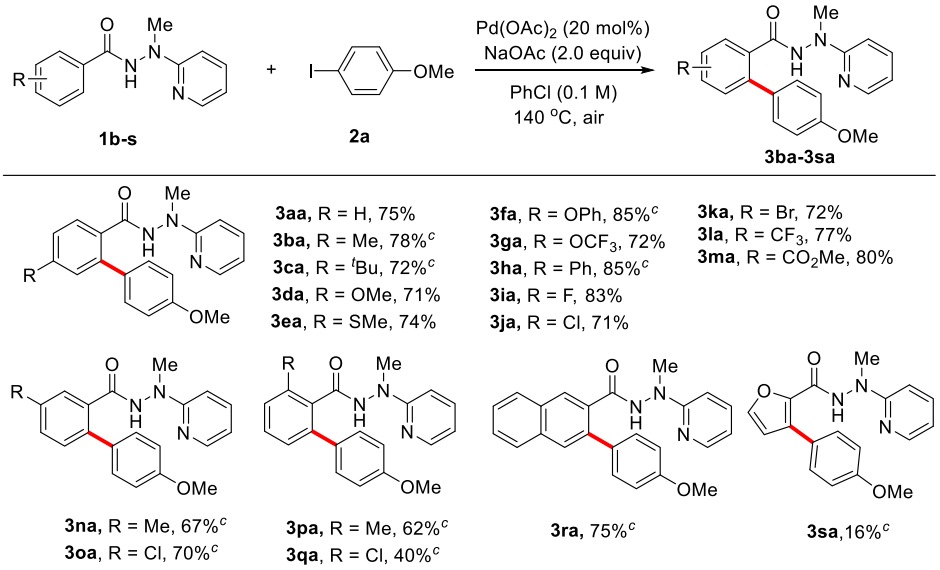
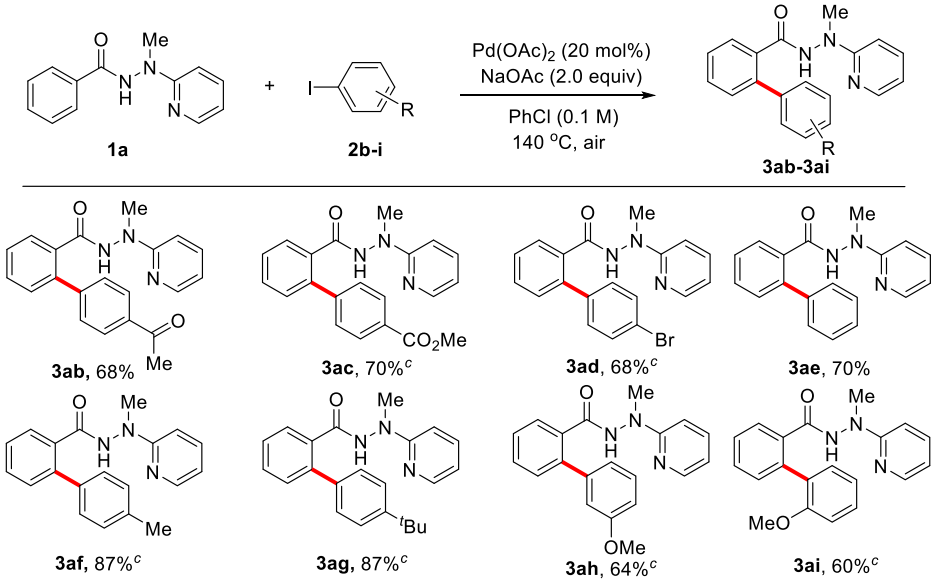
Scheme 2. Substrate Scope of the Benzoylhydrazide[a,b]



[a]Reaction conditions: **1** (0.2 mmol), **2a** (0.6 mmol), $Pd(OAc)_2$ (20 mol %), NaOAc (2.0 equiv), PhCl (2.0 mL), air, 140 °C, 48 h. [b]Isolated yields. [c]The reaction time was 72 h.

Scheme 3. Substrate Scope of the Iodobenzenes[a,b]



[a]Reaction conditions: **1a** (0.2 mmol), **2** (0.6 mmol), $Pd(OAc)_2$ (20 mol %), NaOAc (2.0 equiv), PhCl (2.0 mL), air, 140 °C, 48 h. [b]Isolated yields. [c]The reaction time was 72 h.

standard conditions, delivering the corresponding product in only 16% yield (**3sa**).

The scope of the aryl iodide substrates was then investigated and the results are summarized in Scheme 3. The experiments showed that aryl iodides with electron-withdrawing substituents at the para-position afforded the corresponding coupling products in 68−70% yields (**3ab**−**3ad**). Notably, aryl iodides with a Br atom on the phenyl ring (see **3ad**) worked well and showed excellent chemoselectivity in this reaction. In comparison, aryl iodides with an electron-donating substituent at the para-position performed even better (**3af**, **3ag**). Moreover, when the electron-donating group was located at the ortho- or meta-position of aryl iodides, the reaction still worked but gave the products in slightly lower yields (**3ah**, **3ai**).

Next, replacement of Ar−I with Ar−OTf, Ar−OTs, Ar−Br, and Ar−Cl was evaluated for the reaction (Scheme 4). With Ar−OTf (**2j**), Ar−OTs (**2k**), and Ar−Cl (**2m**, **2o**) as the substrates, no desired products were obtained, while the reaction of aryl bromides **2l**, **2n**, and **2p** did give a trace amount of the products under the standard conditions. This can be accounted for based on the barrier for oxidative addition of aryl halides, which increases in the order of ArI < ArBr < ArCl, consistent with the reactivity order. The speculation is in line with the mechanism proposed in the literature.[18]

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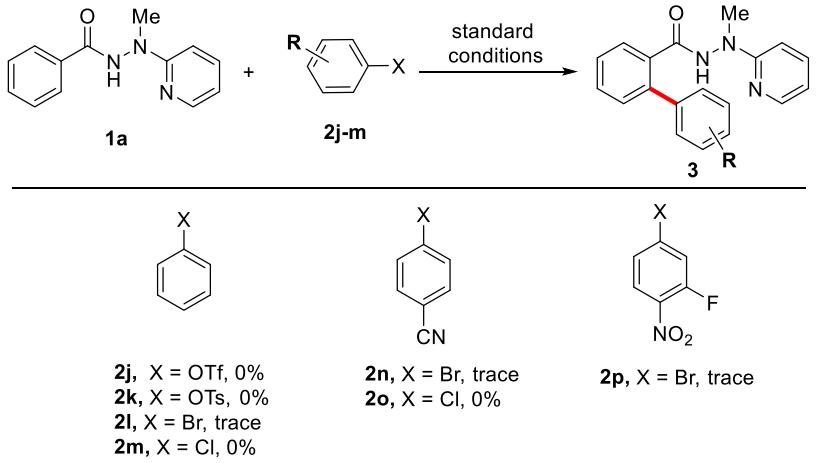
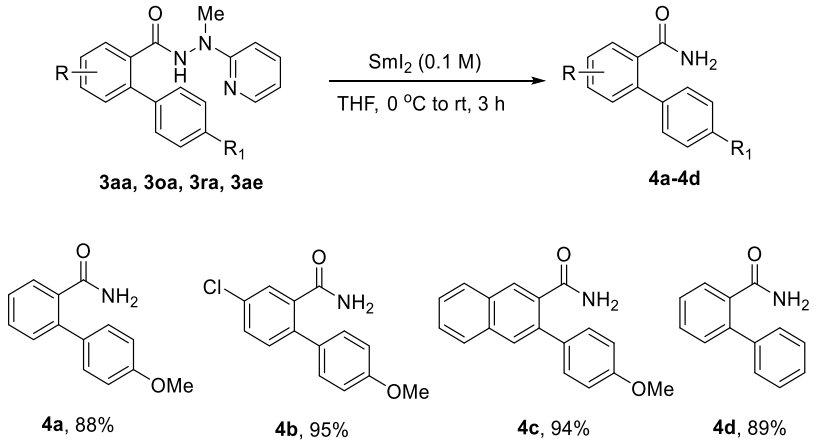
Scheme 4. Substrate Scope of Other Coupling Partners[a,b]

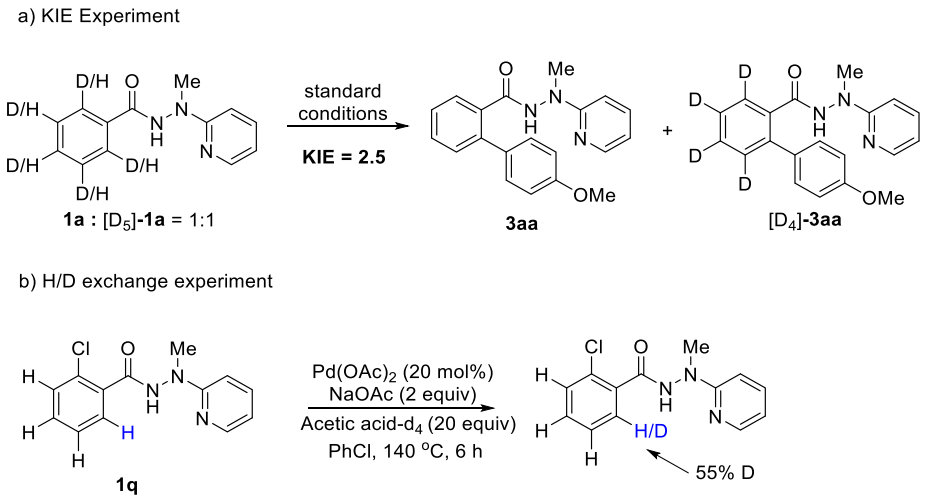


[a]Reaction conditions: **1a** (0.2 mmol), **2** (0.6 mmol), $Pd(OAc)_2$ (20 mol %), NaOAc (2.0 equiv), PhCl (2.0 mL), air, 140 °C, 48 h. [b]Determined by ^1H NMR using 1,3,5-trimethoxybenzene as the internal standard.

Scheme 5. Reductive Removal of the Directing Group



Scheme 6. Mechanistic Studies



Similar to the transformations developed previously in this laboratory,[17] the N−N bond present in the products was easily cleaved under mild reductive conditions. For example, treatment of 2-aryl benzoyl hydrazines **3aa**, **3oa**, **3ra**, and **3ae** with SmI_2 afforded benzamides **4a**−**4d** in 88−95% yields (Scheme 5). Therefore, the current reaction features easy *N*-deprotection that allows further *N*-derivatization.

The reaction kinetics plot revealed that the reaction rate was fast at the start of the reaction and gradually decreased with time (see the Supporting Information). In order to better

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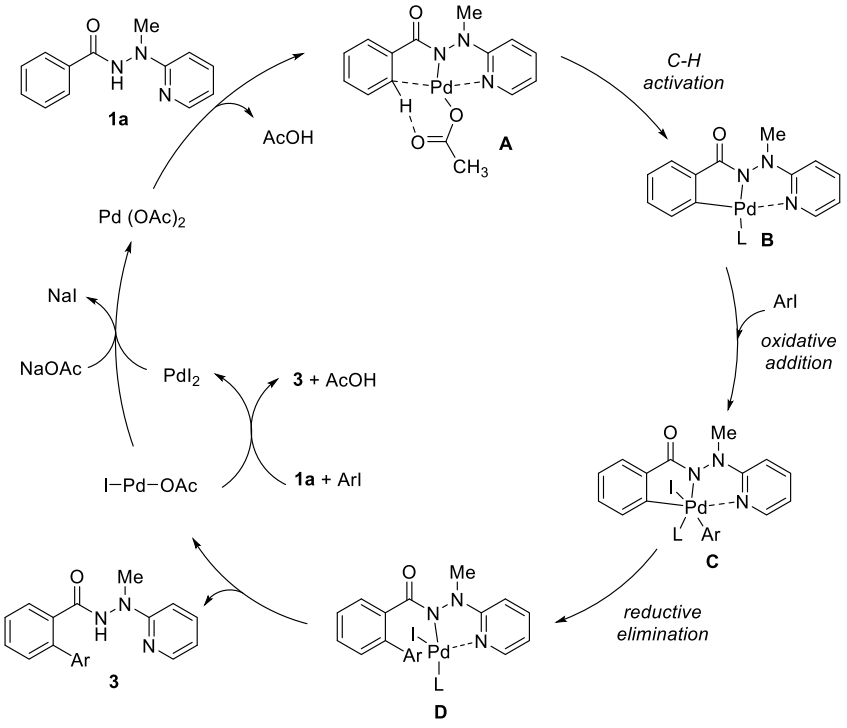
Scheme 7. Proposed Mechanism



understand the reaction mechanism, the kinetic isotope effect of the catalytic reaction was evaluated by the reaction of hydrazide **1a** and isotopically labeled counterpart [D_5]-**1a** with **2a** under the standard reaction conditions (Scheme 6). The k_H/k_D value was determined to be 2.5, indicating that *ortho* C(sp^2)−H bond cleavage took place in the rate-determining step (see the Supporting Information). Furthermore, by employing acetic acid-d_4 as a cosolvent, H/D scrambling was observed at the ortho-position of the carbonyl group in **1q**, suggesting the reversibility of the C−H cleavage step under the reaction conditions.

Based on our preliminary mechanistic studies and the relevant literature reports,[19] a plausible reaction mechanism is proposed in Scheme 7. First, **1a** reacts with $Pd(OAc)_2$ to generate the palladium amidate A, facilitating the subsequent C−H insertion to produce the palladium chelate B. Oxidative addition of B to aryl iodide forms Pd(IV) species C, which undergoes reductive elimination to deliver the desired product **3** along with PdIOAc. The latter (i.e., PdIOAc) could initiate a second catalytic cycle, leading to the unreactive species, PdI_2. However, both PdI_2 and PdIOAc could react with NaOAc to regenerate the catalyst, $Pd(OAc)_2$.

CONCLUSIONS

We have accomplished an efficient palladium-catalyzed C-(sp^2)−H arylation involving the easily accessible and highly efficient MHP as the directing group. With this unique directing group developed by our laboratory, arylations of C−H bonds were carried out under an air atmosphere with good regioselectivity, and a wide range of aryl iodides and benzoic hydrazides were successfully applied. In spite of the involvement of the palladium catalyst, our protocol should still be useful in the facile construction of valuable biaryl scaffolds, considering the superb accessibility and removability of the MHP directing group as well as the potential recyclability of the catalyst in large-scale applications. Studies on the application of MHP as the directing group to other related transformations and to achieve a clearer understanding of the reaction mechanism are ongoing.

EXPERIMENTAL SECTION

General Information. All reactions were carried out under an air atmosphere, unless otherwise noted. All the chemicals were purchased commercially, and used without further purification. Thin-layer chromatography (TLC) was conducted with 0.25 mm Tsingdao silica gel plates (60F-254) and visualized by exposure to UV light (254 nm). Flash column chromatography was performed on the Tsingdao silica gel (200−300 mesh). ^{1}H NMR spectra were recorded on Bruker spectrometers (at 400 or 500 MHz) and reported relative to deuterated solvent signals or tetramethylsilane internal standard signals. Data for ^{1}H NMR spectra were reported as follows: chemical shift (δ/ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, and br = broad), coupling constant (J/Hz), and integration. ^{13}C NMR spectra were recorded on Bruker spectrometers (101 or 126 MHz). Data for ^{13}C NMR spectra were reported in terms of chemical shift. ^{19}F NMR spectra were recorded on Bruker spectrometers (376 MHz). High-resolution mass spectrometry (HRMS) was conducted on Bruker Apex IV RTMS.

General Procedure for the Synthesis of Starting Materials (1a−1s). To a stirred solution of MHP (1.0 equiv, 5.0 mmol) and Et_3N (5.0 equiv) in dry dichloromethane (DCM) (0.5 M) was added benzoyl chloride (1.05 equiv) dropwise under an Ar atmosphere at 0 °C. After stirring for 30 min, the resulting mixture was warmed to room temperature and stirred overnight at this temperature. Upon completion of the reaction indicated by TLC, the reaction mixture was washed with H_2O and extracted with DCM (50 mL × 3). The combined organic phases were washed with brine, dried over

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with anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography (petroleum ether/EtOAc = 3:1 to 1:1) to afford the corresponding product. All spectroscopic data of **1a**−**1s** are in good agreement with the literature reported data.[17]

General Procedure for Palladium-Catalyzed C(sp^2)−H Arylation. A mixture of *N*′-methyl-*N*′-(pyridin-2-yl)-benzohydrazide (0.2 mmol, 1.0 equiv), aryl iodides (0.6 mmol, 3.0 equiv), $Pd(OAc)_2$ (9 mg, 0.2 equiv), NaOAc (33 mg, 2.0 equiv), and PhCl (2.0 mL, 0.1 M) was added to a 10 mL reaction tube. It was stirred at 140 °C for 48 h under air conditions. After cooling to room temperature, the reaction mixture was filtered through a plug of Celite, followed by washing with 10 mL of DCM. The combined residue was concentrated under reduced pressure, and then the resulting crude product was purified by column chromatography to provide **3**.

General Procedure for Reductive Removal of the Directing Group. An oven-dried 25 mL two-neck round bottom flask was charged with **3** (0.1 mmol). After purging with Ar three times, 5 mL fresh distilled THF was added, followed by the dropwise addition of SmI_2 (0.1 M in THF, 5.0 equiv) at 0 °C. After 5 min, the mixture was warmed to room temperature and stirred for 3 h. After that, the mixture was quenched with 5 mL saturated aqueous $Na_2S_2O_3$ and extracted with DCM, dried over Na_2SO_4, filtered, concentrated under reduced pressure, and **4** was obtained via column chromatography.

Characterization Data of Products. 4′-Methoxy-*N*′-methyl-*N*′-(pyridin-2-yl)-[1,1′-biphenyl]-2-carbohydrazide. Compound **3aa** (50 mg, yield = 75%) was isolated (petroleum ether/EtOAc = 10:1 to 3:1) as a white foam. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.11 (ddd, *J* = 5.0, 1.8, 0.8 Hz, 1H), 7.71 (dd, *J* = 7.6, 1.1 Hz, 1H), 7.51 (td, *J* = 7.5, 1.4 Hz, 1H), 7.46−7.37 (m, 4H), 7.34 (ddd, *J* = 8.8, 7.2, 1.9 Hz, 1H), 7.23 (s, 1H), 6.98 (d, *J* = 8.7 Hz, 2H), 6.64 (ddd, *J* = 7.1, 5.0, 0.8 Hz, 1H), 6.30 (d, *J* = 8.5 Hz, 1H), 3.85 (s, 3H), 3.13 (s, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 168.8, 159.6, 159.1, 147.5, 139.5, 137.4, 133.6, 132.2, 130.6, 130.2, 130.2, 128.9, 127.4, 114.6, 114.3, 107.2, 55.4, 37.5. HRMS m/z: $[M + H]^+$ calcd for $C_{20}H_{20}N_3O_2$, 334.1477; found, 334.1550.

4′-methoxy-*N*′,5-dimethyl-*N*′-(pyridin-2-yl)-[1,1′-biphenyl]-2-carbohydrazide. Compound **3ba** (54 mg, yield = 78%) was isolated (petroleum ether/EtOAc = 10:1 to 3:1) as a white foam. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.13 (dd, *J* = 4.9, 1.0 Hz, 1H), 7.66 (d, *J* = 7.8 Hz, 1H), 7.41 (d, *J* = 8.7 Hz, 2H), 7.35 (ddd, *J* = 8.8, 7.3, 1.8 Hz, 1H), 7.25 (d, *J* = 9.5 Hz, 1H), 7.19 (s, 1H), 7.09 (s, 1H), 6.99 (d, *J* = 8.7 Hz, 2H), 6.64 (dd, *J* = 6.7, 5.3 Hz, 1H), 6.33 (d, *J* = 8.5 Hz, 1H), 3.85 (s, 3H), 3.15 (s, 3H), 2.43 (s, 3H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 168.7, 159.6, 159.1, 147.4, 140.9, 139.5, 137.4, 132.4, 131.0, 130.6, 130.1, 129.1, 128.1, 114.5, 114.2, 107.2, 55.4, 37.4, 21.4. HRMS *m*/*z*: $[M + H]^+$ calcd for $C_{21}H_{22}N_3O_2$, 348.1707; found, 348.1706.

5-(*tert*-butyl)-4′-methoxy-*N*′-methyl-*N*′-(pyridin-2-yl)-[1,1′-biphenyl]-2-carbo-hydrazide. Compound **3ca** (55 mg, yield = 72%) was isolated (petroleum ether/EtOAc = 10:1 to 3:1) as a white solid; mp 81−83 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.11 (ddd, *J* = 4.9, 1.8, 0.8 Hz, 1H), 7.69 (d, *J* = 8.1 Hz, 1H), 7.47 (dd, *J* = 8.2, 2.0 Hz, 1H), 7.42 (d, *J* = 8.7 Hz, 2H), 7.38−7.31 (m, 2H), 7.15 (s, 1H), 7.00 (d, *J* = 8.7 Hz, 2H), 6.64 (ddd, *J* = 7.1, 5.0, 0.7 Hz, 1H), 6.32 (d, *J* = 8.5 Hz, 1H), 3.86 (s, 3H), 3.14 (s, 3H), 1.36 (s, 9H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 168.7, 159.6, 159.2, 154.1, 147.5, 139.3, 137.3, 132.9, 130.6, 130.2, 128.9, 127.3, 124.6, 114.5, 114.3, 107.2, 55.4, 37.5, 34.9, 31.2. HRMS *m*/*z*: $[M + H]^+$ calcd for $C_{24}H_{28}N_3O_2$, 390.2176; found, 390.2178.

4′,5-dimethoxy-*N*′-methyl-*N*′-(pyridin-2-yl)-[1,1′-biphenyl]-2-carbohydrazide. Compound **3da** (52 mg, yield = 71%) was isolated (petroleum ether/EtOAc = 10:1 to 3:1) as a white foam. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.12 (dd, *J* = 4.9, 1.0 Hz, 1H), 7.73 (d, *J* = 8.6 Hz, 1H), 7.40 (d, *J* = 8.5 Hz, 2H), 7.35 (ddd, *J* = 8.8, 7.3, 1.8 Hz, 1H), 7.10 (s, 1H), 6.99 (d, *J* = 8.7 Hz, 2H), 6.95 (dd, *J* = 8.6, 2.6 Hz, 1H), 6.85 (d, *J* = 2.5 Hz, 1H), 6.64 (dd, *J* = 6.7, 5.3 Hz, 1H), 6.36 (d, *J* = 8.5 Hz, 1H), 3.87 (s, 3H), 3.85 (s, 3H), 3.14 (s, 3H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 168.2, 161.2, 159.8, 159.2, 147.5, 141.5, 137.3, 132.4, 131.2, 130.1, 125.9, 115.6, 114.5, 114.3, 112.9, 107.2, 55.5, 55.4, 37.5. HRMS *m*/*z*: $[M + H]^+$ calcd for $C_{21}H_{22}N_3O_3$, 364.1656; found, 364.1655.

4′-methoxy-*N*′-methyl-5-(methylthio)-*N*′-(pyridin-2-yl)-[1,1′-biphenyl]-2-carbo-hydrazide. Compound **3ea** (56 mg, yield = 74%) was isolated (petroleum ether/EtOAc = 10:1 to 3:1) as a white foam. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.12 (dd, *J* = 5.0, 1.1 Hz, 1H), 7.67 (d, *J* = 8.2 Hz, 1H), 7.43−7.31 (m, 3H), 7.27 (dd, *J* = 8.1, 2.0 Hz, 1H), 7.18 (d, *J* = 1.9 Hz, 1H), 7.17 (s, 1H), 6.99 (d, *J* = 8.7 Hz, 2H), 6.64 (dd, *J* = 6.8, 5.2 Hz, 1H), 6.32 (d, *J* = 8.4 Hz, 1H), 3.85 (s, 3H), 3.13 (s, 3H), 2.52 (s, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 168.2, 159.8, 159.1, 147.5, 142.4, 140.1, 137.4, 131.9, 130.1, 129.7, 129.6, 127.1, 124.4, 114.6, 114.3, 107.1, 55.4, 37.5, 15.1. HRMS *m*/*z*: $[M + H]^+$ calcd for $C_{21}H_{22}N_3O_2S$, 380.1427; found, 380.1430.

4′-methoxy-*N*′-methyl-5-phenoxy-*N*′-(pyridin-2-yl)-[1,1′-biphenyl]-2-carbohydrazide. Compound **3fa** (72 mg, yield = 85%) was isolated (petroleum ether/EtOAc = 10:1 to 3:1) as a white solid; mp 149−151 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.12 (dd, *J* = 5.0, 1.1 Hz, 1H), 7.73 (d, *J* = 8.5 Hz, 1H), 7.43−7.35 (m, 5H), 7.29 (s, 1H), 7.17 (t, *J* = 7.4 Hz, 1H), 7.11−7.06 (m, 2H), 7.02 (dd, *J* = 8.5, 2.5 Hz, 1H), 6.93−6.99 (m, 3H), 6.67 (dd, *J* = 6.6, 5.2 Hz, 1H), 6.39 (d, *J* = 8.6 Hz, 1H), 3.84 (s, 3H), 3.16 (s, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 168.2, 159.8, 159.3, 159.1, 155.9, 147.5, 141.7, 137.4, 131.8, 131.1, 130.0, 130.0, 127.9, 124.2, 119.7, 119.5, 116.8, 114.6, 114.3, 107.1, 55.4, 37.5. HRMS *m*/*z*: $[M + H]^+$ calcd for $C_{26}H_{24}N_3O_3$, 426.1812; found, 426.1813.

4′-methoxy-*N*′-methyl-*N*′-(pyridin-2-yl)-5-(trifluoromethoxy)-[1,1′-biphenyl]-2-carbohydrazide. Compound **3ga** (60 mg, yield = 72%) was isolated (petroleum ether/EtOAc = 10:1 to 3:1) as a light yellow foam. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.12 (dd, *J* = 5.0, 1.0 Hz, 1H), 7.76 (d, *J* = 8.5 Hz, 1H), 7.41 (d, *J* = 8.7 Hz, 2H), 7.39−7.33 (m, 1H), 7.30−7.26 (m, 2H), 7.24 (s, 1H), 7.00 (d, *J* = 8.7 Hz, 2H), 6.67 (ddd, *J* = 7.1, 5.0, 0.4 Hz, 1H), 6.33 (d, *J* = 8.5 Hz, 1H), 3.86 (s, 3H), 3.14 (s, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 167.6, 160.1, 158.9, 150.4, 147.6, 141.9, 137.5, 132.0, 130.9, 130.8, 130.1, 122.2, 120.4 (q, *J* = 256.8 Hz), 119.4, 114.8, 114.5, 107.1, 55.4, 37.7. ^{19}F NMR (376 MHz, $CDCl_3$): δ −57.60. HRMS *m*/*z*: $[M + H]^+$ calcd for $C_{21}H_{19}F_3N_3O_3$, 418.1373; found, 418.1374.

4″-methoxy-*N*′-methyl-*N*′-(pyridin-2-yl)-[1,1′:3′,1″-terphenyl]-4′-carbohydrazide. Compound **3ha** (65 mg, yield = 80%) was isolated (petroleum ether/EtOAc = 10:1 to 3:1) as a white solid; mp 80−82 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.13 (dd, *J* = 5.0, 1.0 Hz, 1H), 7.81 (d, *J* = 8.0 Hz, 1H), 7.69−

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7.58 (m, 4H), 7.51−7.43 (m, 4H), 7.43−7.36 (m, 2H), 7.35 (s, 1H), 7.01 (d, J = 8.7 Hz, 2H), 6.66 (dd, J = 6.5, 5.1 Hz, 1H), 6.35 (d, J = 8.5 Hz, 1H), 3.86 (s, 3H), 3.16 (s, 3H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 168.5, 159.8, 159.1, 147.5, 143.5, 140.1, 139.9, 137.4, 132.3, 132.2, 130.2, 129.7, 129.0, 128.9, 128.0, 127.2, 126.0, 114.6, 114.3, 107.2, 55.4, 37.6. HRMS m/z: $[M + H]^+$ calcd for $C_{26}H_{24}N_3O_2$, 410.1863; found, 410.1862.

5-fluoro-4′-methoxy-N'-methyl-N'-(pyridin-2-yl)-[1,1′-biphenyl]-2-carbohydrazide. Compound **3ia** (51 mg, yield = 73%) was isolated (petroleum ether/EtOAc = 10:1 to 3:1) as a white foam. ^1H NMR (400 MHz, $CDCl_3$): δ 8.10 (ddd, J = 4.8, 1.6, 0.8 Hz, 1H), 7.70 (dd, J = 8.5, 5.8 Hz, 1H), 7.42−7.29 (m, 4H), 7.14−7.03 (m, 2H), 6.98 (d, J = 8.7 Hz, 2H), 6.65 (ddd, J = 7.1, 5.0, 0.6 Hz, 1H), 6.31 (d, J = 8.5 Hz, 1H), 3.84 (s, 3H), 3.12 (s, 3H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 167.9, 163.5 (d, J = 251.6 Hz), 160.0, 159.0, 147.5, 142.2 (d, J = 8.4 Hz), 137.4, 131.3 (d, J = 9.1 Hz), 131.1 (d, J = 1.6 Hz), 130.0, 129.7 (d, J = 3.1 Hz), 117.0 (d, J = 21.9 Hz), 114.7, 114.4 (d, J = 3.1 Hz), 114.3, 107.1, 55.4, 37.6. ^{19}F NMR (376 MHz, $CDCl_3$): δ −109.23. HRMS m/z: $[M + H]^+$ calcd for $C_{20}H_{19}FN_3O_2$, 352.1456; found, 352.1458.

5-chloro-4′-methoxy-N'-methyl-N'-(pyridin-2-yl)-[1,1′-biphenyl]-2-carbohydrazide. Compound **3ja** (50 mg, yield = 68%) was isolated (petroleum ether/EtOAc = 10:1 to 3:1) as a white foam. ^1H NMR (400 MHz, $CDCl_3$): δ 8.09 (dd, J = 5.0, 1.0 Hz, 1H), 7.62 (dd, J = 7.6, 1.0 Hz, 1H), 7.48 (s, 1H), 7.40−7.31 (m, 5H), 6.96 (d, J = 8.7 Hz, 2H), 6.65 (dd, J = 7.2, 4.8 Hz, 1H), 6.29 (d, J = 8.5 Hz, 1H), 3.84 (s, 3H), 3.10 (s, 3H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 167.8, 160.0, 158.9 147.5, 141.3, 137.4, 136.5, 131.9, 130.9, 130.4, 130.2, 130.1, 127.5, 114.8, 114.4, 107.1, 55.4, 37.6. HRMS: m/z $[M + H]^+$ calcd for $C_{20}H_{19}ClN_3O_2$, 368.1160; found, 368.1159.

5-bromo-4′-methoxy-N'-methyl-N'-(pyridin-2-yl)-[1,1′-biphenyl]-2-carbohydrazide. Compound **3ka** (59 mg, yield = 72%) was isolated (petroleum ether/EtOAc = 10:1 to 3:1) as a white solid; mp 86−88 °C. ^1H NMR (500 MHz, $CDCl_3$): δ 8.10 (d, J = 3.9 Hz, 1H), 7.58−7.52 (m, 3H), 7.39−7.32 (m, 4H), 6.97 (d, J = 8.6 Hz, 2H), 6.65 (dd, J = 6.8, 5.2 Hz, 1H), 6.28 (d, J = 8.5 Hz, 1H), 3.84 (s, 3H), 3.11 (s, 3H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 167.9, 159.9, 158.9, 147.4, 141.4, 137.4, 133.0, 132.3, 130.7, 130.4, 130.3, 130.1, 124.8, 114.7, 114.3, 107.1, 55.4, 37.6. HRMS m/z: $[M + H]^+$ called for $C_{20}H_{19}BrN_3O_2$, 412.0655; found, 412.0658.

4′-methoxy-N'-methyl-N'-(pyridin-2-yl)-5-(trifluoromethyl)-[1,1′-biphenyl]-2-carbohydrazide. Compound **3la** (62 mg, yield = 77%) was isolated (petroleum ether/EtOAc = 10:1 to 3:1) as a white foam. ^1H NMR (400 MHz, $CDCl_3$): δ 8.10 (dd, J = 5.0, 1.0 Hz, 1H), 7.80 (d, J = 7.9 Hz, 1H), 7.66 (d, J = 9.7 Hz, 1H), 7.65 (s, 1H), 7.48 (s, 1H), 7.41 (d, J = 8.7 Hz, 2H), 7.37 (ddd, J = 8.8, 7.2, 1.9 Hz, 1H), 7.00 (d, J = 8.7 Hz, 2H), 6.67 (ddd, J = 7.1, 5.0, 0.7 Hz, 1H), 6.30 (d, J = 8.5 Hz, 1H), 3.86 (s, 3H), 3.13 (s, 3H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 167.6, 160.1, 158.8, 147.5, 140.4, 137.5, 136.8, 132.5 (q, J = 32.7 Hz), 130.7, 130.2, 129.5, 127.1 (d, J = 3.8 Hz), 124.0 (d, J = 3.7 Hz), 123.6 (q, J = 267.9 Hz), 114.9, 114.4, 107.1, 55.4, 37.8. ^{19}F NMR (376 MHz, $CDCl_3$): δ −62.87. HRMS m/z: $[M + H]^+$ calcd for $C_{21}H_{19}F_3N_3O_2$, 402.1424; found, 402.1423.

Methyl 4′-methoxy-6-(2-methyl-2-(pyridin-2-yl)hydrazine-1-carbonyl)-[1,1′-biphenyl]-3-carboxylate. Compound **3ma** (63 mg, yield = 80%) was isolated (petroleum ether/EtOAc = 10:1 to 3:1) as a white foam. ^1H NMR (400 MHz, $CDCl_3$): δ 8.13 (ddd, J = 5.0, 1.8, 0.8 Hz, 1H), 8.09−8.05 (m, 2H), 7.78 (d, J = 8.4 Hz, 1H), 7.44 (d, J = 8.8 Hz, 2H), 7.40−7.33 (m, 1H), 7.28 (s, 1H), 7.00 (d, J = 8.7 Hz, 2H), 6.67 (ddd, J = 7.1, 5.0, 0.8 Hz, 1H), 6.31 (d, J = 8.5 Hz, 1H), 3.95 (s, 3H), 3.86 (s, 3H), 3.16 (s, 3H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 168.0, 166.2, 160.0, 158.9, 147.6, 139.8, 137.5, 137.5, 132.0, 131.4, 131.2, 130.2, 129.1, 128.2, 114.9, 114.4, 107.2, 55.4, 52.5, 37.8. HRMS m/z: $[M + H]^+$ calcd for $C_{22}H_{22}N_3O_4$, 392.1605; found, 392.1603.

4′-methoxy-N′,4-dimethyl-N'-(pyridin-2-yl)-[1,1′-biphenyl]-2-carbohydrazide. Compound **3na** (47 mg, yield = 67%) was isolated (petroleum ether/EtOAc = 10:1 to 4:1) as a white foam. ^1H NMR (400 MHz, $CDCl_3$): δ 8.12 (ddd, J = 5.0, 1.8, 0.8 Hz, 1H), 7.52 (d, J = 0.5 Hz, 1H), 7.38 (d, J = 8.7 Hz, 2H), 7.37−7.30 (m, 2H), 7.27 (d, J = 7.1 Hz, 1H), 7.17 (s, 1H), 6.98 (d, J = 8.7 Hz, 2H), 6.64 (ddd, J = 7.1, 5.0, 0.8 Hz, 1H), 6.31 (d, J = 8.5 Hz, 1H), 3.84 (s, 3H), 3.13 (s, 3H), 2.43 (s, 3H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 168.9, 159.5, 159.1, 147.4, 137.4, 137.3, 136.6, 133.3, 132.2, 131.4, 130.2, 130.1, 129.4, 114.6, 114.2, 107.2, 55.4, 37.5, 20.9. HRMS m/z: $[M + H]^+$ calcd for $C_{21}H_{22}N_3O_2$, 348.1707; found, 348.1708.

4-chloro-4′-methoxy-N'-methyl-N'-(pyridin-2-yl)-[1,1′-biphenyl]-2-carbohydrazide. Compound **3oa** (51 mg, yield = 70%) was isolated (petroleum ether/EtOAc = 10:1 to 4:1) as a white solid; mp 96−98 °C. ^1H NMR (400 MHz, $CDCl_3$): δ 8.13 (dd, J = 4.9, 1.0 Hz, 1H), 7.71 (d, J = 2.2 Hz, 1H), 7.48 (dd, J = 8.3, 2.2 Hz, 1H), 7.43−7.35 (m, 3H), 7.33 (d, J = 8.3 Hz, 1H), 7.19 (s, 1H), 6.99 (d, J = 8.7 Hz, 2H), 6.68 (dd, J = 6.9, 5.2 Hz, 1H), 6.32 (d, J = 8.5 Hz, 1H), 3.85 (s, 3H), 3.14 (s, 3H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 167.3, 159.9, 158.9, 147.6, 138.0, 137.5, 134.9, 133.6, 131.7, 131.0, 130.7, 130.1, 129.0, 114.9, 114.4, 107.2, 55.4, 37.7. HRMS m/z: $[M + H]^+$ calcd for $C_{20}H_{19}ClN_3O_2$, 368.1160; found, 368.1160.

4′-methoxy-N′,3-dimethyl-N'-(pyridin-2-yl)-[1,1′-biphenyl]-2-carbohydrazide. Compound **3pa** (43 mg, yield = 62%) was isolated (petroleum ether/EtOAc = 10:1 to 4:1) as a white foam. ^1H NMR (400 MHz, $CDCl_3$): δ 8.09 (ddd, J = 5.0, 1.8, 0.8 Hz, 1H), 7.41 (d, J = 8.8 Hz, 2H), 7.36 (t, J = 7.6 Hz, 1H), 7.25−7.16 (m, 4H), 6.97 (d, J = 8.8 Hz, 2H), 6.62 (ddd, J = 7.1, 5.0, 0.8 Hz, 1H), 5.93 (d, J = 8.5 Hz, 1H), 3.85 (s, 3H), 3.10 (s, 3H), 2.49 (s, 3H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 168.9, 159.4, 159.0, 147.4, 139.5, 137.3, 136.2, 133.9, 132.7, 130.3, 129.5, 129.0, 127.3, 114.6, 114.0, 107.1, 55.4, 37.5, 19.4. HRMS m/z: $[M + H]^+$ calcd for $C_{21}H_{22}N_3O_2$, 348.1707; found, 348.1707.

3-chloro-4′-methoxy-N'-methyl-N'-(pyridin-2-yl)-[1,1′-biphenyl]-2-carbohydrazide. Compound **3qa** (43 mg, yield = 40%) was isolated (petroleum ether/EtOAc = 10:1 to 4:1) as a white foam. ^1H NMR (400 MHz, $CDCl_3$): δ 8.10 (ddd, J = 5.0, 1.8, 0.8 Hz, 1H), 7.47−7.37 (m, 4H), 7.33−7.27 (m, 2H), 7.21 (ddd, J = 8.8, 7.2, 1.9 Hz, 1H), 6.97 (d, J = 8.8 Hz, 2H), 6.62 (ddd, J = 7.1, 5.0, 0.8 Hz, 1H), 5.99 (d, J = 8.5 Hz, 1H), 3.85 (s, 3H), 3.16 (s, 3H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 166.0, 159.8, 159.0, 147.3, 141.8, 137.3, 133.5, 132.1, 131.1, 130.6, 130.4, 128.4, 128.2, 114.7, 114.1, 107.3, 55.4, 37.5. HRMS m/z: $[M + H]^+$ calcd for $C_{20}H_{19}ClN_3O_2$, 368.1160; found, 368.1161.

3-(4-methoxyphenyl)-N'-methyl-N'-(pyridin-2-yl)-2-naphthohydrazide. Compound **3ra** (57 mg, yield = 75%) was isolated (petroleum ether/EtOAc = 10:1 to 4:1) as a white solid; mp 188−190 °C. ^1H NMR (400 MHz, $CDCl_3$): δ 8.34 (s, 1H), 8.08 (d, J = 4.5 Hz, 1H), 7.98 (br, 1H), 7.93 (d, J = 7.9 Hz, 1H), 7.85 (d, J = 7.9 Hz, 1H), 7.80 (s, 1H), 7.61−7.47

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(m, 4H), 7.39 (t, J = 7.2 Hz, 1H), 6.99 (d, J = 8.5 Hz, 2H), 6.62 (t, J = 6.0 Hz, 1H), 6.38 (d, J = 8.6 Hz, 1H), 3.85 (s, 3H), 3.20 (s, 3H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 168.6, 159.6, 159.1, 147.5, 137.4, 136.4, 134.0, 132.4, 131.9, 131.7, 130.3, 129.5, 129.3, 128.3, 127.9, 127.8, 126.8, 114.6, 114.3, 107.2, 55.4, 37.6. HRMS m/z: $[M + H]^+$ called for $C_{24}H_{22}N_3O_2$, 384.1707; found, 384.1706.

3-(4-methoxyphenyl)-*N*′-methyl-*N*′-(pyridin-2-yl)furan-2-carbohydrazide. Compound **3sa** (11 mg, yield = 16%) was isolated (petroleum ether/EtOAc = 10:1 to 4:1) as a white foam. ^1H NMR (400 MHz, $CDCl_3$): δ 8.35 (s, 1H), 8.20 (dd, J = 5.0, 1.0 Hz, 1H), 7.72 (d, J = 8.9 Hz, 2H), 7.53−7.45 (m, 2H), 6.92 (d, J = 8.9 Hz, 2H), 6.79 (d, J = 8.5 Hz, 1H), 6.73−6.66 (m, 2H), 3.81 (s, 3H), 3.43 (s, 3H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 159.8, 159.3, 158.1, 147.6, 143.4, 139.7, 137.6, 132.7, 130.7, 123.4, 114.6, 114.4, 113.7, 107.1, 55.3, 38.8. HRMS m/z: $[M + H]^+$ calcd for $C_{18}H_{18}N_3O_3$, 324.1343; found, 324.1342.

4′-acetyl-*N*′-methyl-*N*′-(pyridin-2-yl)-[1,1′-biphenyl]-2-carbohydrazide compound **3ab** (47 mg, yield = 68%) was isolated (petroleum ether/EtOAc = 10:1 to 3:1) as a white foam. ^1H NMR (400 MHz, $CDCl_3$): δ 8.12 (dd, J = 5.0, 1.0 Hz, 1H), 8.03 (d, J = 8.4 Hz, 2H), 7.74 (dd, J = 7.6, 1.3 Hz, 1H), 7.61 (d, J = 8.4 Hz, 2H), 7.60−7.54 (m, 1H), 7.51 (td, J = 7.5, 1.3 Hz, 1H), 7.44 (dd, J = 7.6, 1.0 Hz, 1H), 7.43 (s, 1H), 7.36 (ddd, J = 8.7, 7.2, 1.9 Hz, 1H), 6.67 (dd, J = 6.5, 5.0 Hz, 1H), 6.36 (d, J = 8.5 Hz, 1H), 3.16 (s, 3H), 2.64 (s, 3H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 197.6, 168.3, 158.9, 147.6, 144.7, 139.0, 137.5, 136.4, 133.8, 130.8, 130.2, 129.3, 128.8, 128.7, 128.4, 114.9, 107.1, 38.0, 26.7. HRMS m/z: $[M + H]^+$ calcd for $C_{21}H_{20}N_3O_2$, 346.1550; found, 346.1546.

Methyl 2′-(2-methyl-2-(pyridin-2-yl)hydrazine-1-carbonyl)-[1,1′-biphenyl]-4-carboxylate. Compound **3ac** (51 mg, yield = 70%) was isolated (petroleum ether/EtOAc = 10:1 to 3:1) as a white foam. ^1H NMR (400 MHz, $CDCl_3$): δ 8.12 (d, J = 7.9 Hz, 3H), 7.75 (d, J = 7.4 Hz, 1H), 7.61−7.54 (m, 3H), 7.51 (t, J = 7.3 Hz, 1H), 7.43 (d, J = 7.5 Hz, 1H), 7.40−7.29 (m, 2H), 6.67 (dd, J = 6.8, 5.2 Hz, 1H), 6.35 (d, J = 8.6 Hz, 1H), 3.95 (s, 3H), 3.13 (s, 3H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 168.3, 166.7, 158.9, 147.5, 144.5, 139.0, 137.5, 133.7, 130.7, 130.2, 130.0, 129.6, 129.0, 128.8, 128.3, 114.8, 107.1, 52.3, 37.8. HRMS m/z: $[M + H]^+$ calcd for $C_{21}H_{20}N_3O_3$, 362.1499; found, 362.1500.

4′-bromo-*N*′-methyl-*N*′-(pyridin-2-yl)-[1,1′-biphenyl]-2-carbohydrazide. Compound **3ad** (52 mg, yield = 68%) was isolated (petroleum ether/EtOAc = 10:1 to 4:1) as a yellow oil. ^1H NMR (400 MHz, $CDCl_3$): δ 8.13 (ddd, J = 5.0, 1.8, 0.8 Hz, 1H), 7.70 (dd, J = 7.6, 1.2 Hz, 1H), 7.58 (d, J = 8.5 Hz, 2H), 7.57−7.52 (m, 1H), 7.48 (td, J = 7.5, 1.4 Hz, 1H), 7.44−7.34 (m, 5H), 6.69 (ddd, J = 7.2, 5.0, 0.8 Hz, 1H), 6.26 (d, J = 8.5 Hz, 1H), 3.18 (s, 3H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 168.4, 158.9, 147.5, 138.8, 138.8, 137.6, 133.7, 131.9, 130.7, 130.6, 130.1, 128.8, 128.0, 122.4, 114.9, 107.1, 37.9. HRMS m/z: $[M + H]^+$ calcd for $C_{19}H_{17}BrN_3O$, 382.0550; found, 382.0549.

N′-methyl-*N*′-(pyridin-2-yl)-[1,1′-biphenyl]-2-carbohydrazide. Compound **3ae** (42 mg, yield = 70%) was isolated (petroleum ether/EtOAc = 10:1 to 5:1) as a white foam. ^1H NMR (400 MHz, $CDCl_3$): δ 8.12 (ddd, J = 4.9, 1.8, 0.8 Hz, 1H), 7.74 (dd, J = 7.6, 1.2 Hz, 1H), 7.55 (td, J = 7.5, 1.5 Hz, 1H), 7.51−7.40 (m, 7H), 7.35 (ddd, J = 8.9, 7.2, 1.9 Hz, 1H), 7.12 (s, 1H), 6.64 (ddd, J = 7.1, 5.0, 0.7 Hz, 1H), 6.29 (d, J = 8.5 Hz, 1H), 3.08 (s, 3H).$^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 168.5, 159.1, 147.5, 140.0, 140.0, 137.4, 133.6, 130.6, 130.2, 128.97, 128.95, 128.9, 128.1, 127.8, 114.6, 107.1, 37.4. HRMS m/z: $[M + H]^+$ calcd for $C_{19}H_{18}N_3O$, 304.1444; found, 304.1445.

N′,4′-dimethyl-*N*′-(pyridin-2-yl)-[1,1′-biphenyl]-2-carbohydrazide. Compound **3af** (55 mg, yield = 87%) was isolated (petroleum ether/EtOAc = 10:1 to 4:1) as a white foam. ^1H NMR (400 MHz, $CDCl_3$): δ 8.12 (dd, J = 5.0, 1.0 Hz, 1H), 7.74 (dd, J = 7.6, 1.2 Hz, 1H), 7.53 (td, J = 7.5, 1.4 Hz, 1H), 7.45 (td, J = 7.5, 1.3 Hz, 1H), 7.41−7.32 (m, 4H), 7.29 (s, 1H), 7.28 (d, J = 7.9 Hz, 1H), 7.17 (s, 1H), 6.65 (ddd, J = 7.1, 5.0, 0.7 Hz, 1H), 6.31 (d, J = 8.5 Hz, 1H), 3.12 (s, 3H), 2.43 (s, 3H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 168.6, 159.1, 147.4, 139.8, 137.9, 137.3, 137.0, 133.5, 130.6, 130.2, 129.5, 128.9, 128.8, 127.5, 114.5, 107.1, 37.3, 21.2. HRMS m/z: $[M + H]^+$ calcd for $C_{20}H_{20}N_3O$, 318.1601; found, 318.1595.

4′-(*tert*-butyl)-*N*′-methyl-*N*′-(pyridin-2-yl)-[1,1′-biphenyl]-2-carbohydrazide. Compound **3ag** (58 mg, yield = 81%) was isolated (petroleum ether/EtOAc = 10:1 to 4:1) as a white foam. ^1H NMR (400 MHz, $CDCl_3$): δ 8.11 (dd, J = 4.8, 2.0 Hz, 1H), 7.74 (dd, J = 7.5, 0.9 Hz, 1H), 7.53 (td, J = 7.5, 1.4 Hz, 1H), 7.51−7.40 (m, 6H), 7.37 (ddd, J = 8.7, 7.2, 1.9 Hz, 1H), 7.07 (s, 1H), 6.64 (ddd, J = 7.2, 5.2, 0.4 Hz, 1H), 6.41 (d, J = 8.5 Hz, 1H), 3.03 (s, 3H), 1.36 (s, 9H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 168.7, 159.1, 151.3, 147.4, 139.8, 137.4, 136.9, 133.6, 130.6, 130.2, 129.0, 128.6, 127.6, 125.8, 114.6, 107.2, 37.1, 34.6, 31.3. HRMS m/z: $[M + H]^+$ called for $C_{23}H_{26}N_3O$, 360.2070; found, 360.2071.

3′-methoxy-*N*′-methyl-*N*′-(pyridin-2-yl)-[1,1′-biphenyl]-2-carbohydrazide. Compound **3ah** (43 mg, yield = 64%) was isolated (petroleum ether/EtOAc = 10:1 to 3:1) as a white foam. ^1H NMR (400 MHz, $CDCl_3$): δ 8.11 (dd, J = 4.9, 1.1 Hz, 1H), 7.74 (dd, J = 7.6, 1.3 Hz, 1H), 7.53 (td, J = 7.5, 1.4 Hz, 1H), 7.47 (td, J = 7.5, 1.3 Hz, 1H), 7.43−7.33 (m, 3H), 7.19 (s, 1H), 7.06 (d, J = 7.6 Hz, 1H), 7.02−6.95 (m, 2H), 6.64 (dd, J = 6.8, 5.3 Hz, 1H), 6.31 (d, J = 8.5 Hz, 1H), 3.81 (s, 3H), 3.10 (s, 3H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 168.5, 159.8, 159.1, 147.5, 141.3, 139.7, 137.4, 133.6, 130.6, 130.0, 130.0, 129.0, 127.8, 121.2, 114.6, 114.4, 113.8, 107.1, 55.3, 37.3. HRMS m/z: $[M + H]^+$ called for $C_{20}H_{20}N_3O_2$, 334.1550; found, 334.1550.

2′-methoxy-*N*′-methyl-*N*′-(pyridin-2-yl)-[1,1′-biphenyl]-2-carbohydrazide. Compound **3ai** (40 mg, yield = 60%) was isolated (petroleum ether/EtOAc = 10:1 to 3:1) as a light yellow foam. ^1H NMR (400 MHz, $CDCl_3$): δ 8.12 (dd, J = 4.9, 1.1 Hz, 1H), 7.81 (dd, J = 7.6, 1.3 Hz, 1H), 7.57−7.39 (m, 4H), 7.36−7.27 (m, 3H), 7.08 (t, J = 7.4 Hz, 1H), 7.01 (d, J = 8.3 Hz, 1H), 6.63 (dd, J = 6.9, 5.2 Hz, 1H), 6.25 (d, J = 8.5 Hz, 1H), 3.78 (s, 3H), 3.06 (s, 3H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 168.0, 159.2, 156.2, 147.4, 137.4, 136.1, 134.3, 131.0, 131.0, 130.5, 129.8, 129.2, 128.7, 127.8, 121.2, 114.4, 111.1, 107.1, 55.5, 37.3. HRMS m/z: $[M + H]^+$ calcd for $C_{20}H_{20}N_3O_2$, 334.1550; found, 334.1546.

4′-methoxy-[1,1′-biphenyl]-2-carboxamide. Compound **4a** (20 mg, yield = 88%) was isolated (petroleum ether/EtOAc = 5:1 to 3:1) as a white solid; mp 108−110 °C. ^1H NMR (400 MHz, $CDCl_3$): δ 7.76 (dd, J = 7.7, 1.2 Hz, 1H), 7.48 (td, J = 7.5, 1.5 Hz, 1H), 7.42−7.32 (m, 4H), 6.96 (d, J = 8.8 Hz, 2H), 5.70 (br, 1H), 5.30 (br, 1H), 3.84 (s, 3H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 171.5, 159.4, 139.5, 134.2, 132.4, 130.5, 130.4, 129.9, 129.1, 127.2, 114.1, 55.3. HRMS m/z: $[M + H]^+$ calcd for $C_{14}H_{14}NO_2$, 228.1019; found, 228.1018.

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4-chloro-4′-methoxy-[1,1′-biphenyl]-2-carboxamide. Compound **4b** (25 mg, yield = 95%) was isolated (petroleum ether/EtOAc = 5:1 to 3:1) as a white solid; mp 154−156 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.74 (d, J = 2.3 Hz, 1H), 7.42 (dd, J = 8.3, 2.3 Hz, 1H), 7.31 (d, J = 8.8 Hz, 2H), 7.24 (s, 1H), 6.94 (d, J = 8.8 Hz, 2H), 5.63 (br, 1H), 5.28 (br, 1H), 3.83 (s, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 169.8, 159.7, 137.9, 135.5, 133.4, 131.8, 131.2, 130.5, 129.9, 129.2, 114.3, 55.3. HRMS m/z: $[M + H]^+$ called for $C_{14}H_{13}ClNO_2$, 262.0629; found, 262.0629.

3-(4-methoxyphenyl)-2-naphthamide. Compound **4c** (26 mg, yield = 94%) was isolated (petroleum ether/EtOAc = 5:1 to 3:1) as a white solid; mp 224−226 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.33 (s, 1H), 7.92 (d, J = 7.9 Hz, 1H), 7.85 (d, J = 8.0 Hz, 1H), 7.79 (s, 1H), 7.60−7.50 (m, 2H), 7.46 (d, J = 8.7 Hz, 2H), 6.99 (d, J = 8.7 Hz, 2H), 5.77 (br, 1H), 5.43 (br, 1H), 3.86 (s, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 171.2, 159.5, 136.5, 134.0, 132.5, 132.4, 131.7, 130.2, 129.8, 129.4, 128.5, 127.8, 127.6, 126.6, 114.2, 55.3. HRMS m/z: $[M + H]^+$ calcd for $C_{18}H_{16}NO_2$, 278.1176; found, 278.1174.

[1,1′-biphenyl]-2-carboxamide. Compound **4d** (18 mg, yield = 89%) was isolated (petroleum ether/EtOAc = 5:1 to 3:1) as a white solid.^{1}H NMR (400 MHz, $CDCl_3$): δ 7.77 (dd, J = 7.6, 1.2 Hz, 1H), 7.50 (td, J = 7.5, 1.5 Hz, 1H), 7.46−7.38 (m, 6H), 7.36 (dd, J = 7.6, 1.1 Hz, 1H), 5.79 (s, 1H), 5.29 (s, 1H). ^{13}C{1H} NMR (101 MHz, $CDCl_3$): δ 171.4, 140.2, 139.8, 134.3, 130.5, 130.4, 129.0, 128.7, 128.6, 127.9, 127.6. HRMS m/z: $[M + H]^+$ calcd for $C_{13}H_{11}NO$, 198.0913; found, 198.0914.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsomega.1c02481.

Copies of ^{1}H, ^{13}C, and ^{19}F NMR spectra for all new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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