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Palladium-Catalyzed, *ortho*-Selective C−H Halogenation of Benzyl Nitriles, Aryl Weinreb Amides, and Anilides

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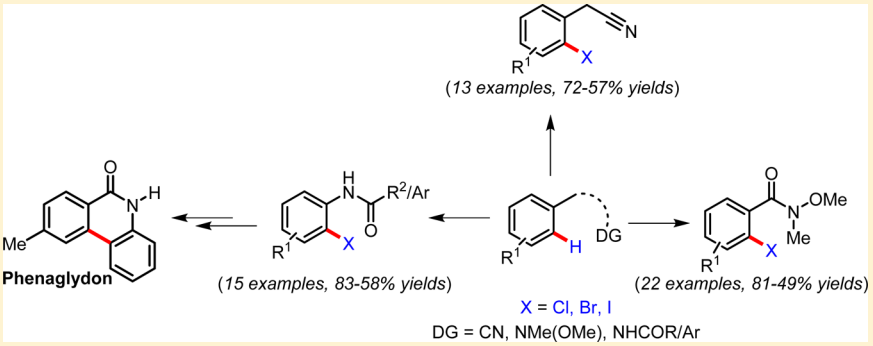
Supporting Information



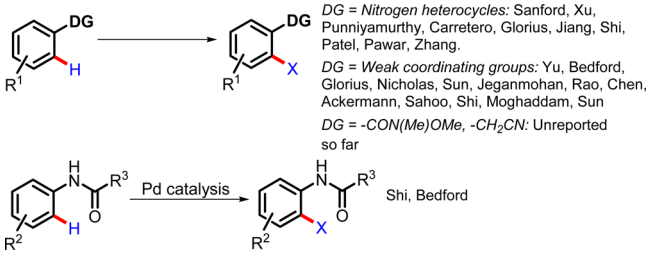
ABSTRACT: A palladium-catalyzed, *ortho*-selective C−H halogenation methodology is reported herein. The highlight of the work is the highly selective C(sp^2)−H functionalization of benzyl nitriles in the presence of activated C(sp^3)−H bond, which results in good yields of the halogenated products with excellent regioselectivity. Along with benzyl nitriles, aryl Weinreb amides and anilides have been evaluated for the transformation using aprotic conditions. Mechanistic studies yield interesting aspects with respect to the pathway of the reaction and the directing group abilities.

INTRODUCTION

Aryl halides are probably one of the most important building blocks in organic synthesis. After the advent of transition metal-catalyzed cross-coupling reactions,[1] the utility of aromatic as well as vinyl halides has seen only an upward trend. Often, low-valent transition metals were employed in such cross-coupling reactions where the oxidative insertion into the carbon−halogen bond is usually the early step in the catalytic cycle. Traditionally, aromatic halides were usually synthesized via aromatic electrophilic substitution (S_EAr)[2] reactions with the Sandmeyer reaction[3] often being the other method of choice. With the recent advances in the area of C−H functionalization,[4] transition metal-catalyzed carbon−halogen bond-forming reactions have emerged as a great alternative to these S_EAr reactions. The most popular mode of proximal C−H functionalization is via the use of Lewis-basic directing groups (DG). The site-selectivity is often governed by the type of directing group employed. In such cases, a distinction can be made between strongly coordinating (such as heterocyclic amines) against weakly coordinating directing groups (such as acyl groups). Thus, the stability of the resulting metallacycle is dependent on the type of directing group employed, and the outcome of the C−H functionalization is then determined by the metallacycle.

Preliminary reports by the groups of Sanford,[5a−c] Shi,[5d] and Yu[5e] set the stage for further exploration in the area of transition metal-catalyzed C−H halogenation (Scheme 1). A review of literature on this topic reveals that almost all of the reports on C−H halogenations utilize directing groups to mediate the proximal C−H bond functionalization. There are very few reports that do not employ DG to govern the site-selectivity in this transformation.[6] We also realized that a majority of the reports involved the use of protic media or protic additives to assist the transformation. A variety of transition-metal catalysts have been employed, the most prominent being Pd, Cu, and Rh catalysts.[7,8]

Scheme 1. Some of the Previous Strategies for C−H Halogenations



RESULTS AND DISCUSSION

We have been interested in the C−H functionalization of C(sp^2)−H bonds,[9] and in this context we report herein a new method for the C−H halogenation of substrates possessing

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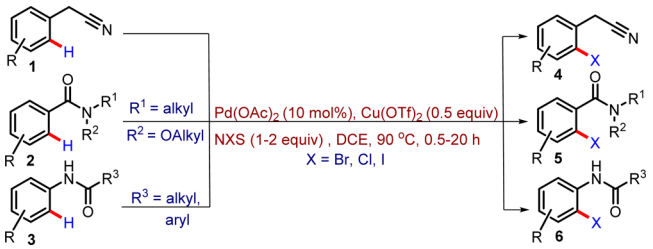
weak coordinating groups, benzyl nitriles,[10] Weinreb amides, and anilides (Scheme 2). To the best of our knowledge,

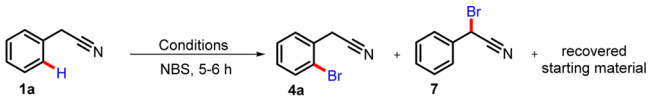
Scheme 2. Present Work: Palladium-Catalyzed C−H Halogenation



transition metal-catalyzed *ortho*-C−H halogenations have not been reported for benzyl cyanides and Weinreb amides. The *ortho*-C−H halogenation of anilides is a big challenge due to poor regiocontrol in transformation. There are only a couple of successful reports for this substrate.[5d,11] The method utilizes aprotic media for the transformation and has good substrate scope. The mechanistic studies bring out interesting aspects of the directing group abilities in this reaction.

The primary concern in such transformations is the functionalization of the benzylic C−H when the reaction is performed with arylmethyl nitriles. To subvert this unwanted transformation, we needed to develop a new method for the selective *ortho*-C−H halogenation of benzyl nitriles. Initial attempts to standardize the reaction conditions for these as well as Weinreb amides resulted in undesired transformations, especially under the protic conditions. In case of the benzyl nitriles, when the reaction was carried out in protic medium, it resulted mostly in benzylic bromination or very poor levels of conversions (Scheme 3). In case of the Weinreb amides, use of

Scheme 3. Side Reactions Observed during C−H Halogenations of Benzyl Nitriles under Protic Conditions



Conditions	Result
$Pd(OAc)_2$, TsOH, MeCN, rt	Mixture of *ortho* C-H bromination (5%) along with benzylic bromination (27%)
$Pd(OAc)_2$, TfOH, DCE, rt	Mixture of *ortho* C-H bromination(13%) along with benzylic bromination (21%)
$Pd(OAc)_2$, AcOH, Ag(TFA), DCE, 90 °C	Benzylic bromination was the major product (48%)
$[RhCp^*Cl_2]_2$, $AgSbF_6$, PivOH, DCE, 90 °C	Complex mixture
$Pd(OAc)_2$, $Cu(OTf)_2$, DCE, 90°C	Exclusively *ortho* C-H bromination (71%)
DCE, 90°C	Exclusively benzylic bromination (75%)

acidic media resulted mostly in bromination at the *meta*-positions. After considerable optimization,[12] the best conditions were found to be $Pd(OAc)_2/Cu(OTf)_2$/NXS in dichloroethane as the solvent.

This reaction condition worked best for all three, the benzyl nitriles, the Weinreb amides, as well as the anilides. The transformation did not work without the palladium catalyst and the copper additive. The substrate scope for the transformation is depicted in Table 1. The reaction worked very well for benzyl nitriles under the aprotic conditions. The benzylic bromination product was not observed under these conditions, and the regioselectivity was exclusive. The reaction conditions were well tolerated by electron-rich as well as electron-deficient benzyl nitriles. The unique feature of this transformation was that halogen functionalities were well tolerated under these conditions, which immensely increases the synthetic utility of this method. The advantage of having two different halogen functional groups in the resulting C−H halogenation product is the amplified scope for further chemoselective functionalization, leading to densely substituted products in fewer steps. For the Weinreb amides, the reaction worked very decently, and a variety of electronic factors were tolerated under these conditions (Table 1).[13]

A nitro-substituent on the arene was not tolerated, and the reaction failed to result in any C−H functionalization product, and, on the other hand, the 4-fluoro substituent worked quite well (Table 1, **5j**, **5k**). In the case of benzyl nitriles, we were unable to synthesize the starting material with a nitro-substituent to check its effect on the reaction. In the case of Weinreb amides too, the halogen functional groups were well tolerated. An olefin functional unit also survived these reaction conditions, although some amount of scrambling of the olefin geometry was nonetheless observed (Table 1, **5r**, **5s**). Also notable is the fact that the Weinreb amide functional group was unaffected under these reaction conditions and the N−O bond was not reductively cleaved.[14]

In case of the anilides, the reaction was very efficient and was completed in a very short period. This is probably due to the high reactivity of the anilides, capable of activating the arene as well as being excellent directing groups themselves. In this case, the nitro-substituent on the arene did not inhibit the transformation, and decent yields were obtained (Table 1, **6j**, **6k**). In some of the substrates, where strong electron-donating or -activating groups were present, the reaction expectedly resulted in the electrophilic halogenation predominating the *ortho*-C−H halogenation pathway (Table 1, **4k**, **4l**, **4m**).

In some cases, both C−H halogenation as well as electrophilic halogenations were obtained in a single product (Table 1, **5u**). In the case of the free anilides (Table 1, **6f**), within 30 min, the transformation resulted in over 50% of *ortho*-C−H halogenation at room temperature, after which the electrophilic halogenation at the *para*-position was also observed. At elevated temperatures, the *o*-,*p*-dihalogenated product was the major product. Reactions carried out in the absence of the palladium catalyst did not result in the arene *ortho*-C−H functionalization. However, a competing copper-catalyzed pathway was also observed in the case of the anilides, but the rate for this pathway was much lower than that for the palladium-catalyzed transformation. In that case, the *para*-substituted product was the major transformation. In the case of π-excessive heterocycles such as furans, benzofurans, and thiophenes, the electrophilic halogenation dominated the directed C−H halogenations, and these were therefore not investigated further. *ortho*-C−H halogenations were also observed for phenol carbamates under our reaction conditions, but, unfortunately, the reaction did not have a broad substrate scope for this functionality and was therefore not developed further.

The synthetic potential of this transformation was demonstrated in the dual functionalization of some of the C−H halogenation products, in which two different halogen substituents were available for sequential transformation (Scheme 4).[15] In another important application, the *ortho*-C−

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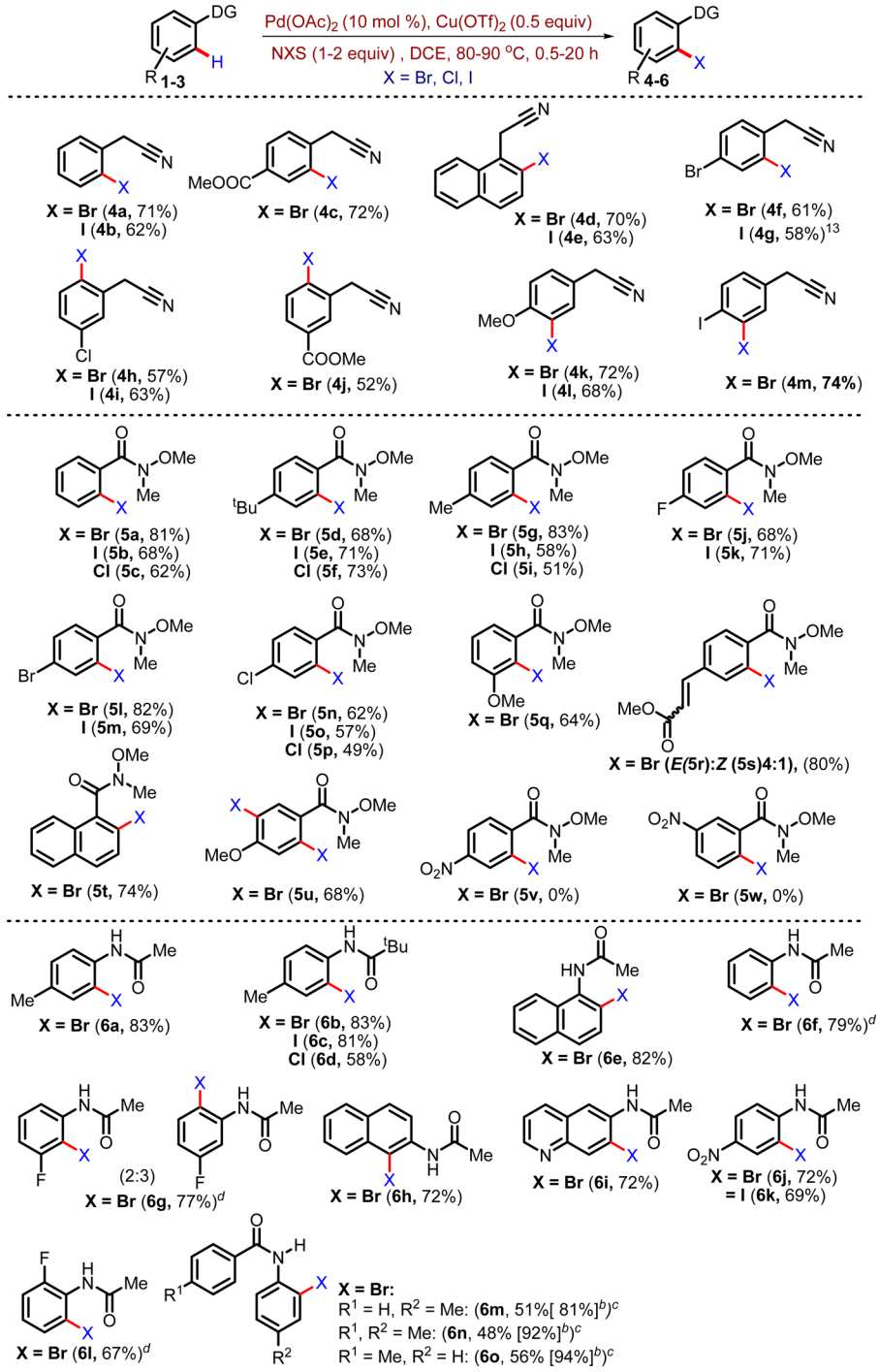
Table 1. Substrate Scope for the C−H Halogenation Reaction[a]



[a]All yields are isolated yields. [b]Based on recovered starting material. [c]Reaction time: 15 min. [d]Carried out at rt.

H halogenation of benzoic acid anilamides resulted in an important starting material for building the phenanthridone skeleton,[16] present in several important alkaloids (Scheme 4).

This sequential halogenation and cyclization provides a quick access to this class of compounds, and a quick assembly of the natural product Phenaglydon (Scheme 4, **11c**)[16] was achieved by employing this strategy. The most interesting observation was that a clear site-selectivity was visible between the reactivity of the two possible C−H in **3j**, **3k**, **3l**, and the anilide *ortho*-C−H was preferentially functionalized over the benzamide *ortho*-C−H, pointing to the possibility of the electrophilic metalation being operational in activation of the anilide *ortho*-C−H (Table 1, **6m**, **6n**, **6o**). Our attempts to effect both of the transformations in a single pot unfortunately did not yield the desired products.

A plausible mechanism for the transformation, based on previous literature,[7c,8f] is depicted in Scheme 5. The first step is the coordination of the metal to the directing group followed by an acetate-assisted proximal C−H bond activation to generate the palladacycle (B). Oxidative addition of NXS gives rise to either a Pd(IV) species or a Pd(III)-bimetallic

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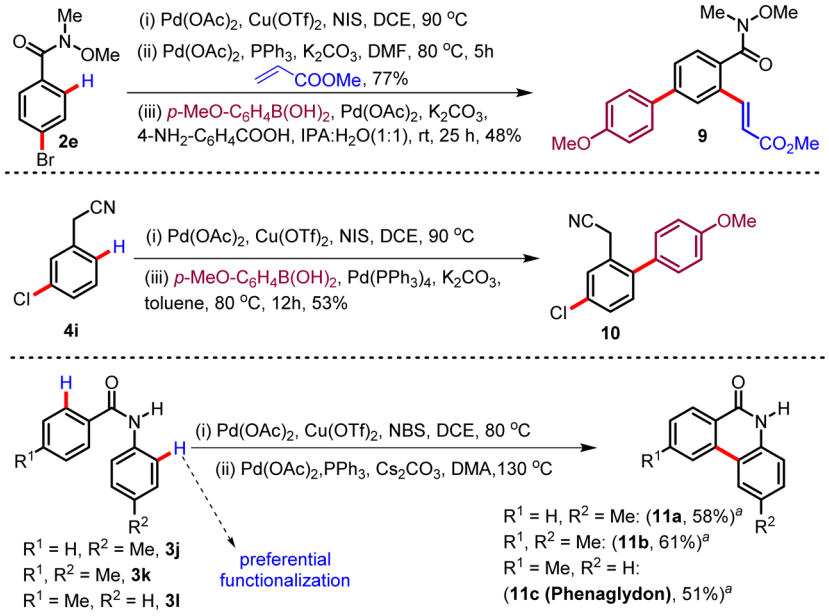
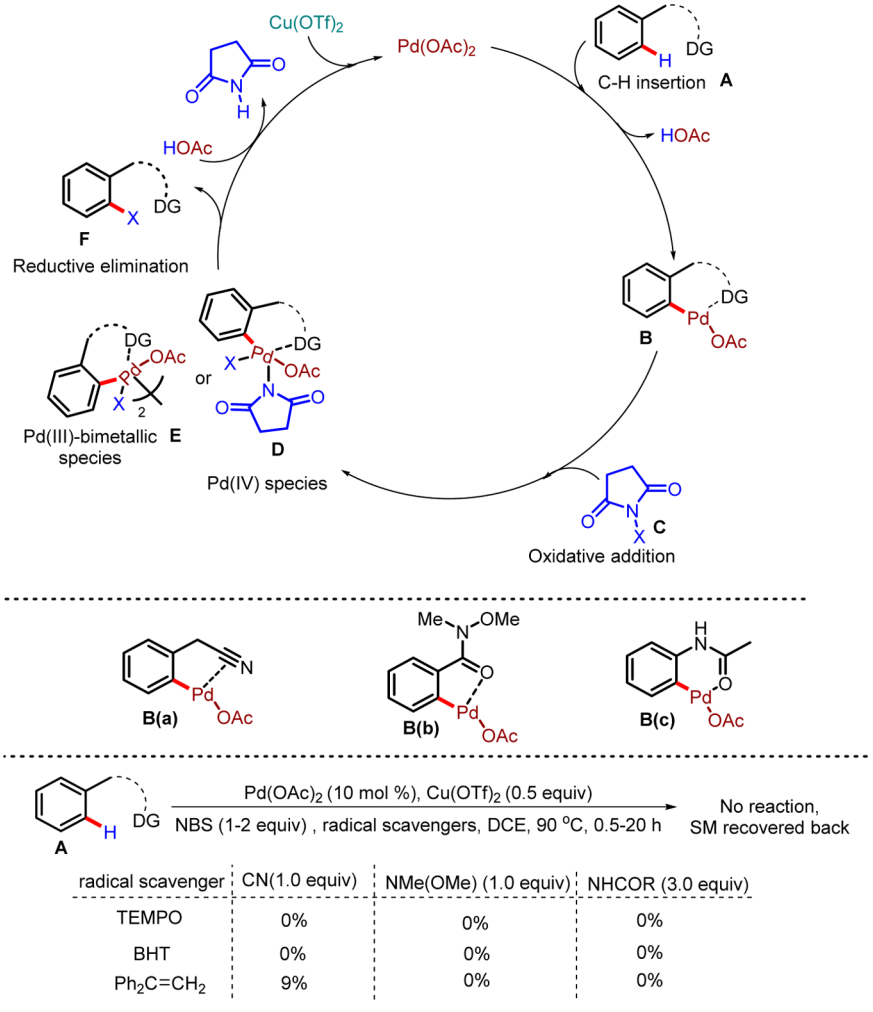
Scheme 4. Synthetic Utility of the Sequential Functionalization of C−H Halogenation Products[a]



[a]Yields are for the annulation step.

Scheme 5. Plausible Mechanism



radical scavenger	CN(1.0 equiv)	NMe(OMe) (1.0 equiv)	NHCOR (3.0 equiv)
TEMPO	0%	0%	0%
BHT	0%	0%	0%
$Ph_2C=CH_2$	9%	0%	0%

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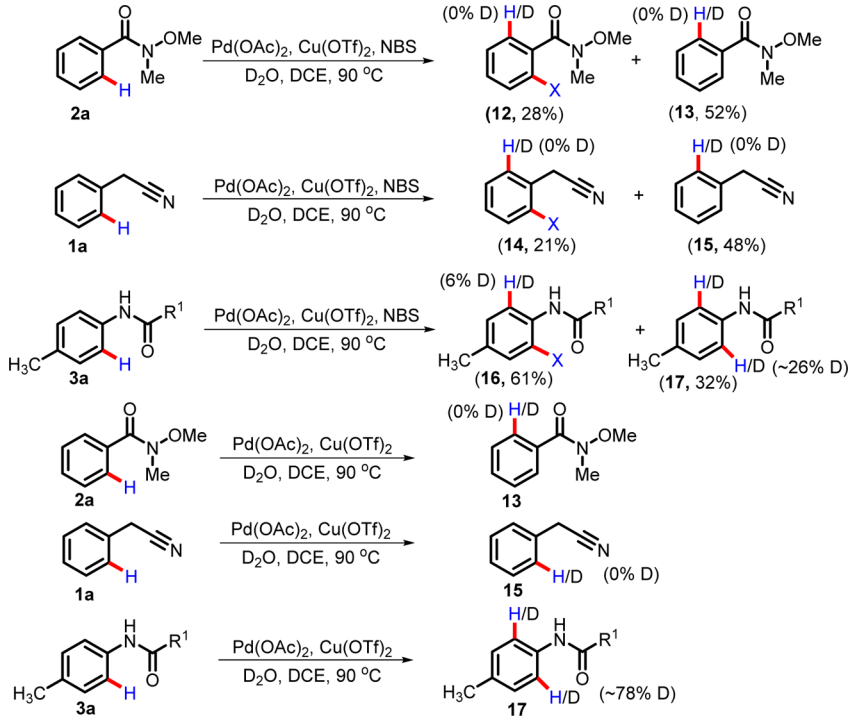
J. Org. Chem. 2017, 82, 1114−1126

Scheme 6. Reversibility of Metalation



species. Reductive elimination from this species results in the product.

The Pd(II) is regenerated via acetic acid-assisted oxidation by Cu(II). The fact that the reaction is completely inhibited in the presence of either TEMPO, BHT, or 1,1-diphenylethylene (>1 equiv) points to a one-electron transfer pathway (Scheme 5).

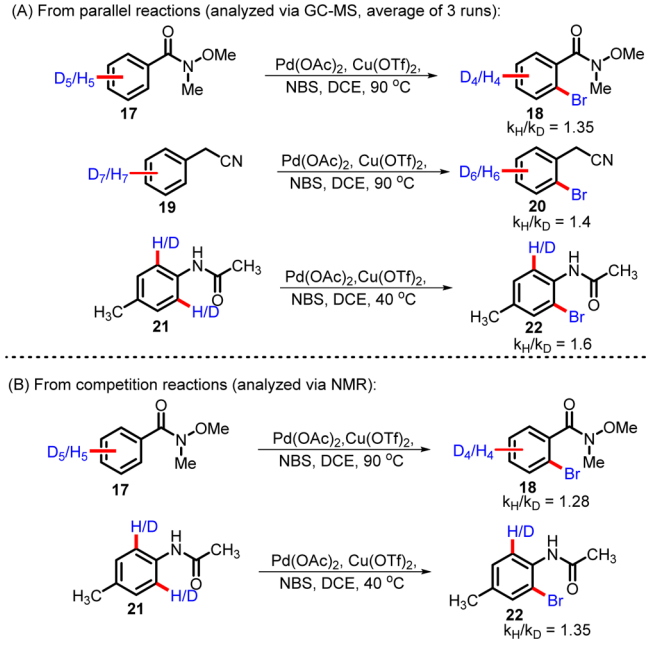
Experiments conducted to check the reversibility of the palladacycle formation resulted in interesting conclusions (Scheme 6). The metalation did not seem to be reversible in case of the Weinreb amides and the benzyl nitriles, both in the presence of the halogenating agent and in the absence of it. However, in case of anilides, it was reversible to a considerable extent.

Studies were performed to determine whether the *ortho*-C−H bond cleavage was the rate-determining step for the transformation (Scheme 7). Moderate values were obtained for the KIE, both via parallel reactions as well as via competition reactions, indicating that the C−H activation was not involved in the rate-determining step.[17]

To check the difference in the directing group abilities of the three weakly coordinating groups, we performed the relative-rate studies (Figure 1). The anilides were invariably the fastest of all, giving rise to complete consumption of the starting material within just 10 min. In this time period, the Weinreb amide had a higher initial rate as compared to the benzyl nitrile, which, however, slowed with time. The reaction rate for the benzyl nitrile was higher in the later part of the reaction. This clearly indicated the ability of the groups to be effective directing groups in this kind of a transformation. The anilide seems to be activating the arene toward C−H activation by a dual mode. Not only does it appear to be a better coordinating group of the three, it seems be assisting the *ortho*-C−H functionalization via an electrophilic palladation mechanism.[18]

The observation of the preferential functionalization of the anilide *ortho*-C−H (**3j−l**, Scheme 4) is also indicative of this fact. This mode of activation is not available to the aryl Weinreb

Scheme 7. Kinetic Isotope Effect Studies



amides and the benzyl nitriles, and this probably could explain the huge difference in rates for the same transformation. The transition state for the anilide *ortho*-C−-H activation could thus be a combination of the electrophilic activation pathway and the acetate-mediated concerted metalation deprotonation (CMD) pathway.[19] The considerable amount of *ortho*-deuteration observed for the anilides (Scheme 6) in a way also supports this hypothesis.

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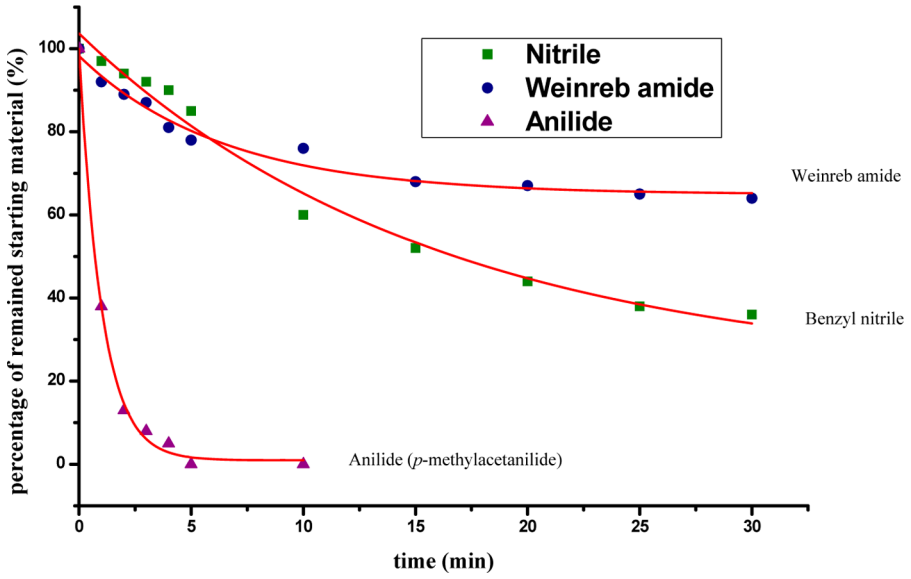

Figure 1. Studies for relative rate determination.

CONCLUSION

In summary, we have developed a new method for the palladium-catalyzed *ortho*-C−H halogenations of arenes bearing weak-coordinating groups. The strategy uses aprotic reaction conditions, suitable for substrates bearing sensitive functional groups. Benzyl nitriles, benzoic acid Weinreb amides, and anilides were evaluated as directing groups, and very interesting observations resulted in intriguing aspects with respect to the pathway of the reaction and the directing group abilities. The utility of this methodology is brought out by quick assembly of densely functionalized molecules, which are normally prepared via several synthetic steps. The methodology is particularly useful for benzyl nitriles, where the more reactive C(sp^3) benzylic C−H are left untouched in the transformation.

EXPERIMENTAL SECTION

1. General Methods. All commercially available compounds were used without purification. Unless otherwise noted, all reactions were performed in oven-dried glassware. All reactions were run under argon or nitrogen atmosphere. All solvents used in the reactions were purified before use. Tetrahydrofuran was distilled from sodium and benzophenone, whereas dry dichloromethane, dimethylformamide, dioxane, toluene, and dichloroethane were distilled from CaH_2. Petroleum ether with a boiling range of 40−60 °C was used. Melting points are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded at 295 K in $CDCl_3$ or DMSO-d_6 using a 400 or 500 MHz spectrometer, and chemical shifts are calibrated to the residual proton and carbon resonance of the solvent: $CDCl_3$ (^{1}H δ 7.25; ^{13}C δ 77.0). HRMS were recorded at HR-LCMS with Q-ToF using electron spray ionization (ESI) or atmospheric pressure chemical ionization (APCI) techniques. IR spectra were recorded on a FT-IR spectrometer. GCMS analysis was performed at GC with methyl silicone column and FID detector, using the electron impact (EI) technique.

2. General Procedures. *2.1. Synthesis of Benzyl Bromide.* In a round-bottom flask was taken the substituted toluene (10 mmol) in CCl_4 (30 mL), followed by addition of NBS (12 mmol) and benzoyl peroxide (0.5 mmol). The reaction mixture was then refluxed, and the progress was followed by TLC. Upon completion of the reaction and subsequent cooling to room temperature, the reaction mixture was concentrated under reduced pressure and then diluted with EtOAc. The organic layer was washed with water, brine, and dried over anhydrous Na_2SO_4. The extract was filtered and concentrated under reduced pressure, and the crude product was purified by silica gel flash column chromatography.

2.1.1. Methyl 4-(Bromomethyl)benzoate. This was prepared according to the general procedure, and the title compound was isolated as a colorless gel (86% yield). Spectral data obtained were in good agreement with those reported in the literature.[20]

2.1.2. Methyl 3-(Bromomethyl)benzoate. This was prepared according to the general procedure, and the title compound was isolated as a colorless gel (84% yield). Spectral data obtained were in good agreement with those reported in the literature.[20]

2.1.3. Methyl 2-(Bromomethyl)benzoate. This was prepared according to the general procedure, and the title compound was isolated as a colorless gel (72% yield). Spectral data obtained were in good agreement with those reported in the literature.[20]

2.1.4. 1-(Bromomethyl)-4-iodobenzene. This was prepared according to the general procedure, and the title compound was isolated as a white solid (79% yield). Spectral data obtained were in good agreement with those reported in the literature.[21]

2.1.5. 1-(Bromomethyl)naphthalene. This was prepared according to the general procedure, and the title compound was isolated as a brown gel (79% yield). Spectral data obtained were in good agreement with those reported in the literature.[21]

3. General Procedure for Cyanation. *3.1. Synthesis of Phenyl Acetonitrile.* In a round-bottom flask was dissolved the substituted benzyl bromide (2.1 mmol) in dry acetonitrile (10 mL) followed by the addition of sodium cyanide (5.8 mmol) and tetrabutylammoniumiodide (0.44 mmol). The reaction mixture was refluxed, and the progress of the transformation was followed by TLC. Upon completion of the reaction and subsequent cooling to room temperature, the reaction mixture was concentrated under reduced pressure and then diluted with EtOAc. The solution was washed with water, brine, and dried over anhydrous Na_2SO_4. The organic extract was filtered and concentrated under a vacuum, and the crude product was purified by silica gel flash column chromatography.

*3.1.1. Methyl 4-(Cyanomethyl)benzoate (**1a**).* This was prepared according to the general procedure, and the title compound was isolated as a white solid (65% yield). Spectral data obtained were in good agreement with those reported in the literature.[22]

*3.1.2. Methyl 3-(Cyanomethyl)benzoate (**1b**).* This was prepared according to the general procedure, and the title compound was isolated as a white solid (62% yield). Spectral data obtained were in good agreement with those reported in the literature.[23]

*3.1.3. Methyl 2-(Cyanomethyl)benzoate (**1c**).* This was prepared according to the general procedure, and the title compound was

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isolated as a white solid (51% yield). Spectral data obtained were in good agreement with those reported in the literature.[23]

*3.1.4. 2-(4-Iodophenyl)acetonitrile (**1d**).* This was prepared according to the general procedure, and the title compound was isolated as a pale yellow gel (59% yield). Spectral data obtained were in good agreement with those reported in the literature.[22]

*3.1.5. 2-(Naphthalen-1-yl)acetonitrile (**1d**).* This was prepared according to the general procedure, and the title compound was isolated as a yellow gel (67% yield). Spectral data obtained were in good agreement with those reported in the literature.[22]

4. General Procedures for the Synthesis of Weinreb Amides. *4.1. Synthesis of Weinreb Amide (**2a**).*[24] Pyridine (2.1 equiv) was slowly added to a mixture of benzoyl chloride (1.0 equiv) and *N*,*O*-dimethylhydroxylamine hydrochloride (1.05 equiv) in dry dichloromethane at 0 °C. The reaction mixture was allowed to warm to room temperature and was stirred for 12 h. After the addition of 1 N HCl (100 mL), the phases were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 25 mL). The combined organic phases were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography to result in the product as a colorless gel (78% yield). Spectral data obtained were in good agreement with those reported in the literature.[25]

5. General Procedures for the Synthesis of Weinreb Amides from Corresponding Acids.[26] In a two-neck round-bottomed flask was added oxalyl chloride (1.2 equiv) dropwise into the stirring solution of the benzoic acid (1 equiv) in CH_2Cl_2 at 0 °C. This was followed by addition of DMF (2 drops). The reaction mixture was allowed to warm to room temperature and stirred for another 1.5 h and then recooled to 0 °C. Et_3N (3 equiv) and *N*,*O*-dimethylhydroxylamine hydrochloride (1.05 equiv) were added. The reaction mixture was once again allowed to warm to room temperature and stirred for a further 6 h. It was quenched at room temperature with a saturated solution of $NaHCO_3$, and the resulting mixture was extracted twice with CH_2Cl_2. The combined organic extracts were washed with brine and dried over anhydrous Na_2SO_4, filtered, and concentrated under vacuum. The crude product was purified by silica gel flash column chromatography.

*5.1. 4-(tert-Butyl)-N-methoxy-N-methylbenzamide (**2b**).* This was prepared according to the general procedure, and the title compound was isolated as a white solid (81% yield). Spectral data obtained were in good agreement with those reported in the literature.[27]

*5.2. N-Methoxy-N,4-dimethylbenzamide (**2c**).* This was prepared according to the general procedure, and the title compound was isolated as a brown gel (86% yield). Spectral data obtained were in good agreement with those reported in the literature.[28]

*5.3. 4-Fluoro-N-methoxy-N-methylbenzamide (**2d**).* This was prepared according to the general procedure, and the title compound was isolated as a pale yellow liquid (91% yield). Spectral data obtained were in good agreement with those reported in the literature.[29]

*5.4. 4-Bromo-N-methoxy-N-methylbenzamide (**2e**).* This was prepared according to the general procedure, and the title compound was isolated as a colorless liquid (87% yield). Spectral data obtained were in good agreement with those reported in the literature.[30]

*5.5. 4-Chloro-N-methoxy-N-methylbenzamide (**2f**).* This was prepared according to the general procedure, and the title compound was isolated as a colorless liquid (83% yield). Spectral data obtained were in good agreement with those reported in the literature.[28]

*5.6. N-3-Dimethoxy-N-methylbenzamide (**2g**).* This was prepared according to the general procedure, and the title compound was isolated as a pale yellow liquid (72% yield). Spectral data obtained were in good agreement with those reported in the literature.[28]

*5.7. N-Methoxy-N-methyl-4-nitrobenzamide (**2h**).* This was prepared according to the general procedure, and the title compound was isolated as a pale yellow solid (83% yield). Spectral data obtained were in good agreement with those reported in the literature.[31]

*5.8. N-Methoxy-N-methyl-1-naphthamide (**2i**).* This was prepared according to the general procedure, and the title compound was isolated as a colorless gel (79% yield). Spectral data obtained were in good agreement with those reported in the literature.[27]

*5.9. 4-Iodo-N-methoxy-N-methylbenzamide (**2j**).* This was prepared according to the general procedure, and the title compound was isolated as a colorless gel (79% yield). Spectral data obtained were in good agreement with those reported in the literature.[31]

*5.10. N-4-Dimethoxy-N-methylbenzamide (**2k**).* This was prepared according to the general procedure, and the title compound was isolated as a colorless gel (81% yield). Spectral data obtained were in good agreement with those reported in the literature.[26]

6. General Procedures. *6.1. Methyl (E)-3-(4-(Methoxy(methyl)-carbamoyl)phenyl)acrylate (**2l**).*[32] In a pressure tube equipped with a stir bar was taken 4-iodo-*N*-methoxy-*N*-methylbenzamide (0.344 mmol) in dry DMSO (2 mL). The reaction mixture was degassed with nitrogen for about 10 min, followed by the addition of $Pd(OAc)_2$ (7 μmol), K_2CO_3 (1.031 mmol), and methyl acrylate (0.515 mmol). The tube was fitted with a Teflon screw cap under nitrogen flow. The reaction mixture was heated to 80 °C and stirred at that temperature, and the progress was followed by TLC. Upon completion of the reaction and subsequent cooling to room temperature, the reaction mixture was diluted with EtOAc and filtered through a short pad of Celite. The organic filtrate was washed with brine and dried over anhydrous Na_2SO_4, filtered, and concentrated under vacuum. The crude product was purified by silica gel flash column chromatography, eluting with petroleum ether−EtOAc (7:3). Yield: 80% (60 mg). Physical appearance: White solid. Mp 82−86 °C, TLC R_f 0.30 (7:3, petroleum ether:EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.74−7.64 (m, 3H), 7.54 (d, J = 8.2 Hz, 1H), 6.47 (d, J = 16.0 Hz, 1H), 3.80 (s, 3H), 3.54 (s, 3H), 3.35 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.1, 167.1, 143.8, 136.4, 135.6, 128.8, 127.6, 119.3, 61.2, 51.8, 33.6. IR (KBr, cm^{-1}): 2913, 2871, 2343, 2318, 1742, 1714, 1685, 1539, 1458, 1316, 1278, 1182, 1064, 984, 851, 781, 658. ESI-HRMS: calcd for $C_{13}H_{15}NO_4$ $[M + H]^+$ 250.1074, found 250.1050.

7. General Procedures for Synthesis of Anilides. *7.1. Synthesis of Anilides and Pivalamides.*[33] In a round-bottom flask was taken the substituted aniline under a nitrogen atmosphere and cooled to 0 °C. Ac_2O (or PivOCl) was added dropwise with stirring. The reaction mixture was allowed to warm to room temperature and stirred until the reaction was complete. The reaction mixture was then diluted with DCM and quenched with a saturated solution of $NaHCO_3$, and the resulting mixture was extracted twice with CH_2Cl_2. The combined organic layer was washed with brine and dried over anhydrous Na_2SO_4, filtered, and concentrated under vacuum. The crude product was purified by silica gel column chromatography.

*7.1.1. N-Phenylacetamide (**3a**).* This was prepared according to the general procedure, and the title compound was isolated as a white solid (98% yield). Spectral data obtained were in good agreement with those reported in the literature.[34]

*7.1.2. N-(p-Tolyl)acetamide (**3b**).* This was prepared according to the general procedure, and the title compound was isolated as a white solid (97% yield). Spectral data obtained were in good agreement with those reported in the literature.[35]

*7.1.3. N-(4-Nitrophenyl)acetamide (**3c**).* This was prepared according to the general procedure, and the title compound was isolated as a pale yellow solid (93% yield). Spectral data obtained were in good agreement with those reported in the literature.[36]

*7.1.4. N-(Naphthalen-2-yl)acetamide (**3d**).* This was prepared according to the general procedure, and the title compound was isolated as a pale brown solid (86% yield). Spectral data obtained were in good agreement with those reported in the literature.[37]

*7.1.5. N-(Quinolin-6-yl)acetamide (**3e**).* This was prepared according to the general procedure, and the title compound was isolated as a pale brown solid (81% yield). Spectral data obtained were in good agreement with those reported in the literature.[38]

*7.1.6. N-(Naphthalen-1-yl)acetamide (**3f**).* This was prepared according to the general procedure, and the title compound was isolated as a purple solid (91% yield). Spectral data obtained were in good agreement with those reported in the literature.[39]

*7.1.7. N-(3-Fluorophenyl)acetamide (**3g**).* This was prepared according to the general procedure, and the title compound was isolated as an off-white solid (84% yield). Spectral data obtained were in good agreement with those reported in the literature.[40]

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J. Org. Chem. 2017, 82, 1114−1126

*7.1.8. N-(2-Fluorophenyl)acetamide (**3h**).* This was prepared according to the general procedure, and the title compound was isolated as an off-white solid (81% yield). Spectral data obtained were in good agreement with those reported in the literature.[41]

*7.1.9. N-(p-Tolyl)pivalamide (**3i**).* This was prepared according to the general procedure, and the title compound was isolated as a purple solid (91% yield). Spectral data obtained were in good agreement with those reported in the literature.[42]

8. General Procedure for the Synthesis of *N*-Arylbenzamides. In a two-neck round-bottomed flask, oxalyl chloride (1.2 equiv) was added dropwise into the stirring solution of the benzoic acid (1 equiv) in CH_2Cl_2 at 0 °C. This was followed by addition of DMF (2 drops). The reaction mixture was allowed to warm to room temperature and stirred for another 1.5 h and then recooled to 0 °C. Et_3N (3 equiv) and aniline (1.05 equiv) were added. The reaction mixture was once again allowed to warm to room temperature and stirred for a further 6 h. The reaction was quenched at room temperature with a saturated solution of $NaHCO_3$, and the resulting mixture was extracted twice with CH_2Cl_2. The combined organic layer was washed with brine and dried over anhydrous Na_2SO_4, filtered, and concentrated under vacuum. The crude product was purified by silica gel column chromatography.

*8.1. N-(p-Tolyl)benzamide (**3j**).* This was prepared according to the general procedure, and the title compound was isolated as a white solid (89% yield). Spectral data obtained were in good agreement with those reported in the literature.[43]

*8.2. 4-Methyl-N-(p-tolyl)benzamide (**3k**).* This was prepared according to the general procedure, and the title compound was isolated as a white solid (86% yield). Spectral data obtained were in good agreement with those reported in the literature.[44]

*8.3. 4-Methyl-N-phenylbenzamide (**3l**).* This was prepared according to the general procedure, and the title compound was isolated as white solid (91% yield). Spectral data obtained were in good agreement with those reported in the literature.[45]

9. General Procedure for the Pd-Catalyzed *ortho*-C−H Halogenation Reaction. In a pressure tube equipped with a stir bar was taken the substrate (0.303 mmol) in dry dichloroethane (1.5 mL). The solution was degassed with nitrogen for about 10 min, followed by the addition of $Pd(OAc)_2$ (0.03 mmol), $Cu(OTf)_2$ (0.151 mmol), and *N*-halosuccinimide (0.606 mmol). The tube was fitted with a Teflon screw cap under nitrogen flow, and the reaction mixture was heated to 80 °C and stirred at that temperature. The progress was followed either by GCMS or by TLC. Upon completion of the reaction and subsequent cooling to room temperature, the reaction mixture was diluted with EtOAc and filtered through a short pad of Celite, and the filtrate was washed with brine. The organic layer was dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure, and the crude product was purified by silica gel flash column chromatography.

*9.1. 2-(2-Bromophenyl)acetonitrile (**4a**).* Yield: 71% (59 mg). Physical appearance: yellow gel, TLC R_f 0.30 (19:1, petroleum ether:EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.62 (d, J = 8.1 Hz, 1H), 7.55 (d, J = 7.7 Hz, 1H), 7.38 (t, J = 7.6 Hz, 1H), 7.24 (t, J = 7.7 Hz, 1H), 3.83 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 133.1, 129.9, 129.7, 128.2, 123.6, 116.2, 24.9. IR (KBr, cm^{-1}): 3063, 2928, 2252, 1571, 1472, 1441, 1413, 1194, 1120, 1028, 951, 817, 752, 661, 427. APCI-HRMS: calcd for C_8H_7BrN $[M + H]^+$ 195.9846 and 197.9834, found 195.9846 and 197.9834.

*9.2. 2-(2-Iodophenyl)acetonitrile (**4b**).* Yield: 62% (65 mg). Physical appearance: pale yellow gel, TLC R_f 0.30 (19:1, petroleum ether:EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.86 (d, J = 7.9 Hz, 1H), 7.52 (d, J = 7.9 Hz, 1H), 7.39 (t, J = 7.9 Hz, 1H), 7.03 (t, J = 7.9 Hz, 1H), 3.80 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 139.8, 133.3, 129.9, 129.1, 129.0, 117.1, 99.0, 30.0. IR (KBr, cm^{-1}): 2961, 2352, 1462, 1407, 1245, 1184, 1065, 800, 657. APCI-HRMS: calcd for C_8H_5IN $[M - H]^-$ 241.9461, found 241.9489.

*9.3. Methyl 3-Bromo-4-(cyanomethyl)benzoate (**4c**).* Yield: 72% (78 mg). Physical appearance: pale yellow semisolid, mp less than 40 °C, TLC R_f 0.30 (9:1, petroleum ether:EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.25 (s, 1H), 8.04 (d, J = 8.0 Hz, 1H), 7.61 (d, J = 8.0 Hz, 1H), 3.92 (s, 3H), 3.87 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.1, 134.6, 134.1, 131.9, 129.6, 129.1, 123.5, 116.2, 52.6, 25.1. IR (KBr, cm^{-1}): 2953, 2916, 2847, 2361, 1728, 1605, 1562, 1435, 1292, 1260, 1194, 1119, 1042, 972, 758. APCI-HRMS: calcd for $C_{10}H_7BrNO_2$ $[M - H]^-$ 251.9655 and 253.9635, found 251.9648 and 253.9624.

*9.4. 2-(2-Bromonaphthalen-1-yl)acetonitrile (**4d**).* Yield: 70% (51 mg). Physical appearance: brownish gel, TLC R_f 0.30 (9:1, petroleum ether:EtOAc). ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.26−8.12 (m, 1H), 8.11−8.04 (m, 1H), 7.89 (d, J = 7.7 Hz, 1H), 7.79−7.63 (m, 2H), 7.50 (d, J = 7.7 Hz, 1H), 4.49 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 132.4, 132.3, 131.9, 131.7, 131.1, 130.3, 128.9, 128.7, 128.5, 128.3, 128.1, 128.0, 127.9, 127.7, 127.6, 127.4, 124.8, 124.3, 123.2, 122.7, 119.3, 119.2, 21.2, 21. IR (KBr, cm^{-1}): 2918, 2340, 2253, 1595, 1506, 1414, 1379, 1198, 1039, 945, 893, 785, 667. APCI-HRMS: calcd for $C_{12}H_8BrN$ $[M]^+$ 244.9835 and 246.9814, found 244.9818 and 246.9797.

*9.5. 2-(2-Iodonaphthalen-1-yl)acetonitrile (**4e**).* Yield: 63% (55 mg). Physical appearance: yellow solid, mp 77−81 °C, TLC R_f 0.30 (9:1, petroleum ether:EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.20−8.02 (m, 2H), 7.86−7.73 (m, 1H), 7.65−7.50 (m, 1H), 7.26 (d, J = 7.6 Hz, 1H), 4.06 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 138.2, 137.1, 134.4, 133.6, 133.5, 131.3, 128.2, 128.0, 127.5, 127.4, 127.2, 126.9, 126.4, 123.3, 123.0, 117.4, 100.9, 100.7, 21.7, 21.7. IR (KBr, cm^{-1}): 2975, 2353, 1601, 1572, 1431, 1380, 1211, 1020, 945, 900, 708. APCI-HRMS: calcd for $C_{12}H_7IN$ $[M - H]^+$ 291.9618, found 291.9597.

*9.6. 2-(2,4-Dibromophenyl)acetonitrile (**4f**).* Yield: 61% (43 mg). Physical appearance: white solid, mp 59−60 °C, TLC R_f 0.30 (9:1, petroleum ether:EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.76 (d, J = 1.9 Hz, 1H), 7.49 (dd, J = 8.3, 1.9 Hz, 1H), 7.39 (d, J = 8.3 Hz, 1H), 3.78 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 135.5, 131.4, 130.7, 129.0, 124.2, 116.4, 24.5. IR (KBr, cm^{-1}): 2924, 2389, 2313, 2249, 1578, 1406, 1377, 1088, 1038, 926, 816, 704. APCI-HRMS: calcd for $C_8H_4Br_2N$ $[M - H]^-$ 271.8707, 273.8685, and 275.8664, found 271.8702, 273.8687, and 275.8662.

*9.7. 2-(4-Bromo-2-iodophenyl)acetonitrile (**4g**).* Yield: 58% (49 mg). Physical appearance: white solid, mp 88−91 °C, TLC R_f 0.30 (9:1, petroleum ether:EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.01 (s, 1H), 7.52 (d, J = 8.2 Hz, 1H), 7.38 (d, J = 8.2 Hz, 1H), 3.75 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 141.7, 132.4, 131.2, 130.0, 122.7, 116.7, 99.4, 29.5. IR (KBr, cm^{-1}): 2963, 2332, 1464, 1400, 1261, 1085, 1024, 800, 687. APCI-HRMS: calcd for C_8H_4BrIN $[M - H]^-$ 319.8566 and 321.8546, found 319.8590 and 321.8560.

*9.8. 2-(2-Bromo-3-chlorophenyl)acetonitrile (**4h**).* Yield: 47% (36 mg). Physical appearance: white solid, mp 92−93 °C, TLC R_f 0.30 (19:1, petroleum ether:EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.53−7.51 (m, 2H), 7.20 (dd, J = 8.5, 2.4 Hz, 1H), 3.80 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 134.3, 134.1, 131.6, 129.7, 121.4, 116.2, 24.8. IR (KBr, cm^{-1}): 2937, 2914, 2369, 2246, 1649, 1457, 1403, 1095, 1029, 931, 856, 824. APCI-HRMS: calcd for C_8H_4ClBrN $[M - H]^-$ 227.9210 and 229.9189, found 227.9215 and 229.9184.

*9.9. 2-(5-Chloro-2-iodophenyl)acetonitrile (**4i**).* Yield: 53% (49 mg). Physical appearance: white solid, mp 89−94 °C, TLC R_f 0.30 (19:1, petroleum ether:EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.76 (d, J = 8.4 Hz, 1H), 7.51 (d, J = 2.4 Hz, 1H), 7.03 (dd, J = 8.4, 2.4 Hz, 1H), 3.77 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 140.7, 135.4, 135.0, 130.2, 129.2, 116.5, 96.0, 29.8. IR (KBr, cm^{-1}): 2359, 2334, 1643, 1452, 1397, 1259, 1093, 1012, 818, 740. APCI-HRMS: calcd for C_8H_4ClIN $[M - H]^-$ 275.9071, found 275.9054.

*9.10. Methyl 4-Bromo-3-(cyanomethyl)benzoate (**4j**).* Yield: 52% (38 mg). Physical appearance: white solid, mp 88−90 °C, TLC R_f 0.30 (9:1, petroleum ether:EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.16 (d, J = 1.7 Hz, 1H), 7.87 (dd, J = 8.3, 1.9 Hz, 1H), 7.69 (d, J = 8.3 Hz, 1H), 3.92 (s, 3H), 3.87 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.7, 133.4, 130.8, 130.7, 130.5, 130.3, 129.0, 116.3, 52.3, 24.9. IR (KBr, cm^{-1}): 2360, 2330, 1718, 1303, 1256, 1195, 1109, 1032, 758. APCI-HRMS: calcd for $C_{10}H_7BrNO_2$ $[M - H]^-$ 251.9655 and 253.9635, found 251.9632 and 253.9601.

*9.11. 2-(3-Bromo-4-methoxyphenyl)acetonitrile (**4k**).* Yield: 72% (55 mg). Physical appearance: yellow solid, mp 45−47 °C, TLC R_f

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J. Org. Chem. 2017, 82, 1114−1126

0.30 (9:1, petroleum ether:EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.47 (d, J = 2.1 Hz, 1H), 7.22 (dd, J = 8.4, 2.1 Hz, 1H), 6.86 (d, J = 8.5 Hz, 1H), 3.87 (s, 3H), 3.65 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 155.8, 132.8, 128.1, 123.2, 117.6, 112.3, 112.2, 56.4, 22.4. IR (KBr, cm^{-1}): 2963, 2839, 2251, 1603, 1501, 1462, 1414, 1285, 1259, 1184, 2153, 1055, 1020, 923, 856, 803, 754, 675. APCI-HRMS: calcd for C_9H_7BrNO $[M - H]^-$ 223.9706 and 225.9685, found 223.9712 and 225.9698.

*9.12. 2-(3-Iodo-4-methoxyphenyl)acetonitrile (**4l**).* Yield: 68% (63 mg). Physical appearance: greenish-yellow solid, mp 59−61 °C, TLC R_f 0.30 (9:1, petroleum ether:EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.69 (d, J = 2.1 Hz, 1H), 7.25 (dd, J = 8.6, 1.9 Hz, 1H), 6.78 (d, J = 8.5 Hz, 1H), 3.86 (s, 3H), 3.64 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 158.0, 138.8, 129.1, 123.7, 117.7, 111.1, 86.4, 56.5, 22.2. IR (KBr, cm^{-1}): 2247, 1599, 1489, 1260, 1094, 1047, 1018, 802. APCI-HRMS: calcd for C_9H_7INO $[M - H]^-$ 271.9567, found 271.9563.

*9.13. 2-(3-Bromo-4-iodophenyl)acetonitrile (**4m**).* Yield: 58% (38 mg). Physical appearance: yellow gel, TLC R_f 0.30 (9:1, petroleum ether:EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.84 (d, J = 8.2 Hz, 1H), 7.60 (s, 1H), 6.97 (d, J = 8.2 Hz, 1H), 3.67 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 140.9, 132.1, 131.7, 130.6, 128.0, 116.7, 100.8, 22.9. APCI-HRMS: calcd for C_8H_4BrIN $[M - H]^-$ 319.8566 and 321.8546, found 319.8548 and 321.8516.

*9.14. 2-Bromo-N-methoxy-N-methylbenzamide (**5a**).* Yield: 81% (60 mg). Physical appearance: colorless gel, TLC R_f 0.30 (4:1, petroleum ether:EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.56 (d, J = 8.0 Hz, 1H), 7.39−7.19 (m, 3H), 4.19−2.88 (m, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.1, 137.5, 132.5, 130.3, 127.6, 127.0, 119.3, 61.3, 32.3. IR (KBr, cm^{-1}): 3459, 2098, 1644, 982, 767, 741, 662. ESI-HRMS: calcd for $C_9H_{11}BrNO_2$ $[M + H]^+$ 243.9968 and 245.9947, found 243.9964 and 245.9947.

*9.15. 2-Iodo-N-methoxy-N-methylbenzamide (**5b**).* Yield: 68% (60 mg). Physical appearance: colorless gel, TLC R_f 0.30 (4:1, petroleum ether:EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.80 (d, J = 7.9 Hz, 1H), 7.39 (t, J = 7.3 Hz, 1H), 7.27−7.20 (m, 1H), 7.07 (td, J = 7.8, 1.5 Hz, 1H), 4.31−2.84 (m, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 138.9, 133.4, 130.3, 128.4, 127.6, 127.2, 92.5, 61.4, 32.6. IR (KBr, cm^{-1}): 3475, 2091, 1645, 1420, 1385, 1263, 1215, 1176, 1115, 1674, 1016, 984, 886, 769, 653. ESI-HRMS: calcd for $C_9H_{11}INO_2$ $[M + H]^+$ 291.9829, found 291.9849.

*9.16. 2-Chloro-N-methoxy-N-methylbenzamide (**5c**).* Yield: 62% (37 mg). Physical appearance: colorless gel, TLC R_f 0.40 (4:1, petroleum ether:EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.39−7.37 (m, 1H), 7.35−7.26 (m, 3H), 4.17−2.87 (m, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.5, 135.2, 130.7, 130.2, 129.5, 127.6, 126.5, 61.3, 32.3. IR (KBr, cm^{-1}): 3484, 2098, 1646, 1437, 1386, 1267, 1214, 1175, 1128, 1080, 1048, 986, 889, 768, 743, 678, 576. ESI-HRMS: calcd for $C_9H_{11}ClNO_2$ $[M + H]^+$ 200.0473, found 200.0497.

*9.17. 2-Bromo-4-(tert-butyl)-N-methoxy-N-methylbenzamide (**5d**).* Yield: 68% (46 mg). Physical appearance: yellow gel, TLC R_f 0.30 (4:1, petroleum ether:EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.54 (s, 1H), 7.33 (d, J = 8.0 Hz, 1H), 7.21 (d, J = 8.0 Hz, 1H), 4.10−2.84 (m, 6H), 1.28 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 154.0, 137.5, 130.2, 129.7, 127.5, 124.2, 119.2, 61.4, 34.9, 32.3, 31.1. IR (KBr, cm^{-1}): 3449, 2966, 2246, 1652, 1602, 1547, 1417, 1383, 1277, 1259, 1175, 1113, 1037, 987, 881, 832, 750, 677, 660. ESI-HRMS: calcd for $C_{13}H_{19}BrNO_2$ $[M + H]^+$ 300.0594 and 302.0574, found 300.0614 and 302.0595.

*9.18. 2-Iodo-4-(tert-butyl)-N-methoxy-N-methylbenzamide (**5e**).* Yield: 71% (56 mg). Physical appearance: pale yellow solid, mp 46−47 °C, TLC R_f 0.30 (4:1, petroleum ether:EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.78 (s, 1H), 7.36 (d, J = 8.0 Hz, 1H), 7.16 (d, J = 8.0 Hz, 1H), 4.34−2.79 (m, 6H), 1.28 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 154.0, 138.5, 136.2, 128.1, 126.9, 124.9, 92.6, 61.4, 34.7, 32.6, 31.1. IR (KBr, cm^{-1}): 3448, 1646, 1261, 985, 884, 833, 748. ESI-HRMS: calcd for $C_{13}H_{19}INO_2$ $[M + H]^+$ 348.0455, found 348.0477.

*9.19. 2-Chloro-4-(tert-butyl)-N-methoxy-N-methylbenzamide (**5f**).* Yield: 73% (42 mg). Physical appearance: colorless gel, TLC R_f 0.30 (4:1, petroleum ether:EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.34 (s, 1H), 7.29−7.16 (m, 2H), 4.28−2.57 (m, 6H), 1.25 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 154.1, 132.1, 130.3, 127.4, 126.6, 123.7, 61.9, 34.9, 32.3, 31.3. IR (KBr, cm^{-1}): 3431, 2092, 1638, 748, 438. ESI-HRMS: calcd for $C_{13}H_{19}ClNO_2$ $[M + H]^+$ 256.1099, found 256.1090.

*9.20. 2-Bromo-N-methoxy-N,4-dimethylbenzamide (**5g**).* Yield: 83% (59 mg). Physical appearance: colorless gel, TLC R_f 0.30 (4:1, petroleum ether:EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.34 (s, 1H), 7.14 (d, J = 7.7 Hz, 1H), 7.09 (d, J = 7.8 Hz, 1H), 4.18−2.86 (m, 6H), 2.29 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.4, 140.8, 134.4, 133.0, 127.7, 127.5, 119.1, 61.3, 32.3, 21.0. IR (KBr, cm^{-1}): 3457, 2093, 1645, 814, 747, 676, 583. ESI-HRMS: calcd for $C_{10}H_{13}BrNO_2$ $[M + H]^+$ 258.0124 and 260.0104, found 258.0131 and 260.0113.

*9.21. 2-Iodo-N-methoxy-N,4-dimethylbenzamide (**5h**).* Yield: 58% (49 mg). Physical appearance: colorless gel, TLC R_f 0.30 (4:1, petroleum ether:EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.16 (s, 1H), 7.60 (d, J = 7.8 Hz, 1H), 7.27 (d, J = 8.0 Hz, 1H), 3.57 (s, 3H), 3.36 (s, 3H), 2.47 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.7, 144.2, 138.7, 133.1, 129.1, 128.1, 100.2, 61.1, 33.7, 28.1. IR (KBr, cm^{-1}): 3464, 2934, 1637, 1380, 1210, 1069, 1034, 980, 898, 832, 807, 743, 660. ESI-HRMS: calcd for $C_{10}H_{13}INO_2$ $[M + H]^+$ 305.9985, found 305.9982.

*9.22. 2-Chloro-N-methoxy-N,4-dimethylbenzamide (**5i**).* Yield: 51% (30 mg). Physical appearance: pale yellow gel, TLC R_f 0.30 (4:1, petroleum ether:EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.21−7.13 (m, 2H), 7.05 (d, J = 8.0 Hz, 1H), 3.54−3.11 (s, 6H), 2.30 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.0, 140.7, 130.4, 129.9, 128.6, 128.3, 127.6, 61.3, 32.3, 21.1. IR (KBr, cm^{-1}): 3464, 2938, 1652, 1418, 1386, 1270, 1173, 1117, 1081, 1045, 986, 901, 856, 749, 688. ESI-HRMS: calcd for $C_{10}H_{13}ClNO_2$ $[M + H]^+$ 214.0629, found 214.0658.

*9.23. 2-Bromo-4-fluoro-N-methoxy-N-methylbenzamide (**5j**).* Yield: 68% (48 mg). Physical appearance: colorless gel, TLC R_f 0.30 (4:1, petroleum ether:EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.30−7.24 (m, 2H), 7.09−6.98 (m, 1H), 4.33−2.58 (m, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.4, 162.4 (d, J = 252.2 Hz, 1C), 133.5, 130.8 (d, J = 8.6 Hz, 1C), 129.0, 120.1 (d, J = 9.6 Hz, 1C), 114.8 (d, J = 53.0 Hz, 1C), 61.3, 32.4. IR (KBr, cm^{-1}): 3484, 3090, 2975, 2938, 2084, 1651, 1600, 1420, 1385, 1264, 1203, 1168, 1072, 986, 858, 748, 678. ESI-HRMS: calcd for $C_9H_{10}BrFNO_2$ $[M + H]^+$ 261.9873 and 263.9853, found 261.9886 and 263.9863.

*9.24. 2-Iodo-4-fluoro-N-methoxy-N-methylbenzamide (**5k**).* Yield: 71% (60 mg). Physical appearance: colorless gel, TLC R_f 0.30 (4:1, petroleum ether:EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.55 (dd, J = 8.1, 2.4 Hz, 1H), 7.28−7.20 (m, 1H), 7.09 (td, J = 8.1, 2.3 Hz, 1H), 4.39−2.63 (m, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.0, 162.0 (d, J = 249.9 Hz, 1C), 137.8, 129.5, 128.5, 126.2 (d, J = 23.2 Hz, 1C), 115.1 (d, J = 21.5 Hz, 1C), 93.4 (d, J = 8.1 Hz, 1C), 61.4, 32.6. IR (KBr, cm^{-1}): 3479, 3086, 2936, 1652, 1592, 1418, 1264, 1222, 1071, 1030, 986, 851, 748, 584. ESI-HRMS: calcd for $C_9H_{10}FINO_2$ $[M + H]^+$ 309.9735, found 309.9756.

*9.25. 2,4-Dibromo-N-methoxy-N-methylbenzamide (**5l**).* Yield: 82% (54 mg). Physical appearance: pale yellow gel, TLC R_f 0.30 (4:1, petroleum ether:EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.72 (s, 1H), 7.60−7.39 (m, 1H), 7.16 (d, J = 8.1 Hz, 1H), 4.44−2.74 (m, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.3, 135.1, 131.2, 130.3, 130.0, 128.8, 120.2, 61.5, 32.4. IR (KBr, cm^{-1}): 3448, 1646, 1261, 983, 884, 833, 748. ESI-HRMS: calcd for $C_9H_{10}Br_2NO_2$ $[M + H]^+$ 321.9073, 323.9053, and 325.9032, found 321.9074, 323.9061, and 325.9041.

*9.26. 4-Bromo-2-iodo-N-methoxy-N-methylbenzamide (**5m**).* Yield: 69% (52 mg). Physical appearance: pale yellow gel, TLC R_f 0.30 (4:1, petroleum ether:EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.65−7.41 (m, 3H), 4.09−2.90 (m, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.7, 141.0, 132.8, 131.2, 130.0, 125.1, 93.1, 61.1, 33.5. IR (KBr, cm^{-1}): 3489, 2971, 2935, 2096, 1644, 1589, 1573, 1456, 1417, 1382, 1214, 1177, 1111, 1072, 981, 887, 836, 744. ESI-HRMS: calcd for $C_9H_{10}BrNO_2I$ $[M + H]^+$ 369.8934 and 371.8914, found 369.8938 and 371.8913.

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J. Org. Chem. 2017, 82, 1114−1126

*9.27. 2-Bromo-4-chloro-N-methoxy-N-methylbenzamide (**5n**).* Yield: 62% (43 mg). Physical appearance: colorless gel, TLC R_f 0.30 (4:1, petroleum ether:EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.57 (s, 1H), 7.40−7.13 (m, 2H), 4.04−2.96 (m, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.2, 135.9, 135.5, 132.4, 128.5, 127.4, 120.0, 61.5, 32.3. IR (KBr, cm^{-1}): 3450, 2067, 1647, 1213, 1037, 983, 824, 782, 673. ESI-HRMS: calcd for $C_9H_{10}BrClNO_2$[M + H]$^+$ 277.9578 and 279.9557, found 277.9594 and 279.9579.

*9.28. 2-Iodo-4-chloro-N-methoxy-N-methylbenzamide (**5o**).* Yield: 62% (46 mg). Physical appearance: colorless gel, TLC R_f 0.30 (4:1, petroleum ether:EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.86 (d, J = 1.9 Hz, 1H), 7.39 (d, J = 8.1 Hz, 1H), 7.21 (d, J = 8.1 Hz, 1H), 4.33−2.41 (m, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.7, 140.0, 138.5, 135.3, 128.8, 128.0, 92.7, 61.5, 32.6. IR (KBr, cm^{-1}): 3432, 2098, 1638, 984, 826, 745. ESI-HRMS: calcd for $C_9H_{10}ClINO_2$ [M + H]$^+$ 325.9439, found 325.9455.

*9.29. 2,4-Dichloro-N-methoxy-N-methylbenzamide (**5p**).* Yield: 49% (29 mg). Physical appearance: colorless gel, TLC R_f 0.30 (4:1, petroleum ether:EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.61 (d, J = 8.5 Hz, 1H), 7.41 (s, 1H), 7.33 (d, J = 8.5 Hz, 1H), 4.36−2.78 (m, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.6, 136.7, 132.4, 131.7, 129.5, 128.3, 61.1, 33.5. IR (KBr, cm^{-1}): 3450, 2090, 1647, 1388, 1213, 1092, 984, 839, 801, 746. ESI-HRMS: calcd for $C_9H_{10}Cl_2NO_2$ [M + H]$^+$ 234.0083, found 234.0086.

*9.30. 2-Bromo-N,3-dimethoxy-N-methylbenzamide (**5q**).* Yield: 64% (29 mg). Physical appearance: pale yellow gel, TLC R_f 0.30 (4:1, petroleum ether:EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.42 (d, J = 8.8 Hz, 1H), 6.90−6.74 (m, 2H), 4.20−2.84 (m, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 158.5, 138.2, 133.4, 133.3, 116.4, 113.2, 109.6, 61.4, 55.6, 32.3. IR (KBr, cm^{-1}): 3448, 2066, 1649, 1290, 1082, 1019, 825, 745, 601. ESI-HRMS: calcd for $C_{10}H_{13}BrNO_3$ [M + H]$^+$ 274.0073 and 276.0053, found 274.0063 and 276.0037.

*9.31. Methyl (E)-3-(3-Bromo-4-(methoxy(methyl)carbamoyl)-phenyl)acrylate (**5r**).* Yield: 80% (42 mg). Physical appearance: white solid, mp 51−53 °C, TLC R_f 0.30 (7:3, petroleum ether:EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.71 (s, 1H), 7.58 (d, J = 16.1 Hz), 7.46 (d, J = 7.8 Hz, 1H), 7.30 (d, J = 7.8 Hz, 1H), 6.43 (dd, J = 16.1, 1.5 Hz, 1H), 3.79 (d, J = 2.4 Hz, 3H), 3.64−3.04 (m, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.5, 166.7, 142.3, 138.8, 136.7, 131.8, 128.1, 126.5, 120.1, 120.1, 61.5, 53.8. IR (KBr, cm^{-1}): 2943, 2820, 2363, 1726, 1650, 1433, 1385, 1317, 1296, 1110, 1175, 1078, 1037, 986, 833, 739, 677. ESI-HRMS: calcd for $C_{13}H_{15}BrNO_4$ [M + H]$^+$ 328.0179 and 330.0159, found 328.0198 and 330.0187.

*9.32. Methyl (Z)-3-(4-(Methoxy(methyl)carbamoyl)phenyl)-acrylate (**5s**).* Yield: 80% (10 mg). Physical appearance: colorless gel, TLC R_f 0.40 (7:3, petroleum ether:EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.61 (d, J = 1.4 Hz, 1H), 7.49−7.25 (m, 2H), 5.25 (d, J = 11.7 Hz, 1H), 4.37 (d, J = 11.7 Hz, 1H), 3.88 (s, 3H), 3.58−2.78 (m, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.5, 166.7, 142.3, 138.8, 136.7, 131.8, 128.1, 126.5, 120.1, 120.0, 61.5, 53.8. IR (KBr, cm^{-1}): 2943, 2820, 2363, 1726, 1650, 1433, 1385, 1317, 1296, 1110, 1175, 1078, 1037, 986, 833, 739, 677. ESI-HRMS: calcd for $C_{13}H_{15}BrNO_4$ [M + H]$^+$ 328.0179 and 330.0159, found 328.0198 and 330.0187.

*9.33. 2-Bromo-N-methoxy-N-methyl-1-naphthamide (**5t**).* Yield: 74% (50 mg). Physical appearance: colorless gel, TLC R_f 0.30 (3:2, petroleum ether:EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.88 (d, J = 7.7 Hz, 1H), 7.83 (d, J = 7.8 Hz, 2H), 7.57−7.47 (m, 2H), 7.35−7.26 (m, 1H), 3.40 (s, 2H), 3.29 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.1, 135.3, 134.1, 132.9, 130.4, 128.8, 127.0, 126.5, 125.3, 119.3, 60.6, 34.0.IR (KBr, cm^{-1}): 2970, 2934, 2359, 1715, 1655, 1497, 1460, 1379, 1360, 1182, 1105, 1016, 978, 822, 768. ESI-HRMS: calcd for $C_{13}H_{13}BrNO_2$ [M + H]$^+$ 294.0124 and 296.0104, found 294.0149 and 296.0124.

*9.34. 2,5-Dibromo-N,4-dimethoxy-N-methylbenzamide (**5u**).* Yield: 68% (61 mg). Physical appearance: pale yellow gel, TLC R_f 0.30 (4:1, petroleum ether:EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.48 (s, 1H), 7.05 (s, 1H), 3.90 (s, 3H), 3.65−3.11 (m, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 156.8, 132.1, 130.5, 119.1, 116.0, 61.3, 56.6, 29.7. IR (KBr, cm^{-1}): 3591, 2940, 1658, 1579, 1424, 1362, 1268, 1246, 1183, 1107, 874, 830, 752, 651. ESI-HRMS: calcd for $C_{10}H_{12}Br_2NO_3$ [M + H]$^+$ 351.9178, 353.9162, and 355.9132, found 351.9179, 353.9174, and 355.9138.

*9.35. N-(2-Bromo-4-methylphenyl)acetamide (**6a**).* Yield: 83% (63 mg). Physical appearance: white solid, mp 88−89 °C, TLC R_f 0.30 (3:2, petroleum ether:EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.13 (d, J = 8.3 Hz, 1H), 7.49 (s, 1H), 7.33 (s, 1H), 7.09 (d, J = 8.3 Hz, 1H), 2.27 (s, 3H), 2.20 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.1, 135.2, 133.2, 129.0, 121.9, 113.2, 24.8, 20.5. IR (KBr, cm^{-1}): 3277, 2355, 2325, 1650, 1292, 1042, 821, 680. ESI-HRMS: calcd for $C_9H_{11}BrNO$ [M + H]$^+$ 228.0019 and 229.9998, found 228.0035 and 230.0013.

*9.36. N-(2-Bromo-4-methylphenyl)pivalamide (**6b**).* Yield: 83% (58 mg). Physical appearance: white solid, mp 49−51 °C, TLC R_f 0.40 (9:1, petroleum ether:EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.21 (d, J = 8.4 Hz, 1H), 7.89 (s, 1H), 7.09 (d, J = 8.4 Hz, 1H), 2.27 (s, 3H), 1.33 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 176.5, 134.9, 133.3, 132.3, 129.0, 121.5, 113.5, 40.1, 27.6, 20.5. IR (KBr, cm^{-1}): 3318, 2970, 2351, 1650, 1517, 1169, 1040, 809, 737, 601. ESI-HRMS: calcd for $C_{12}H_{17}BrNO$ [M + H]$^+$ 270.0488 and 272.0468, found 270.0517 and 272.0495.

*9.37. N-(2-Iodo-4-methylphenyl)pivalamide (**6c**).* Yield: 81% (67 mg). Physical appearance: greenish solid, mp 52−55 °C, TLC R_f 0.40 (9:1, petroleum ether:EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.10 (d, J = 8.1 Hz, 1H), 7.71 (s, 1H), 7.60 (s, 1H), 7.14 (d, J = 8.1 Hz, 1H), 2.20 (s, 3H), 1.37 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 176.6, 138.8, 135.9, 135.6, 129.9, 121.6, 40.0, 27.7, 20.3. IR (KBr, cm^{-1}): 3402, 2960, 1681, 1600, 1506, 1395, 1295, 1158, 1037, 920, 870, 768, 542, 438. ESI-HRMS: calcd for $C_{12}H_{17}INO$ [M + H]$^+$ 318.0349, found 318.0365.

*9.38. N-(2-Chloro-4-methylphenyl)pivalamide (**6d**).* Yield: 58% (34 mg). Physical appearance: white solid, mp 52−55 °C, TLC R_f 0.40 (9:1, petroleum ether:EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.26 (d, J = 8.4 Hz, 1H), 7.92 (s, 1H), 7.07 (d, J = 8.4 Hz, 1H), 2.30 (s, 3H), 1.35 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 176.5, 134.4, 132.2, 129.1, 128.3, 122.8, 121.4, 40.1, 27.6, 20.6. IR (KBr, cm^{-1}): 3317, 2957, 2356, 1658, 1509, 1492, 1398, 1248, 1176, 1056, 937, 890, 865, 841, 815, 777, 687. ESI-HRMS: calcd for $C_{12}H_{17}NOCl$ [M + H]$^+$ 226.0993, found 226.1019.

*9.39. N-(2-Bromonaphthalen-1-yl)acetamide (**6e**).* Yield: 82% (58 mg). Physical appearance: white solid, mp 170−174 °C, TLC R_f 0.30 (3:2, petroleum ether:EtOAc). ^{1}H NMR (400 MHz, CD_3OD): δ 8.25−8.20 (m, 1H), 8.04−8.01 (m, 1H), 7.79 (d, J = 8.0 Hz, 1H), 7.67−7.56 (m, 2H), 7.50 (d, J = 8.0 Hz, 1H), 2.26 (s, 3H). ^{13}C NMR (100 MHz, CD_3OD): δ 171.5, 133.2, 132.5, 132.1, 131.8, 131.4, 129.2, 128.9, 128.1, 127.9, 127.2, 126.3, 123.8, 123.0, 122.0, 120.5, 120.0, 21.2. IR (KBr, cm^{-1}): 2334, 1647, 1373, 1116, 754, 677. ESI-HRMS: calcd for $C_{12}H_{11}BrNO$ [M + H]$^+$ 264.0019 and 265.9998, found 264.0016 and 265.9995.

*9.40. N-(2-Bromophenyl)acetamide (**6f**).* This was prepared according to the general procedure, and the title compound was isolated as a white solid (79% (62 mg) yield). Spectral data obtained were in agreement with those reported in the literature.[46]

*9.41. N-(2-Bromo-5-fluorophenyl)acetamide and N-(2-Bromo-3-fluorophenyl)acetamide (**6g**).* This was prepared according to the general procedure, and the title compounds were isolated as a white solid (mixture of isomers, 77% (59 mg) yield). Spectral data obtained were in good agreement with those reported in the literature.[11b]

*9.42. N-(1-Bromonaphthalen-2-yl)acetamide (**6h**).* Yield: 78% (54 mg). Physical appearance: off-white solid, mp 103−107 °C, TLC R_f 0.30 (2:3, petroleum ether:EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.40 (d, J = 8.6 Hz, 1H), 8.13 (d, J = 8.6 Hz, 1H), 7.88 (s, 1H), 7.76 (d, J = 8.6 Hz, 2H), 7.54 (t, J = 7.3 Hz, 1H), 7.43 (t, J = 7.3 Hz, 1H), 2.26 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.5, 134.3, 131.9, 131.6, 128.3, 128.2, 127.7, 126.6, 125.6, 121.0, 111.7, 24.9. IR (KBr, cm^{-1}): 3268, 2355, 2329, 1664, 1519, 1290, 1018, 811, 747, 668. ESI-HRMS: calcd for $C_{12}H_{11}BrNO$ [M + H]$^+$ 264.0019 and 265.9998, found 264.0021 and 266.0000.

*9.43. N-(7-Bromoquinolin-6-yl)acetamide (**6i**).* Yield: 72% (51 mg). Physical appearance: white solid, mp 123−125 °C, TLC R_f 0.30 (2:3, petroleum ether:EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.85

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J. Org. Chem. 2017, 82, 1114−1126

(d, J = 3.2 Hz, 1H), 8.69 (d, J = 8.6 Hz, 1H), 8.45 (d, J = 8.6 Hz, 1H), 8.07 (d, J = 8.6 Hz, 1H), 7.87 (s, 1H), 7.53−7.40 (m, 1H), 2.30 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 177.3, 168.5, 149.7, 145.9, 143.0, 135.0, 129.7, 127.6, 124.3, 122.5, 29.6. IR (KBr, cm^{-1}): 3271, 2963, 2335, 1707, 1670, 1518, 1437, 1335, 1277, 1186, 934, 808; ESI-HRMS: calcd for $C_{11}H_{10}BrN_2O$ $[M + H]^+$ 264.9971 and 266.9951, found 264.9966 and 266.9945.

*9.44. N-(2-Bromo-4-nitrophenyl)acetamide (**6j**).* Yield: 72% (51 mg). Physical appearance: pale-yellow solid, mp 88−89 °C, TLC R_f 0.30 (3:2, petroleum ether:EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.63 (d, J = 9.2 Hz, 1H), 8.42 (s, 1H), 8.17 (d, J = 9.2 Hz, 1H), 7.88 (s, 1H), 2.29 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.5, 143.2, 141.4, 127.9, 124.2, 120.2, 111.9, 25.1. IR (KBr, cm^{-1}): 3292, 3099, 1672, 1587, 1538, 1505, 1389, 1348, 1308, 1278, 1139, 1118, 1041, 903, 831, 746, 633, 591, 443. ESI-HRMS: calcd for $C_8H_8BrN_2O_3$ $[M + H]^+$ 258.9713 and 260.9693, found 258.9732 and 260.9720.

*9.45. N-(2-Iodo-4-nitrophenyl)acetamide (**6k**).* Yield: 69% (58 mg). Physical appearance: pale yellow solid, mp 109−112 °C, TLC R_f 0.30 (3:2, petroleum ether:EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.60 (d, J = 2.5 Hz, 1H), 8.49 (d, J = 9.2 Hz, 1H), 8.18 (dd, J = 9.2 Hz, 2.5 Hz, 1H), 7.72 (s, 1H), 2.28 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.5, 143.8, 143.4, 134.2, 124.9, 119.8, 87.3, 25.1. IR (KBr, cm^{-1}): 3393, 2365, 2330, 1649, 1263, 1031, 743. ESI-HRMS: calcd for $C_8H_8IN_2O_3$ $[M + H]^+$ 306.9574, found 306.9592.

*9.46. N-(2-Bromo-6-fluorophenyl)acetamide (**6l**).* This was prepared according to the general procedure, and the title compound was isolated as a white solid (67% (50 mg) yield). Spectral data obtained were in good agreement with those reported in the literature.[11b]

*9.47. N-(2-Bromo-4-methylphenyl)benzamide (**6m**).* This was prepared according to the general procedure, and the title compound was isolated as a white solid (52% (18 mg) isolated yield, 81% yield based on recovered starting material). Spectral data obtained were in good agreement with those reported in the literature.[47]

*9.48. N-(2-Bromo-4-methylphenyl)-4-methylbenzamide (**6n**).* This was prepared according to the general procedure, and the title compound was isolated as a white solid (48% (16 mg) isolated yield, 92% yield based on recovered starting material). Mp 80−85 °C, TLC R_f 0.40(4:1, petroleum ether:EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.38 (d, J = 8.4 Hz, 1H), 8.33 (s, 1H), 7.81 (d, J = 8.4 Hz, 2H), 7.38 (s, 1H), 7.29 (d, J = 8.4 Hz, 2H), 7.15 (d, J = 8.4 Hz, 1H), 2.43 (s, 3H), 2.31 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.1, 142.7, 135.2, 133.4, 132.5, 131.9, 129.6, 129.1, 127.1, 113.6, 21.5, 20.6. IR (KBr, cm^{-1}): 3303, 2386, 2352, 1650, 1301, 1075, 698. ESI-HRMS: calcd for $C_{15}H_{15}BrNO[M + H]^+$ 304.0332 and 306.0312, found 304.0334 and 306.0306.

*9.49. N-(2-Bromophenyl)-4-methylbenzamide (**6o**).* This was prepared according to the general procedure, and the title compound was isolated as a white solid (56% (19 mg) isolated yield, 94% yield based on recovered starting material). Mp 61−64 °C, TLC R_f 0.40 (4:1, petroleum ether:EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.54 (dd, J = 8.3, 1.3 Hz, 1H), 8.43 (s, 1H), 7.82 (d, J = 8.3 Hz, 2H), 7.55 (dd, J = 8.3, 1.3 Hz, 1H), 7.35 (t, J = 8.3 Hz, 1H), 7.30 (d, J = 8.3 Hz, 2H), 6.99 (td, J = 8.3, 1.3 Hz, 1H), 2.42 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.2, 142.8, 136.0, 132.2, 131.8, 129.6, 128.5, 127.1, 125.1, 121.7, 113.7, 21.5. IR (KBr, cm^{-1}): 3346, 2403, 2358, 1665, 1281, 1026, 800. ESI-HRMS: calcd for $C_{14}H_{13}BrNO$ $[M + H]^+$ 290.0175 and 292.0155, found 290.0170 and 292.0149.

10. Synthetic Utility. *10.1. Synthesis of Methyl (E)-3-(5-Bromo-2-(methoxy(methyl)carbamoyl)phenyl)acrylate (**8**).* In a pressure tube equipped with a stir bar was dissolved the substrate (0.081 mmol) in dry dimethylformamide (0.5 mL). The solution was degassed with nitrogen for about 10 min, followed by the addition of $Pd(OAc)_2$ (0.004 mmol), PPh_3 (0.008 mmol), K_2CO_3 (0.243 mmol), and the methyl acrylate (0.01 mmol). The tube was fitted with a Teflon screw cap under nitrogen flow. The reaction mixture was heated to 80 °C and stirred at that temperature. The reaction was followed either by GCMS or by TLC. Upon completion of the reaction and cooling to room temperature, the reaction mixture was diluted with EtOAc and filtered through a short pad of Celite. The organic filtrate was washed with water and brine and dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure, and the crude product was purified by silica gel column chromatography. Pure product was isolated as a colorless gel (77% (21 mg) yield). TLC R_f 0.30(4:1, petroleum ether:EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.80 (d, J = 1.7 Hz, 1H), 7.68 (d, J = 15.9 Hz, 1H), 7.55 (dd, J = 8.2, 1.7 Hz, 1H), 7.37 and 7.29 (d, J = 4.6 Hz, 1H), 3.81 (s, 3H), 3.63−3.13 (m, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.5, 140.1, 134.6, 133.9, 132.5, 129.4, 128.9, 128.5, 127.6, 127.0, 121.4, 61.3, 53.4, 51.9. IR (KBr, cm^{-1}): 3598, 3472, 3103, 2936, 2369, 1932, 1699, 1680, 1501, 1471, 1229, 1184, 743. ESI-HRMS: calcd for $C_{13}H_{15}BrNO_4$ $[M + H]^+$ 328.0179 and 330.0159, found 328.0180 and 330.0175.

*10.2. Synthesis of Methyl (E)-3-(4′-Methoxy-4-(methoxy(methyl)-carbamoyl)-[1,1′-biphenyl]-3-yl)acrylate (**9**).* In a RB flask, the substrate (0.06 mmol) was dissolved in IPA−H_2O mixture (0.6 mL, 1:1). This was followed by the addition of $Pd(OAc)_2$ (4 μmol), 4-aminobenzoic acid (8 μmol), K_2CO_3 (0.18 mmol), and the 4-methoxy phenylboronic acid (0.12 mmol). The reaction mixture was stirred at room temperature. Upon completion of the reaction, it was concentrated under reduced pressure and then diluted with EtOAc and filtered through a short pad of Celite. The mixture was extracted with EtOAc and washed with brine. The organic layer was dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure, and the crude product was purified by silica gel flash column chromatography. Pure product was isolated as colorless gel (48% (10 mg) yield). TLC R_f 0.20 (4:1, petroleum ether:EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.81−7.77 (m, 2H), 7.57 (dd, J = 8.0, 1.6 Hz, 1H), 7.52 (d, J = 8.0 Hz, 2H), 7.42 (d, J = 8.0 Hz, 1H), 6.98 (d, J = 8.0 Hz, 2H), 6.47 (d, J = 16.0 Hz, 1H), 3.84 (s, 3H), 3.78 (s, 3H), 3.63−3.27 (m, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.9, 159.8, 142.3, 141.7, 134.0, 132.3, 132.2, 128.2, 127.9, 124.7, 120.3, 114.4, 61.2, 56.4, 55.4, 51.8. IR (KBr, cm^{-1}): 3498, 3103, 2875, 2392, 1852, 1671, 1652, 1468, 1235, 1031, 654. ESI-HRMS: calcd for $C_{20}H_{22}NO_5$ $[M + H]^+$ 356.1492, found 356.1498.

*10.3. Synthesis of 2-(4-Chloro-4′-methoxy-[1,1′-biphenyl]-2-yl)-acetonitrile (**10**).* In a pressure tube equipped with a stir bar was dissolved substrate (0.20 mmol) in dry toluene (1.5 mL). The reaction mixture was degassed with nitrogen for about 10 min, followed by the addition of $Pd(PPh_3)_4$ (0.02 mmol), K_2CO_3 (0.55 mmol), and 4-methoxy phenylboronic acid (0.40 mmol). The tube was fitted with a Teflon screw cap under nitrogen flow. The reaction mixture was heated to 80 °C and stirred at that temperature. The reaction was followed either by GCMS or by TLC. Upon completion of the reaction and subsequent cooling to room temperature, the reaction mixture was diluted with EtOAc and filtered through a short pad of Celite, and the organic filtrate was washed with brine. The organic layer was dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure, and the crude product was purified by silica gel flash column chromatography. Pure product was isolated as pale yellow gel (53% (24 mg) yield). TLC R_f 0.20 (9:1, petroleum ether:EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.52 (d, J = 2.2 Hz, 1H), 7.34 (dd, J = 8.2, 2.2 Hz, 1H), 7.13 (m, 3H), 6.97 (d, J = 8.2 Hz, 2H), 3.85 (s, 3H), 3.59 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 159.5, 140.0, 133.7, 131.9, 130.9, 130.0, 129.7, 128.9, 128.4, 117.7, 114.2, 55.4, 22.0. IR (KBr, cm^{-1}): 2346, 1651, 1457, 1400, 1258, 1074, 791. ESI-HRMS: calcd for $C_{15}H_{11}ClNO_2$ $[M - H]^-$ 256.0524, found 256.0553.

10.4. General Procedure for the Synthesis of Substituted Phenanthridones. In a pressure tube equipped with a stir bar was dissolved substrate (0.05 mmol) in dry dimethylacetamide (0.5 mL). The reaction mixture was degassed with nitrogen for about 10 min, followed by the addition of $Pd(OAc)_2$ (5 μmol), PPh_3 (0.01 mmol), and Cs_2CO_3 (0.06 mmol). The tube was fitted with a Teflon screw cap under nitrogen flow. The reaction mixture was heated to 130 °C and stirred at that temperature. The reaction was followed either by GCMS or by TLC. Upon completion of the reaction and subsequent cooling to room temperature, the reaction mixture was diluted with EtOAc and filtered through a short pad of Celite, and the organic filtrate was washed with brine. The organic layer was dried over anhydrous

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J. Org. Chem. 2017, 82, 1114−1126

Na_2SO_4, filtered, and concentrated under reduced pressure, and the crude product was purified by silica gel flash column chromatography.

*10.4.1. 2-Methylphenanthridin-6(5H)-one (**10a**).* This was prepared according to the general procedure, and the title compound was isolated as a white solid (58% (8 mg) yield). Spectral data obtained were in good agreement with those reported in the literature.[48]

*10.4.2. 2,9-Dimethylphenanthridin-6(5H)-one (**10b**).* This was prepared according to the general procedure, and the title compound was isolated as a white solid (61% (9 mg) yield). Mp 203−206 °C, TLC R_f 0.30 (3:2, petroleum ether:EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.94 (s, 1H), 8.41 (d, J = 8.1 Hz, 1H), 8.06 (s, 1H), 7.99 (s, 1H), 7.40 (d, J = 8.1 Hz, 1H), 7.27 (d, J = 8.1 Hz, 1H), 7.16 (d, J = 8.1 Hz, 1H), 2.57 (s, 3H), 2.47 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 162.6, 150.8, 143.4, 132.2, 130.5, 129.2, 128.3, 122.9, 122.1, 118.5, 116.2, 96.9, 22.2, 21.3. IR (KBr, cm^{-1}): 3390, 2339, 1652, 1395, 1003, 753. ESI-HRMS: calcd for $C_{15}H_{14}NO$ $[M + H]^+$ 224.1070, found 224.1078.

*10.4.3. 9-Methylphenanthridin-6(5H)-one (**10c**).* This was prepared according to the general procedure, and the title compound was isolated as a white solid (51% (7 mg) yield). Spectral data obtained were in good agreement with those reported in the literature.[48]

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b02731.

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

X-ray crystallographic information file for compound **4g** (CIF)

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Notes

The authors declare no competing financial interest.

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