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# Palladium-Catalyzed Ortho-Alkoxylation of Anilides via C−H Activation

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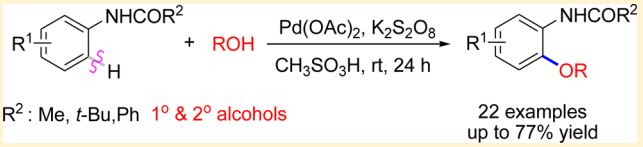
Supporting Information

**ABSTRACT:** A palladium-catalyzed ortho-alkoxylation of anilides with both primary and secondary alcohols via ligand-directed C−H activation has been explored. This alkoxylation promoted by catalytic methanesulfonic acid proceeds well at room temperature in most cases and affords aryl alkyl ethers in moderate to good yields.




## INTRODUCTION

Aryl alkyl ethers are important motifs in many natural products and pharmaceuticals.[1] For their preparation, C−O bond-forming reactions catalyzed by transition metals such as copper[2] and palladium[3] as well as other methods[4] become effective strategies. Early studies on the palladium-catalyzed acetoxylation of arenes under strong oxidants represent seminal works in C−H oxygenation.[5] Over the past decade, numerous endeavors have been focused on the palladium-catalyzed C−H functionalizations with the aid of directing groups by many groups including Sanford,[6] Daugulis,[7] Yu,[8] and others.[9] In this area, the C−H oxygenation reaction developed by the groups of Sanford[10] and Yu[11] represents a critical advance in C−O bond formation reactions. Despite the success of other C−H oxygenation methods,[12,13] C−H alkoxylation reactions remain relatively scarce and are limited to the ligand-directed ortho-alkoxylation mainly using MeOH or EtOH.[10a,d,12c] Alkoxylation with secondary alcohols and at ambient temperature is still a challenging task. Some potential difficulties may be encountered in alkoxylations with alcohols. First, the in situ formed palladium alkoxide (Pd−OR) species would weaken the electrophilicity of Pd(II) if alcohols were used. Second, Pd(II) is known to oxidize primary and secondary alcohols.[14] Third, strong oxidants ($PhI(OAc)_2$, $K_2S_2O_8$, Oxone) and high temperature used in these reactions limit the reaction scopes. Despite these difficulties, we set forth to develop a more mild and efficient C−H alkoxylation reaction, particularly with secondary alcohols as well as other primary alcohols.

We have recently reported the palladium-catalyzed ortho-alkoxylation of *N*-methoxybenzamides.[12c] When acetanilide was chosen as the substrate, in which the $NHCOCH_3$ moiety was the directing group, only poor yield (≤31%) was obtained for the methoxylation reaction. We reasoned that the efficiency and scope of the reaction would be improved after further condition optimization. Herein, we disclose the Pd-catalyzed alkoxylation of acetanilides with both primary and secondary alcohols under mild conditions.[15]

## RESULTS AND DISCUSSION

To overcome the low efficiency of our previous ortho-methoxylation of acetanilide,[12c] we searched for better reaction conditions. The large beneficial effect of *p*-toluenesulfonic acid (PTSA) in promoting the Pd-catalyzed C−H activation reaction of anilides was first revealed by de Vries, van Leeuwen, and co-workers in 2002.[16] Inspired by this discovery, we initially tested the reaction by using 10 mol % of $Pd(OAc)_2$, 2 equiv of $K_2S_2O_8$, 0.5 equiv of PTSA, and 50 equiv of MeOH in 2 mL of dioxane for 24 h at room temperature, and the desired product **2a** was obtained in 12% yield (Table 1, entry 1). To our delight, when methanesulfonic acid, a stronger organic acid, was employed, the methoxylated product could be obtained in 25% yield (Table 1, entry 2). Other solvents including 1,2-dichloroethane (DCE), 1,2-dimethoxyethane (DME), and dichloromethane (DCM) were screened, the best yield was 42% in DME (Table 1, entries 3−5). Compared with $(NH_4)_2S_2O_8$ and Oxone, $K_2S_2O_8$ was better (Table 1, entries 6 and 7 vs entry 4). It is noteworthy that the yield could be increased dramatically to 62% when 15 equiv of $CH_3OH$ was employed (Table 1, entry 8). The yield of **2a** could be further improved to 64% when only 10 equiv of $CH_3OH$ was used (Table 1, entry 9). However, the yield dropped to 59% from 64% if the amount of $CH_3OH$ was reduced to 5 equiv (Table 1, entry 10 vs entry 9). Interestingly, decreasing the amount of $CH_3SO_3H$ to 0.2 equiv could give a better result, and a yield of 68% was achieved (Table 1, entries 11−13). Nevertheless, the usage of $CF_3SO_3H$ as the additive, which is a stronger organic acid and has played an important role on palladium-catalyzed ligand-directed C−H activation,[17] did not improve the efficiency in our catalytic system (Table 1, entry 14). The desired product was not obtained in the absence of the $Pd(OAc)_2$ catalyst (Table 1, entry 15). Finally, when 0.3 mmol of **1a**, 10 mol % of $Pd(OAc)_2$, 0.2 equiv of $CH_3SO_3H$, and 2 equiv of $K_2S_2O_8$ were used, the reaction at ambient temperature

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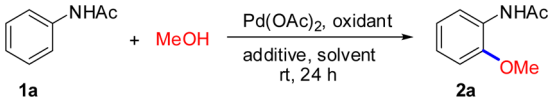
**Table 1. Screening Conditions for the $Pd(OAc)_2$-Catalyzed Direct Ortho-Methoxylation of Acetanilide**[a]




1a 2a

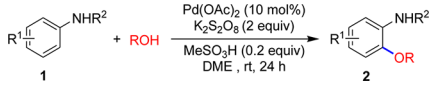
| entry | $CH_3OH$ (equiv) | additive (equiv) | oxidant | solvent | yield (%) |
|---|---|---|---|---|---|
| 1 | 50 | PTSA (0.5) | $K_2S_2O_8$ | dioxane | 12 |
| 2 | 50 | $CH_3SO_3H$ (0.5) | $K_2S_2O_8$ | dioxane | 25 |
| 3 | 50 | $CH_3SO_3H$ (0.5) | $K_2S_2O_8$ | DCE | 21 |
| 4 | 50 | $CH_3SO_3H$ (0.5) | $K_2S_2O_8$ | DME | 42 |
| 5 | 50 | $CH_3SO_3H$ (0.5) | $K_2S_2O_8$ | DCM | 15 |
| 6 | 50 | $CH_3SO_3H$ (0.5) | $(NH_4)_2S_2O_8$ | DME | 29 |
| 7 | 50 | $CH_3SO_3H$ (0.5) | Oxone | DME | 37 |
| 8 | 15 | $CH_3SO_3H$ (0.5) | $K_2S_2O_8$ | DME | 62 |
| 9 | 10 | $CH_3SO_3H$ (0.5) | $K_2S_2O_8$ | DME | 64 |
| 10 | 5 | $CH_3SO_3H$ (0.5) | $K_2S_2O_8$ | DME | 59 |
| 11 | 10 | $CH_3SO_3H$ (0.3) | $K_2S_2O_8$ | DME | 67 |
| 12 | 10 | $CH_3SO_3H$ (0.2) | $K_2S_2O_8$ | DME | 68 |
| 13 | 10 | $CH_3SO_3H$ (0.1) | $K_2S_2O_8$ | DME | 65 |
| 14 | 10 | $CF_3SO_3H$ (0.2) | $K_2S_2O_8$ | DME | 54 |
| 15[b] | 10 | $CH_3SO_3H$ (0.2) | $K_2S_2O_8$ | DME | 0 |
| 16[c] | 10 | $CH_3SO_3H$ (0.2) | $K_2S_2O_8$ | DME | 66 |

[a]Unless otherwise specified, all the reactions were carried out with 0.2 mmol of **1a**, 0.02 mmol of $Pd(OAc)_2$, and 0.4 mmol of oxidant in 2 mL of solvent at room temperature for 24 h. [b]The reaction was performed in the absence of $Pd(OAc)_2$. [c]0.3 mmol of **1a**, 0.03 mmol of $Pd(OAc)_2$, and 0.6 mmol of oxidant were used.

for 24 h gave **2a** in 66%, comparable to 0.2 mmol scale (Table 1, entry 16 vs entry 12).

With the optimal conditions in hand (Table 1, entry 16), we next investigated the scope of this reaction. As summarized in Table 2, a variety of anilides with either electron-donating or electron-withdrawing groups on the phenyl ring could be applied to afford the desired alkoxylated products (**2a**–**v**). We first conducted the alkoxylation reaction with primary alcohols. Methoxylated and ethoxylated products **2a**–**e** could be obtained in 45–74% yields by employing 10 equiv of MeOH and EtOH. For the substrate with the electron-withdrawing chorine group, increasing the reaction temperature from room temperature to 60 °C was required. We found that the room-temperature reaction could be extended to other primary alcohols such as *n*-PrOH, *n*-BuOH, and $MeOCH_2CH_2OH$, and the corresponding alkoxylated products **2f**–**h** were obtained in 37–69% yields although a larger amount (1 mL) of alcohols was demanded. 2-Chloroethanol, a halogenated alcohol, could also be employed to provide **2i** in 38% yield. Generally, primary alcohols bearing a longer alkyl chain afforded lower yields (**2b**, **2e**, and **2f** vs **2g** and **2h**). Intriguingly, alkoxylation of anilides using 1 mL of secondary alcohols proceeded well in this

**Table 2. Pd-Catalyzed Directed Ortho-Alkoxylation of Anilides**[a]




1 2

| entry | anilides | ROH | product | yield(%) |
|---|---|---|---|---|
| 1 | NHAc 1a | MeOH[b] | NHAc 2a OMe | 66 |
| 2 | NHAc 1b | MeOH[b] | NHAc 2b OMe | 74 |
| 3 | NHAc Cl 1c | MeOH[b,c] | NHAc Cl 2c OMe | 45 |
| 4 | NHAc 1a | EtOH[b] | NHAc 2d OEt | 53 |
| 5 | NHAc 1b | EtOH[b] | NHAc 2e OEt | 70 |
| 6 | NHAc 1b | *n*-PrOH[d] | NHAc 2f O*n*Pr | 69 |
| 7 | NHAc 1b | *n*-BuOH[d] | NHAc 2g O*n*Bu | 51 |
| 8 | NHAc 1b | $MeO(CH_2)_2OH$[d] | NHAc 2h $O(CH_2)_2OMe$ | 37 |
| 9 | NHAc 1b | $Cl(CH_2)_2OH$[b] | NHAc 2i $O(CH_2)_2Cl$ | 38 |
| 10 | NHAc 1a | *i*-PrOH[d] | NHAc 2j O*i*Pr | 55 |
| 11 | NHAc 1b | *i*-PrOH[d] | NHAc 2k O*i*Pr | 77 |
| 12 | NHAc 1d | *i*-PrOH[d] | NHAc 2l O*i*Pr | 48 |
| 13 | NHAc 1e | *i*-PrOH[c,d] | NHAc 2m O*i*Pr | 51 |
| 14 | NHAc O 1f | *i*-PrOH[c,d,e] | NHAc O 2n O*i*Pr | 48 |
| 15 | NHAc I 1g | *i*-PrOH[c,d] | NHAc I 2o O*i*Pr | 36 |
| 16 | NHAc 1b | *s*-BuOH[d] | NHAc 2p O*s*Bu | 70 |
| 17 | NHAc 1b | *c*-HexOH[d] | NHAc 2q O*c*Hex | 63 |
| 18 | NHAc 1b | *c*-PenOH[d] | NHAc 2r O*c*Pen | 71 |
| 19 | NHPiv 1h | MeOH[b] | NHPiv 2s OMe | 60 |
| 20 | NHPiv 1h | *i*-PrOH[d] | NHPiv 2t O*i*Pr | 69 |
| 21 | NHCOPh 1i | MeOH[b] | NHCOPh 2u OMe | 49 |
| 22 | NHCOPh 1i | *i*-PrOH[d] | NHCOPh 2v O*i*Pr | 56 |

[a]Unless otherwise specified, all the reactions were carried out with 0.3 mmol of **1**, 0.03 mmol of $Pd(OAc)_2$, 0.6 mmol of oxidant, and 0.06 mmol of $CH_3SO_3H$ in 2 mL of solvent at 25 °C for 24 h. [b]10 equiv of alcohol was used. [c]The reaction was performed at 60 °C. [d]1 mL of alcohol was used. [e]$CF_3SO_3H$ was used instead of $CH_3SO_3H$.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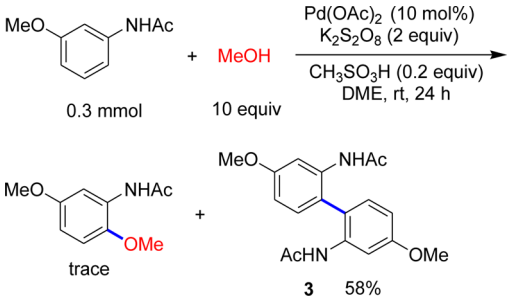
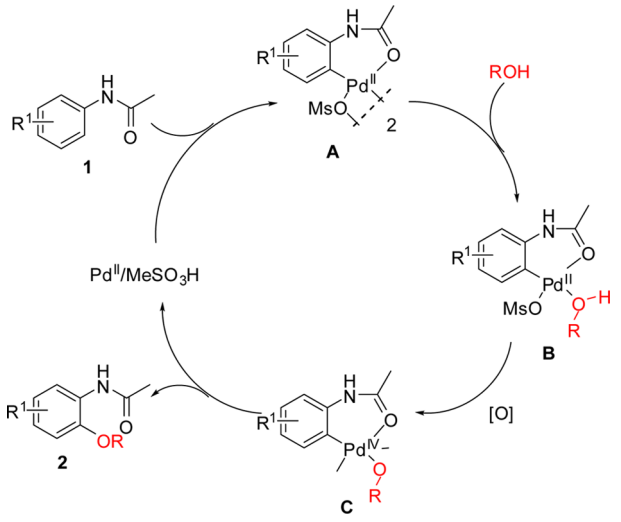
catalytic system and afforded **2j−r** in 36−77% yields. The electronic property and position of substituents on the phenyl ring exhibited significant effects on the reactivity. For example, alkoxylation of acetanilide bearing a methyl group at the meta position of the phenyl ring with *i*-PrOH was more efficient and afforded a higher yield (77% for **2k**) than those for the unsubstituted and substituted substrates (36−55% for **2j** and **2l−o**). Other commonly used secondary alcohols including 2-butanol (*s*-BuOH), cyclohexanol (*c*-HexOH), and cyclopentanol (*c*-PenOH) could be employed and afforded the desired products in 63−71% yields (**2p−r**). To further expand the substrate scope, we performed the reactions of anilides bearing other directing groups, i.e., *N*-(*m*-tolyl)pivalamide (**1h**) and *N*-(*m*-tolyl)benzamide (**1i**), with MeOH and *i*-PrOH, respectively. Although desired products (**2s−v**) could be obtained, their yields (49−69%) were lower than those for the corresponding methoxylation and isopropoxylation of *N*-*m*-tolylacetamide (**1b**) (**2s−v** vs **2b** and **2k**). Unfortunately, tertiary alcohols such as *t*-BuOH failed to react with acetanilide under otherwise identical conditions. It should be pointed out that the alkoxylation of acetanilides gave exclusively one regioisomer, and trace or no dialkoxylation was observed. The reason for the low yields of some products was that the starting material could not be consumed completely even after longer reaction time. It is somewhat surprising that the electron-rich acetanilide bearing a methoxyl group at the meta-position afforded only a trace amount of the desired cross-coupling product; instead, the oxidative C−H homocoupling product **3** was obtained in 58% yield (Scheme 1).[18]

**Scheme 1. Homocoupling Reaction of *N*-(3-Methoxyphenyl)acetamide**




Based on the previous literature,[6,10,12c] a possible mechanism for the alkoxylation of acetanilides is outlined in Scheme 2. We believe that the role of methanesulfonic acid may be 2-fold: (1) compared to PTSA, $CH_3SO_3H$ is a stronger acid and it will generate more electrophilic Pd(II) species toward C−H activation. The palladacycle **A**, which resembles that reported by Yu,[19] is formed with two $CH_3SO_3^-$ anions bridging two Pd(II). In this system, *m*-methoxyl-substituted anilide mainly affords oxidative C−H homocoupling product; this phenomenon is similar to that reported by Sanford[18a] and Greaney[18b] for the electron-neutral and electron-rich arenes. (2) Palladacycle **A** can be easily substituted by an alcohol to afford intermediate **B** since the $CH_3SO_3^-$ anion is a good leaving group. Pd(IV) complex **C** is formed by the oxidation of $K_2S_2O_8$; subsequent reduction elimination affords the alkoxylated product along with the regeneration of the Pd(II) species. It should be noted that a mechanism involving a recently formulated bimetallic Pd(II)/Pd(III) pathway by Ritter[20] or Pd(II)/Pd(0) process proposed by Sunoj[21] cannot be excluded.

**Scheme 2. Proposed Mechanism for the C−H Alkoxylation Reaction**




## CONCLUSION

In summary, we have successfully accomplished the intermolecular ortho C−H alkoxylation of anilides with primary or secondary alcohols under mild conditions and found that methanesulfonic acid was crucial for the success of this transformation. We believe that methanesulfonic acid not only promotes the C−H functionalization but also serves as a good leaving group, which can be easily substituted by an alcohol. The final products could be further transformed into various useful derivatives.

## EXPERIMENTAL SECTION

**General Procedure for the Direct Ortho-Alkoxylation of Acetanilides.** A mixture of acetanilide **1** (0.3 mmol, 1 equiv), $Pd(OAc)_2$ (0.03 mmol, 0.1 equiv), $K_2S_2O_8$ (0.6 mmol, 2 equiv), alcohol (3.0 mmol, 10 equiv; or 1 mL), $CH_3SO_3H$ (0.06 mmol, 0.2 equiv), and 1,2-dimethoxyethane (2 mL) was stirred at 25 °C (or 60 °C in a few cases) (see Table 2) for 24 h. After the reaction was complete, the mixture was filtered by a silica gel plug with ethyl acetate as the eluent and evaporated in vacuum. The residue was purified by flash column chromatography on a silica gel using petroleum ether/EtOAc (3:1 to 5:1) as the eluent to give product **2**.

***N*-(2-Methoxyphenyl)acetamide (2a).**[22] By following the general procedure, the reaction of **1a** (40.6 mg, 0.3 mmol) with $CH_3OH$ (122 μL, 3.0 mol) at 25 °C gave **2a** (32.7 mg, 66% yield): $^1$H NMR (400 MHz, $CDCl_3$) δ 8.35 (dd, *J* = 8.0 Hz, *J* = 1.2 Hz, 1H), 7.75 (br, 1H), 7.03 (td, *J* = 8.0 Hz, *J* = 1.2 Hz, 1H), 6.96 (td, *J* = 8.0 Hz, *J* = 1.2 Hz, 1H), 6.87 (dd, *J* = 8.0 Hz, *J* = 1.2 Hz, 1H), 3.88 (s, 3H), 2.20 (s, 3H).

***N*-(2-Methoxy-5-methylphenyl)acetamide (2b).**[23] By following the general procedure, the reaction of **1b** (44.8 mg, 0.3 mmol) with $CH_3OH$ (122 μL, 3.0 mol) at 25 °C gave **2b** (39.8 mg, 74% yield): $^1$H NMR (400 MHz, $CDCl_3$) δ 8.18 (d, *J* = 1.2 Hz, 1H), 7.72 (br, 1H), 6.82 (dd, *J* = 8.4 Hz, *J* = 1.2 Hz, 1H), 6.75 (d, *J* = 8.4 Hz, 1H), 3.84 (s, 3H), 2.29 (s, 3H), 2.19 (s, 3H).

***N*-(4-Chloro-2-methoxyphenyl)acetamide (2c).** By following the general procedure, the reaction of **1c** (50.9 mg, 0.3 mmol) with $CH_3OH$ (122 μL, 3.0 mol) at 60 °C afforded **2c** (27.0 mg, 45% yield): $^1$H NMR (400 MHz, $CDCl_3$) δ 8.30 (d, *J* = 8.8 Hz, 1H), 7.66 (br, 1H), 6.93 (dd, *J* = 8.8 Hz, *J* = 2.4 Hz, 1H), 6.85 (d, *J* = 2.4 Hz, 1H), 3.88 (s, 3H), 2.19 (s, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) δ 168.1, 148.2, 128.4, 126.4, 120.9, 120.4, 110.7, 55.9, 24.8; IR (KBr) ν 3295, 2959, 2921, 1669, 1596, 1528, 1488, 1400, 1250, 1122, 1022, 875, 813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$cm^{-1}$; HRMS (ESI-Orbitrap) $m/z$ [M + $H^+$] calcd for $C_9H_{11}O_2N^{35}Cl$ 200.0473, found 200.0472.

***N*-(2-Ethoxyphenyl)acetamide (2d).**[24] By following the general procedure, the reaction of **1a** (40.6 mg, 0.3 mmol) with $C_2H_5OH$ (175 μL, 3.0 mol) at 25 °C gave **2d** (28.5 mg, 53% yield): $^1H$ NMR (400 MHz, $CDCl_3$) δ 8.35 (dd, $J$ = 8.0 Hz, $J$ = 1.2 Hz, 1H), 7.78 (br, 1H), 7.01 (td, $J$ = 8.0 Hz, $J$ = 1.2 Hz, 1H), 6.94 (td, $J$ = 8.0 Hz, $J$ = 1.2 Hz, 1H), 6.85 (dd, $J$ = 8.0 Hz, $J$ = 1.2 Hz, 1H), 4.10 (q, $J$ = 6.9 Hz, 2H), 2.20 (s, 3H), 1.45 (t, $J$ = 6.9 Hz, 3H).

***N*-(2-Ethoxy-5-methylphenyl)acetamide (2e).** By following the general procedure, the reaction of **1b** (44.8 mg, 0.3 mmol) with $C_2H_5OH$ (175 μL, 3.0 mol) at 25 °C provided **2e** (40.6 mg, 70% yield): $^1H$ NMR (400 MHz, $CDCl_3$) δ 8.19 (s, 1H), 7.73 (br, 1H), 6.80 (d, $J$ = 8.0 Hz, 1H), 6.74 (d, $J$ = 8.0 Hz, 1H), 4.07 (q, $J$ = 6.9 Hz, 2H), 2.29 (s, 3H), 2.19 (s, 3H), 1.44 (t, $J$ = 6.9 Hz, 3H); $^{13}C$ NMR (100 MHz, $CDCl_3$) δ 168.0, 144.8, 130.5, 127.6, 123.7, 120.4, 110.8, 64.3, 25.0, 20.9, 14.9; IR (KBr) ν 3327, 2986, 2929, 1669, 1540, 1470, 1392, 1371, 1254, 1227, 1130, 1043, 914, 881, 795, 735, 682, 609, 530 $cm^{-1}$; HRMS (ESI-Orbitrap) $m/z$ [M + $H^+$] Calcd for $C_{11}H_{16}O_2N$ 194.1176, found 194.1174.

***N*-(5-Methyl-2-propoxyphenyl)acetamide (2f).** By following the general procedure, the reaction of **1b** (44.8 mg, 0.3 mmol) with *n*-PrOH (1 mL) at 25 °C provided **2f** (42.9 mg, 69% yield): $^1H$ NMR (400 MHz, $CDCl_3$) δ 8.19 (s, 1H), 7.73 (br, 1H), 6.80 (d, $J$ = 8.0 Hz, 1H), 6.75 (d, $J$ = 8.0 Hz, 1H), 3.96 (t, $J$ = 6.6 Hz, 2H), 2.29 (s, 3H), 2.19 (s, 3H), 1.88−1.79 (m, 2H), 1.05 (t, $J$ = 7.4 Hz, 3H); $^{13}C$ NMR (100 MHz, $CDCl_3$) δ 168.0, 145.0, 130.5, 127.6, 123.8, 120.4, 110.9, 70.3, 24.9, 22.6, 21.0, 10.5; IR (KBr) ν 3342, 2970, 2919, 1669, 1594, 1538, 1489, 1458, 1254, 1226, 1130, 1068, 979, 879, 797, 667, 605 $cm^{-1}$; HRMS (ESI-Orbitrap) $m/z$ [M + $H^+$] calcd for $C_{12}H_{18}O_2N$ 208.1332, found 208.1335.

***N*-(2-Butoxy-5-methylphenyl)acetamide (2g).** By following the general procedure, the reaction of **1b** (44.8 mg, 0.3 mmol) with *n*-BuOH (1 mL) at 25 °C gave **2g** (33.9 mg, 51% yield): $^1H$ NMR (400 MHz, $CDCl_3$) δ 8.18 (s, 1H), 7.73 (br, 1H), 6.80 (dd, $J$ = 8.4 Hz, $J$ = 1.2 Hz, 1H), 6.75 (d, $J$ = 8.4 Hz, 1H), 4.00 (t, $J$ = 6.6 Hz, 2H), 2.29 (s, 3H), 2.18 (s, 3H), 1.83−1.76 (m, 2H), 1.54−1.45 (m, 2H), 1.00 (t, $J$ = 7.4 Hz, 3H); $^{13}C$ NMR (100 MHz, $CDCl_3$) δ 168.0, 145.0, 130.4, 127.6, 123.7, 120.3, 110.9, 68.5, 31.2, 24.9, 20.9, 19.3, 13.8; IR (KBr) ν 3312, 2957, 2925, 1663, 1593, 1544, 1492, 1462, 1374, 1259, 1226, 1133, 1023, 808 $cm^{-1}$; HRMS (ESI-Orbitrap) $m/z$ [M + $H^+$] calcd for $C_{13}H_{20}O_2N$ 222.1489, found 222.1488.

***N*-(2-(2-Methoxyethoxy)-5-methylphenyl)acetamide (2h).** By following the general procedure, the reaction of **1b** (44.8 mg, 0.3 mmol) with $MeOCH_2CH_2OH$ (1 mL) at 25 °C gave **2h** (24.8 mg, 37% yield): $^1H$ NMR (400 MHz, $CDCl_3$) δ 8.21 (s, 1H), 8.16 (br, 1H), 6.83 (d, $J$ = 8.0 Hz, 1H), 6.79 (dd, $J$ = 8.0 Hz, $J$ = 1.2 Hz, 1H), 4.13−4.11 (m, 2H), 3.70−3.68 (m, 2H), 3.46 (s, 3H), 2.30 (s, 3H), 2.17 (s, 3H); $^{13}C$ NMR (100 MHz, $CDCl_3$) δ 168.3, 144.8, 132.4, 129.5, 123.9, 120.6, 114.8, 70.9, 70.3, 59.0, 24.8, 21.1; IR (KBr) ν 3303, 2924, 1666, 1613, 1552, 1488, 1449, 1431, 1371, 1302, 1260, 783, 694 $cm^{-1}$; HRMS (ESI-Orbitrap) $m/z$ [M + $H^+$] calcd for $C_{12}H_{18}O_3N$ 224.1281, found 224.1280.

***N*-(2-(2-Chloroethoxy)-5-methylphenyl)acetamide (2i).** By following the general procedure, the reaction of **1b** (44.8 mg, 0.3 mmol) with 2-chloroethanol (201 μL, 3.0 mol) at 25 °C provided **2i** (26.0 mg, 38% yield): $^1H$ NMR (400 MHz, $CDCl_3$) δ 8.20 (s, 1H), 7.89 (br, 1H), 6.81 (dd, $J$ = 8.4 Hz, $J$ = 1.2 Hz, 1H), 6.78 (d, $J$ = 8.0 Hz, 1H), 4.27−4.24 (m, 2H), 3.85−3.82 (m, 2H), 2.30 (s, 3H), 2.19 (s, 3H); $^{13}C$ NMR (100 MHz, $CDCl_3$) δ 168.2, 154.2, 144.1, 132.3, 123.9, 120.7, 113.0, 69.8, 42.6, 24.9, 21.1; IR (KBr) ν 3407, 2922, 1677, 1598, 1540, 1484, 1327, 1294, 1253, 1220, 1132, 1078, 1034, 886, 805, 664, 599, 540 $cm^{-1}$; HRMS (ESI-Orbitrap) $m/z$ [M + $H^+$] calcd for $C_{11}H_{15}O_2N^{35}Cl$ 228.0786, found 228.0782.

***N*-(2-Isopropoxyphenyl)acetamide (2j).** By following the general procedure, the reaction of **1a** (40.6 mg, 0.3 mmol) with *i*-PrOH (1 mL) at 25 °C gave **2j** (31.9 mg, 55% yield): $^1H$ NMR (400 MHz, $CDCl_3$) δ 8.36 (dd, $J$ = 8.0 Hz, $J$ = 1.2 Hz, 1H), 7.79 (br, 1H), 7.00 (td, $J$ = 8.0 Hz, $J$ = 1.2 Hz, 1H), 6.93 (td, $J$ = 8.0 Hz, $J$ = 1.2 Hz, 1H), 6.87 (dd, $J$ = 8.0 Hz, $J$ = 1.2 Hz, 1H), 4.59 (heptet, $J$ = 6.0 Hz, 1H), 2.20 (s, 3H), 1.37 (d, $J$ = 6.0 Hz, 6H); $^{13}C$ NMR (100 MHz, $CDCl_3$) δ 168.0, 145.8, 128.6, 123.4, 120.9, 119.8, 112.5, 71.2, 24.9, 22.2 (2C); IR (KBr) ν 3364, 2974, 2931, 1675, 1596, 1536, 1484, 1452, 1369, 1330, 1289, 1254, 1120, 1048, 1007, 950, 751, 649, 591, 540 $cm^{-1}$; HRMS (ESI-Orbitrap) $m/z$ [M + $H^+$] calcd for $C_{11}H_{16}O_2N$ 194.1176, found 194.1173.

***N*-(2-Isopropoxy-5-methylphenyl)acetamide (2k).** By following the general procedure, the reaction of **1b** (44.8 mg, 0.3 mmol) with *i*-PrOH (1 mL) at 25 °C afforded **2k** (47.9 mg, 77% yield): $^1H$ NMR (400 MHz, $CDCl_3$) δ 8.19 (s, 1H), 7.75 (br, 1H), 6.80 (dd, $J$ = 8.8 Hz, $J$ = 1.2 Hz, 1H), 6.76 (d, $J$ = 8.4 Hz, 1H), 4.53 (heptet, $J$ = 6.0 Hz, 1H), 2.29 (s, 3H), 2.18 (s, 3H), 1.35 (d, $J$ = 6.0 Hz, 6H); $^{13}C$ NMR (100 MHz, $CDCl_3$) δ 168.0, 143.7, 130.6, 128.5, 123.8, 120.4, 112.7, 71.5, 24.9, 22.2 (2C), 20.9; IR (KBr) ν 3313, 2980, 2927, 1669, 1590, 1544, 1485, 1374, 1316, 1258, 1224, 1133, 1106, 951, 800, 732, 663, 605, 571, 534 $cm^{-1}$; HRMS (ESI-Orbitrap) $m/z$ [M + $H^+$] calcd for $C_{12}H_{18}O_2N$ 208.1332, found 208.1330.

***N*-(2-Isopropoxy-4-methylphenyl)acetamide (2l).** By following the general procedure, the reaction of **1d** (44.8 mg, 0.3 mmol) with *i*-PrOH (1 mL) at 25 °C afforded **2l** (29.8 mg, 48% yield): $^1H$ NMR (400 MHz, $CDCl_3$) δ 8.20 (d, $J$ = 8.4 Hz, 1H), 7.69 (br, 1H), 6.73 (d, $J$ = 8.4 Hz, 1H), 6.69 (s, 1H), 4.57 (heptet, $J$ = 6.0 Hz, 1H), 2.29 (s, 3H), 2.17 (s, 3H), 1.36 (d, $J$ = 6.0 Hz, 6H); $^{13}C$ NMR (100 MHz, $CDCl_3$) δ 167.8, 145.8, 133.3, 126.1, 121.3, 119.7, 113.5, 71.2, 24.9, 22.2 (2C), 21.3; IR (KBr) ν 3425, 3333, 2979, 2926, 1673, 1603, 1527, 1489, 1452, 1417, 1375, 1329, 1281, 1259, 1128, 1008, 980, 812, 581 $cm^{-1}$; HRMS (ESI-Orbitrap) $m/z$ [M + $H^+$] calcd for $C_{12}H_{18}O_2N$ 208.1332, found 208.1333.

***N*-(2-Isopropoxy-4,5-dimethylphenyl)acetamide (2m).** By following the general procedure, the reaction of **1e** (49.0 mg, 0.3 mmol) with *i*-PrOH (1 mL) at 60 °C provided **2m** (33.9 mg, 51% yield): $^1H$ NMR (400 MHz, $CDCl_3$) δ 8.11 (s, 1H), 7.65 (br, 1H), 6.67 (s, 1H), 4.52 (heptet, $J$ = 6.0 Hz, 1H), 2.19 (s, 6H), 2.17 (s, 3H), 1.34 (d, $J$ = 6.0 Hz, 6H); $^{13}C$ NMR (100 MHz, $CDCl_3$) δ 167.7, 144.0, 131.5, 128.9, 126.4, 121.1, 114.7, 71.6, 24.9, 22.3 (2C), 19.7, 19.2; IR (KBr) ν 3424, 3332, 2975, 2926, 1673, 1594, 1527, 1453, 1406, 1375, 1326, 1263, 1202, 1114, 1010, 945, 882 $cm^{-1}$; HRMS (ESI-Orbitrap) $m/z$ [M + $H^+$] calcd for $C_{13}H_{20}O_2N$ 222.1489, found 222.1488.

***N*-(4-Acetyl-2-isopropoxyphenyl)acetamide (2n).** By following the general procedure, the reaction of **1f** (53.2 mg, 0.3 mmol) with *i*-PrOH (1 mL) and $CF_3SO_3H$ (5.3 μL, 0.06 mmol) replacing $CH_3SO_3H$ at 60 °C afforded **2n** (33.9 mg, 48% yield): $^1H$ NMR (400 MHz, $CDCl_3$) δ 8.48 (d, $J$ = 8.4 Hz, 1H), 7.97 (br, 1H), 7.54 (dd, $J$ = 8.4 Hz, $J$ = 2.0 Hz, 1H), 7.52 (d, $J$ = 2.0 Hz, 1H), 4.74 (heptet, $J$ = 6.0 Hz, 1H), 2.57 (s, 3H), 2.24 (s, 3H), 1.40 (d, $J$ = 6.0 Hz, 6H); $^{13}C$ NMR (100 MHz, $CDCl_3$) δ 197.0, 168.4, 145.6, 133.0, 132.3, 122.8, 118.4, 110.7, 71.4, 26.3, 25.0, 22.0 (2C); IR (KBr) ν 3326, 2981, 2930, 1672, 1589, 1524, 1485, 1410, 1367, 1328, 1269, 1236, 1197, 1117, 969, 872, 832, 727, 638, 600 $cm^{-1}$; HRMS (ESI-Orbitrap) $m/z$ [M + $H^+$] calcd for $C_{13}H_{18}O_3N$ 236.1281, found 236.1281.

***N*-(4-Iodo-2-isopropoxyphenyl)acetamide (2o).** By following the general procedure, the reaction of **1g** (78.3 mg, 0.3 mmol) with *i*-PrOH (1 mL) at 60 °C gave **2o** (34.5 mg, 36% yield): $^1H$ NMR (400 MHz, $CDCl_3$) δ 8.13 (d, $J$ = 8.4 Hz, 1H), 7.69 (br, 1H), 7.25 (dd, $J$ = 8.4 Hz, $J$ = 1.6 Hz, 1H), 7.15 (d, $J$ = 1.6 Hz, 1H), 4.56 (heptet, $J$ = 6.0 Hz, 1H), 2.19 (s, 3H), 1.37 (d, $J$ = 6.0 Hz, 6H); $^{13}C$ NMR (100 MHz, $CDCl_3$) δ 168.0, 146.4, 130.0, 128.5, 121.4, 121.3, 85.9, 71.8, 25.0, 22.0 (2C); IR (KBr) ν 3318, 2983, 2925, 1669, 1587, 1523, 1481, 1395, 1326, 1247, 1209, 1127, 1105, 954, 812 $cm^{-1}$; HRMS (ESI-Orbitrap) $m/z$ [M + $H^+$] calcd for $C_{11}H_{15}O_2NI$ 320.0142, found 320.0142.

***N*-(2-*sec*-Butoxy-5-methylphenyl)acetamide (2p).** By following the general procedure, the reaction of **1b** (44.8 mg, 0.3 mmol) with 2-butyl alcohol (1 mL) at 25 °C provided **2p** (46.5 mg, 70% yield): $^1H$ NMR (400 MHz, $CDCl_3$) δ 8.20 (s, 1H), 7.76 (br, 1H), 6.80 (dd, $J$ = 8.4 Hz, $J$ = 1.2 Hz, 1H), 6.75 (d, $J$ = 8.4 Hz, 1H), 4.30 (sextet, $J$ = 6.0 Hz, 1H), 2.29 (s, 3H), 2.18 (s, 3H), 1.81−1.70 (m, 1H), 1.69−1.59 (m, 1H), 1.30 (d, $J$ = 6.0 Hz, 3H), 0.99 (t, $J$ = 7.4 Hz, 3H); $^{13}C$ NMR (100 MHz, $CDCl_3$) δ 167.9, 143.9, 130.6, 128.6, 123.7, 120.4, 112.8, 76.6, 29.2, 24.9, 21.0, 19.4, 9.7. IR (KBr) ν 3425, 3337, 2971, 2930, 1685, 1593, 1533, 1472, 1427, 1373, 1253, 1128, 1026, 992, 917, 802,


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599 $cm^{-1}$; HRMS (ESI-Orbitrap) $m/z$ [M + $H^+$] calcd for $C_{13}H_{20}O_2N$ 222.1489, found 222.1490.

***N*-(2-(Cyclohexyloxy)-5-methylphenyl)acetamide (2q).** By following the general procedure, the reaction of **1b** (44.8 mg, 0.3 mmol) with cyclohexanol (1 mL) at 25 °C provided **2q** (46.7 mg, 63% yield): $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 8.19 (s, 1H), 7.78 (br, 1H), 6.81−6.75 (m, 2H), 4.26−4.19 (m, 1H), 2.29 (s, 3H), 2.18 (s, 3H), 2.01−1.97 (m, 2H), 1.82−1.76 (m, 2H), 1.63−1.34 (m, 6H); $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$ 167.9, 143.6, 130.6, 128.7, 123.7, 120.4, 113.0, 76.9, 31.9 (2C), 25.5, 25.0, 23.8 (2C), 21.0; IR (KBr) $\nu$ 3422, 3340, 2932, 2857, 1682, 1593, 1532, 1473, 1427, 1368, 1253, 1218, 1127, 1045, 1020, 966, 801, 598 $cm^{-1}$; HRMS (ESI-Orbitrap) $m/z$ [M + $H^+$] calcd for $C_{15}H_{22}O_2N$ 248.1645, found 248.1639.

***N*-(2-(Cyclopentyloxy)-5-methylphenyl)acetamide (2r).** By following the general procedure, the reaction of **1b** (44.8 mg, 0.3 mmol) with cyclopentanol (1 mL) at 25 °C afforded **2r** (49.7 mg, 71% yield): $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 8.18 (s, 1H), 7.69 (br, 1H), 6.79 (dd, $J$ = 8.4 Hz, $J$ = 1.2 Hz, 1H), 6.75 (d, $J$ = 8.4 Hz, 1H), 4.80−4.75 (m, 1H), 2.29 (s, 3H), 2.17 (s, 3H), 1.93−1.65 (m, 8H); $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$ 167.9, 143.9, 130.3, 128.2, 123.7, 120.3, 112.3, 80.5, 32.9 (2C), 25.0, 24.0 (2C), 20.9; IR (KBr) $\nu$ 3424, 3340, 2959, 2945, 1683, 1593, 1534, 1474, 1428, 1366, 1253, 1221, 1168, 1126, 987, 801, 598 $cm^{-1}$; HRMS (ESI-Orbitrap) $m/z$ [M + $H^+$] calcd for $C_{14}H_{20}O_2N$ 234.1489, found 234.1485.

***N*-(2-Methoxy-5-methylphenyl)pivalamide (2s).** By following the general procedure, the reaction of **1h** (57.5 mg, 0.3 mmol) with $CH_3OH$ (122 $\mu$L, 3.0 mol) at 25 °C afforded **2s** (39.8 mg, 60% yield): $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 8.27 (d, $J$ = 2.4 Hz, 1H), 8.10 (br, 1H), 6.83−6.80 (m, 1H), 6.75 (d, $J$ = 8.0 Hz, 1H), 3.86 (s, 3H), 2.29 (s, 3H), 1.31 (s, 9H); $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$ 176.5, 145.9, 130.6, 127.6, 123.5, 120.2, 109.6, 55.9, 40.0, 27.6, 20.9; IR (KBr) $\nu$ 3443, 2960, 1682, 1597, 1533, 1485, 1464, 1427, 1253, 1226, 1169, 1123, 1029, 798 $cm^{-1}$; HRMS (APCI-Orbitrap) $m/z$ [M + $H^+$] calcd for $C_{13}H_{20}O_2N$ 222.1489, found 222.1482.

***N*-(2-Isopropoxy-5-methylphenyl)pivalamide (2t).** By following the general procedure, the reaction of **1h** (57.5 mg, 0.3 mmol) with *i*-PrOH (1 mL) at 25 °C provided **2t** (51.6 mg, 69% yield): $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 8.27 (s, 1H), 8.22 (br, 1H), 6.80−6.76 (m, 2H), 4.52 (heptet, $J$ = 6.0 Hz, 1H), 2.28 (s, 3H), 1.35 (d, $J$ = 6.0 Hz, 6H), 1.31 (s, 9H); $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$ 176.3, 144.1, 130.8, 128.9, 123.5, 120.2, 113.0, 71.8, 40.0, 27.6, 22.3, 21.0; IR (KBr) $\nu$ 3438, 2974, 2929, 1683, 1595, 1533, 1480, 1428, 1251, 1218, 1178, 1120, 1106, 960, 921, 803, 624 $cm^{-1}$; HRMS (APCI-Orbitrap) $m/z$ [M + $H^+$] calcd for $C_{15}H_{24}O_2N$ 250.1802, found 250.1796.

***N*-(2-Methoxy-5-methylphenyl)benzamide (2u).** By following the general procedure, the reaction of **1i** (63.4 mg, 0.3 mmol) with $CH_3OH$ (122 $\mu$L, 3.0 mol) at 25 °C afforded **2u** (35.5 mg, 49% yield): $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 8.53 (br, 1H), 8.39 (d, $J$ = 2.0 Hz, 1H), 7.91−7.88 (m, 2H), 7.57−7.53 (m, 1H), 7.52−7.48 (m, 2H), 6.88 (dd, $J$ = 8.4 Hz, 2.0 Hz, 1H), 6.81 (d, $J$ = 8.4 Hz, 1H), 3.90 (s, 3H), 2.35 (s, 3H); $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$ 165.2, 146.1, 135.4, 131.6, 130.7, 128.7, 127.5, 127.0, 124.0, 120.5, 109.8, 55.9, 21.0; IR (KBr) $\nu$ 3428, 2922, 1675, 1596, 1534, 1478, 1427, 1252, 1224, 1139, 1028, 799, 707 $cm^{-1}$; HRMS (APCI-Orbitrap) $m/z$ [M + $H^+$] calcd for $C_{15}H_{16}O_2N$ 242.1176, found 242.1169.

***N*-(2-Isopropoxy-5-methylphenyl)benzamide (2v).** By following the general procedure, the reaction of **1i** (63.4 mg, 0.3 mmol) with *i*-PrOH (1 mL) at 25 °C provided **2v** (45.3 mg, 56% yield): $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 8.66 (br, 1H), 8.42 (d, $J$ = 1.6 Hz, 1H), 7.91−7.88 (m, 2H), 7.58−7.54 (m, 1H), 7.53−7.49 (m, 2H), 6.86 (dd, $J$ = 8.4 Hz, 2.0 Hz, 1H), 6.82 (d, $J$ = 8.4 Hz, 1H), 4.58 (heptet, $J$ = 6.0 Hz, 1H), 2.35 (s, 3H), 1.39 (d, $J$ = 6.0 Hz, 1H); $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$ 164.8, 144.2, 135.4, 131.6, 130.8, 128.8, 128.7, 126.9, 124.0, 120.4, 112.8, 71.7, 22.3, 21.0; IR (KBr) $\nu$ 3426, 2976, 2925, 1676, 1594, 1533, 1472, 1428, 1249, 1136, 1111, 959, 798, 706 $cm^{-1}$; HRMS (APCI-Orbitrap) $m/z$ [M + $H^+$] calcd for $C_{17}H_{20}O_2N$ 270.1489, found 270.1482.

***N*,*N*′-(4,4′-Dimethoxy[1,1′-biphenyl]-2,2′-diyl)diacetamide (3).** A mixture of *N*-(3-methoxyphenyl)acetamide (49.6 mg, 0.3 mmol), $Pd(OAc)_2$ (6.7 mg, 0.03 mmol), $K_2S_2O_8$ (162.0 mg, 0.6 mmol), $CH_3OH$ (122 $\mu$L, 3.0 mmol), $CH_3SO_3H$ (3.9 $\mu$L, 0.06 mmol), and 1,2-dimethoxyethane (2 mL) was stirred at 25 °C for 24 h. After the reaction was complete, the mixture was filtered by a silica gel plug with ethyl acetate as the eluent and evaporated in vacuum. The residue was purified by flash column chromatography on a silica gel using EtOAc as the eluent to give product **3** (28.7 mg, 58% yield): $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 7.88 (d, $J$ = 2.8 Hz, 2H), 7.08 (d, $J$ = 8.4 Hz, 2H), 6.88 (br, 2H), 6.77 (dd, $J$ = 8.4 Hz, $J$ = 2.8 Hz, 2H), 3.87 (s, 6H), 1.98 (s, 6H); $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$ 168.9, 160.2, 137.0, 131.5, 119.6, 111.3, 107.4, 55.5, 24.5; IR (KBr) $\nu$ 3378, 3272, 2963, 1674, 1610, 1580, 1531, 1460, 1423, 1370, 1300, 1254, 1194, 1163, 1126, 1052, 871, 805, 734, 628 $cm^{-1}$; HRMS (ESI-Orbitrap) $m/z$ [M + $H^+$] calcd for $C_{18}H_{21}O_4N_2$ 329.1496, found 329.1494.

## ■ ASSOCIATED CONTENT

### Ⓢ Supporting Information

NMR spectra of products **2a**−**v** and **3**. This material is available free of charge via the Internet at http://pubs.acs.org.

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### Notes

The authors declare no competing financial interest.

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