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Iodine(III)-Mediated C−H Alkoxylation of Aniline Derivatives with Alcohols under Metal-Free Conditions

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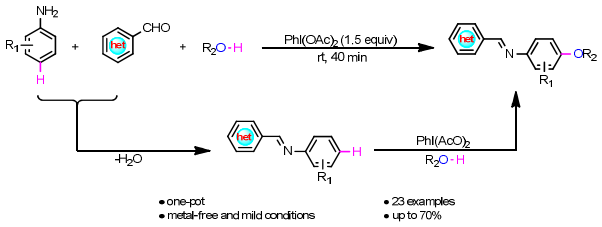
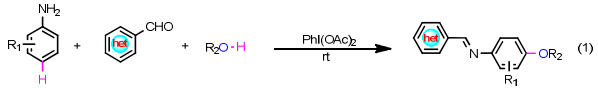


ABSTRACT: The development of a novel intermolecular oxidative C−H alkoxylation of aniline derivatives is described under metal-free conditions with high reaction rates at ambient temperature. In the presence of an I(III) oxidant, a range of aldehydes, anilines and alcohol substrates undergo three-component coupling to produce synthetically useful alkoxyl-substituted *N*-arylimines. The preliminary mechanism investigations revealed that the transformation proceeds via imines as intermediates.

INTRODUCTION

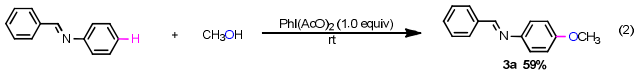
Direct functionalization of inert C−H bonds is an area of widespread and active research that has seen enormous growth over the past decades, owing to the omnipresent nature of C–H bonds in organic molecules.[1,2] A wide variety of C−H functionalization methods for the formation of C−C bonds have already been developed to date and have had a significant impact in the field of organic chemistry. In parallel, the development of C−O bond formation reactions has greatly accelerated in recent years.[3-8] Despite the success of C−H oxygenation methods, C(sp^2)−H

alkoxylation reactions[8] remain scarce; existing reports have been limited to the directed *ortho* alkoxylation of the C(sp^2)−H bonds of arenes and require the use of expensive palladium as catalyst. However, to the best of our knowledge, intermolecular oxidative C−H alkoxylation of arenes utilizing alcohols as oxygen source under metal-free conditions has not yet been achieved. Herein, we report a metal-free oxidative C−H alkoxylation of aniline derivatives with alcohols in the presence of phenyliodonium diacetate ($PhI(AcO)_2$): the present C(sp^2)−H alkoxylation is achieved via three-component reaction from commercial available aldehydes, anilines and alcohols under mild, metal-free conditions. Most importantly, as shown in Eq. 1, the $PhI(AcO)_2$-mediated C−H alkoxylation of anilines with alcohols occurred at the *para* position to afford a range of aryl ether derivatives, which are important structural motifs found in various biologically active compounds and functional materials[9] and useful intermediates in organic synthesis.[10]



RESULTS AND DISCUSSION

Recently, the application of hypervalent iodine compounds in organic synthesis has attracted immense research interests due to their low toxicity, simple handling, commercial availability, and mild reactivity, and has resulted in the discovery of numerous novel synthetic methods for the construction of carbon−carbon and carbon−heteroatom bonds.[11-14] Among them, the most impressive is that such iodine compounds could be utilized to catalyze or mediate C−H/C−H coupling[13] and C−H/N−H coupling.[14] More recently, we reported the hypervalent iodine reagents mediated nitrogenation of alkenes[15a] and esterification of alkynes[15b] via C−C bonds oxidative cleavage. On the basis of these observations, we wondered whether C−N double bond was used in

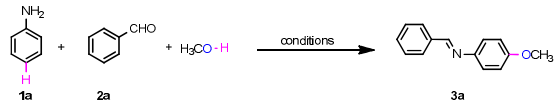


(2)

place of C−C double bond and C−C triple bond that would lead to aromatic ring C−H functionalization mediated by such iodine compound. To test our hypothesis, the reaction of *N*-benzylidenebenzenamine was carried out with 1.0 equiv of $PhI(AcO)_2$ (PIDA) in CH_3OH at room temperature for 30 min. To our delight, the expected C−H oxidation product **3a** was obtained in 59% yield (Eq. 2). Inspired by this result and the fact that the imines can be prepared easily from aldehydes and anilines in alcohols as solvents, we questioned whether the present alkoxylation could also be achieved through three-component reaction[16] fashion from readily available aldehydes, aniline and alcohols in the presence of PIDA. When the three-component reaction of benzaldehyde, aniline and methanol was carried out in the presence of 1.0 equiv of PIDA at room temperature for 40 min, the desired product 3a was obtained in 56% yield (Table 1, entry 1). Optimization of the reaction was straightforward and provided conditions that enable the selective oxidation of **1a** to **3a** in moderate yield (Table 1). The best yield (74%) was achieved when increasing the amount of PIDA to 1.5 equiv (Table 1, entries 2 and 3), while further increase of PIDA dropped the yield to 71% (Table 1, entry 4). Addition of other solvents as the co-solvent such as DCM, benzene and cyclohexane did not promote the reaction (Table 1, entries 5-6). The reaction temperature ranging from 0 ^{o}C to 60 ^{o}C had little effect on the reaction efficiency (Table 1, entries 8-10). Prolonging the reaction time to 1 h did not improve the yield (Table 1, entry 11). Control reaction confirms that C−H alkoxylation product **3a** is not formed in the absence of PIDA. It should be noted that no *ortho*- or *meta*-C−H alkoxylation were detected in all cases. Thus, the optimized conditions were found to include anilines (0.2 mmol), aldehydes (0.2 mmol), PIDA (1.5

equiv) in alcohols (6 mL) at room temperature for 40 min. In addition, under optimal conditions, only <5% of the starting materials were observed by GC, and the reaction by-products were benzoic acid, *N*-benzylidenebenzenamine, azobenzene and unidentified products, determined by GC-MS.

Table 1. Discovery and Optimization of Metal-Free C−H Alkoxylation[a]



1a 2a 3a

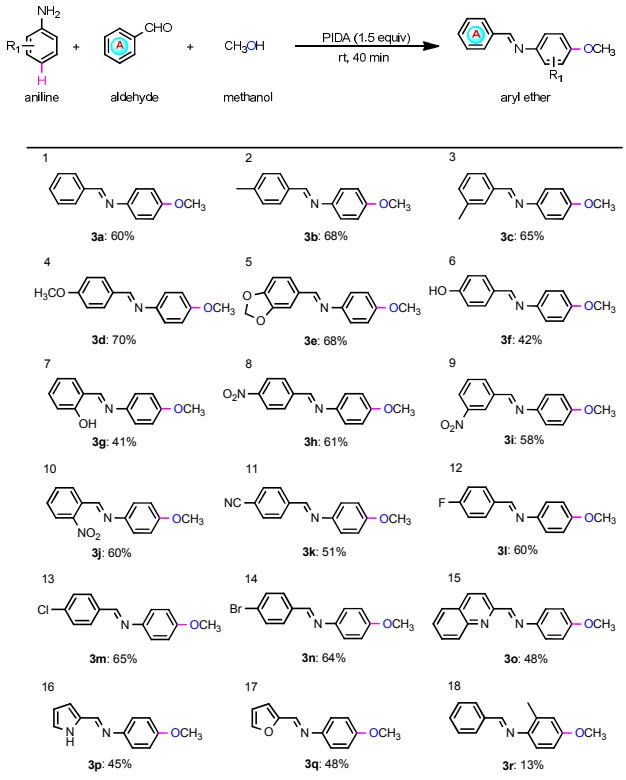
entry	conditions	yield (%)[b]
1	PIDA (1.0 equiv), rt, 40 min	56
2	PIDA (1.2 equiv), rt, 40 min	70
3	PIDA (1.5 equiv), rt, 40 min	74 (60)
4	PIDA (2.0 equiv), rt, 40 min	71
5[c]	PIDA (1.5 equiv), DCM, rt, 40 min	25
6[d]	PIDA (1.5 equiv), benzene, rt, 40 min	28
7[e]	PIDA (1.5 equiv), cyclohexane, rt, 40 min	32
8	PIDA (1.5 equiv), 0 °C, 40 min	70
9	PIDA (1.5 equiv), 40 °C, 40 min	70
10	PIDA (1.5 equiv), 60 °C, 40 min	67
11	PIDA (1.5 equiv), rt, 1 h	72

[a] Reaction conditions: **1a** (0.2 mmol), **2a** (0.2 mmol), CH_3OH (6 mL). [b] GC yields. [c] DCE/ CH_3OH (1/1, 6 mL). [d] Benzene/ CH_3OH (1/1, 6 mL). [e] Cyclohexane/ CH_3OH (1/1, 6 mL). The isolated yield is given in parentheses.

With the establishment of the optimal conditions, the scope and limitation of this three-component coupling system were next explored. The scope of the adehyde in the coupling with aniline and methanol was examined first. As shown in Table 2, the reaction worked very well for a wide variety of substituted benzaldehydes, and the products were isolated in yields ranging from 41% to 68% (entries 1-17). Benzaldehydes bearing nitro substituents at different positions on the phenyl ring afforded similar results (entries 8-10, 58%-61% yield). Moreover, the **A** ring is not limited to benzene rings. Quinolines, pyrroles and furans, are also viable substrates, providing the

corresponding alkoxylation products in moderate yields (entries 15-17, 45%-48%). While the results of aryl aldehydes were all favorable, the reactions of aliphatic aldehydes were messy, and the desired alkoxylation products were not detected by GC-MS. However, anilines bearing substituents is inefficient. Reaction of *N*-benzylidene-2-methylbenzenamine with methanol yielded only 13% of the product **3r** (entry 18), whereas the reactions of *N*-benzylidene-2-methoxybenzenamine and *N*-benzylidene-2-chlorobenzenamine were messy and only trace amounts of the corresponding alkoxylation products were observed by GC-MS.

Table 2: C−H Alkoxylation: Scope of the aldehyde and aniline Coupling Component[a,b]

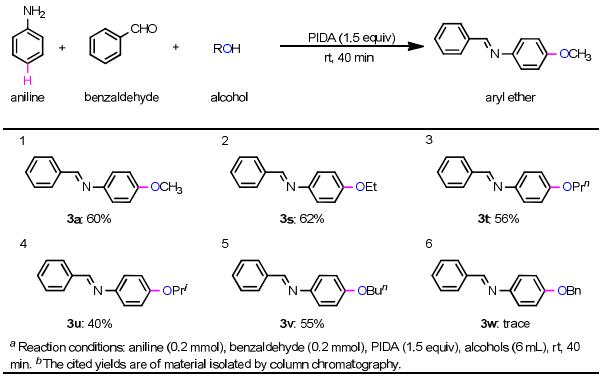


[a] Reaction conditions:anilines (0.2 mmol), aldehydes (0.2 mmol), PIDA (1.5 equiv), CH_3OH (6 mL), rt, 40 min.
[b] The cited yields are of material isolated by column chromatography.

The scope of the alcohol substrate was next explored in the coupling with aniline and benzaldehyde, and the results are summarized in Table 3. For example, common simple alcohols such as ethanol, *n*-propanol, *i*-propanol, and *n*-butanol all reacted smoothly to generate the corresponding alkoxylation products in 41%-65% yields (entries 2-5). Unfortunately, benzylic

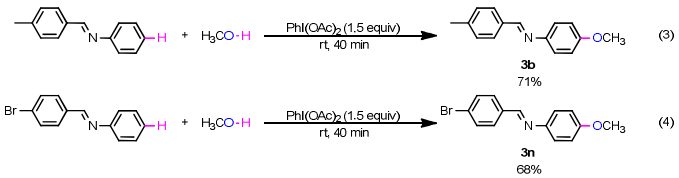
alcohols such as phemethylol only provided a trace amount of the desired product (entry 6).

Table 3: C−H Alkoxylation: Scope of the Alcohol Coupling Component[a,b]



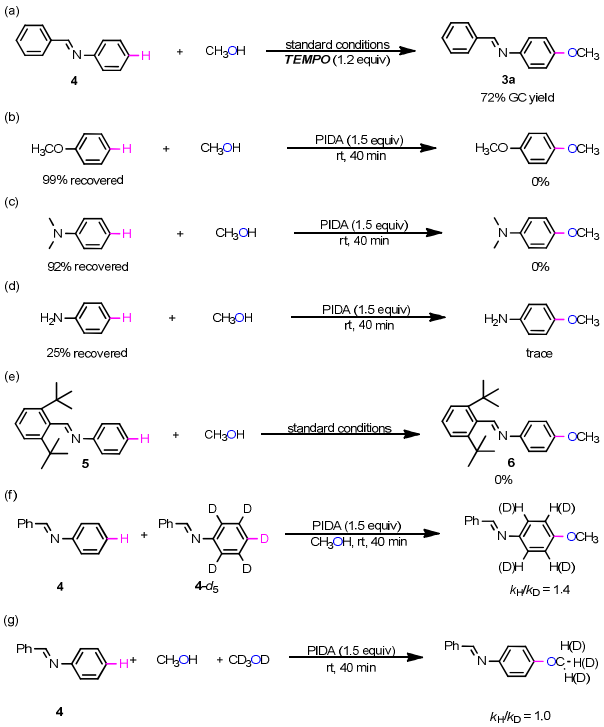
[a] Reaction conditions: aniline (0.2 mmol), benzaldehyde (0.2 mmol), PIDA (1.5 equiv), alcohols (6 mL), rt, 40 min. [b] The cited yields are of material isolated by column chromatography.

To further verify whether the imine is possible intermediate in the reaction, we attempted to synthesize various imines from benzaldehydes and anilines, and subjected them to the standard conditions. As demonstrated in Eqns. 3 and 4, reaction of *N*-(4-methylbenzylidene)aniline and *N*-(4-bromobenzylidene)aniline with methanol provided the corresponding desired alkoxylation products 3b and 3n in 71% and 68% yield, respectively. The data indicate that the alkoxylation reaction proceeds via imines as intermediates.



For related iodine(III)-mediated C−H functionalization reactions, radical pathways were often postulated. In our case, a control experiment showed that the presence of 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO), a well-known radical inhibitor, does not affect the conversion of **4** to **3a** (Scheme 1a). To gain more insight into the mechanism of the present C−H alkoxylation process, several control experiments were conducted. When the reaction was tried with anisole or *N*,*N*-dimethyl aniline under the optimized conditions, the corresponding C−H alkoxylation products were not detected by GC-MS (Schemes 1b and 1c), whereas aniline gave a

complex mixture and only a trace amount of the desired product was observed by GC-MS (Scheme 1d). The results suggest that C=N double bond is essential for the reaction to proceed efficiently. Moreover, no reaction occurred when sterically hindered imine **5**, wherein C=N bond is shielded by two *tert*-butyl groups, was subjected to the standard conditions (Scheme 1e). This result indicates that the reaction might be initiated by the interaction of C=N double bond with iodine(III). Furthermore, the isotope effect of the reaction was examined. The reaction was conducted under the standard conditions using equimolar amounts of **4** and **4**-d_5 coupling with methanol in the presence of PIDA. The labeling experiment gave a relatively small kinetic isotope effect k_H/k_D = 1.4 (Scheme 1f). The observation implies the C−H bond cleavage of arenes might be involved in the rate-limiting step. The intermolecular kinetic isotope experiments are performed

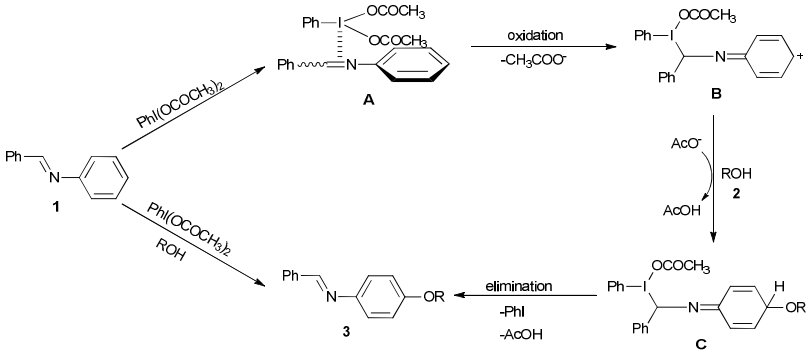


Scheme 1. Control experiments

in Scheme 1g. No kinetic isotope effect (k_H/k_D = 1.0) was observed.

On the basis of the data above and precedent literature,[11,12] a plausible mechanism for the

present oxidative *para*-C(sp^2)−H alkoxylation reaction is illustrated in Scheme 2. First, this reaction is initiated via an interaction between the PIDA and the C=N double bond of imine **1** to give intermediate **A**.[12b,c] Then the intermediate **A** is oxidized to generate carbon cation intermediate **B**.[11b,13j] Finally, nucleophilic attack of alcohol to B affords intermediate **C**, and subsequent elimination gives rise to the final product **3**.



Scheme 2 Possible reaction mechanism

CONCLUSIONS

In summary, we have developed a metal-free C−H alkoxylation for aniline derivatives. A range of substrates are compatible with this process, and to the best of our knowledge this represents the first example of metal-free intermolecular oxidative C−H alkoxylation of anilines that proceeds at room temperature with high reaction rates. The reaction is operationally simple using only commercially available phenyliodonium diacetate (PIDA) as a reagent and alcohols as an oxygen source. Moreover, the present C−H alkoxylation is achieved via three-component reaction fashion from commercially available aromatic aldehydes, aniline, and alcohols in the presence of PIDA. However, substituted anilines did not react satisfactorily in the presence of aromatic aldehydes, some alcohols and PIDA. Further experimental studies to elucidate the mechanistic details and further investigation of relevant reactions based on this room temperature metal-free C−H

activation are currently underway, and these studies will be reported in due course.

EXPERIMENTAL SECTION

General Comments. All reagents and solvent used were obtained commercially and used without further purification unless indicated otherwise. All products were characterized by ^{1}H NMR and ^{13}C NMR. ^{1}H NMR spectra were recorded on 400 MHz in $CDCl_3$, and ^{13}C NMR spectra were recorded on 101 MHz in $CDCl_3$ using TMS as internal standard. Multiplicities are indicated as s (singlet), d (doublet), t (triplet), q (quartet), and m (multiplet), and coupling constants (*J*) are reported in Hertz. Copies of ^{1}H NMR and ^{13}C NMR spectra are provided as Supporting Information.

General procedure for the oxidative C−H alkoxylation of aniline derivatives mediated by PIDA. A 25-mL flask was charged with aldehydes (0.2 mmol, 1 equiv), aniline (0.2mmol, 1 equiv), phenyliodonium diacetate (PIDA) (0.3 mmol, 1.5 equiv) and alcohols (6 mL). The reaction was stirred at room temperature for 40 min. Upon completion of the reaction, the crude reaction mixture was concentrated in vacuo followed by neutral alumina column purification (EtOAc:Hexane as eluents) to give the desired alkoxylation products.

*N-Benzylidene-4-methoxyaniline (**3a**).*[17a] Isolated as a pale yellow solid, 25.3 mg (60%), mp = 68.3-70.5 ^{o}C; ^{1}HNMR (400 MHz, $CDCl_3$) δ 8.47 (s, 1 H), 7.87-7.89 (m, 2 H), 7.45-7.46 (m, 3 H), 7.24 (d, J = 8.0 Hz, 2 H), 6.93 (d, J = 8.0 Hz, 2 H), 3.81 (s, 3 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.6, 158.3, 144.8, 136.4, 131.2, 128.8, 128.7, 122.3, 114.4, 55.5; Anal. Calcd for $C_{14}H_{13}NO$ Elemental Analysis: C, 79.59; H, 6.20; N, 6.63; Found: C, 79.56; H, 6.18; N, 6.61.

*4-Methoxy-N-(4-methylbenzylidene)aniline (**3b**).* [17a] Isolated as a pale yellow oil, 30.6 mg (68%); ^{1}HNMR (400 MHz, $CDCl_3$) δ 8.44 (s, 1 H), 7.78 (d, J = 8.0 Hz, 2 H), 7.22-7.28 (m, 4 H), 6.93 (d,

J = 8.0 Hz 2H), 3.83 (s, 3 H), 2.41 (s, 3 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.5, 158.2, 145.0, 141.6, 133.8, 129.5, 128.7, 122.2, 114.4, 55.5, 21.6.

*N-(3-Methylbenzylidene)-4-methoxyaniline (**3c**).* [17b] Isolated as a pale yellow oil, 29.3 mg (65%); ^{1}HNMR (400 MHz, $CDCl_3$) δ 8.42 (s, 1 H), 7.73 (s, 1 H), 7.63 (d, *J* = 12.0 Hz, 2 H), 7.33 (t, *J* = 8.0 Hz, 2 H), 7.21-7.26 (m, 3 H), 6.92 (d, *J* = 6.8 Hz, 2 H), 3.80 (s, 3 H), 2.40 (s, 3 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.8, 158.3, 145.0, 138.5, 136.4, 132.0, 128.8, 128.7, 126.3, 122.2, 114.5, 55.5, 21.4.

*4-Methoxy-N-(4-methoxybenzylidene)aniline (**3d**).* [17c] Isolated as a pale yellow solid, 33.7 mg (70%), mp = 142.2-144.4 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.41 (s, 1 H), 7.86 (d, *J* = 8.0 Hz, 2 H), 7.22-7.25 (m, 2 H), 6.98 (d, *J* = 8.0 Hz, 2 H), 6.93 (d, *J* = 8.0 Hz, 2 H), 3.87 (s, 3 H), 3.83 (s, 3 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.0, 130.4, 122.1, 114.4, 114.2, 55.5, 55.4; Anal. Calcd for $C_{15}H_{15}NO_2$ Elemental Analysis: C, 74.67; H, 6.27; N, 5.81; Found: C, 74.69; H, 6.30; N, 5.84.

*N-(Benzo[d][1,3]dioxol-5-ylmethylene)-4-methoxyaniline (**3e**).* [17d] Isolated as an off-white solid, 34.7 mg (68%), mp = 113.3-115.2 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.35 (s, 1 H), 7.52 (s, 1 H), 7.19-7.24 (m, 3 H), 6.86-6.94 (m, 3 H), 6.02 (s, 2 H), 3.82 (s, 3 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.1, 157.6, 150.3, 148.4, 144.9, 131.4, 125.4, 122.1, 114.4, 108.2, 106.8, 101.6, 55.5; Anal. Calcd for $C_{15}H_{13}NO_3$ Elemental Analysis: C, 70.58; H, 5.13; N, 5.49; Found: C, 70.56; H, 5.13; N, 5.46.

*4-Methoxy-N-(4-hydroxylbenzylidene)aniline (**3f**).* [17e] Isolated as a greenish white solid, 19.1 mg (42%), mp = 212.1-214.3 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.06 (brs, 1 H), 8.47 (s, 1 H), 7.75 (d, J = 8.0 Hz, 2 H), 7.22 (d, *J* = 8.0 Hz, 2 H), 6.96 (d, *J* = 12.0 Hz, 2 H), 6.67 (d, *J* = 8.0 Hz, 2 H), 3.77 (s, 3 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 160.7, 158.4, 157.9, 145.2, 130.8, 128.2, 122.6,

116.1, 114.8, 55.7; Anal. Calcd for $C_{14}H_{13}NO_2$ Elemental Analysis: C, 73.99; H, 5.77; N, 6.16; Found: C, 74.04; H, 5.74; N, 6.18.

*4-Methoxy-N-(2-hydroxylbenzylidene)aniline (**3g**).* [17f] Isolated as a greenish white solid, 18.6 mg (41%), mp = 85.2-87.3 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 13.39 (brs, 1 H), 8.59 (s, 1 H), 7.32-7.37 (m, 2 H), 7.24-7.28 (m, 2 H), 7.01 (d, J = 8.0 Hz, 1 H), 6.90-6.96 (m, 3 H), 7.96 (d, J = 8.0 Hz, 2 H), 3.83 (s, 3 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 161.0, 160.5, 158.9, 141.4, 132.7, 132.0, 122.3, 119.4, 119.0, 117.2, 114.6, 55.5; Anal. Calcd for $C_{14}H_{13}NO_2$ Elemental Analysis: C, 73.99; H, 5.77; N, 6.16; Found: C, 73.96; H, 5.76; N, 6.12.

*4-Methoxy-N-(4-nitrobenzylidene)aniline (**3h**).* [17c] Isolated as a yellow solid, 31.2 mg (61%), mp = 131.1-133.5 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.54 (s, 1 H), 8.27 d, J = 8.0 Hz, 2 H), 8.02 (d, J = 8.0 Hz, 2 H), 7.29 (d, J = 8.0 Hz, 2 H), 6.94 (d, J = 8.0 Hz, 2 H), 3.83 (s, 3 H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 159.3, 154.8, 149.0, 143.5, 142.0, 129.1, 124.0, 122.7, 114.6, 55.5; Anal. Calcd for $C_{14}H_{12}N_2O_3$ Elemental Analysis: C, 65.62; H, 4.72; N, 10.93; Found: C, 65.66; H, 4.77; N, 10.91.

*4-Methoxy-N-(3-nitrobenzylidene)aniline (**3i**).* [17c] Isolated as a yellow solid, 30.0 mg (58%), mp = 77.6-79.8 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.97 (s, 1 H), 8.31-8.33 (m, 1 H), 8.05-8.07 (m, 1 H), 7.73 (t, J = 8.0 Hz, 1 H), 7.58-7.62 (m, 1 H), 7.30-7.34 (m, 2 H), 7.26 (s, 1H), 6.94-6.98 (m, 2 H), 3.85 (s, 3 H); ^{13}C NMR (101 MHz, $CDCl_3$): 159.0, 154.8, 148.7, 143.6, 138.2, 133.9, 129.7, 125.2, 123.3, 122.5, 114.5, 55.5; Anal. Calcd for $C_{14}H_{12}N_2O_3$ Elemental Analysis: C, 65.62; H, 4.72; N, 10.93; Found: C, 65.64; H, 4.75; N, 10.96.

*4-Methoxy-N-(2-nitrobenzylidene)aniline (**3j**).* [17c] Isolated as a yellow solid, 30.7 mg (60%), mp = 78.2-80.5 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.73-8.74 (m, 1 H), 8.57 (s, 1 H), 8.23-8.32 (m, 2 H),

7.65 (t, J = 8.0 Hz, 1 H), 7.29-7.31 (m, 2 H), 7.96 (d, J = 8.0 Hz, 2 H), 3.85 (s, 3 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.1, 153.3, 149.2, 143.9, 133.5, 131.4, 130.8, 129.6, 124.6, 122.8, 114.5, 55.5; Anal. Calcd for $C_{14}H_{12}N_2O_3$ Elemental Analysis: C, 65.62; H, 4.72; N, 10.93; Found: C, 65.64; H, 4.71; N, 10.95.

*4-(((4-Methoxyphenyl)imino)methyl)benzonitrile (**3k**).* [17a] Isolated as a yellow solid, 24.1 mg (51%), mp = 116.4-118.7 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.51 (s, 1 H), 7.98 (d, J = 8.0 Hz, 2 H), 7.73 (d, J = 12.0 Hz, 2 H), 7.28 (d, J = 8.0 Hz, 2 H), 6.95 (d, J = 8.0 Hz, 2 H), 3.84 (s, 3 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.1, 155.4, 143.7, 140.3, 132.5, 128.9, 122.6, 118.6, 114.5, 113.9, 55.5; Anal. Calcd for $C_{15}H_{12}N_2O$ Elemental Analysis: C, 76.25; H, 5.12; N, 11.86; Found: C, 76.21; H, 5.10; N, 11.89.

*N-(4-Fluorobenzylidene)-4-methoxyaniline (**3l**).* [17c] Isolated as acolorless solid, 27.5 mg (60%), mp = 92.4-94.7 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.45 (s, 1 H), 7.89 (t, J = 8.0 Hz, 2 H), 7.24 (t, J = 12.0 Hz, 2 H), 7.15 (t, J = 8.0 Hz, 2 H), 6.94 (d, J = 8.0 Hz, 2 H), 3.84 (s, 3 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.5 (d, $J_{C\text{-}F}$ = 250.0 Hz), 158.3, 156.9, 144.7, 132.8, 130.5 (d, $J_{C\text{-}F}$ = 8.0 Hz), 122.2, 115.9 (d, $J_{C\text{-}F}$ = 22.0 Hz), 114.4, 55.5; Anal. Calcd for $C_{14}H_{12}FNO$ Elemental Analysis: C, 73.35; H, 5.28; N, 6.11; Found: C, 73.32; H, 5.24; N, 6.15;

*N-(4-Chlorobenzylidene)-4-methoxyaniline (**3m**).* [17f] Isolated as acolorless solid, 31.9 mg (65%), mp = 135.6-137.8 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.44 (s, 1 H), 7.83 (d, J = 8.0 Hz, 2 H), 7.44 (d, J = 12.0 Hz, 2 H), 7.23-7.26 (m, 2 H), 6.94 (d, J = 12.0 Hz, 2 H), 3.84 (s, 3 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.5, 156.7, 144.4, 137.0, 134.9, 129.8, 129.0, 122.3, 114.4, 55.5; Anal. Calcd for $C_{14}H_{12}ClNO$ Elemental Analysis: C, 68.44; H, 4.92; N, 5.70; Found: C, 68.41; H, 4.91; N, 5.68.

*N-(4-Bromobenzylidene)-4-methoxyaniline (**3n**).* [17g] Isolated as a yellow solid, 37.1 mg (64%), mp = 144.2-146.2 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.42 (s, 1 H), 7.75 (d, J = 8.0 Hz, 2 H), 7.58 (d, J = 12.0 Hz, 2 H), 7.23 (J = 8.0 Hz, 2 H), 6.93 (d, J = 8.0 Hz, 2 H), 3.83 (s, 1 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.3, 154.8, 149.0, 143.5, 142.0, 129.1, 124.0, 122.7, 114.6, 55.5; Anal. Calcd for $C_{14}H_{12}BrNO$ Elemental Analysis: C, 57.95; H, 4.17; N, 4.83; Found: C, 57.93; H, 4.16; N, 4.84.

*4-Methoxy-N-(quinolin-2-ylmethylene)aniline (**3o**).* [17h] Isolated as an off-white solid, 25.2 mg (48%), mp = 87.5-89.8 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.82 (s, 1 H), 8.36 (d, J = 8.0 Hz, 1 H), 8.23 (d, J = 8.60 Hz, 1 H), 8.16 (d, J = 8.0 Hz, 1 H), 7.85 (d, J = 8.0 Hz, 1 H), 7.73 – 7.77 (m, 1 H), 7.59 (t, J = 8.0Hz, 1 H), 7.41 (d, J = 8.0 Hz, 2H), 6.97 (d, J = 8.0 Hz, 2 H), 3.84 (s, 3 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.2, 158.3, 155.1, 147.9, 143.5, 136.7, 130.0, 129.5, 128.8, 127.8, 127.6, 122.9, 118.6, 114.5, 58.2; Anal. Calcd for $C_{17}H_{14}N_2O$ Elemental Analysis: C, 77.84; H, 5.38; N, 10.68; Found: C, 77.86; H, 5.39; N, 10.70.

*N-((1H-Pyrrol-2-yl)methylene)-4-methoxyaniline (**3p**).* [17i] Isolated as a pale yellow solid, 18.0 mg (45%), mp = 95.6-97.8 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.43 (brs, 1 H), 8.27 (s, 1 H), 7.18 (d, J = 8.0 Hz, 2 H), 6.90 (d, J = 8.0 Hz, 2 H), 6.73 (s, 1 H), 6.63 (s, 1 H), 6.23 (s, 1H), 3.80 (s, 1 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 157.8, 148.7, 144.8, 130.9, 123.4, 122.1, 116.5, 114.5, 110.2, 55.5; Anal. Calcd for $C_{12}H_{12}N_2O$ Elemental Analysis: C, 71.98; H, 6.04; N, 13.99; Found: C, 71.99; H, 6.07; N, 14.02.

*N-(Furan-2-ylmethylene)-4-methoxyaniline (**3q**).* [17j] Isolated as an off-white solid, 19.3 mg (48%), mp = 70.1-72.3 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.30 (s, 1 H), 7.59 (s, 1 H), 7.26 (d, J = 8.0 Hz, 2 H), 6.92 (d, J = 8.0 Hz, 3 H), 6.53-6.55 (m, 1H), 3.82 (s, 1 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ

158.5, 152.3, 145.8, 145.4, 144.2, 122.3, 115.6, 114.4, 112.1, 55.5; Anal. Calcd for $C_{12}H_{11}NO_2$ Elemental Analysis: C, 71.63; H, 5.51; N, 6.96; Found: C, 71.62; H, 5.54; N, 6.98.

*N-Benzylidene-4-methoxy-3-methylaniline (**3r**).* [17k] Isolated as a yellow oil, 5.9 mg (13%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.37 (s, 1 H), 7.90 (t, J = 4.0 Hz, 2 H), 7.45 (s, 3 H), 6.95 (d, J = 12.0 Hz, 1 H), 6.79 (s, 1 H), 6.74 (d, J = 6.8 Hz, 2 H), 3.80 (s, 3 H), 2.39 (s, 3 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.0, 157.7, 144.1, 136.8, 134.3, 130.9, 128.7, 128.6, 118.1, 115.8, 111.7, 55.4, 18.2.

*N-Benzylidene-4-ethoxyaniline (**3s**).* [17l] Isolated as a yellow solid, 27.9 mg (62%), mp = 72.1-74.3 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.47 (s, 1 H), 7.88 (m, 2 H), 7. 45 (m, 3 H), 7.22 (d, J = 8.0 Hz, 2 H), 6.91 (d, J = 8.0 Hz, 2 H), 4.04 (q, J = 8.0 Hz, 2 H), 1.42 (t, J = 8.0 Hz, 3 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.3, 157.7, 144.8, 136.5, 131.0, 128.8, 128.6, 122.2, 115.0, 63.7, 14.9; Anal. Calcd for $C_{15}H_{15}NO$ Elemental Analysis: C, 79.97; H, 6.71; N, 6.22; Found: C, 79.91; H, 6.74; N, 6.16

*N-Benzylidene-4-propoxyaniline (**3t**).* Isolated as a yellow solid, 26.8 mg (56%), mp = 71.8-74.1 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.48 (s, 1 H), 7.88-7.90 (m, 2 H), 7.45-7.47 (m, 3 H), 7.23 (d, J = 8.0 Hz, 2 H), 6.93 (d, J = 8.0 Hz, 2 H), 3.94 (t, J = 8.0 Hz, 2 H), 1.78-1.87 (m, 2 H), 1.05 (t, J = 8.0 Hz, 3 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.3, 157.9, 144.7, 136.5, 131.1, 128.8, 128.6, 122.2, 115.0, 69.8, 22.7, 10.6; Anal. Calcd for $C_{16}H_{17}NO$ Elemental Analysis: C, 80.30; H, 7.16; N, 5.85; Found: C, 80.27; H, 7.26; N, 5.85.

*N-Benzylidene-4-isopropoxyaniline (**3u**).* [17m] Isolated as a yellow solid, 19.1 mg (40%), mp = 88.2-90.6 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.47 (s, 1 H), 7.86-7.89 (m, 2 H), 7.43-7.45 (m, 3 H), 7.22 (d, J = 12.0 Hz, 2 H), 6.91 (d, J = 8.0 Hz, H), 4.49-4.58 (m, 1H), 1.34 (d, J = 8.0 Hz, 6 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.3, 156.6, 144.7, 136.5, 131.0, 128.8, 128.6, 122.3, 116.5, 70.2,

22.1; Anal. Calcd for $C_{16}H_{17}NO$ Elemental Analysis: C, 80.30; H, 7.16; N, 5.85; Found: C, 80.34; H, 7.18; N, 5.89.

*N-Benzylidene-4-butoxyaniline (**3v**).* Isolated as an off-white solid, 27.8 mg (55%), mp = 66.2-68.3 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.48 (s, 1 H), 7.88-7.90 (m, 2 H), 7.45-7.46 (m, 3 H), 7.23 (d, J = 8.0 Hz, 2 H), 6.92 (d, J = 8.0 Hz, 2 H), 3.98 (t, J = 8.0 Hz, 2 H), 1.74-1.81 (m, 2 H), 1.44-1.55 (m, 2 H), 0.98 (t, J = 8.0 Hz, 3 H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.3, 157.9, 144.7, 136.5, 131.0, 128.8, 128.6, 122.2, 115.0, 68.0, 31.4, 19.3, 13.9; Anal. Calcd for $C_{17}H_{19}NO$ Elemental Analysis: C, 80.60; H, 7.56; N, 5.53; Found: C, 80.65; H, 7.58; N, 5.59.

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Supporting Information. Kinetic isotopic effect (KIE) studies and copies of ^{1}H and ^{13}C NMR spectra for the products. This material is available free of charge via the Internet at http://pubs.acs.org.

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