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Note

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Palladium-Catalyzed *N*-Nitroso-Directed C−H Alkoxylation of Arenes and Subsequent Formation of 2-Alkoxy-*N*-alkylarylamines

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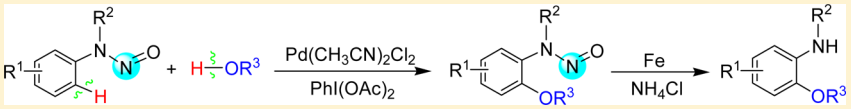
Supporting Information



ABSTRACT: A palladium-catalyzed direct *ortho*-alkoxylation of *N*-alkyl-*N*-nitrosoarylamines was developed in which alcohols were used as the alkoxylation reagents and $PhI(OAc)_2$ was employed as the oxidant. The protocol was available for both primary and secondary alcohols. The products were transformed to *o*-alkoxy-*N*-alkylanilines expediently by a simple reduction.

Aromatic ethers represent an important structural motif in many naturally occurring medicinal compounds and functional materials.[1] Palladium-catalyzed alkoxylation to arene derivatives is a remarkable route to access this type of compounds.[1c] Besides the coupling of aryl halides with alcohols,[2] the transition-metal-catalyzed direct alkoxylation of the inert C(sp^2)−H bond with alcohols is considered to be an efficient strategy in recent years due to the advantages that no preactivation of arenes is required and wasteful byproducts are minimized. For these Pd-catalyzed ligand-directed alkoxylations, the coordinating groups such as oxime ether,[3] carbamoyl (CONHOMe),[4] acylamino,[5] picolinamide (NHPA),[6] cyano,[7] azo,[8] 2-(pyridin-2-yl)propan-2-amine (CONHPIP),[9] 2-pyridyloxyl,[10] and triazole[11] were employed as the efficient *ortho*-directing groups in the C(sp^2)−H bond oxidative activation process. A few other works disclosed the intramolecular C(sp^2)−H bond alkoxylation.[12] Still, compared with the various transition-metal-catalyzed direct aromatic C−C and C−heteroatom bond formation reactions, the alkoxylation of inert C−H remains relatively rare because the transition-metal-catalyzed C−O bond formation is generally considered more difficult.[13,2e,f]

N-Nitrosoanilines are a class of very useful medicinal compounds and synthetic materials for the preparation of various nitrogencontaining compounds.[14] They are usually prepared by the *N*-nitrosation of secondary amines using nitrous acid or related compounds.[15] The moderate coordination effect of nitroso to transition metals is well-known,[15a,16] which made this group act as a favorable directing group to carry out the functionalization of inert C−H bond. Thus, a few rhodium-catalyzed C−C bond formation reactions selective on the *ortho* C(sp^2)−H bond of arenes directed by nitroso were developed recently. Zhu and co-workers[17] first reported a Rh-catalyzed *ortho*-olefination, this research group[18] and Huang[19] then independently described a Rh-catalyzed cyclization of *N*-nitrosoanilines with alkynes for streamlined synthesis of indoles. A Rh-catalyzed *ortho* C−H alkynylation of arenes was also developed.[20] Our continued efforts to develop concise syntheses of arene derivatives led us to explore the application of this protocol to the C−heteroatom bond formation reaction to get the useful skeletons in complex molecules. Herein we want to describe a Pd-catalyzed *ortho*-alkoxylation of the C(sp^2)−H bond at aromatic ring directed by nitroso group using alcohols as the alkoxylation reagents, and the products could be transformed to *o*-alkoxyanilines expediently by a simple reduction.

Initially, we chose *N*-methyl-*N*-nitrosobenzenamine (**1a**) as the substrate and methanol as both alkoxylation reagent and the solvent to explore and optimize this new alkoxylation reaction via C−H bond activation (Table 1). We were pleased to find that under the catalysis of $Pd(OAc)_2$ (10 mol %) and $PhI(OAc)_2$ as an oxidant, the desired methoxylation product, 2-methoxy-*N*-methyl-*N*-nitrosobenzenamine (**3aa**), was isolated after 24 h at 30 °C in 47% yield, (entry 1). For getting a better yield, various palladium catalysts, such as $PdCl_2$, $Pd(PPh_3)_4$, $PdCl_2(PPh_3)_2$, and $Pd(CH_3CN)_2Cl_2$, were screened in the reaction (entries 2−5). Among them, $Pd(CH_3CN)_2Cl_2$ was proven to be the most effective; the product **3aa** was generated in 83% yield; and a 10 mol % catalyst loading was required (entries 5 and 6). We then tried a series of oxidants. When BQ (benzoquinone) was used, a very low yield (<10%) was obtained (entry 7), while the oxidants $Na_2S_2O_8$, $K_2S_2O_8$, and O_2 were completely ineffective for this reaction (entries 8−10). $PhI(OAc)_2$ was therefore selected as the oxidant for this transformation. The appropriate amount of $PhI(OAc)_2$ seemed to be 3 equiv. Increasing the amount to 5 equiv did not bring an obvious improvement (entry 11), while a lower loading of 2 equiv reduced the yield of **3aa** remarkably (entry 12). Particularly, the reaction proceeded at 30 °C, and the higher

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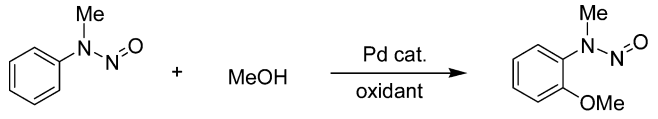
Table 1. Optimization of Reaction Conditions[a]



1a 2a 3aa

entry	catalyst	oxidant (equiv)	solvent	yield (%)
1	$Pd(OAc)_2$	$PhI(OAc)_2$ (3)	MeOH	47
2	$PdCl_2$	$PhI(OAc)_2$ (3)	MeOH	72
3	$Pd(PPh_3)_4$	$PhI(OAc)_2$ (3)	MeOH	0
4	$PdCl_2(PPh_3)_2$	$PhI(OAc)_2$ (3)	MeOH	65
5	$Pd(CH_3CN)_2Cl_2$	$PhI(OAc)_2$ (3)	MeOH	83
6	$Pd(CH_3CN)_2Cl_2$	$PhI(OAc)_2$ (3)	MeOH	68[b]
7	$Pd(CH_3CN)_2Cl_2$	BQ (3)	MeOH	<10
8	$Pd(CH_3CN)_2Cl_2$	$Na_2S_2O_8$ (3)	MeOH	0
9	$Pd(CH_3CN)_2Cl_2$	$K_2S_2O_8$ (3)	MeOH	0
10	$Pd(CH_3CN)_2Cl_2$	O_2 (1 atm)	MeOH	0
11	$Pd(CH_3CN)_2Cl_2$	$PhI(OAc)_2$ (5)	MeOH	85
12	$Pd(CH_3CN)_2Cl_2$	$PhI(OAc)_2$ (2)	MeOH	57
13	$Pd(CH_3CN)_2Cl_2$	$PhI(OAc)_2$ (3)	MeOH/DCE (1:1)	54
14	$Pd(CH_3CN)_2Cl_2$	$PhI(OAc)_2$ (3)	MeOH/toluene (1:1)	52
15	$Pd(CH_3CN)_2Cl_2$	$PhI(OAc)_2$ (3)	MeOH/dioxane (1:1)	41
16	$Pd(CH_3CN)_2Cl_2$	$PhI(OAc)_2$ (3)	MeOH	80[c]
17	$Pd(CH_3CN)_2Cl_2$	$PhI(OAc)_2$ (3)	MeOH	75[d], 56[e]
18	$Pd(CH_3CN)_2Cl_2$	$PhI(OAc)_2$ (3)	MeOH	65[f]

[a]Unless otherwise specified, the reactions were carried out in a sealed tube in the presence of **1a** (0.5 mmol), **2a** (2 mL), catalyst (10 mol %), and oxidant (1.5 mmol) under an air atmosphere at 30 °C for 24 h. All listed yields are isolated ones. [b]$Pd(CH_3CN)_2Cl_2$ (5 mol %) was used. [c]At 60 °C. [d]AcOH (5 equiv) was added. [e]$MeSO_3H$ (5 equiv) was added. [f]The reaction took place in an open flask.

temperature did not improve the conversion (entry 16). Mixed solvents were also tested. The results indicated that the addition of DCE, toluene, or dioxane reduced the yield obviously (entries 13−15), which revealed that a low concentration of alcohol was unfavorable for this reaction. Furthermore, the presence of AcOH or $MeSO_3H$ as additive also did not show positive effect for this methoxylation reaction (entry 17). The moist air may be unfavorable for the reaction. When the reaction took place in an open flask, a lower yield of 65% was obtained (entry 18).

Having established the optimal reaction conditions, the substrate scope was next examined. The results are summarized in Table 2. The methoxylation reaction was first investigated by using methanol as the coupling partner with a series of *N*-methyl-*N*-nitrosoarylamines. The protocol was found to be broadly applicable for the C−H methoxylation of this type of arylamine derivatives bearing electron-donating or -withdrawing substituents on the phenyl ring. The reactants with methyl group showed a high reactivity (**3ba**, **3ca**), but the presence of an electron-withdrawing group (Cl, Br, COOMe) on the phenyl ring led to a decrease of the yields (**3da**, **3ea**, **3fa**, and **3ia**). Surprisingly, when a methoxyl group was substituted on the *para*-position of the phenyl ring, only a 30% yield was obtained (**3ha**). It is interesting that for the *meta*-substituted reactants the methoxylation selectively took place on the side with smaller steric hindrance (**3ba**, **3da**, **3ga**). For *N*-methyl-*N*-nitrosonaphthalen-2-amine, a 3-position methoxylated product was obtained (**3ja**). We next examined some other *N*-alkyl-substituted reactants. Compared with *N*-methyl-*N*-nitrosoarylamine, the yields reduced obviously when *N*-ethyl-*N*-nitrosobenzenamine, *N*-isopropyl-*N*-nitrosobenzenamine, and *N*-phenyl-*N*-nitrosobenzenamine were employed as the substrates (**3ka**, **3la**, **3ma**), presumably due to the steric hindrance. It is noteworthy that because of the restricted rotation around the *N*-nitroso N−N bond in these molecules, the *syn* and *anti* isomers were detected in these products.

The ethoxylation, propoxylation, and isopropoxylation were next studied using the corresponding alcohols as the alkoxylation reagents, and the desired *ortho*-alkoxylation products were obtained with high selectivity. When primary alcohols were used, similar to the methoxylation above, methyl-substituted substrates provided good yields (**3bb**, **3cb**, **3bc**, and **3cc**). When alkoxylation of *N*-methyl-*N*-nitrosoarylamines used a secondary alcohol 2-propanol, however, lower yields were obtained compared with the reactions of the primary alcohols (**3ad**−**ed**).

Developing a large-scale reaction is desirable, especially for industry. We then attempted to conduct the reaction on gram scale. When 10 mmol (1.50 g) of *N*,3-dimethyl-*N*-nitrosobenzenamine was used as the reactant, under the established methoxylation reaction conditions, 1.45 g (yield 81%) of 2-methoxy-*N*,5-dimethyl-*N*-nitrosobenzenamine (**3ba**) was obtained, which revealed that the decrease of the yield was less than 8% when the reaction proceeded on a gram scale. The present reaction is capable as a general synthetic method in organic synthesis.

It is well-known that *o*-alkoxyanilines are a class of very useful compounds in the synthesis of medicines, dyes, and various materials.[21] As an expansion of the alkoxylation of *N*-nitrosoarylamines, we used the alkoxylation products as the substrates via a simple reduction obtained *o*-alkoxyanilines. The reduction reaction was taken out in the presence of Fe (4 equiv) and NH_4Cl (3 equiv) in 75% ethanol at 80 °C, and the corresponding *o*-alkoxyaniline derivatives were obtained in high yields (Scheme 1).

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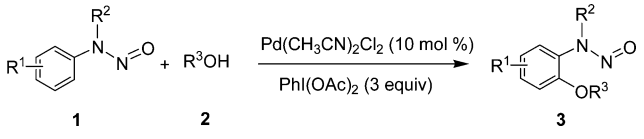
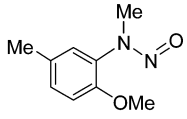
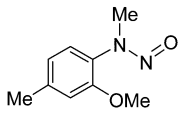
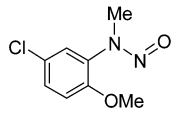
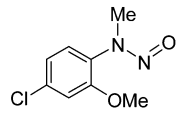
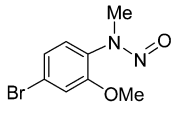
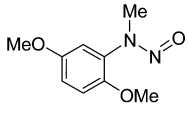
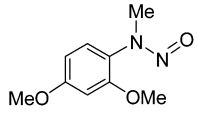
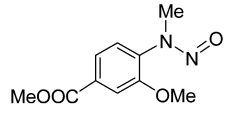
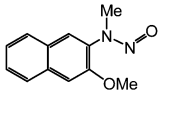
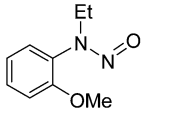
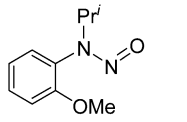
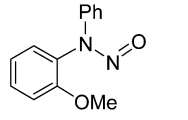
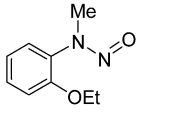
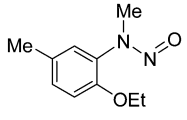
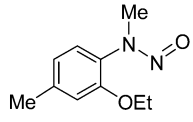
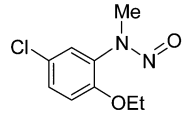
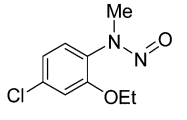
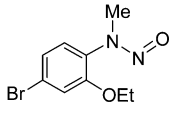
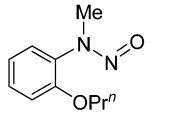
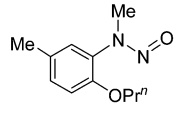
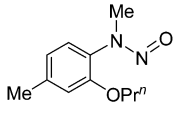
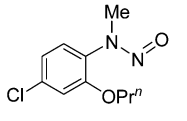
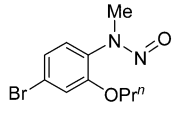
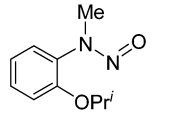
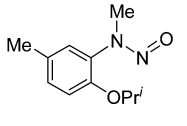
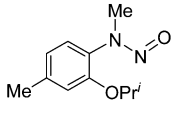
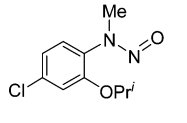
Table 2. ***ortho*-Alkoxylation of *N*-Alkyl-*N*-nitrosoarylamines with Alcohols**[a,b]



1 2 3

 **3ba**, 88%	 **3ca**, 86%	 **3da**, 62%	 **3ea**, 53%
 **3fa**, 63%	 **3ga**, 68%	 **3ha**, 30%	 **3ia**, 62%
 **3ja**, 68%	 **3ka**, 60% (74%)[c] (3:1)[d]	 **3la**, 36%[c] (2:1)[d]	 **3ma**, 44%[c] (5:1)[d]
 **3ab**, 64%	 **3bb**, 89%	 **3cb**, 70%	 **3db**, 28%
 **3eb**, 34%	 **3fb**, 39%	 **3ac**, 49%	 **3bc**, 86%
 **3cc**, 80%	 **3ec**, 31%	 **3fc**, 30%	 **3ad**, 23%
 **3bd**, 37%	 **3cd**, 44%	 **3ed**, 20%	

[a]Unless otherwise specified, the reactions were carried out with **1** (0.50 mmol), **2** (2 mL), $Pd(CH_3CN)_2Cl_2$ (10 mol %), and $PhI(OAc)_2$ (1.5 mmol) under an air atmosphere at 30 °C for 24 h. [b]Isolated yields. [c]$PhI(OAc)_2$ (2.5 mmol) was used. [d]The ratio of the *syn* to *anti* isomers relative to N−N bond, determined by the ^1H NMR spectra.

In summary, we have successfully developed an efficient and mild palladium-catalyzed alkoxylation of *N*-nitrosoarylamines using a synthetically versatile directing group nitroso which is capable of undergoing further synthetic manipulations. This alkoxylation protocol was available for both primary and secondary alcohols. The result presented here should be of

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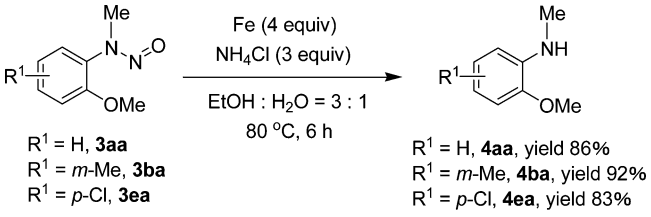
Scheme 1. Removal of Directing Group



R^1 = H, **3aa**
R^1 = *m*-Me, **3ba**
R^1 = *p*-Cl, **3ea**

R^1 = H, **4aa**, yield 86%
R^1 = *m*-Me, **4ba**, yield 92%
R^1 = *p*-Cl, **4ea**, yield 83%

considerable interest for valuable synthetic building blocks in organic synthesis.

EXPERIMENTAL SECTION

General Methods. All reactions were run in oven-dried flasks under air. *N*-Alkyl-*N*-nitrosoarylamines were prepared according to the literature;[15b,17] alcohols were dried using general method; other reagents were commercially available and were used without purification. NMR spectra were recorded at 400 MHz (^{1}H) and 100 MHz (^{13}C) using TMS as an internal standard. Chemical shifts are given relative to $CDCl_3$ (7.28 ppm for ^{1}H NMR, 77.16 ppm for ^{13}C NMR). The following abbreviations are used to explain the multiplicities: s = singlet, d = doublet, dd = doublet of doublet, t = triplet, q = quartet, m = multiplet, br = broad. Melting points are uncorrected. For the HRMS measurements, Q-TOF was used.

General Experimental Procedures and Characterizations. *Palladium-Catalyzed Alkoxylation of N-Nitrosoarylamines.* *N*-Alkyl-*N*-nitrosoarylamine (0.5 mmol), $PhI(OAc)_2$ (1.5 mmol), $Pd(CH_3CN)_2Cl_2$ (0.05 mmol), and alcohol (2 mL) were added in a 25 mL sealed tube with a Teflon-lined cap. The mixture was stirred at 30 °C (oil bath temperature) for 24 h. After the reaction was complete, the mixture was diluted with dichloromethane, washed with water, and dried. The solution was concentrated in vacuo and separated on a silica gel column using hexane/EtOAc (20:1, v/v) as eluent to give the corresponding pure *o*-alkoxylated products. For the solid products, the melting points were obtained after further recrystallization from hexane.

Reduction of o-Alkoxy-N-alkyl-N-nitrosoarylamines. *o*-Alkoxy-*N*-alkyl-*N*-nitrosoarylamines (0.25 mmol), Fe powder (4 equiv), NH_4Cl (3 equiv), and 75% ethanol (2 mL) were added in a 25 mL reaction tube. The mixture was stirred at 80 °C for 6 h. After being cooled to room temperature, the mixture was extracted with dichloromethane and then washed and dried. The solution was concentrated by vacuum and separated on a silica gel column using hexane/EtOAc (10:1, v/v) as eluent to give the corresponding pure *o*-alkoxy-*N*-alkylarylamines.

*2-Methoxy-N-methyl-N-nitrosobenzenamine (**3aa**):* yield 83% (70 mg); brown oil; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.44−7.39 (m, 1H), 7.35 (dd, J_1 = 8.0 Hz, J_2 = 1.6 Hz, 1H), 7.06−7.02 (m, 2H), 3.85 (s, 3H), 3.36 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 153.0, 131.2, 130.3, 126.6, 120.8, 112.1, 55.7, 35.0; HRMS-ESI (m/z) calcd for $C_8H_{10}N_2O_2Na$ $[M + Na]^+$ 189.0634, found 189.0636.

*2-Methoxy-N,5-dimethyl-N-nitrosobenzenamine (**3ba**):* yield 88% (79 mg); brown oil; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.24−7.16 (m, 2H), 6.94 (d, J = 8.0 Hz, 1H), 3.84 (s, 3H), 3.37 (s, 3H), 2.34 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 150.8, 130.9, 130.6, 130.5, 127.2, 112.0, 55.8, 35.0, 20.3; HRMS-ESI (m/z) calcd for $C_9H_{12}N_2O_2Na$ $[M + Na]^+$ 203.0796, found 203.0789.

*2-Methoxy-N,4-dimethyl-N-nitrosobenzenamine (**3ca**):* yield 86% (77 mg); brown oil; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.24 (d, J = 8.4 Hz, 1H), 6.87−6.86 (m, 2H), 3.86 (s, 3H), 3.36 (s, 3H), 2.43 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 152.8, 140.8, 128.9, 126.4, 121.4, 112.9, 55.7, 35.1, 21.7; HRMS-ESI (m/z) calcd for $C_9H_{12}N_2O_2Na$ $[M + Na]^+$ 203.0796, found 203.0798.

*5-Chloro-2-methoxy-N-methyl-N-nitrosobenzenamine (**3da**):* yield 62% (62 mg); yellow solid; mp 68−69 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.41−7.38 (m, 2H), 6.99 (d, J = 9.2 Hz, 1H), 3.88 (s, 3H), 3.36 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 151.7, 132.0, 129.8, 126.6, 125.7, 113.1, 56.1, 34.8; HRMS-ESI (m/z) calcd for $C_8H_9ClN_2O_2K$ $[M + K]^+$ 238.9990, found 238.9986.

*4-Chloro-2-methoxy-N-methyl-N-nitrosobenzenamine (**3ea**):* yield 53% (53 mg); yellow solid; mp 35−37 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.31 (dd, J_1 = 7.2 Hz, J_2 = 1.6 Hz, 1H), 7.07−7.04 (m, 2H), 3.88 (s, 3H), 3.35 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 153.5, 135.7, 130.0, 127.3, 120.9, 112.8, 56.1, 34.9; HRMS-ESI (m/z) calcd for $C_8H_9ClN_2O_2K$ $[M + K]^+$ 238.9990, found 238.9995.

*4-Bromo-2-methoxy-N-methyl-N-nitrosobenzenamine (**3fa**):* yield 63% (77 mg); yellow solid; mp 53−54 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.23 (dd, J_1 = 7.2 Hz, J_2 = 1.2 Hz, 1H), 7.21−7.18 (m, 2H), 3.88 (s, 3H), 3.33 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 153.5, 130.5, 127.6, 123.9, 123.5, 115.7, 56.1, 34.9; HRMS-ESI (m/z) calcd for $C_8H_9BrN_2O_2Na$ $[M + Na]^+$ 266.9739, found 266.9738.

*2, 5-Dimethoxy-N-methyl-N-nitrosobenzenamine (**3ga**):* yield 68% (67 mg); brown solid; mp 64−66 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.98 (s, 3H), 3.84 (s, 3H), 3.82 (s, 3H), 3.39 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 153.7, 146.9, 131.8, 115.3, 113.2, 112.4, 56.4, 55.9, 35.0; HRMS-ESI (m/z) calcd for $C_9H_{13}N_2O_3$ $[M + H]^+$ 197.0926, found 197.0918.

*2, 4-Dimethoxy-N-methyl-N-nitrosobenzenamine (**3ha**):* yield 30% (29 mg); brown oil; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.27 (d, J = 8.8 Hz, 1H), 6.60−6.55 (m, 2H), 3.87 (s, 3H), 3.85 (s, 3H), 3.35 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 161.4, 154.3, 127.4, 124.9, 104.3, 99.6, 55.8, 55.7, 35.2; HRMS-ESI (m/z) calcd for $C_9H_{12}N_2O_3Na$ $[M + Na]^+$ 219.0745, found 219.0749.

*Methyl 3-methoxy-4-(methyl(nitroso)amino)benzoate (**3ia**):* yield 62% (69 mg); yellow solid; mp 82−84 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.74 (dd, J_1 = 8.0 Hz, J_2 = 1.6 Hz, 1H), 7.71 (d, J = 1.6 Hz, 1H), 7.45 (d, J = 8.0 Hz, 1H), 3.95 (s, 3H), 3.94 (s, 3H), 3.37 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 166.2, 152.4, 134.9, 131.6, 126.1, 122.4, 113.1, 58.3, 56.0, 34.8; HRMS-ESI (m/z) calcd for $C_{10}H_{12}N_2O_4Na$ $[M + Na]^+$ 247.0695, found 247.0689.

*3-Methoxy-N-methyl-N-nitrosonaphthalen-2-amine (**3ja**):* yield 68% (73 mg); orange solid; mp 81−83 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.85−7.79 (m, 3H), 7.55−7.50 (m, 1H), 7.44−7.40 (m, 1H), 7.28 (s, 1H), 3.96 (s, 3H), 3.46 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 151.6, 134.3, 131.9, 128.1, 127.9, 127.4, 126.6, 125.6, 124.8, 107.2, 55.8, 35.2; HRMS-ESI (m/z) calcd for $C_{12}H_{12}N_2O_2Na$ $[M + Na]^+$ 239.0791, found 239.0795.

*N-Ethyl-2-methoxy-N-nitrosobenzenamine (**3ka**):* yield 74% (67 mg); brown oil. The title compound was obtained as an inseparable mixture of *syn* and *anti* isomers, and the isomers' ratio was determined by ^{1}H NMR to be approximately 3:1: ^{1}H NMR ($CDCl_3$, 400 MHz) (*syn* and *anti* isomers) δ 7.46−7.42 (m, 1H), 7.40−7.36 (m, 0.4H), 7.31−7.29 (m, 1H), 7.08−7.01 (m, 2H), 6.99−6.94 (m, 0.6H), 6.93−6.92 (m, 0.3H), 4.48 (q, J = 7.3 Hz, 0.6H), 3.97 (q, J = 7.1 Hz, 2H), 3.86 (s, 3H), 3.77 (s, 1H), 1.34 (t, J = 7.4 Hz, 1H), 1.07 (t, J = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 154.2, 153.8, 131.4, 131.2, 130.8, 130.5, 128.4, 128.1, 120.8, 120.8, 112.1, 112.1, 55.7, 55.7, 48.5, 41.5, 13.9, 11.2; HRMS-ESI (m/z) calcd for $C_9H_{12}N_2O_2K$ $[M + K]^+$ 219.0536, found 219.0534.

*N-Isopropyl-2-methoxy-N-nitrosobenzenamine (**3la**):* yield 36% (35 mg); brown oil. The title compound was obtained as an inseparable mixture of *syn* and *anti* isomers, and the isomers' ratio was determined by ^{1}H NMR to be approximately 2:1: ^{1}H NMR ($CDCl_3$, 400 MHz) (*syn* and *anti* isomers) δ 7.48−7.46 (m, 1H), 7.45−7.38 (m, 2H), 7.26−7.24 (m, 1H), 7.09−6.99 (m, 6H), 6.93−6.90 (m, 2H), 5.11−5.04 (m, 1H), 5.01−4.91 (m, 2H), 3.84 (s, 3H), 3.77 (s, 3H), 1.49 (s, 12H), 1.14 (d, J = 6.8 Hz, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 155.8, 154.7, 130.9, 130.8, 129.8, 128.8, 128.3, 125.7, 120.8, 120.6, 112.1, 112.0, 56.3, 55.6, 47.7, 19.1; HRMS-ESI (m/z) calcd for $C_{10}H_{14}N_2O_2K$ $[M + K]^+$ 233.0692, found 233.0687.

*N-(2-Methoxyphenyl)-N-nitrosobenzenamine (**3ma**):* yield 44% (50 mg); brown oil. The title compound was obtained as an inseparable mixture of *syn* and *anti* isomers, and the isomers' ratio was determined by ^{1}H NMR to be approximately 5:1: ^{1}H NMR ($CDCl_3$, 400 MHz) (*syn* and *anti* isomers) δ 7.52−7.38 (m, 6H), 7.37−7.30 (m, 1H), 7.11−6.98 (m, 4H), 3.88 (s, 0.6H), 3.76 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 154.9, 142.8, 142.4, 131.4, 129.6, 129.3, 129.2,

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128.9, 128.6, 127.0, 126.9, 126.6, 125.5, 121.9, 121.3, 119.5, 118.8, 115.0, 114.5, 112.4, 55.8, 55.5; HRMS-ESI (m/z) calcd for $C_{13}H_{12}N_2O_2Na$ $[M + Na]^+$ 251.0796, found 251.0799.

*2-Ethoxy-N-methyl-N-nitrosobenzenamine (**3ab**):* yield 64% (58 mg); brown oil; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.43−7.37 (m, 2H), 7.07−7.03 (m, 2H), 4.11 (q, J = 7.0 Hz, 2H), 3.40 (s, 3H), 1.40 (t, J = 7.0 Hz, 3H); ^{13}C NMR (CDCl3, 100 MHz) δ 152.3, 131.5, 130.2, 126.6, 120.7, 112.9, 64.3, 35.0, 14.7; HRMS-ESI (m/z) calcd for $C_9H_{12}N_2O_2Na$ $[M + Na]^+$ 203.0796, found 203.0781.

*2-Ethoxy-N,5-dimethyl-N-nitrosobenzenamine (**3bb**):* yield 89% (86 mg); brown oil; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.21−7.18 (m, 2H), 6.92 (dd, J_1 = 6.0 Hz, J_2 = 2.8 Hz, 1H), 4.06 (q, J = 7.2 Hz, 2H), 3.38 (s, 3H), 2.34 (s, 3H), 1.37 (t, J = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 150.1, 131.2, 130.5, 130.4, 127.1, 112.9, 64.4, 35.0, 20.3, 14.7; HRMS-ESI (m/z) calcd for $C_{10}H_{14}N_2O_2Na$ $[M + Na]^+$ 217.0948, found 217.0954.

*2-Ethoxy-N,4-dimethyl-N-nitrosobenzenamine (**3cb**):* yield 70% (68 mg); brown oil; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.25 (d, J = 8.4 Hz, 1H), 6.86−6.84 (m, 2H), 4.09 (q, J = 7.2 Hz, 2H), 3.38 (s, 3H), 2.41 (s, 3H), 1.39 (t, J = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 152.1, 140.6, 129.1, 126.3, 121.3, 113.7, 64.2, 35.1, 21.6, 14.7; HRMS-ESI (m/z) calcd for $C_{10}H_{14}N_2O_2Na$ $[M + Na]^+$ 217.0948, found 217.0954.

*5-Chloro-2-ethoxy-N-methyl-N-nitrosobenzenamine (**3db**):* yield 28% (30 mg); yellow solid; mp 54−55 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.41−7.36 (m, 2H), 6.97 (d, J = 8.8 Hz, 1H), 4.10 (q, J = 7.0 Hz, 2H), 3.38 (s, 3H), 1.41 (t, J = 7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 150.9, 132.2, 129.7, 126.6, 125.6, 113.9, 64.7, 34.9, 14.6; HRMS-ESI (m/z) calcd for $C_9H_{11}ClN_2O_2Na$ $[M + H]^+$ 237.0401, found 237.0403.

*4-Chloro-2-ethoxy-N-methyl-N-nitrosobenzenamine (**3eb**):* yield 34% (36 mg); yellow solid; mp 61−63 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.32 (d, J = 8.0 Hz, 1H), 7.06−7.03 (m, 2H), 4.11 (q, J = 7.0 Hz, 2H), 3.37 (s, 3H), 1.42 (t, J = 7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 152.8, 135.6, 130.1, 127.3, 120.8, 113.5, 64.7, 34.9, 14.5; HRMS-ESI (m/z) calcd for $C_9H_{11}ClN_2O_2Na$ $[M + Na]^+$ 237.0401, found 237.0403.

*4-Bromo-2-ethoxy-N-methyl-N-nitrosobenzenamine (**3fb**):* yield 39% (50 mg); orange solid; mp 63−64 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.26 (d, J = 8.4 Hz, 1H), 7.21−7.18 (m, 2H), 4.11 (q, J = 6.8 Hz, 2H), 3.37 (s, 3H), 1.42 (t, J = 6.8 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 152.8, 130.6, 127.6, 123.8, 123.4, 116.5, 64.8, 34.9, 14.5; HRMS-ESI (m/z) calcd for $C_9H_{12}BrN_2O_2$ $[M + H]^+$ 259.0077, found 259.0076.

*N-Methyl-N-nitroso-2-propoxybenzenamine (**3ac**):* yield 49% (48 mg); brown oil; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.41 (dd, J_1 = 8.0 Hz, J_2 = 1.6 Hz, 1H), 7.39 (dd, J_1 = 8.0 Hz, J_2 = 1.6 Hz, 1H), 7.06−7.02 (m, 2H), 4.00 (t, J = 6.4 Hz, 2H), 3.40 (s, 3H), 1.84−1.75 (m, 2H), 1.00 (t, J = 7.4 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 152.5, 131.4, 130.2, 126.6, 120.7, 112.9, 70.1, 35.1, 22.5, 10.6; HRMS-ESI (m/z) calcd for $C_{10}H_{14}N_2O_2Na$ $[M + Na]^+$ 217.0947, found 217.0943.

*N,5-Dimethyl-N-nitroso-2-propoxybenzenamine (**3bc**):* yield 86% (90 mg); brown oil; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.22−7.19 (m, 2H), 6.93 (d, J = 8.8 Hz, 1H), 3.96 (t, J = 6.4 Hz, 2H), 3.39 (s, 3H), 2.34 (s, 3H), 1.80−1.75 (m, 2H), 1.00 (t, J = 7.4 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 150.3, 131.1, 130.5, 130.3, 127.1, 112.9, 70.3, 35.1, 22.5, 21.3, 10.6; HRMS-ESI (m/z) calcd for $C_{11}H_{17}N_2O_2$ $[M + H]^+$ 209.1285, found 209.1289.

*N,4-Dimethyl-N-nitroso-2-propoxybenzenamine (**3cc**):* yield 80% (83 mg); brown oil; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.25 (d, J = 8.0 Hz, 1H), 6.85−6.84 (m, 2H), 3.98 (t, J = 6.4 Hz, 2H), 3.38 (s, 3H), 2.41 (s, 3H), 1.811.76 (m, 2H), 1.00 (t, J = 7.4 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 153.3, 140.6, 128.9, 126.3, 121.2, 113.6, 70.1, 35.2, 22.5, 21.6, 10.6; HRMS-ESI (m/z) calcd for $C_{11}H_{17}N_2O_2$ $[M + H]^+$ 209.1285, found 209.1278.

*4-Chloro-N-methyl-N-nitroso-2-propoxybenzenamine (**3ec**):* yield 31% (35 mg); brown oil; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.32 (dd, J_1 = 7.2 Hz, J_2 = 1.2 Hz, 1H), 7.06−7.03 (m, 2H), 4.00 (t, J = 6.4 Hz, 2H), 3.37 (s, 3H), 1.86−1.77 (m, 2H), 1.01 (t, J = 7.4 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 152.9, 135.6, 130.1, 127.3, 120.8, 113,5, 70.6, 35.0, 22.3, 10.5; HRMS-ESI (m/z) calcd for $C_{10}H_{14}ClN_2O_2$ $[M + H]^+$ 229.0738, found 229.0742.

*4-Bromo-N-methyl-N-nitroso-2-propoxybenzenamine (**3fc**):* yield 30% (41 mg); brown oil; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.26 (d, J = 7.6 Hz, 1H), 7.21−7.18 (m, 2H), 4.00 (t, J = 6.4 Hz, 2H), 3.37 (s, 3H), 1.84−1.78 (m, 2H), 1.02 (t, J = 7.4 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 153.0, 130.5, 127.6, 123.8, 123.4, 116.4, 70.6, 34.9, 22.3, 10.5; HRMS-ESI (m/z) calcd for $C_{10}H_{14}BrN_2O_2$ $[M + H]^+$ 273.0233, found 273.0232.

*2-Isopropoxy-N-methyl-N-nitrosobenzenamine (**3ad**):* yield 23% (22 mg); brown oil; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.43−7.38 (m, 2H), 7.06−7.02 (m, 2H), 4.68−4.59 (m, 1H), 3.40 (s, 3H), 1.34 (d, J = 6.0 Hz, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 151.3, 132.4, 130.1, 126.9, 120.7, 114.5, 71.1, 35.2, 21.9; HRMS-ESI (m/z) calcd for $C_{10}H_{14}N_2O_2Na$ $[M + Na]^+$ 217.0948, found 217.0956.

*2-Isopropoxy-N,5-dimethyl-N-nitrosobenzenamine (**3bd**):* yield 37% (38 mg); red oil; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.21−7.19 (m, 2H), 6.94 (d, J = 9.2 Hz, 1H), 4.61−4.51 (m, 1H), 3.39 (s, 3H), 2.35 (s, 3H), 1.31 (d, J = 6.0 Hz, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 149.0, 132.2, 130.5, 130.4, 127.3, 114.8, 71.3, 35.2, 22.0, 20.3; HRMS-ESI (m/z) calcd for $C_{11}H_{17}N_2O_2$ $[M + H]^+$ 209.1285, found 209.1289.

*2-Isopropoxy-N,4-dimethyl-N-nitrosobenzenamine (**3cd**):* yield 44% (46 mg); brown oil; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.25 (d, J = 7.6 Hz, 1H), 6.86−6.83 (m, 2H), 4.66−4.57 (m, 2H), 3.37 (s, 3H), 2.41 (s, 3H), 1.33 (d, J = 6.0 Hz, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 151.1, 140.5, 129.9, 126.5, 121.3, 115.2, 71.0, 35.2, 22.0, 21.7; HRMS-ESI (m/z) calcd for $C_{11}H_{17}N_2O_2$ $[M + H]^+$ 209.1285, found 209.1279.

*4-Chloro-2-isopropoxy-N-methyl-N-nitrosobenzenamine (**3ed**):* yield 20% (23 mg); brown oil; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.32 (d, J = 9.2 Hz, 1H), 7.05−7.02 (m, 2H), 4.66−4.57 (m, 1H), 3.36 (s, 3H), 1.36 (d, J = 6.0 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 151.8, 135.5, 130.9, 127.5, 120.7, 114.8, 71.7, 35.0, 21.8; HRMS-ESI (m/z) calcd for $C_{10}H_{14}ClN_2O_2$ $[M + H]^+$ 229.0738, found 229.0740.

*2-Methoxy-N-methylbenzenamine (**4aa**):* yield 86% (29 mg); brown oil; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.00−6.96 (m, 1H), 6.84 (dd, J_1 = 8.0 Hz, J_2 = 1.6 Hz, 1H), 6.77−6.73 (m, 1H), 6.68 (dd, J_1 = 8.0 Hz, J_2 = 1.6 Hz, 1H), 4.14 (br, 1H), 3.91 (s, 3H), 2.93 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 146.9, 139.4, 121.4, 116.4, 109.4, 109.3, 55.4, 30.4.

*2-Methoxy-N,5-dimethylbenzenamine (**4ba**):* yield 92% (35 mg); yellow oil; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.72 (d, J = 8.0 Hz, 1H), 6.54 (d, J = 8.0 Hz, 1H), 6.50 (s, 1H), 4.18 (br, 1H), 3.88 (s, 3H), 2.92 (s, 3H), 2.36 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 145.0, 139.2, 130.8, 116.4, 110.5, 109.3, 55.6, 30.4, 21.2.

*4-Chloro-2-methoxy-N-methylbenzenamine (**4ea**):* yield 83% (36 mg); yellow oil; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.88 (dd, J_1 = 8.4 Hz, J_2 = 2.4 Hz, 1H), 6.75 (d, J = 2.0 Hz, 1H), 6.49 (d, J = 8.4 Hz, 1H), 4.17 (br, 1H), 3.85 (s, 3H), 2.86 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 147.3, 138.0, 120.9, 120.8, 109.9, 109.6, 55.6, 30.4.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

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

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Notes

The authors declare no competing financial interest.

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