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Palladium-Catalyzed Alkoxylation of *N*-Methoxybenzamides via Direct sp^2 C−H Bond Activation

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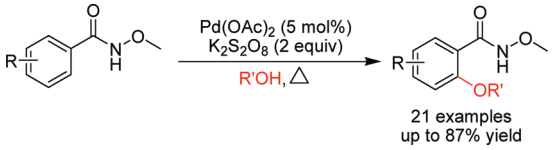

The palladium-catalyzed ortho-alkoxylation of *N*-methoxybenzamides has been demonstrated. With the CONHOMe group as a directing group, the aromatic C−H bond can be functionalized efficiently to generate ortho-alkoxylated derivatives in moderate to good yields.

The direct functionalization of arene and alkane C−H bonds is an exceedingly valuable process in contemporary organic and organometallic chemistry and still remains a tremendous challenge.[1,2] The recent development of the palladium-catalyzed C−H activation reaction has widely demonstrated its versatility and practicality in organic synthesis.[3]

Recently, the employment of substrates containing a directing group holds a promise for the selective functionalization of C−H bonds.[4−12] Significant endeavors have been focused on exploiting directing groups such as acylaminos,[4,5] pyridines,[5,6] quinolines/isoquinolines,[5,6] oxime ethers,[5c,7] oxazolines,[8] carboxylic acids,[9] *N*-methoxy amides,[10] triflamides,[11] and pyrimidinyloxy groups.[12] The *N*-methoxy amides can be readily transformed to esters[13a] and amides,[13b] or reduced to alkanes.[13b] Therefore, the C−H activation with this functionality would be synthetically useful. In Yu's recent work, the C−H bond in *N*-methoxy amides has been activated to construct the C−C bond[10a] and the C−N bond[10b] with high selectivity. Herein, we describe a highly selective alkoxylation of *N*-methoxybenzamides, i.e., C−O bond formation, through Pd-catalyzed sp^2 C−H bond oxidative activation.

We have recently reported the palladium-catalyzed direct ortho-acetoxylation of anilides.[14] Therefore, we first attempted the methoxylation of acetanilide by replacing acetic acid with methanol. The reaction was performed with acetanilide **1**, 5 mol % of $Pd(OAc)_2$, and 2 equiv of $K_2S_2O_8$ in MeOH for 48 h, and gave the methoxylated product **2** in 13% yield (entry 1, Table 1). When 1,2-dichloroethane (DCE) or dioxane was added as a cosolvent, the yields were improved to 31% and 26%, respectively (entries 2 and 3, Table 1). While $K_2S_2O_8$ was replaced with Oxone in MeOH/DCE, nearly the same product yield was obtained (entry 4 vs. entry 2, Table 1). Other oxidants such as $PhI(OAc)_2$, *m*-chloroperbenzoic acid (MCPBA), ^{t}BuOOH, $Cu(OAc)_2$, $Cu(OTf)_2$, and O_2 gave only a trace amount of product **2** (entries 5−10, Table 1).

Previously, it has already been observed that a subtle change of the directing groups exerts significant effect on

(1) (a) Shilov, A. E.; Shul'pin, G. B. *Chem. Rev.* **1997**, *97*, 2879. (b) Stahl, S. S.; Labinger, J. A.; Bercaw, J. E. *Angew. Chem., Int. Ed.* **1998**, *37*, 2180. (c) Sen, A. *Acc. Chem. Res.* **1998**, *31*, 550. (d) Fekl, U.; Goldberg, K. I. *Adv. Inorg. Chem.* **2003**, *54*, 259.

(2) Selected recent examples: (a) Yoneyama, T.; Crabtree, R. H. *J. Mol. Catal. A* **1996**, *108*, 35. (b) Periana, R. A.; Taube, D. J.; Gamble, S.; Taube, H.; Satoh, T.; Fujii, H. *Science* **1998**, *280*, 560. (c) Mukhopadhyay, S.; Bell, A. T. *Angew. Chem., Int. Ed.* **2003**, *42*, 2990.

(3) For reviews, see: (a) Dyker, G. *Angew. Chem., Int. Ed.* **1999**, *38*, 1698. (b) Jia, C.; Kitamura, T.; Fujiwara, Y. *Acc. Chem. Res.* **2001**, *34*, 633. (c) Ritleng, V.; Sirlin, C.; Pfeffer, M. *Chem. Rev.* **2002**, *102*, 1731. (d) Dick, A. R.; Sanford, M. S. *Tetrahedron* **2006**, *62*, 2439. (e) Catellani, M.; Motti, E.; Della Ca', N. *Acc. Chem. Res.* **2008**, *41*, 1512. (f) Daugulis, O.; Do, H.-Q.; Shabashov, D. *Acc. Chem. Res.* **2009**, *42*, 1074. (g) Chen, X.; Engle, K. M.; Wang, D.-H.; Yu, J.-Q. *Angew. Chem., Int. Ed.* **2009**, *48*, 5094.

(4) (a) Tremont, S. J.; Rahman, H. U. *J. Am. Chem. Soc.* **1984**, *106*, 5759. (b) Wang, Z.; Zhang, Z.; Lu, X. *Organometallics* **2000**, *19*, 775. (c) Boele, M. D. K.; van Strijdonck, G. P. F.; de Vries, A. H. M.; Kamer, P. C. J.; de Vries, J. G.; Leeuwen, P. W. N. M. *J. Am. Chem. Soc.* **2002**, *124*, 1586. (d) Lee, G. T.; Jiang, X.; Prasad, K.; Repič, O.; Blacklock, T. J. *Adv. Synth. Catal.* **2005**, *347*, 1921. (e) Zaitsev, V. G.; Daugulis, O. *J. Am. Chem. Soc.* **2005**, *127*, 4156. (f) Tsang, W. C. P.; Zheng, N.; Buchwald, S. L. *J. Am. Chem. Soc.* **2005**, *127*, 14560. (g) Yang, S.; Li, B.; Wan, X.; Shi, Z. *J. Am. Chem. Soc.* **2007**, *129*, 6066. (h) Shi, Z.; Li, B.; Wan, X.; Cheng, J.; Fang, Z.; Cao, B.; Qin, C.; Wang, Y. *Angew. Chem., Int. Ed.* **2007**, *46*, 5554. (i) Shabashov, D.; Daugulis, O. *J. Org. Chem.* **2007**, *72*, 7720. (j) Li, B.; Tian, S.; Fang, Z.; Shi, Z. *Angew. Chem., Int. Ed.* **2008**, *47*, 1115.

(5) (a) Kalyani, D.; Deprez, N. R.; Desai, L. V.; Sanford, M. S. *J. Am. Chem. Soc.* **2005**, *127*, 7330. (b) Kalyani, D.; Sanford, M. S. *Org. Lett.* **2005**, *7*, 4149. (c) Kalyani, D.; Dick, A. R.; Anani, W. Q.; Sanford, M. S. *Org. Lett.* **2006**, *8*, 2523. (d) Zhang, Y.; Feng, J.; Li, C.-J. *J. Am. Chem. Soc.* **2008**, *130*, 2900.

(6) (a) Dick, A. R.; Hull, K. L.; Sanford, M. S. *J. Am. Chem. Soc.* **2004**, *126*, 2300. (b) Hull, K. L.; Anani, W. Q.; Sanford, M. S. *J. Am. Chem. Soc.* **2006**, *128*, 7134. (c) Chen, X.; Goodhue, C. E.; Yu, J.-Q. *J. Am. Chem. Soc.* **2006**, *128*, 12634.

(7) (a) Desai, L. V.; Hull, K. L.; Sanford, M. S. *J. Am. Chem. Soc.* **2004**, *126*, 9542. (b) Desai, L. V.; Malik, H. A.; Sanford, M. S. *Org. Lett.* **2006**, *8*, 1141.

(8) (a) Giri, R.; Liang, J.; Lei, J.-G.; Li, J.-J.; Wang, D.-H.; Chen, X.; Naggar, I. C.; Guo, C.-Y.; Foxman, B. M.; Yu, J.-Q. *Angew. Chem., Int. Ed.* **2005**, *44*, 7420. (b) Chen, X.; Li, J.-J.; Hao, X.-S.; Goodhue, C. E.; Yu, J.-Q. *J. Am. Chem. Soc.* **2006**, *128*, 78.

(9) (a) Giri, R.; Maugel, N.; Li, J.-J.; Wang, D.-Q.; Breazzano, S. P.; Saunders, L. B.; Yu, J.-Q. *J. Am. Chem. Soc.* **2007**, *129*, 3510. (b) Giri, R.; Yu, J.-Q. *J. Am. Chem. Soc.* **2008**, *130*, 14082. (c) Wang, D.-H.; Mei, T.-S.; Yu, J.-Q. *J. Am. Chem. Soc.* **2008**, *130*, 17676. (d) Zhang, Y.-H.; Yu, J.-Q. *J. Am. Chem. Soc.* **2009**, *131*, 14654.

(10) (a) Wang, D.-H.; Wasa, M.; Giri, R.; Yu, J.-Q. *J. Am. Chem. Soc.* **2008**, *130*, 7190. (b) Wasa, M.; Yu, J.-Q. *J. Am. Chem. Soc.* **2008**, *130*, 14058.

(11) (a) Li, J.-J.; Mei, T.-S.; Yu, J.-Q. *Angew. Chem., Int. Ed.* **2008**, *47*, 6452. (b) Mei, T.-S.; Wang, X.; Yu, J.-Q. *J. Am. Chem. Soc.* **2009**, *131*, 10806.

(12) Gu, S.; Chen, C.; Chen, W. *J. Org. Chem.* **2009**, *74*, 7203.

(13) (a) De Almeida, M. V.; Barton, D. H. R.; Bytheway, I.; Ferreira, J. A.; Hall, M. B.; Liu, W.; Taylor, D. K.; Thomson, L. *J. Am. Chem. Soc.* **1995**, *117*, 4870. (b) Yus, M.; Radivoy, G.; Alonso, F. *Synthesis* **2001**, 914.

(14) Wang, G.-W.; Yuan, T.-T.; Wu, X.-L. *J. Org. Chem.* **2008**, *73*, 4717.

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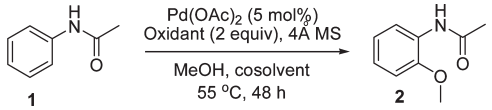
TABLE 1. Screening Conditions for the $Pd(OAc)_2$-Catalyzed Direct Ortho-Methoxylation of Acetanilide[a]

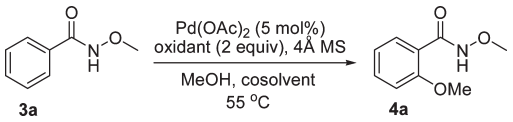


entry	oxidant	cosolvent	yield
1	$K_2S_2O_8$		13%
2	$K_2S_2O_8$	DCE	31%
3	$K_2S_2O_8$	dioxane	26%
4	oxone	DCE	30%
5	$PhI(OAc)_2$	DCE	trace
6	MCPBA	DCE	trace
7	^{t}BuOOH	DCE	trace
8	$Cu(OAc)_2$	DCE	trace
9	$Cu(OTf)_2$	DCE	trace
10	O_2	DCE	trace

[a]Unless otherwise specified, all the reactions were carried out with 0.25 mmol of **1**, 0.0125 mmol of $Pd(OAc)_2$, 0.5 mmol of oxidant, 30 mg of 4 Å MS in 2 mL of MeOH, and 2 mL of cosolvent at 55 °C.

the C−H bond activations.[4c,e,g,14] We then turned our attention to other directing groups due to the poor yield for the methoxylation of acetanilide, of which the $NHCOCH_3$ moiety was the directing group. A number of substrates including 4-methylbenzamide, *N*-benzylidene-4-methylbenzenesulfonamide, *N*′-phenylbenzohydrazide, *N*-methoxy-2-phenylacetamide, and *N*-ethylbenzamide failed to give the corresponding methoxylated products in MeOH. Much to our pleasure, *N*-methoxybenzamide (**3a**) was found to generate the ortho-methoxylated product **4a** in 42% yield in MeOH (entry 1, Table 2). When DCE was used as cosolvent, the yield was increased to 66% (entry 2, Table 2). Other cosolvents such as THF, toluene, and acetonitrile were also screened, and all of them proved to be deleterious to the reaction (entries 3−5 vs. entry 2, Table 2). However, when the reaction was performed in MeOH/dioxane, the product yield of **4a** could be further improved to 73% (entry 6, Table 2). The efficiency of various oxidants was also examined. $PhI(OAc)_2$, which was used as a privileged oxidant in Sanford's systems,[5b,6a,7a] afforded only a trace amount of product (entry 7, Table 2). Several peroxides have been employed as the oxidants for Pd-catalyzed C−H oxidation,[5d,7b,8a,14] and the first used peroxide was $MeCOOO^tBu$.[8a] Organic peroxidants including ^{t}BuOOH and MCPBA were investigated, but both of them failed to facilitate this reaction (entries 8 and 9, Table 2). When Oxone was employed as the oxidant, the methoxylation product could be isolated in moderate yield (entry 10, Table 2). Cu(II) salts were also ineffective in the methoxylation process (entries 11 and 12, Table 2). Finally, the reaction conducted in oxygen atmosphere proved to be infeasible (entry 13, Table 2). The amount of $K_2S_2O_8$ and $Pd(OAc)_2$ was further varied to examine their effect on the product yield. Reducing or increasing the loading of oxidant $K_2S_2O_8$ resulted in lower product yield (entries 14 and 15 vs. entry 6, Table 2). Reducing the catalyst loading (2.5 mol %) gave a decreased yield (entry 16, Table 2). Surprisingly, a larger amount of $Pd(OAc)_2$ (10 mol %) was also harmful to the reaction, affording product **4a** in only 35% yield (entry 17, Table 2). This methoxylation process was very sensitive to water; the yield was decreased dramatically to 40% from 73% when the reaction was carried out without molecular sieve (entry 18 vs. entry 6, Table 2). As a result, we found that treating **3a** with 5 mol % of $Pd(OAc)_2$ and 2 equiv of $K_2S_2O_8$ in the presence of 4 Å MS in MeOH/dioxane (1:1) at 55 °C afforded the best result.

TABLE 2. Screening Conditions for the $Pd(OAc)_2$-Catalyzed Direct Ortho-Methoxylation of *N*-Methoxybenzamide 3a[a]

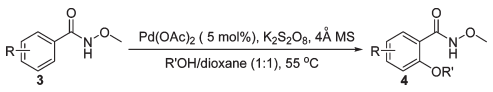


entry	oxidant	cosolvent	time	yield
1	$K_2S_2O_8$		8 h	42%
2	$K_2S_2O_8$	DCE	10 h	66%
3	$K_2S_2O_8$	THF	12 h	31%
4	$K_2S_2O_8$	PhMe	9 h	50%
5	$K_2S_2O_8$	CH_3CN	24 h	trace
6	$K_2S_2O_8$	dioxane	6.5 h	73%
7	$PhI(OAc)_2$	dioxane	24 h	trace
8	MCPBA	dioxane	24 h	trace
9	^{t}BuOOH	dioxane	24 h	trace
10	Oxone	dioxane	11 h	57%
11	$Cu(OAc)_2$	dioxane	24 h	trace
12	$Cu(OTf)_2$	dioxane	24 h	trace
13	O_2	dioxane	24 h	trace
14[b]	$K_2S_2O_8$	dioxane	12 h	55%
15[c]	$K_2S_2O_8$	dioxane	6.5 h	67%
16[d]	$K_2S_2O_8$	dioxane	11 h	53%
17[e]	$K_2S_2O_8$	dioxane	5 h	35%
18[f]	$K_2S_2O_8$	dioxane	9 h	40%

[a]Unless otherwise specified, all the reactions were carried out with 0.25 mmol of **3a**, 0.0125 mmol of $Pd(OAc)_2$, 0.5 mmol of oxidant, 30 mg of 4 Å MS in 2 mL of MeOH, and 2 mL of cosolvent at 55 °C. [b]0.25 mmol of $K_2S_2O_8$ was employed. [c]0.75 mmol of $K_2S_2O_8$ was employed. [d]0.00625 mmol of $Pd(OAc)_2$ was used. [e]0.025 mmol of $Pd(OAc)_2$ was used. [f]4 Å MS was not added.

With the optimized conditions in hand, the scope of the Pd-catalyzed methoxylation reaction was investigated with a diverse array of substituted *N*-methoxybenzamides. The results are summarized in Table 3. Substrates with either electron-donating or electron-withdrawing groups on the phenyl group of *N*-methoxybenzamides could be applied to afford the desired products **4b**−**n** (entries 2−14, Table 3). Substrates with a methyl group at the meta-position and/or para-position of the phenyl ring (**3b**−**d**) gave comparable product yields to that of unsubstituted *N*-methoxybenzamide (**3a**) (entries 2−4 vs. entry 1, Table 3). When both of the meta-positions of the phenyl ring were occupied by a methyl group, the product yield was lower than that of **3d** (entry 5 vs entry 4, Table 3) due to the steric hindrance. It is known that ortho-substitution on phenyl rings hampers[4c,d,14] the Pd-catalyzed ortho C−H insertions. Hence, it was not surprising that the *o*-methyl substitution on the phenyl ring of **3f** reduced product yield significantly (entry 6 vs. entries 2−3, Table 3). The product yield of **4f** could not be improved even if the reaction time was prolonged to 48 h, and a lot of **3f** was recovered. Substrates with the strong electron-donating methoxy group at the meta-position (**3g**) or at both meta- and para-positions (**3h**) of the phenyl ring gave lower yields than their counterparts substituted by the methyl group (entry 7 vs. entry 3 and entry 8 vs. entry 4, Table 3) because they tended to react faster and generate more byproducts.

TABLE 3. Pd-Catalyzed Direct Ortho-Alkoxylation of *N*-Methoxybenzamides[a]



entry	substrate	product	time (h)	yield (%)
1	3a	4a	6.5	73
2	3b	4b	6.5	70
3	3c	4c	8	62
4	3d	4d	6	72
5	3e	4e	11	56
6	3f	4f	6.5	48
7	3g	4g	6	46
8	3h	4h	12	45
9	3i	4i	9	65
10	3j	4j	6	53
11	3k	4k	36	61
12	3l	4l	9	43
13	3m	4m	12	46
14	3n	4n	24	32
15[b]	3a	4o	7	64
16[b]	3b	4p	7	79
17[b]	3c	4q	12	63
18[b]	3d	4r	7	87
19[b]	3i	4s	48	61
20[b]	3l	4t	48	47
21[c]	3a	4u	72	20

[a]Unless otherwise specified, all the reactions were carried out with 0.25 mmol of **3**, 0.0125 mmol of $Pd(OAc)_2$, 0.5 mmol of $K_2S_2O_8$, 30 mg of 4 Å MS, 2 mL of MeOH, and 2 mL of dioxane at 55 °C. [b]EtOH was used. [c]^{i}PrOH was used.

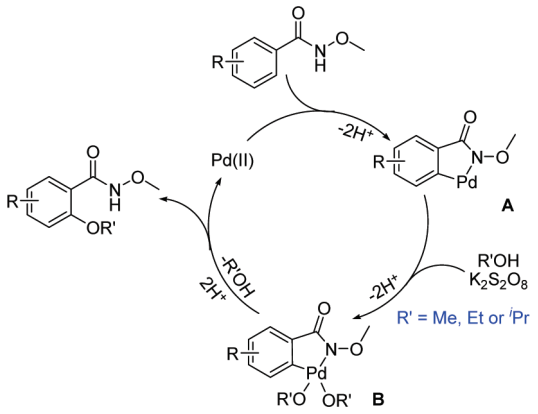
The same phenomenon has also been observed in the ortho-acetoxylation of anilides.[14] Benzamide **3i**, which had a weak electron-withdrawing chloro group at the para-position of the phenyl ring, afforded a comparable yield to that of the corresponding *p*-methyl-substituted **3c** (entry 9 vs. entry 3, Table 3). Introduction of an additional chloro atom at the meta-position caused a slightly lower yield (entry 10 vs. entry 9, Table 3). Interestingly, *o*-Cl-substituted benzamide **3k** provided nearly the same product yield as the *p*-Cl-substituted **3i** (entry 11 vs. entry 9, Table 3), not displaying the obvious "ortho-substituent" effect.[4c,d,14] The exact reason for this behavior is unknown now. Benzamide **3*l*** bearing a *p*-Br on the phenyl ring delivered a lower yield than that of the counterpart with a *p*-Cl (entry 12 vs. entry 9, Table 3). A similar behavior was also observed previously by us.[14] Benzamide **3m** with a moderate electron-withdrawing COOMe group at the para-position was successfully ortho-methoxylated in a yield of 46% (entry 13, Table 3). Gratifyingly, benzamide **3n** with the strong electron-withdrawing *p*-NO_2 group could also be functionalized to give the desired product, albeit in a low yield even with a prolonged reaction time (entry 14, Table 3). This result is still significant because the attempted acetoxylation of anilides with strong electron-withdrawing groups such as NO_2 failed. The above substituent effects clearly disclose the electrophilic nature for the C−H activation process. To our satisfaction, other alkoxylation of *N*-methoxybenzamides could be realized by simply changing the alcohol. Ethoxylated *N*-methoxybenzamides were obtained in similar product yields to those of the corresponding methoxylated *N*-methoxybenzamides when methanol was replaced with ethanol in the reaction mixtures (entries 15−20, Table 3). To our delight, *N*-methoxybenzamide could even be ortho-alkoxylated by isopropanol, a secondary alcohol, albeit in 20% yield (entry 21, Table 3). However, tertiary alcohol such as ^{t}BuOH failed to react with *N*-methoxybenzamide under otherwise identical conditions. It should be noted that the alkoxylation of *N*-methoxybenzamides bearing meta-substituents gave only one regioisomer (entries 2, 4, 8, 10, 16, and 18, Table 3) due to the steric factor.

We believe that the alkoxylation of *N*-methoxybenzamides most likely proceeds through a similar pathway to that for the acetoxylation of anilides.[14] A possible mechanism for the alkoxylation is outlined in Scheme 1. The fist step involves chelate-directed C−H activation of the substrate to afford the cyclopalladated intermediate **A**, followed by oxidation of the Pd(II) intermediate **A** to the Pd(IV) intermediate **B** by $K_2S_2O_8$ in the presence of an alcohol. In the final step, carbon−heteroatom bond formation via reductive elimination affords the alkoxylated product and regenerates the Pd(II) species. It should be noted that a mechanism involving the common Pd(0)/Pd(II) catalytic cycle or a recently formulated bimetallic Pd(II)/Pd(III) pathway[15] could not be completely excluded.

In conclusion, we have found that the *N*-methoxy amide group (CONHOMe) could be employed as an efficient ortho-directing group in the Pd-catalyzed sp^2 C−H bond oxidative activation process. Directing groups of the substrates were found to play a crucial role in the C−H functionalizations. While substrates with the $NHCOCH_3$ group gave methoxylated products in low yields, those with

(15) (a) Powers, D. C.; Ritter, T. *Nat. Chem.* **2009**, *1*, 302. (b) Powers, D. C.; Geibel, M. A. L.; Klein, J. E. M. N.; Ritter, T. *J. Am. Chem. Soc.* **2009**, *131*, 17050.

SCHEME 1. Possible Reaction Mechanism



the CONHOMe group afforded the desired methoxylated products in much higher yields. Various *N*-methoxybenzamides with either electron-donating or electron-withdrawing groups could be alkoxylated directly and efficiently. The current Pd-catalyzed alkoxylation of *N*-methoxybenzamides could tolerate functional groups such as chloro, bromo, ether, ester, and nitro. The final products could be further manipulated into various derivatives, broadening the potential synthetic application of the current methodology.

Experimental Section

Typical Procedure for the Direct Ortho-Alkoxylation of *N*-Methoxybenzamides 3 Catalyzed by $Pd(OAc)_2$. To a stirred solution of *N*-methoxybenzamide **3a** (**3b**−**n**, 0.25 mmol), $Pd(OAc)_2$ (3.3 mg, 0.0125 mmol), $K_2S_2O_8$ (135 mg, 0.5 mmol), and 4 Å MS (30 mg) in fresh distilled dioxane (2 mL) at 55 °C was added MeOH, EtOH, or ^{i}PrOH (2 mL). The reaction was monitored by TLC. Upon completion, the solvent was evaporated to dryness in vacuo. The residual was separated on a silica gel column with petroleum ether/ethyl acetate 3:2 as the eluent to obtain the desired product **4a** (**4b**−**u**).

Compounds **2**[16] and **4a**[17] have been previously reported, and their identities were confirmed by comparison of their spectral data with reported ones.

***N*,2-Dimethoxy-5-methylbenzamide (4b):** white solid, mp 77−79 °C; IR (KBr) ν 3255, 2980, 2937, 1640, 1611, 1502, 1469, 1307, 1258, 1181, 1116, 1054, 1022, 946, 817, 735, 670, 539 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.23 (1H, br s), 8.00 (1H, d, J = 1.8 Hz), 7.25 (1H, dd, J = 8.4, 1.8 Hz), 6.86 (1H, d, J = 8.4 Hz), 3.94 (3H, s), 3.89 (3H, s), 2.33 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.3, 155.0, 133.8, 132.3, 131.0, 119.1, 111.3, 64.4, 56.1, 20.3; HRMS (EITOF) m/z [M^+] calcd for $C_{10}H_{13}NO_3$ 195.0895, found 195.0902.

2-Ethoxy-*N*-methoxybenzamide (4o): white solid, mp 68−69 °C; IR (KBr) ν 3246, 2974, 2932, 1649, 1602, 1492, 1474, 1302, 1246, 1165, 1120, 1035, 945, 883, 756, 604 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.30 (1H, br s), 8.20 (1H, dd, J = 7.8, 1.8 Hz), 7.44 (1H, ddd, J = 8.4, 7.8, 1.8 Hz), 7.09 (1H, t, J = 7.8 Hz), 6.95 (1H, d, J = 8.4 Hz), 4.22 (2H, q, J = 6.9 Hz), 3.89 (3H, s), 1.54 (3H, t, J = 6.9 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.3, 156.4, 133.3, 132.1, 121.5, 119.8, 112.3, 65.0, 64.5, 14.8; HRMS (EI-TOF) m/z [M^+] calcd for $C_{10}H_{13}NO_3$ 195.0895, found 195.0903.

2-Isopropoxy-*N*-methoxybenzamide (4u): yellow oil; IR (KBr) ν 3357, 2978, 2935, 1672, 1600, 1473, 1291, 1231, 1112, 1038, 949, 886, 756, 665 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.36 (1H, br s), 8.18 (1H, dd, J = 7.8, 1.8 Hz), 7.43 (1H, ddd, J = 8.4, 7.5, 1.8 Hz), 7.07 (1H, dd, J = 7.8, 7.5 Hz), 6.96 (1H, d, J = 8.4 Hz), 4.75 (1H, heptet, J = 6.0 Hz), 3.88 (3H, s), 1.44 (6H, d, J = 6.0 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.5, 155.5, 133.2, 132.4, 121.6, 120.8, 114.0, 72.5, 64.6, 22.3 (2C); HRMS (EI-TOF) m/z [M^+] calcd for $C_{10}H_{15}NO_3$ 209.1052, found 209.1058.

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Supporting Information Available: Spectral data of **2**, **4a**, **4c**−**n**, and **4p**−**t**, and NMR spectra of **2** and **4a**−**u**. This material is available free of charge via the Internet at http://pubs.acs.org.

(16) Kraska, J.; Teodorczyk, Z. *Pol. J. Chem.* **1984**, *58*, 1025.
(17) Miyata, O.; Koizumi, T.; Asai, H.; Iba, R.; Naito, T. *Tetrahedron* **2004**, *60*, 3893.