JOC The Journal of Organic Chemistry

NOTE

pubs.acs.org/joc

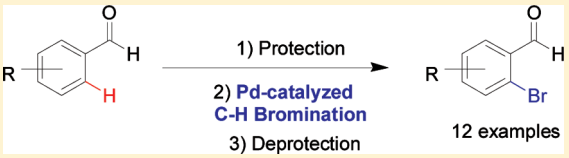
Selective *ortho*-Bromination of Substituted Benzaldoximes Using Pd-Catalyzed C−H Activation: Application to the Synthesis of Substituted 2-Bromobenzaldehydes

Emmanuelle Dubost, Christine Fossey, Thomas Cailly, Sylvain Rault, and Frederic Fabis*

Centre d'Etudes et de Recherche sur le Médicament de Normandie, UPRES EA 4258, INC3M FR-CNRS 3038, UFR des Sciences Pharmaceutiques, Université de Caen Basse-Normandie, boulevard Becquerel, 14032 Caen cedex France

Supporting Information

ABSTRACT: Substituted 2-bromobenzaldehydes were synthesized from benzaldehydes using a three-step sequence involving a selective palladium-catalyzed *ortho*-bromination as the key step. *O*-Methyloxime serves as a directing group in this reaction. A rapid deprotection of substituted 2-bromobenzaldoximes afforded substituted 2-bromobenzaldehydes with good overall yields.



2-Bromobenzaldehydes are useful synthetic intermediates as they offer the possibility of reaction either at the carboxaldehyde, which can be considered as one of the most easily transformable functional group, or at the bromine site by diverse transition-metal-catalyzed cross-coupling reactions. Moreover, combinations of these two reactive sites in cascade reactions have been successfully used for the synthesis of diverse heterocycles[1−4] and natural compounds[5] and have found applications in medicinal chemistry.[6] Nevertheless, the broad synthetic utility of 2-bromobenzaldehydes remains hampered by the difficulty to selectively synthesize these compounds, leading to low commercial availability and prohibitive costs. The synthesis of 2-bromobenzaldehydes can be classified in three main groups including (1) electrophilic aromatic bromination of aldehydes or precursors,[7] (2) metal−halogen exchange from *ortho*-dibrominated arenes followed by formylation,[8] and (3) directed *ortho*-metalation using bromine or DMF as the electrophile.[9,10] In these three methods, the selective formation of 2-bromobenzaldehydes remains very substituent-dependent and a strong directing group is most often required, limiting their general applicability.

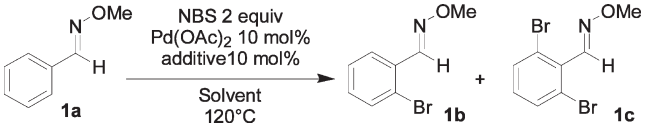
Recently, the transition-metal-catalyzed transformation of inactivated C−H bonds has emerged as a new powerful synthetic tool to create C−C and C−heteroatom bonds.[11−14] This method has found broad applications in the functionalization of aromatic C−H bonds, allowing the successful selective introduction of numerous substituents including halogens,[15−24] aryl groups,[11] ethers,[15] esters,[25] sulfones,[26] or amines.[27,28] In most of these transformations, a directing group is required to achieve a high selectivity. In the case of a bromination reaction by C−H activation, Sandford first described the use of *N*-bromosuccinimide and pyridines or pyrimidines as the directing group. The group developed a powerful palladium-catalyzed halogenation method that led to a large number of 2-halogenated compounds.[15,17,18] Yu's group described the use of more flexible functional groups such as carboxylic acids and acetanilides to direct the *ortho*-halogenation of arenes.[19,22,24] Very recently, the use of *O*-acetyl oximes as a transformable directing group in C−H functionalization of C sp^2 and sp^3 has been reported. This directing group has been shown to be stable in C−H activation conditions and has been used as a precursor of acetophenones, oxazolines, aminophenols, and diols.[29]

Considering that aldehydes are poor directing groups in Pd-catalyzed C−H functionalization,[18,30,31] some authors used successfully *O*-methylbenzaldoximes as directing groups.[25,27,32,33] We thought *O*-methylbenzaldoximes could serve as an *ortho*-directing group for palladium-catalyzed bromination reactions and should be able to lead selectively to 2-bromobenzaldehydes after deprotection of the oxime group. Moreover, *O*-methylbenzaldoximes are easily obtained from the corresponding benzaldehydes using standard procedures.[32]

Our initial investigations focused on the $Pd(OAc)_2$-catalyzed bromination of *O*-methylbenzaldoxime **1a** under various conditions (solvent, additives, and reaction times). In all of our experiments, only starting material and mono- and dibrominated compounds were observed, allowing the easy monitoring of the reactions by ^1H NMR (Table 1). Using Sanford's conditions, NBS (2 equiv) and $PdOAc_2$ (10 mol %) in MeCN at 120 °C for 2 h, 2-bromobenzaldoxime **1b** was obtained along with starting material **1a** in a 7:3 ratio (entry 1). Without palladium, the starting material was recovered unchanged (entry 2). In order to improve the conversion, we screened some additives commonly used in C−H activation reactions (entries 3−8). Whereas the use of $AgOCOCF_3$ (entry 7) led to the same result, other additives were detrimental to the reaction. Replacing MeCN by DCE as a solvent led to a lower conversion of the starting material (entry 9). Nevertheless, using $AgOCOCF_3$ (10 mol %) led to an almost total conversion, but in this case, significant amounts of dibrominated compound **1c** were observed (entry 10).

Received: May 11, 2011
Published: June 20, 2011

Table 1. Palladium-Catalyzed Bromination of *O*-Methylbenzaldoxime 1a



entry	solvent	time (h)	additives	1a/1b/1c[a]
1[b]	MeCN	2		31/69/0
2[b,c,d]	MeCN	1		100/0/0
3[b]	MeCN	2	$Cu(OAc)_2$	94/6/0
4[b]	MeCN	2	$CuBr_2$	100/0/0
5[b]	MeCN	2	$K_2S_2O_8$	66/34/0
6[b]	MeCN	2	AgOAc	63/37/0
7[b]	MeCN	2	$AgOCOCF_3$	39/61/0
8[b]	MeCN	2	$PhI(OAc)_2$	43/57/0
9	DCE	2.5		47/47/6
10	DCE	2.5	$AgOCOCF_3$	4/75/21
11[d]	DCE	2.5	$AgOCOCF_3$	50/50/ε
12[d]	DCE	24	$AgOCOCF_3$	24/71/5
13[d,e]	DCE	24	$AgOCOCF_3$	24/76/ε
14[c]	AcOH	2.5	$AgOCOCF_3$	27/65/8
15[d,f]	DCE	2.5	$AgOCOCF_3$	16/76/8

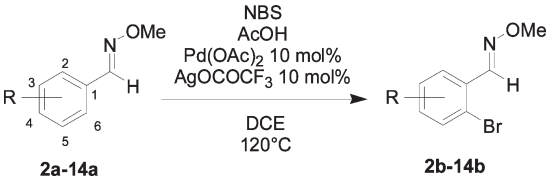
[a] ^{1}H NMR ratio. [b] Microwave heating. [c] No catalyst. [d] NBS 1 equiv. [e] 20 mol % $AgOCOCF_3$. [f] 1 equiv of AcOH.

Decreasing the amount of NBS to 1 equiv led to the decrease of both the conversion of the starting material and the quantity of dibrominated compound (entry 11). A good conversion was obtained in 24 h without significantly increasing the formation of **1c** (entry 12). Compared to DCE, the use of AcOH as a solvent seemed to accelerate the bromination reaction (entry 14), and we finally found that using 1 equiv of AcOH in DCE (entry 15) appeared to us as the best compromise between a high conversion and low byproduct formation.

In order to extend the scope of this methodology, we explored the bromination of substituted *O*-methylbenzaldoximes. For each substrate, reaction conditions were adjusted to give the monobrominated compound as a major product. The best results are summarized in Table 2.

As expected, 2-substituted benzaldoximes **2a**−**5a** were selectively monobrominated in moderate to good yields. For compound **2a** bearing the strongly activating methoxy group, a lower heating temperature was crucial to avoid the formation of the electrophilic aromatic substitution (EAS) product observed at 120 °C. For 3-substituted benzaldoximes a selective monobromination was obtained with bulky groups, whereas for small substituents such as fluorine **6a** or chlorine **9a** dibromination occurred, leading to lower yields. Monobromination was very difficult to achieve with 4-substituted benzaldoximes, and significant dibromination was generally observed. Lowering the reaction temperature to 90 °C did not change the dibrominated/monobrominated ratio but led to a lower conversion of starting material. Overall, electron-donating groups seemed to favor the formation of monobrominated products, whereas electron-withdrawing groups led to lower yields. In many cases, the use of AcOH led to higher yields but with an excessive formation of dibrominated compounds.[34]

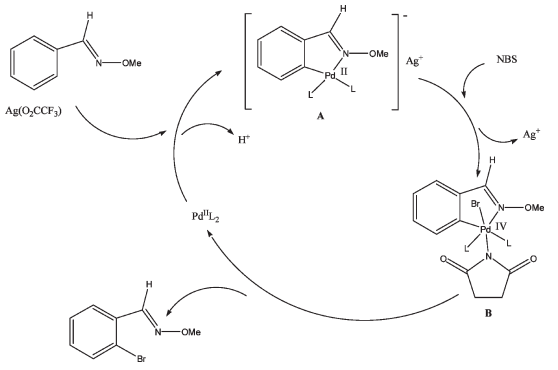
Table 2. Palladium-Catalyzed *ortho*-Bromination of Substituted *O*-Methylbenzaldoximes



starting material	conditions[a]	^{1}H NMR yield (%)[b]
2-OMe **2a**	A[c] − 24 h	**2b** 93 (64)
2-Me **3a**	B − 4 h	**3b** 74 (45)
2-F **4a**	C − 5 h	**4b** 91 (71)
2-Cl **5a**	C − 24 h	**5b** 99 (81)
3-Cl **6a**	B − 24 h	**6b** 76 (37)
3-NO_2**7a**	B − 24 h	**7b** 53 (32)
3-Br **8a**	C − 24 h	**8b** 89 (40)
3-F **9a**	B − 2.5 h	**9b** 47 (18)
4-CF_3**10a**	C − 2.5 h	**10b** 63 (41)
4-CN **11a**	C − 24 h	**11b** 66 (32)
		11b 34[c]
3,4-diCl **12a**	C − 24 h	**12b** 98 (50)
4,6-diCl **13a**	C − 24 h	**13b** 64 (50)
2,3-diMeO **14a**	A[c] − 24 h	**14b** 98 (72)

[a] Conditions: (A) NBS 1 equiv; (B) NBS 2 equiv; (C) NBS 2 equiv, AcOH 1 equiv. [b] Isolated yields are written in parentheses (close polarity between brominated compounds and starting material led to purification difficulties and differences between ^{1}H NMR and isolated yields), [c] 90 °C.

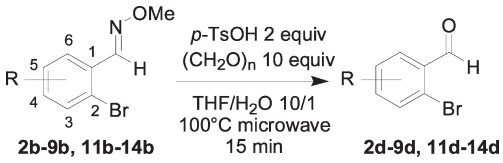
Scheme 1. Mechanistic Proposal for *ortho*-Bromination



Mechanistic investigations on C−H chlorination of arylpyridines or benzo[*h*]quinolines with NCS seem to involve a Pd^{II}−Pd^{IV} catalytic cycle[35,36] or a bimetallic Pd^{III}-complex.[37] Although the role of $AgOCOCF_3$ is not well understood in our reaction, it seems to act as a co-catalyst. The use of this silver salt seems to be crucial (Table 1, entries 9 and 10), but increasing its quantity to 20 mol % has marginal influence on the reaction (Table 1, entries 12 and 13). Cheng et al. recently reported a Pd^{II}-catalyzed C−H arylation reaction starting from *O*-methylbenzaldoximes using Ag_2O as an additive. Their mechanistic investigations have been supported by the isolation of an anionic cyclopalladacycle where silver acts as a counterion leading to an activated catalytic Pd^{II} species.[32] Based on these literature data

dx.doi.org/10.1021/jo200853j |*J. Org. Chem.* 2011, 76, 6414–6420

Table 3. Deprotection of Benzaldoximes to Benzaldehydes



2b-9b, 11b-14b **2d-9d, 11d-14d**

starting material	product	yields %[a]
2b 6-OMe	**2d**	95
3b 6-Me	**3d**	90
4b 6-F	**4d**	92
5b 6-Cl	**5d**	79
6b 5-Cl	**6d**	86
7b 5-NO_2	**7d**	88
8b 5-Br	**8d**	86
9b 5-F	**9d**	87
11b 4-CN	**11d**	97
12b 4,5-diCl	**12d**	83
13b 4,6-diCl	**13d**	79[b]
14b 5,6-diMeO	**14d**	93

[a] Isolated yields. [b] 1.5 h.

and our own observation of a catalytic role of $AgOCOCF_3$, we propose a catalytic cycle involving the formation of the cyclometalated complex **A**, which after oxidative addition of NBS should form a Pd^{IV} intermediate **B** leading to the brominated compound after reductive elimination along with regeneration of the Pd^{II} catalyst (scheme 1).

The isolated brominated benzaldoximes were then subjected to deprotection using a modified procedure of Sakamoto and Kikugawa.[38] Heating the benzaldoximes **2b**−**14b** in a THF/H_2O mixture (10/1) with *p*-TsOH (2 equiv) and *p*-formaldehyde (10 equiv) at 100 °C under microwave irradiation afforded the expected substituted 2-bromobenzaldehydes **2d**−**14d** in high yields within 15 min (Table 3).

In summary, we have developed a selective *ortho*-bromination of benzaldoximes through a palladium-catalyzed C−H activation. The facile deprotection of the *O*-methylaldoxime group led to substituted 2-bromobenzaldehydes, which are useful key intermediates in organic synthesis. This method offers an alternative and complementary approach to the directed *ortho*-metalation and allows the use of sensitive functional groups (e.g., NO_2, Br, CN).

EXPERIMENTAL SECTION

General Procedure for the Synthesis of Substituted Benzaldehyde *O*-Methyloximes 1a−14a. Substituted benzaldehyde (1 equiv) was added to a solution of *O*-methylhydroxylamine hydrochloride (1.2 equiv) and pyridine (4 equiv) in dichloromethane (15 mL/5 mmol). The solution was stirred for 1 h at room temperature and evaporated *in vacuo*. The remaining residue was dissolved in dichloromethane and filtered through a short pad of silica gel. All compounds were obtained in almost quantitative yields. The mixtures of (*Z*)- and (*E*)-diastereoisomers were not purified and were used in the bromination reaction.

(*E*)-Benzaldehyde *O*-Methyloxime 1a[39]. Colorless oil. ^1H NMR (400 MHz, $CDCl_3$) δ 3.98 (s, 3H), 7.36−7.38 (m, 3H), 7.57−7.58 (m, 2H), 8.07 (s, 1H).

(*Z*,*E*)-2-Methoxybenzaldehyde *O*-Methyloxime 2a[40]. Colorless oil; *Z*:*E* ratio 1:9. (*E*): ^1H NMR (400 MHz, $CDCl_3$) δ 3.84 (s, 3H), 3.96 (s, 3H), 6.88 (d, 1H, ^3J = 8.8 Hz), 6.94 (t, 1H, ^3J = 7.8 Hz), 7.33 (dt, 1H, ^3J = 8.8 Hz, ^4J = 2.0 Hz), 7.77 (dd, 1H, ^3J = 7.8 Hz, ^4J = 2.0 Hz), 8.46 (s, 1H). (*Z*): ^1H NMR (400 MHz, $CDCl_3$) δ 3.86 (s, 3H), 3.99 (s, 3H), 6.88 (d, 1H, ^3J = 8.8 Hz), 6.94 (t, 1H, ^3J = 7.8 Hz), 7.33 (dt, 1H, ^3J = 8.8 Hz, ^4J = 2.0 Hz), 7.73 (s, 1H), 8.22 (dd, 1H, ^3J = 7.8 Hz, ^4J = 2.0 Hz).

(*E*)-2-Methylbenzaldehyde *O*-Methyloxime 3a[33]. Colorless oil. ^1H NMR (400 MHz, $CDCl_3$) δ 2.41 (s, 3H), 3.99 (s, 3H), 7.16−7.28 (m, 3H), 7.70 (d, 1H, ^3J = 8.8 Hz), 8.34 (s, 1H).

(*E*)-2-Fluorobenzaldehyde *O*-Methyloxime 4a[41]. Colorless oil. ^1H NMR (400 MHz, $CDCl_3$) δ 3.99 (s, 3H), 7.07 (dd, 1H, ^3J = 9.8 Hz, ^3J = 8.8 Hz), 7.14 (t, 1H, ^3J = 7.8 Hz), 7.32−7.37 (m, 1H), 7.82 (dt, 1H, ^3J = 7.8 Hz, ^4J = 1.9 Hz), 8.31 (s, 1H).

(*E*)-2-Chlorobenzaldehyde *O*-Methyloxime 5a[39]. Colorless oil. ^1H NMR (400 MHz, $CDCl_3$) δ 4.00 (s, 3H), 7.24−7.38 (m, 3H), 7.89 (dd, 1H, ^3J = 6.8 Hz, ^4J = 2.0 Hz), 8.49 (s, 1H).

(*E*)-3-Chlorobenzaldehyde *O*-Methyloxime 6a. Colorless oil. ^1H NMR (400 MHz, $CDCl_3$) δ 3.99 (s, 3H), 7.28−7.36 (m, 2H), 7.43 (dd, 1H, ^3J = 6.8 Hz, ^4J = 2.0 Hz), 7.61 (d, 1H, ^4J = 2.0 Hz), 8.00 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 62.2, 125.3, 126.6, 129.7, 129.9, 134.0, 134.8, 147.1. HRMS/EI: calcd for C_8H_8NOCl 169.0294, found 169.0297.

(*E*)-3-Nitrobenzaldehyde *O*-Methyloxime 7a[42]. White solid, mp 53−55 °C. ^1H NMR (400 MHz, $CDCl_3$) δ 4.02 (s, 3H), 7.55 (t, 1H, ^3J = 7.8 Hz), 7.89 (d, 1H, ^3J = 7.8 Hz), 8.10 (s, 1H), 8.20 (dd, 1H, ^3J = 7.8 Hz, ^4J = 2.0 Hz), 8.43 (d, 1H, ^4J = 2.0 Hz).

(*E*)-3-Bromobenzaldehyde *O*-Methyloxime 8a. Colorless oil. ^1H NMR (400 MHz, $CDCl_3$) δ 3.98 (s, 3H), 7.23 (d, 1H, ^3J = 7.8 Hz), 7.47−7.50 (m, 2H), 7.77 (s, 1H), 7.99 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 62.2, 122.8, 125.7, 129.5, 130.2, 132.6, 134.2, 147.0. HRMS/EI: calcd for C_8H_8NOBr 212.9789, found 212.9780.

(*E*)-3-Fluorobenzaldehyde *O*-Methyloxime 9a. Colorless oil. ^1H NMR (400 MHz, $CDCl_3$) δ 3.98 (s, 3H), 7.03−7.09 (m, 1H), 7.30−7.36 (m, 3H), 8.03 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 62.2, 113.2 (d, ^2J = 23 Hz), 116.7 (d, ^2J = 21 Hz), 123.1 (d, J = 3 Hz), 130.2 (d, J = 8 Hz), 134.4 (d, J = 8 Hz), 147.3 (d, J = 3 Hz), 162.9 (d, ^1J = 245 Hz). HRMS/EI: calcd for C_8H_8NOF 153.0590, found 153.0584.

(*E*)-4-Trifluoromethylbenzaldehyde *O*-Methyloxime 10a[43]. Colorless oil. ^1H NMR (400 MHz, $CDCl_3$) δ 4.01 (s, 3H), 7.63 (d, 2H, ^3J = 7.8 Hz), 7.70 (d, 2H, ^3J = 7.8 Hz), 8.09 (s, 1H).

(*E*)-4-Cyanobenzaldehyde *O*-Methyloxime 11a. White solid, mp 111−113 °C. ^1H NMR (400 MHz, $CDCl_3$) δ 4.02 (m, 3H), 7.64−7.70 (m, 4H), 8.06 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 62.4, 112.9, 118.4, 127.3 (2C), 132.4 (2C), 136.5, 146.5. HRMS/EI: calcd for $C_9H_8N_2O$ 160.0636, found 160.0628.

(*E*)-2,4-Dichlorobenzaldehyde *O*-Methyloxime 12a. White solid, mp 63−65 °C. ^1H NMR (400 MHz, $CDCl_3$) δ 4.00 (s, 3H), 7.24 (dd, 1H, ^3J = 8.8 Hz, ^4J = 1.9 Hz), 7.39 (d, 1H, ^4J = 1.9 Hz), 7.83 (d, 1H, ^3J = 7.8 Hz), 8.41 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 62.4, 127.4, 127.8, 128.6, 129.6, 134.2, 136.0, 144.6. HRMS/EI: calcd for $C_8H_7NOCl_2$ 202.9905, found 202.9910.

(*E*)-3,4-Dichlorobenzaldehyde *O*-Methyloxime 13a. White solid, mp 57−59 °C. ^1H NMR (400 MHz, $CDCl_3$) δ 3.98 (s, 3H), 7.39 (dd, 1H, ^3J = 8.8 Hz, ^4J = 2.0 Hz), 7.43 (d, 1H, ^3J = 8.8 Hz), 7.68 (d, 1H, ^4J = 2.0 Hz), 7.95 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 62.3, 126.1, 128.4, 130.7, 132.2, 133.1, 133.7, 146.2. HRMS/EI: calcd for $C_8H_7NOCl_2$ 202.9905, found 202.9899.

(*E*)-2,3-Dimethoxybenzaldehyde *O*-Methyloxime 14a. White solid, mp 58−59 °C. ^1H NMR (400 MHz, $CDCl_3$) δ 3.84 (s, 3H), 3.87 (s, 3H), 3.98 (s, 3H), 6.92 (d, 1H, ^3J = 6.8 Hz), 7.05 (t, 1H, ^3J = 7.8 Hz), 7.41 (d, 1H, ^3J = 7.8 Hz), 8.41 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$)

δ 55.7, 61.5, 61.9, 113.4, 117.7, 124.2, 126.0, 144.5, 147.9, 152.8. HRMS/EI: calcd for $C_{10}H_{13}NO_3$ 195.0895, found 195.0900.

General Procedure for the Synthesis of Substituted 2-Bromobenzaldehyde *O*-Methyloximes 1b−14b. In a sealed flask, substituted benzaldehyde *O*-methyloxime **1a**−**15a** (1 equiv) was added to a solution of *N*-bromosuccinimide (see Table 2), silver trifluoroacetate (10 mol %), palladium acetate (10 mol %), and acetic acid (see Table 2) in 1,2-dichloroethane (2 mL/0.60 mmol of oxime). The resulting mixture was stirred and heated at 120 °C (see Table 2 for conditions), partitioned between water and dichloromethane, and filtered through a pad of Celite. The aqueous layer was extracted with dichloromethane. The combined organic layers were dried on $MgSO_4$, filtered, evaporated *in vacuo*, and purified by silica gel chromatography.

(*E*)-2-Bromobenzaldehyde *O*-Methyloxime 1b. Starting from benzaldehyde *O*-methyloxime **1a** (500 mg, 3.70 mmol), **1b** was obtained as a colorless oil (403 mg, 51%, cyclohexane as eluent). **(*E*)-2-Bromobenzaldehyde *O*-methyloxime 1b:** IR (KBr) ν cm^{-1}) 3434, 2935, 1591, 1438, 1468, 1059, 924, 753. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.00 (s, 3H), 7.22 (dt, 1H, ^3J = 7.8 Hz, ^4J = 2.0 Hz), 7.30 (t, 1H, ^3J = 6.8 Hz), 7.56 (dd, 1H, ^3J = 7.8 Hz, ^4J = 2.0 Hz), 7.87 (dd, 1H, ^3J = 7.8 Hz, ^4J = 2.0 Hz), 8.45 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 62.3, 123.8, 127.5, 127.6, 131.0, 131.5, 133.1, 147.9. HRMS/EI: calcd for C_8H_8NOBr 212.9789, found 212.9790. **(*E*)-2,6-Dibromobenzaldehyde *O*-methyloxime 1c:** Obtained as a byproduct during the screening of conditions. White solid, mp 78−80 °C. IR (KBr) (cm^{-1}) 3074, 2940, 1547, 1423, 1189, 1054, 923, 772. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.03 (s, 3H), 7.06 (t, 1H, ^3J = 8.8 Hz), 7.58 (d, 2H, ^3J = 8.8 Hz), 8.15 (s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 62.5, 124.1 (2C), 130.9, 132.4 (2C), 147.3. HRMS/EI: calcd for $C_8H_7NOBr_2$ 290.8894, found 290.8885.

(*E*)-2-Bromo-6-methoxybenzaldehyde *O*-Methyloxime 2b. Starting from 2-methoxybenzaldehyde *O*-methyloxime **2a** (495 mg, 3.00 mmol), **2b** was obtained as a colorless oil (470 mg, 64%, petroleum ether/diethyl ether 98/2 as eluent). IR (KBr) ν cm^{-1}) 3004, 2935, 2837, 1586, 1563, 1459, 1429, 1261, 1032, 918. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.83 (s, 3H), 4.01 (s, 3H), 6.87 (d, 1H, ^3J = 7.8 Hz), 7.14−7.23 (m, 2H), 8.27 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 56.2, 62.1, 110.2, 111.7, 124.1, 125.5, 130.7, 145.8, 158.9. HRMS/EI: calcd for $C_9H_{10}NO_2Br$ 242.9895, found 242.9889.

(*E*)-2-Bromo-6-methylbenzaldehyde *O*-Methyloxime 3b. Starting from 2-methylbenzaldehyde *O*-methyloxime **3a** (448 mg, 3.00 mmol), **3b** was obtained as a colorless oil (306 mg, 45%, petroleum ether as eluent). IR (KBr) ν (cm^{-1}) 3435, 2934, 1449, 1052, 925, 771. ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.50(s, 3H), 4.00 (s, 3H), 7.09 (t, 1H, ^3J = 7.8 Hz), 7.18 (d, 1H, ^3J = 6.8 Hz), 7.43 (d, 1H, ^3J = 7.8 Hz), 8.41 (s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 22.2, 62.2, 124.9, 129.8, 130.2, 130.5, 139.9, 149.0. HRMS/EI: calcd for $C_9H_{10}NOBr$ 226.9946, found 226.9953.

2-Bromo-6-fluorobenzaldehyde *O*-Methyloxime 4b[40]. Starting from 2-fluorobenzaldehyde *O*-methyloxime **4a** (310 mg, 2.02 mmol), **4b** was obtained as a colorless oil in a 1:0.9 *Z*:*E* ratio (334 mg, 71%, petroleum ether/acetone 99/1 as eluent). IR (KBr) ν (cm^{-1}) 3085, 2938, 2820, 1599, 1564, 1460, 1443, 1251, 1051, 925, 874, 780. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.96 (s, 3H), 4.04 (s, 3H), 7.05−7.10 (m, 2H), 7.12−7.25 (m, 2H), 7.39−7.42 (m, 3H), 8.30 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) (*E*) δ 62.6, 115.7 (d, ^2J = 22 Hz), 120.6 (d, ^2J = 14 Hz), 124.4 (d, J = 4 Hz), 129.1 (d, J = 4 Hz), 131.1 (d, J = 9 Hz), 144.6 (d, J = 4 Hz), 160.8 (d, ^1J = 258 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) (*Z*) δ 62.6, 114.8 (d, ^2J = 22 Hz), 121.0 (d, ^2J = 21 Hz), 122.5 (d, J = 5 Hz), 128.2 (d, J = 4 Hz), 131.4 (d, J = 9 Hz), 140.5 (d, J = 2 Hz), 159.7 (d, ^1J = 255 Hz).

2-Bromo-6-chlorobenzaldehyde *O*-Methyloxime 5b. Starting from 2-chlorobenzaldyde *O*-methyloxime **5a** (500 mg, 2.95 mmol), **5b** was obtained as a colorless oil in a 1:2 *E*:*Z* ratio (591 mg, 81%, cyclohexane as eluent). IR (KBr) ν (cm^{-1}) 2968, 2938, 1577, 1554, 1427, 1189, 1078, 1058, 920, 776. ^{1}H NMR (400 MHz, $CDCl_3$), diastereoisomer (*Z*) δ 3.95 (s, 3H), 7.18 (d, 1H, ^3J = 7.8 Hz), 7.39 (t, 1H, ^3J = 8.8 Hz), 7.42 (s, 1H), 7.51 (d, 1H, ^3J = 8.8 Hz). ^{1}H NMR (400 MHz, $CDCl_3$), diastereoisomer (*E*) δ 4.03 (s, 3H), 7.13 (d, 1H, ^3J = 7.8 Hz,), 7.39 (t, 1H, ^3J = 8.8 Hz), 7.54 (d, 1H, ^3J = 7.8 Hz), 8.21 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 62.4, 62.4, 122.4, 124.2, 128.3, 129.3, 130.5, 130.6, 130.8, 131.8, 132.1, 133.5, 133.9, 134.9, 143.2, 145.8. HRMS/EI: calcd for $C_8H_7NOBrCl$ 246.9399, found 246.9401.

(*E*)-2-Bromo-5-chlorobenzaldehyde *O*-Methyloxime 6b. Starting from 3-chlorobenzaldehyde *O*-methyloxime **6a** (529 mg, 3.12 mmol), **6b** was obtained as a white solid (284 mg, 37%, petroleum ether as eluent). Mp 70−72 °C. IR (KBr) ν (cm^{-1}) 3084, 2938, 1461, 1394, 1059, 1027, 931, 896, 884, 808. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.01 (s, 3H), 7.19 (dd, 1H, ^3J = 8.8 Hz, ^4J = 2.9 Hz), 7.47 (d, 1H, ^3J = 8.8 Hz), 7.86 (d, 1H, ^4J = 2.0 Hz), 8.36 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 62.5, 121.4, 127.2, 130.8, 132.9, 133.8, 134.1, 146.7. HRMS/EI: calcd for $C_8H_7NOClBr$ 246.9399, found 246.9404.

(*E*)-2-Bromo-5-nitrobenzaldehyde *O*-Methyloxime 7b. Starting from 3-nitrobenzaldehyde *O*-methyloxime **7a** (500 mg, 1.93 mmol), **7b** was obtained as a white solid (230 mg, 32%, cyclohexane/diethyl ether 99/1 as eluent). Mp 117−119 °C. IR (KBr) ν (cm^{-1}) 3097, 3078, 2937, 1560, 1594, 1523, 1345, 1054, 1029, 918, 740. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.06 (s, 3H), 7.75 (d, 1H, ^3J = 8.8 Hz), 8.05 (dd, 1H, ^3J = 8.8 Hz, ^4J = 2.0 Hz), 8.44 (s, 1H), 8.72 (d, 1H, ^4J = 2.0 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ 62.9, 122.3, 124.7, 129.9, 133.3, 134.2, 145.8, 147.3. HRMS/EI: calcd for $C_8H_7N_2O_3Br$ 257.9640, found 257.9637.

(*E*)-2,5-Dibromobenzaldehyde *O*-Methyloxime 8b. Starting from 5-bromobenzaldehyde *O*-methyloxime **8a** (500 mg, 2.34 mmol), **8b** was obtained as a white solid (270 mg, 40%, petroleum ether/acetone 99/1 as eluent). Mp 80−82 °C. IR (KBr) ν (cm^{-1}) 3080, 2937, 1458, 1388, 1198, 1059, 1025, 930. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.01 (s, 3H), 7.33 (dd, 1H, ^3J = 8.8 Hz, ^4J = 2.9 Hz), 7.42 (d, 1H, ^3J = 8.8 Hz), 8.01 (d, 1H, ^4J = 2.9 Hz), 8.35 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 62.5, 121.5, 122.1, 130.1, 133.2, 133.7, 134.3, 146.6. HRMS/EI: calcd for $C_8H_7NOBr_2$ 290.8894, found 290.8890.

(*E*)-2-Bromo-5-fluorobenzaldehyde *O*-Methyloxime 9b. Starting from 3-fluorobenzaldehyde *O*-methyloxime **9a** (518 mg, 3.38 mmol), **9b** was obtained as a white solid (67 mg, 18%, petroleum ether as eluent). 2,6-dibromo-3-fluorobenzaldehyde *O*-methyloxime **9c** as a byproduct was obtained in a 1:1 *Z*:*E* ratio as a white solid (440 mg, 42%). **(*E*)-2-Bromo-5-fluorobenzaldehyde *O*-methyloxime 9b:** Mp < 50 °C. IR (KBr) ν (cm^{-1}) 2932, 1599, 1568, 1460, 1417, 1263, 1158, 1058, 1031, 917. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.01 (s, 3H), 6.95 (dt, 1H, ^3J = 7.8 Hz, ^4J = 2.9 Hz), 7.51 (dd, 1H, ^3J = 8.8 Hz, ^4J = 8.8 Hz), 7.60 (dd, 1H, ^3J = 9.8 Hz, ^4J = 2.9 Hz), 8.38 (d, 1H, ^5J = 1.9 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ 62.5, 114.0 (d, ^2J = 25 Hz), 117.8 (d, J = 2 Hz), 118.3 (d, ^2J = 23 Hz), 133.2 (d, J = 8 Hz), 134.3 (d, J = 8 Hz), 147.0 (d, J = 2 Hz), 161.8 (d, ^1J = 246 Hz). HRMS/EI: calcd for C_8H_7NOFBr 232.9675, found 232.9679. **(*Z*,*E*)-2,6-Dibromo-3-fluorobenzaldehyde *O*-methyloxime 9c:** Mp < 50 °C. IR (KBr) ν (cm^{-1}) 2938, 2820, 1564, 1443, 1400, 1271, 1194, 1056, 998, 897, 813. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.94 (s, 3H), 4.04 (s, 3H), 7.00 (dt, 2H, ^3J = 7.8 Hz, ^4J = 2.9 Hz), 7.34 (s, 1H), 7.48−7.56 (m, 2H), 8.11 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 62.4, 62.5, 110.0 (d, ^2J = 22 Hz), 111.7 (d, ^2J = 22 Hz), 116.3 (d, J = 3 Hz), 117.3 (d, J = 11 Hz), 117.6 (d, J = 11 Hz), 118.1 (d, J = 4 Hz), 132.3 (d, J = 7 Hz), 132.9 (d, J = 7 Hz), 133.7, 135.8, 143.4 (d, J = 2 Hz), 146.4 (d, J = 2 Hz), 158.4 (d, ^1J = 248 Hz), 158.6 (d, ^1J = 246 Hz). HRMS/EI: calcd for $C_8H_6NOFBr_2$ 308.8800, found 308.8808.

(*E*)-2-Bromo-4-trifluoromethylbenzaldehyde *O*-Methyloxime 10b. Starting from 4-trifluoromethylbenzaldehyde *O*-methyloxime **10a** (406 mg, 2.00 mmol), **10b** was obtained as a white solid (230 mg, 41%, petroleum ether as eluent). Mp < 50 °C. IR (KBr) ν (cm^{-1}) 3080, 2949, 1597, 1466, 1399, 1325, 1171, 1038, 925, 863, 836. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.03 (s, 3H), 7.55 (d, 1H, ^3J = 8.8 Hz), 7.83 (s, 1H), 8.00 (d, 1H, ^3J = 7.8 Hz), 8.44 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 62.5,

123.0 (q, ^1J = 271 Hz), 123.4, 124.2 (q, ^3J = 3 Hz), 127.7, 130.0 (q, ^3J = 4 Hz), 132.5 (q, ^2J = 33 Hz), 135.0, 146.6. HRMS/EI: calcd for $C_9H_7NOF_3Br$ 282.9643, found 282.9636.

(*E*)-2-Bromo-4-cyanobenzaldehyde *O*-Methyloxime 11b. Starting from 4-cyanobenzaldehyde *O*-methyloxime **11a** (500 mg, 3.12 mmol), **11b** was obtained as a white solid (237 mg, 32%, petroleum ether/diethyl ether 98/2 as eluent). Mp < 50 °C. IR (KBr) ν (cm^{-1}) 2939, 2232, 1594, 1388, 1061, 1039, 928, 838. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.04 (s, 3H), 7.57 (dd, 1H, ^3J = 7.8 Hz, ^4J = 2.0 Hz), 7.85 (d, 1H, ^4J = 2.0 Hz), 7.99 (d, 1H, ^3J = 7.8 Hz), 8.42 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 62.8, 114.2, 117.1, 123.5, 127.7, 130.7, 136.1, 136.4, 146.3. HRMS/EI: calcd for $C_9H_7N_2OBr$ 237.9742, found 237.9742.

(*E*)-2-Bromo-4,5-dichlorobenzaldehyde *O*-Methyloxime 12b. Starting from 3,4-dichlorobenzaldehyde *O*-methyloxime **12a** (500 mg, 2.45 mmol), **12b** was obtained as a white solid (344 mg, 50%, petroleum ether/diethyl ether 98/2 as eluent). Mp 93−95 °C. IR (KBr) ν (cm^{-1}) 3088, 2966, 2930, 1594, 1448, 1359, 1202, 1130, 1047, 905, 892. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.01 (s, 3H), 7.67 (s, 1H), 7.97 (s, 1H), 8.31 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 62.6, 121.2, 128.2, 131.4, 132.3, 134.1, 134.3, 145.9. HRMS/EI: calcd for $C_8H_6NOBrCl_2$ 280.9010, found 280.9005.

2-Bromo-4,6-dichlorobenzaldehyde *O*-Methyloxime 13b. Starting from 2,4-dichlorobenzaldehyde *O*-methyloxime **13a** (400 mg, 1.96 mmol), **13b** was obtained in a 1:2 *Z*:*E* ratio as a white solid (356 mg, 64%, petroleum ether/diethyl ether 99/1 as eluent). Mp 77−79 °C. IR (KBr) ν (cm^{-1}) 3075, 2928, 1576, 1536, 1364, 1182, 1078, 1047, 922, 856, 767. ^{1}H NMR (400 MHz, $CDCl_3$), (*E*) δ 4.03 (s, 3H), 7.42 (d, 1H, ^4J = 2.0 Hz), 7.56 (d, 1H, ^4J = 2.0 Hz), 8.15 (s, 1H). ^{1}H NMR (400 MHz, $CDCl_3$), (*Z*) δ 3.94 (s, 3H), 7.37 (s, 1H), 7.40 (d, 1H, ^4J = 2.0 Hz), 7.53 (d, 1H, ^4J = 2.0 Hz). ^{13}C NMR (100 MHz, $CDCl_3$), (*E*) δ 62.5, 124.4, 129.1, 129.3, 131.7, 135.3, 135.4, 145.0. ^{13}C NMR (100 MHz, $CDCl_3$), (*Z*) δ 62.5, 122.7, 128.4, 130.7, 130.8, 134.1, 135.6, 142.3. HRMS/EI: calcd for $C_8H_6NOBrCl_2$ 280.9010, found 280.9016.

2-Bromo-5,6-dimethoxybenzaldehyde *O*-Methyloxime 14b. Starting from 2,3-dimethoxybenzaldehyde *O*-methyloxime **14a** (500 mg, 2.56 mmol), **14b** was obtained in a 1:1 *Z*:*E* ratio as a white solid (505 mg, 72%, petroleum ether/acetone 96/4 as eluent). Mp 48−50 °C. IR (KBr) ν (cm^{-1}) 2938, 1569, 1468, 1413, 1297, 1261, 1234, 1050. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.82 (s, 3H), 3.84 (s, 3H), 3.85 (s, 3H), 3.86 (s, 3H), 3.93 (s, 3H), 4.02 (s, 3H), 6.80 (d, 1H, ^3J = 8.8 Hz), 6.81 (d, 1H, ^3J = 8.8 Hz), 7.27 (d, 1H, ^3J = 8.8 Hz), 7.30 (d, 1H, ^3J = 8.8 Hz), 7.41 (s, 1H), 8.24 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 55.9, 56.1, 61.0, 61.6, 62.1, 62.2, 111.6, 113.5, 113.9, 114.1, 126.5, 127.4, 127.5, 128.4, 143.1, 145.5, 147.3, 148.8, 152.0, 152.7. HRMS/EI: calcd for $C_{10}H_{12}NO_3Br$ 273.0001, found 273.0003.

General Procedure for the Synthesis of Substituted 2-Bromobenzaldehydes 2d−14d. In a sealed microwave vial, *p*-toluenesulfonic acid (2 equiv) and formaldehyde (10 equiv) were added to a solution of substituted *O*-methyl-2-bromobenzaldoximes **1b**−**14b** (1 equiv) in a mixture of THF/water 10/1 (5 mL/mmol of oxime). The solution was stirred at 100 °C for 15 min under microwave irradiation. The solvent was evaporated *in vacuo*, and the crude residue was dissolved in dichloromethane and filtered through a short pad of silica gel.

2-Bromo-6-methoxybenzaldehyde 2d[44]. Starting from 2-bromo-6-methoxybenzaldehyde *O*-methyloxime **2b** (100 mg, 0.41 mmol), **2d** was obtained as a white solid (84 mg, 95%). Mp 55−57 °C. IR (KBr) ν (cm^{-1}) 3075, 2953, 1692, 1589, 1566, 1458, 1407, 1266, 1024, 784. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.92 (s, 3H), 6.96 (d, 1H, ^3J = 7.8 Hz), 7.25 (d, 1H, ^3J = 7.8 Hz), 7.33 (t, 1H, ^3J = 7.8 Hz), 10.42 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 56.2, 111.0, 123.3, 124.9, 126.4, 134.8, 161.9, 190.5.

2-Bromo-6-methylbenzaldehyde 3d[45]. Starting from 2-bromo-6-methylbenzaldehyde *O*-methyloxime **3b** (200 mg, 0.88 mmol), **3d** was obtained as a white solid (157 mg, 90%). Mp 46−48 °C. IR (KBr) ν (cm^{-1}) 2926, 1695, 1450, 1187, 777. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.58 (s, 3H), 7.23 (d, 1H, ^3J = 7.8 Hz), 7.33 (t, 1H, ^3J = 7.8 Hz), 7.50 (d, 1H, ^3J = 7.8 Hz), 10.53 (s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.2, 128.3, 131.4, 131.6, 131.7, 133.7, 142.7, 194.6.

2-Bromo-6-fluorobenzaldehyde 4d[46]. Starting from 2-bromo-6-fluorobenzaldehyde *O*-methyloxime **4b** (150 mg, 0.65 mmol), **4d** was obtained as a white solid (121 mg, 92%). Mp < 50 °C. IR (KBr) ν (cm^{-1}) 2956, 1706, 1598, 1452, 1250, 1189, 889, 787. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.16 (t, 1H, ^3J = 9.0 Hz), 7.42 (dt, 1H, ^3J = 7.8 Hz, ^4J = 5.9 Hz), 7.50 (d, 1H, ^3J = 7.8 Hz), 10.37 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 116.3 (d, ^2J = 21 Hz), 122.8 (d, J = 9 Hz), 125.3 (d, J = 2 Hz), 130.1 (d, J = 3 Hz), 135.3 (d, J = 11 Hz), 163.1 (d, ^1J = 264 Hz), 188.5 (d, J = 2 Hz).

2-Bromo-6-chlorobenzaldehyde 5d[10]. Starting from 2-bromo-6-chlorobenzaldehyde *O*-methyloxime **5b** (200 mg, 0.81 mmol), **5d** was obtained as a white solid (140 mg, 79%). Mp 74−76 °C. IR (KBr) ν (cm^{-1}) 3087, 2888, 1699, 1573, 1555, 1431, 1400, 1185, 780. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 (t, 1H, ^3J = 7.8 Hz), 7.44 (d, 1H, ^3J = 7.8 Hz), 7.61 (d, 1H, ^3J = 7.8 Hz), 10.38 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 124.9, 130.4, 131.7, 133.0, 133.7, 136.7, 190.0.

2-Bromo-5-chlorobenzaldehyde 6d[47]. Starting from 2-bromo-5-chlorobenzaldehyde *O*-methyloxime **6b** (100 mg, 0.40 mmol), **6d** was obtained as a white solid (76 mg, 86%). Mp 71−73 °C. IR (KBr) ν (cm^{-1}) 3060, 2925, 1692, 1455, 1189, 1092, 1030, 897, 819. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 (dd, 1H, ^3J = 8.8 Hz, ^4J = 3.0 Hz), 7.52 (d, 1H, ^3J = 8.8 Hz), 7.79 (d, 1H, ^4J = 3.0 Hz), 10.30 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 124.6, 129.6, 134.4, 134.5, 135.0, 135.1, 190.4.

2-Bromo-5-nitrobenzaldehyde 7d[48]. Starting from 2-bromo-5-nitrobenzaldehyde *O*-methyloxime **7b** (100 mg, 0.39 mmol), **7d** was obtained as a white solid (78 mg, 88%). Mp 105−107 °C. IR (KBr) ν (cm^{-1}) 3100, 1687, 1606, 1535, 1351, 1037, 736. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90 (d, 1H, ^3J = 8.8 Hz), 8.31 (dd, 1H, ^3J = 8.8 Hz, ^4J = 3.0 Hz), 8.72 (d, 1H, ^4J = 3.0 Hz), 10.39 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 124.7, 128.8, 133.0, 134.3, 135.3, 147.6, 189.4.

2,5-Dibromobenzaldehyde 8d[49]. Starting from 2,5-dibromobenzaldehyde *O*-methyloxime **8b** (100 mg, 0.34 mmol), **8d** was obtained as a white solid (78 mg, 86%). Mp 93−95 °C. IR (KBr) ν (cm^{-1}) 3076, 2924, 2864, 1686, 1571, 1453, 1380, 1247, 1188, 1078, 1022, 884, 824. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53 (d, 1H, ^3J = 8.8 Hz), 7.57 (dd, 1H, ^3J = 8.8 Hz, ^4J = 2.9 Hz), 8.02 (d, 1H, ^4J = 2.9 Hz), 10.28 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 122.2, 125.4, 132.6, 134.6, 135.2, 138.0, 190.4.

2-Bromo-5-fluorobenzaldehyde 9d. Starting from 2-bromo-5-fluorobenzaldehyde *O*-methyloxime **9b** (42 mg, 0.18 mmol), **9d** was obtained as a white solid (32 mg, 87%). Mp 53−55 °C. IR (KBr) ν (cm^{-1}) 3071, 1692, 1597, 1578, 1465, 1393, 1262, 1213, 1146, 1033, 752. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.18−7.23 (m, 1H), 7.611−7.66 (m, 2H), 10.31 (d, 1H, ^5J = 2.9 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ 116.3 (d, ^2J = 24 Hz), 121.1 (d, J = 3 Hz), 122.7 (d, ^2J = 23 Hz), 134.8 (d, J = 6 Hz), 135.3 (d, J = 7 Hz), 162.1 (d, ^1J = 248 Hz), 190.7. HRMS/EI: calcd for C_7H_4FOBr 201.9430, found 201.9433.

2-Bromo-4-cyanobenzaldehyde 11d. Starting from 2-bromo-4-cyanobenzaldehyde *O*-methyloxime **11b** (150 mg, 0.63 mmol), **11d** was obtained as a white solid (128 mg, 97%). Mp 118−120 °C. IR (KBr) ν (cm^{-1}) 3077, 2891, 2231, 1691, 1596, 1381, 1259, 1194, 1045, 838, 766. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73 (d, 1H, ^3J = 7.8 Hz), 7.97 (s, 1H), 8.00 (d, 1H, ^3J = 7.8 Hz), 10.38 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 116.3, 118.6, 126.8, 130.2, 131.3, 136.2, 137.2, 190.2. HRMS/EI: calcd for C_8H_4NOBr 208.9476, found 208.9481.

2-Bromo-4,5-dichlorobenzaldehyde 12d. Starting from 2-bromo-4,5-dichlorobenzaldehyde *O*-methyloxime **12b** (100 mg, 0.35 mmol), **12d** was obtained as a white solid (75 mg, 83%). Mp 116−118 °C. IR (KBr) ν (cm^{-1}) 3082, 2997, 1690, 1569, 1442, 1342,

1193, 1178, 1059, 923, 899. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 (s, 1H), 7.97 (s, 1H), 10.24 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 124.3, 130.9, 132.7, 133.3, 135.0, 139.5, 189.4. HRMS/EI: calcd for $C_7H_3OBrCl_2$ 251.8744, found 251.8740.

2-Bromo-4,6-dichlorobenzaldehyde 13d. Starting from 2-bromo-4,5-dichlorobenzaldehyde *O*-methyloxime **13b** (54 mg, 0.19 mmol), **13d** was obtained as a white solid (35 mg, 79%). Mp 59−61 °C. IR (KBr) ν (cm^{-1}) 3073, 2924, 2852, 1700, 1570, 1535, 1361, 855. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47 (d, 1H, ^4J = 1.9 Hz), 7.63 (d, 1H, ^4J = 1.9 Hz), 10.32 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 125.5, 129.8, 130.4, 132.9, 137.5, 139.4, 188.8. HRMS/EI: calcd for $C_7H_3OBrCl_2$ 251.8744, found 251.8743.

2-Bromo-5,6-dimethoxybenzaldehyde 14d[50]. Starting from 2-bromo-5,6-dimethoxybenzaldehyde *O*-methyloxime **14b** (100 mg, 0.37 mmol), **14d** was obtained as a white solid (83 mg, 93%). Mp 83−85 °C. IR (KBr) ν (cm^{-1}) 2950, 1702, 1687, 1571, 1474, 1434, 1390, 1298, 1269, 1236, 993, 923, 814. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.89 (s, 3H), 3.93 (s, 3H), 6.96 (d, 1H, ^3J = 8.8 Hz), 7.35 (d, 1H, ^3J = 8.8 Hz), 10.35 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 56.2, 62.4, 112.8, 117.5, 128.6, 129.4, 152.1, 152.8, 190.5.

■ ASSOCIATED CONTENT

Supporting Information. ^{1}H spectra for compounds **1a**−**14a**, **1b**−**14b**. and **1d**−**14d**; ^{13}C NMR spectra for compounds **6a**, **8a**, **9a**, **11a**−**14a**, **1b**−**14b**. and **1d**−**14d**; RX-(ORTEP) of **7b** and table presenting the influence of AcOH on the bromination reaction. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author
*E-mail: frederic.fabis@unicaen.fr.

■ ACKNOWLEDGMENT

We thank Mr. Albert Marcual (Bio-organic Mass Spectrometry, UMR-CNRS 6014, COBRA, University of Rouen) for HRMS data and Dr. J. Sopkova-de Oliveira Santos for RX data.

■ REFERENCES

(1) Cai, Q.; Li, Z.; Wei, J.; Ha, C.; Pei, D.; Ding, K. *Chem. Commun.* **2009**, *48*, 7581.
(2) Cho, C. S.; Lim, D. K.; Heo, N. H.; Kim, T. J.; Shim, S. C. *Chem. Commun.* **2004**, 104.
(3) Cai, Q.; Li, Z.; Wei, J.; Fu, L.; Ha, C.; Pei, D.; Ding, K. *Org. Lett.* **2010**, *12*, 1500.
(4) Kim, Y. H.; Lee, H.; Kim, Y. J.; Kim, B. T.; Heo, J. N. *J. Org. Chem.* **2008**, *73*, 495.
(5) Lin, J.; Zhang, W.; Jiang, N.; Niu, Z.; Bao, K.; Zhang, L.; Liu, D.; Pan, C.; Yao, X. *J. Nat. Prod.* **2008**, *71*, 1938.
(6) Roberts, L. R.; Fish, P. V.; Storer, R. I.; Whitlock, G. A. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 3113.
(7) Wang, L.; Jing, H.; Bu, X.; Chang, T.; Jin, L.; Liang, Y. *Catal. Commun.* **2007**, *8*, 80 and references therein.
(8) Menzel, K.; Machrouhi, F.; Bodenstein, M.; Alorati, A.; Cowden, C.; Gibson, A. W.; Bishop, B.; Ikemoto, N.; Nelson, T. D.; Kress, M. H.; Frantz, D. E. *Org. Process Res. Dev.* **2009**, *13*, 519.
(9) Meyers, A. I.; Himmelsbach, R. J.; Reuman, M. *J. Org. Chem.* **1983**, *48*, 4053.
(10) Dabrowski, M.; Kubicka, J.; Lulinski, S.; Serwatowski, J. *Tetrahedron Lett.* **2005**, *46*, 4175.
(11) Alberico, D.; Scott, M. E.; Lautens, M. *Chem. Rev.* **2007**, *107*, 174.
(12) Chen, X.; Engel, K. M.; Wang, D. H.; Yu, J. Q. *Angew. Chem., Int. Ed.* **2009**, *48*, 5094.
(13) Muñiz, K. *Angew. Chem., Int. Ed.* **2009**, *48*, 9412.
(14) Lyons, T. W.; Sandford, M. S. *Chem. Rev.* **2010**, *110*, 1147.
(15) Dick, A. R.; Hull, K. L.; Sanford, M. S. *J. Am. Chem. Soc.* **2004**, *126*, 2300.
(16) Wan, X.; Ma, Z.; Li, B.; Zhang, K.; Cao, S.; Zhang, S.; Shi, Z. *J. Am. Chem. Soc.* **2006**, *128*, 7416.
(17) Kalyani, D.; Dick, A. R.; Anani, W. Q.; Sanford, M. S. *Org. Lett.* **2006**, *8*, 2523.
(18) Kalyani, D.; Dick, A. R.; Anani, W. Q.; Sanford, M. S. *Tetrahedron* **2006**, *62*, 11483.
(19) Mei, T. S.; Giri, R.; Maugel, N.; Yu, J. Q. *Angew. Chem., Int. Ed.* **2008**, *47*, 5215.
(20) Kakiuchi, F.; Kochi, T.; Mutsutani, H.; Kobayashi, N.; Urano, S.; Sato, M.; Nishiyama, S.; Tanabe, T. *J. Am. Chem. Soc.* **2009**, *131*, 11310.
(21) Song, B.; Zheng, X.; Mo, J.; Xu, B. *Adv. Synth. Catal.* **2010**, *352*, 329.
(22) Mei, T. S.; Wang, D. H.; Yu, J. Q. *Org. Lett.* **2010**, *12*, 3140.
(23) Hull, K. L.; Anani, W. Q.; Sanford, M. S. *J. Am. Chem. Soc.* **2006**, *128*, 7134.
(24) Li, J. J.; Mei, T. S.; Yu, J. Q. *Angew. Chem., Int. Ed.* **2008**, *47*, 6452.
(25) Yu, W. Y.; Sit, W. N.; Lai, K. M.; Zhou, Z.; Chan, A. S. C. *J. Am. Chem. Soc.* **2008**, *130*, 3304.
(26) Zhao, X.; Dimitrijević, E.; Dong, V. M. *J. Am. Chem. Soc.* **2009**, *131*, 3466.
(27) Thu, H. Y.; Yu, W. Y.; Che, C. M. *J. Am. Chem. Soc.* **2006**, *128*, 9048.
(28) Ng, K. H.; Chan, A. S. C.; Yu, W. Y. *J. Am. Chem. Soc.* **2010**, *132*, 12862.
(29) Neufeldt, S. R.; Sanford, M. S. *Org. Lett.* **2010**, *12*, 532.
(30) Terao, Y.; Kametani, Y.; Wakui, H.; Satoh, T.; Miura, M.; Nomura, M. *Tetrahedron* **2001**, *57*, 5967.
(31) Gürbüz, N.; Ozdemir, I.; Cetinkaya, B. *Tetrahedron Lett.* **2005**, *46*, 2273.
(32) Thirunavukkarasu, V. S.; Parthasarathy, K.; Cheng, C. H. *Angew. Chem., Int. Ed.* **2008**, *47*, 9462.
(33) Sun, C. L.; Liu, N.; Li, B. J.; Yu, D. G.; Wang, Y.; Shi, Z. J. *Org. Lett.* **2010**, *12*, 184.
(34) See Supporting Information for details.
(35) Whitfield, S. R.; Sanford, M. S. *J. Am. Chem. Soc.* **2007**, *129*, 15142.
(36) Stowers, K. J.; Sanford, M. S. *Org. Lett.* **2009**, *11*, 4584.
(37) Powers, D. C.; Xiao, D. Y.; Geibel, M. A. L.; Ritter, T. *J. Am. Chem. Soc.* **2010**, *132*, 14530.
(38) Sakamoto, T.; Kikugawa, Y. *Synthesis* **1993**, 563.
(39) Tanimoto, S.; Yamadera, T.; Sugimoto, T.; Okano, M. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 627.
(40) Chang, C.-J.; Shieh, T.-L.; Floss, H. G. *J. Med. Chem.* **1977**, *20*, 176.
(41) Lukin, K.; Hsu, M. C.; Fernando, D.; Leanna, R. *J. Org. Chem.* **2006**, *71*, 8166.
(42) Said, S. B.; Skarzewski, S.; Mlochowski, J. *Synth. Commun.* **1992**, *22*, 1851.
(43) Medwid, J. B.; Paul, R.; Baker, J. S.; Brockman, J. A.; Du, M. T.; Hallett, W. A.; Hanifin, J. W.; Hardy, R. A.; Tarrant, M. E.; Torley, L. W.; Wrenn, S. *J. Med. Chem.* **1990**, *33*, 1230.
(44) Glennon, R. A.; Raghupathi, R.; Bartyzel, P.; Teitler, M.; Leonhardt, S. *J. Med. Chem.* **1992**, *35*, 734.
(45) Fleckenstein, C. A.; Plenio, H. *Chem.—Eur. J.* **2007**, *13*, 2701.
(46) Lee, S.; Lee, H.; Yi, K. Y.; Lee, B. H.; Yoo, S. E.; Lee, K.; Cho, L. S. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 2998.
(47) Spring, D. R.; Krishnan, S.; Blackwell, H. E.; Schreiber, S. L. *J. Am. Chem. Soc.* **2002**, *124*, 1354.

(48) Kabawata, T.; Jiang, C.; Hayashi, K.; Tsubaki, K.; Yoshimura, T.; Majumdar, S.; Sasamori, T.; Takitoh, N. *J. Am. Chem. Soc.* **2009**, *131*, 54.
(49) Cade, I.; Long, N. J.; White, A. J. P.; Williams, D. J. *J. Organomet. Chem.* **2006**, *691*, 1389.
(50) Kessar, S. V.; Gupta, Y. P.; Balakrishnan, P.; Sawal, K. K.; Mohammad, T.; Dutt, M. *J. Org. Chem.* **1988**, *53*, 1708.