JOC The Journal of Organic Chemistry

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# 2,2,6,6-Tetramethylpiperidine-Catalyzed, Ortho-selective Chlorination of Phenols by Sulfuryl Chloride

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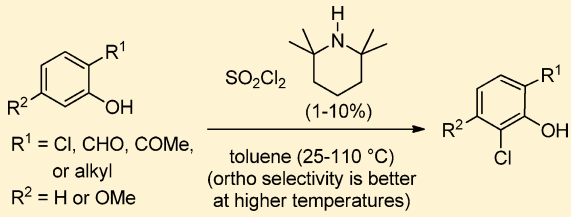
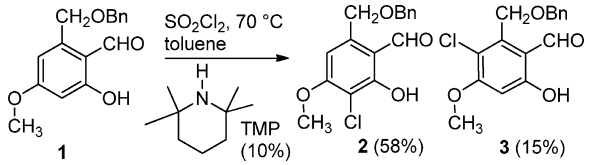
Supporting Information

**ABSTRACT:** 2,2,6,6-Tetramethylpiperidine (TMP)-catalyzed (1–10%) chlorinations of phenols by $SO_2Cl_2$ in aromatic solvents are more ortho selective than with primary and less hindered secondary amine catalysts. Ortho-selective chlorination is successful even with electron deficient phenols such as 2-hydroxybenzaldehyde and 2′-hydroxyacetophenone. Notably, ortho selectivity increases with the reaction temperature. On the other hand, tetraalkylammonium chloride-catalyzed chlorinations are moderately para selective.




For the synthesis of maldoxin, we needed to selectively ortho-chlorinate phenol **1** to give **2** rather than the *para*-chlorophenol **3** (see Scheme 1).[1] The ortho-selective

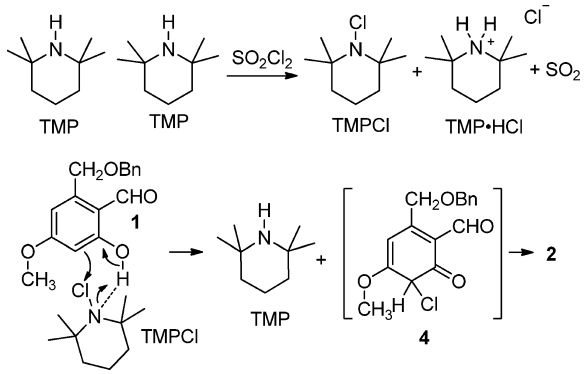
**Scheme 1. Ortho-selective Chlorination of 1 with $SO_2Cl_2$ and Catalytic TMP**




chlorination of phenol itself with $SO_2Cl_2$ and catalytic primary or secondary amines in toluene at 70 °C was reported by Gnaim and Sheldon, who suggested that the high regioselectivity results from the formation of an *N*-chloroamine in situ, which hydrogen bonds to the phenol forming a complex that delivers chlorine intramolecularly to the ortho-position.[2,3] We were disappointed to find that chlorination of **1** with $SO_2Cl_2$ and *t*-butylamine in toluene provided only a 1:2.6 mixture of **2** and **3**, although these conditions are quite ortho selective with phenol. We speculated that the selectivity might be favored by more hindered secondary amines that would favor ortho-selective chlorination via the hydrogen bonded complex. We were pleased to find that the ortho selectivity improved with more hindered secondary amines, increasing to 1.8:1 with dipropylamine, 3.3:1 with diisopropylamine, and 3.9:1 with 2,2,6,6-tetramethylpiperidine (TMP). Fortunately the products are easily separated so that using the latter amine we were able to obtain pure **2** (58%) and **3** (15%) on a gram scale.

Two molecules of TMP could react with $SO_2Cl_2$ to give one molecule of the *N*-chloroamine TMPCl, one molecule of TMP·HCl, and one molecule of $SO_2$ (see Scheme 2). TMPCl could hydrogen bond to the phenolic OH group making the chlorine more electrophilic and the phenol more nucleophilic, thereby facilitating intramolecular chlorination to give TMP and

**Scheme 2. Possible Mechanism for TMP-Catalyzed Ortho-selective Chlorination**




chlorocyclohexadienone **4**, which tautomerizes to **2**. The ortho-selective halogenation of phenols by stoichiometric *N*-bromo- and *N*-chloroamines in nonpolar solvents is well precedented,[4] although these reagents effect para-chlorination in TFA or other acidic media.[5] However, the pathway in Scheme 2 converts catalytic TMP to TMP·HCl, which suggests either that there is a pathway to generate TMPCl from TMP·HCl and $SO_2Cl_2$ or that this mechanism is not correct.

We report here our studies on the scope of the TMP-catalyzed ortho-selective chlorination of phenols that also provide further mechanistic insight. We started by examining the chlorination of 2-*t*-butylphenol (**5**) with $SO_2Cl_2$ and varying amounts of different amines at 25 °C in benzene-$d_6$ as shown in Table 1. With no amine, chlorination was slow, reaching 56% conversion after 405 min, but gave 70% of **6**, indicating that ortho-selective chlorination is preferred for **5** even without a hydrogen bonding pathway (entry 1). The ortho selectivity and conversion increase significantly on changing the catalyst from

**Received:** October 31, 2013
**Published:** December 13, 2013

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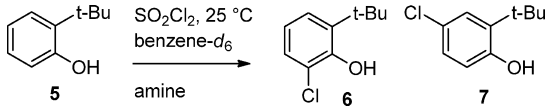
**Table 1. Chlorination of 2-*t*-Butylphenol (5)**




| entry | amine (%) | time (min) | conv[a] (%) | 6[b] (%) |
|---|---|---|---|---|
| 1 | none | 405 | 56 | 70 |
| 2 | *t*-BuNH$_2$ (1) | 50 | 8 | 79 |
| 3 | *t*-BuNH$_2$ (10) | 43 | 21 | 86 |
| 4 | Pr$_2$NH (1) | 42 | 39 | 92 |
| 5 | TMP (1) | 45 | 30 | 97 |
| 6 | TMP (10) | 24 | 95 | 96 |
| 7 | TMP·HCl (10) | 18 | 99 | 94 |
| 8 | Bu$_4$NCl (10) | 1 | 97 | 34[c] |
| 9 | cetylBnMe$_2$NCl (10) | 1 | 98 | 33[d] |
| 10 | cetylBnMe$_2$NCl (1) | 1 | 95 | 29[e] |
| 11 | cetylBnMe$_2$NCl (0.1) | 23 | 95 | 28 |
| 12 | Et$_4$NCl (10) | 1 | 99 | 25[f] |
| 13 | (*i*-Pr)$_2$EtN (1) | 10 | 69 | 55 |

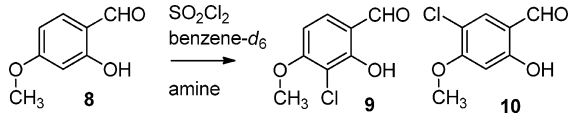
[a](**6** + **7**)/(**5** + **6** + **7**). [b]**6**/(**6** + **7**). [c]30% dichlorophenol. [d]36% dichlorophenol. [e]10% dichlorophenol. [f]22% dichlorophenol.

*t*-butylamine (entries 2 and 3), to dipropylamine (entry 4), and finally TMP (entries 5 and 6). With 10% TMP, the chlorination reached 95% conversion after 24 min with 96% ortho selectivity. On a preparative scale, we obtained **6** in 87% isolated yield by treatment of **5** with $SO_2Cl_2$ and 1% TMP in toluene at 25 °C for 24 h. Similar selectivity was observed with *o*-cresol, although the isolated yield was slightly lower because of the volatility and water solubility of the product.

Tetraethylammonium trichloride in $CH_2Cl_2$ is known to chlorinate aromatic rings,[6] so we thought that TMP·HCl might react with $SO_2Cl_2$ to form $SO_2$ and the chlorinating agent TMP·HCl$_3$. Chlorination with $SO_2Cl_2$ and the soluble tetraalkylammonium salts Bu$_4$NCl, cetylBnMe$_2$NCl, and Et$_4$NCl in benzene-$d_6$ was much faster than with TMP, but the ortho selectivity dropped to 25−34% (entries 8−12). Reaction with only 0.1% cetylBnMe$_2$NCl was complete in just 23 min, indicating that it is a very effective catalyst (entry 11). However, the low ortho selectivity suggests that the chlorination, which might proceed through the trichloride anion,[6] is mechanistically different than with primary or secondary amine catalysts. Chlorination with 10% TMP·HCl (entry 7) was 94% ortho selective suggesting that the trichloride anion is not involved. Chlorination with 1% of the hindered tertiary amine (*i*-Pr)$_2$EtN (entry 13) was slightly faster (69% conversion after 10 min) than with 1% of primary or secondary amines, but the ortho selectivity dropped to 55%.

Phenol **8** is less reactive than **5**, so we examined the effect of varying amounts of primary and secondary amines at different temperatures as shown in Table 2. Chlorination with $SO_2Cl_2$ and no amine was slow even at 70 °C and was para selective (entries 1−2). Chlorination was still slow and para selective with 1 or 10% *t*-BuNH$_2$ at 25 or 70 °C (entries 3−6). Chlorination proceeded effectively with 1 or 10% Pr$_2$NH at 25 or 70 °C (entries 7−10). Notably the ortho selectivity increased from 25−30% at 25 °C to 52−56% at 70 °C. The chlorination was even more ortho selective with TMP (entries 11−15). With 1% TMP, ortho selectivity increased from 36 to 53% on increasing the temperature from 25 to 70 °C (entries 11 and 13). With 10% TMP, ortho selectivity increased from 43 to 67 to 82% on increasing the temperature from 25 to 70 and

**Table 2. Chlorination of 2-Hydroxy-4-methoxybenzaldehyde (8)**




| entry | amine (%) | temp (°C) | time (min) | conv[a] (%) | 9[b] (%) |
|---|---|---|---|---|---|
| 1 | none | 25 | 1440 | 16 | 16 |
| 2 | none | 70 | 30 | 20 | 38 |
| 3 | *t*-BuNH$_2$ (1) | 25 | 21 | 34 | 17 |
| 4 | *t*-BuNH$_2$ (10) | 25 | 5 | 64 | 19 |
| 5 | *t*-BuNH$_2$ (1) | 70 | 53 | 53 | 23 |
| 6 | *t*-BuNH$_2$ (10) | 70 | 72 | 72 | 28 |
| 7 | Pr$_2$NH (1) | 25 | 27 | 80 | 25 |
| 8 | Pr$_2$NH (10) | 25 | 10 | 94 | 30 |
| 9 | Pr$_2$NH (1) | 70 | 10 | 92 | 52 |
| 10 | Pr$_2$NH (10) | 70 | 4 | 91 | 56 |
| 11 | TMP (1) | 25 | 16 | 53 | 36 |
| 12 | TMP (10) | 25 | 6 | 85 | 43 |
| 13 | TMP (1) | 70 | 13 | 86 | 53 |
| 14 | TMP (10) | 70 | 4 | 95 | 67 |
| 15 | TMP (10) | 110[c] | 30 | 90 | 82 (56)[d] |
| 16 | Bu$_4$NCl (10) | 25 | 2 | 87 | 21 |
| 17 | Bu$_4$NCl (10) | 70 | 2 | 77 | 28 |

[a](**9** + **10**)/(**8** + **9** + **10**). [b]**9**/(**9** + **10**). [c]Reaction carried out in toluene. [d]Isolated yield.

then to 110 °C (entries 12, 14, and 15). Under the latter conditions, we isolated **9** in 56% yield. As expected from our results with **5**, chlorination of **8** with 10% Bu$_4$NCl at 25 °C was both very rapid and para selective (entry 16). As with secondary amines, ortho selectivity was slightly better at 70 than 25 °C (entry 17).

The results in Tables 1 and 2 provide further insight into the mechanism of amine-catalyzed chlorination with $SO_2Cl_2$. The best ortho selectivity is obtained at higher temperatures with TMP, a hindered secondary amine. Hydrophobic tetraalkylammonium chlorides, which presumably react with $SO_2Cl_2$ to form the trichloride anion, are very effective catalysts that are para-, rather than ortho-, selective. Since chlorination with either TMP·HCl and TMP is equally ortho selective, the trichloride anion is unlikely to be the chlorinating agent. Although $SO_2Cl_2$ reacts with secondary amines to give $R_2NSO_2Cl$[7] and with phenol to give $PhOSO_2Cl$[8] under basic conditions, these compounds are not formed under acidic conditions and do not function as chlorinating reagents.

We have established that TMP reacts with 0.5 equiv of $SO_2Cl_2$ in either benzene-$d_6$ or $CDCl_3$ to give an approximately 1:1 mixture of TMP·HCl and TMPCl as proposed in Scheme 2. The $^{13}$C NMR data are most informative in that the quaternary carbon absorbs at $\delta$ 49.6 in TMP, $\delta$ 56.9 in TMP·HCl, and $\delta$ 62.6 in TMPCl.[9] However, neither TMPCl[9] nor the above 1:1 mixture of TMPCl and TMP·HCl chlorinates phenol **8** in benzene-$d_6$, so the mechanism is more complex than proposed in Scheme 2. Smith reported that silica gel catalyzes the ortho-selective chlorination of phenols by *N*-chlorodialkylamines in $CCl_4$, which is consistent with a more complex mechanism.[4d] Addition of 1 equiv of $SO_2Cl_2$ to phenol **8** and 10% of the above 1:1 mixture of TMPCl and TMP·HCl in benzene-$d_6$ afforded exactly the same result (43% ortho selectivity, entry 12, Table 2) as addition of $SO_2Cl_2$ to phenol **8** and 10% TMP. Notably, addition of 1 equiv of $SO_2Cl_2$ to phenol **8** and 10% of


dx.doi.org/10.1021/jo402424h | J. Org. Chem. 2014, 79, 809−813

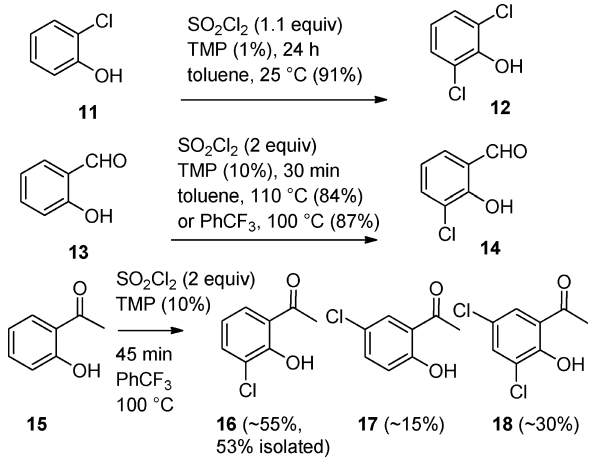
TMPCl[9] in benzene-$d_6$ at 25 °C proceeded with higher (67%) ortho selectivity. Thus TMP, TMPCl, and TMP·HCl all catalyze the chlorination of **8** by $SO_2Cl_2$ and the ortho selectivity is somewhat better with TMPCl.

The chlorination mechanism(s) need to be consistent with the very rapid, para-selective chlorination with $SO_2Cl_2$ and tetraalkylammonium chlorides and the somewhat slower, ortho-selective chlorination with $SO_2Cl_2$ and either TMP, TMPCl, or TMP·HCl. The ortho-selective reaction likely proceeds through an unknown chlorinating species that forms a hydrogen-bonded complex with the phenol that transfers chlorine intramolecularly by a pathway related to that proposed in Scheme 2.[4,10,11] On the other hand, tetraalkylammonium chlorides likely react with $SO_2Cl_2$ to give the trichloride anion, which rapidly chlorinates the phenol with para selectivity.

The reasons for the improved ortho selectivity at higher temperature are also not clear. The higher solubility of TMP·HCl in benzene-$d_6$ or toluene at higher temperatures could play a role. Regeneration of TMP by dissociation of TMP·HCl to TMP and HCl, which will evaporate more effectively at higher temperatures, could also play a role. Amines are about $10^{-6}$ times less basic in toluene than in water[12] so that partial dissociation of TMP·HCl to TMP may be possible. It is worth noting that chloroamines are $10^{-10}$ less basic than amines[13] so that TMPCl will not be protonated by HCl in benzene or toluene. Other less hindered amines may be less ortho selective because they form a less hindered chlorinating species that may be better able to chlorinate the para-position without hydrogen bonding. Analogous differences have been observed in the photochlorination of alkanes in TFA-10% $H_2SO_4$ with $Pr_2NCl$ or TMPCl, which is more selective for the least hindered position.[14]

We examined the regioselectivity with a variety of ortho-substituted phenols as shown in Scheme 3. Chlorination of 2-

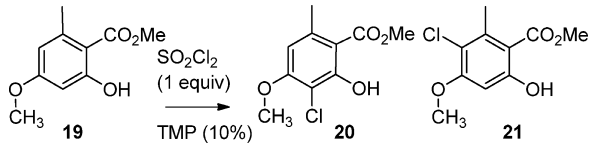
**Scheme 3**




chlorophenol (**11**) with $SO_2Cl_2$ and 1% TMP in toluene at 25 °C for 24 h provided 2,6-dichlorophenol (**12**) in 91% yield. 2-Hydroxybenzaldehyde (**13**), with an electron withdrawing aldehyde group and only one electron donating oxygen, is much less reactive than **8**. Reaction of 13 in toluene at 110 °C with 10% TMP and 2 equiv of $SO_2Cl_2$ afforded **14** in 84% yield. Unfortunately, competing ring and side chain chlorination of toluene occurred under these conditions. Fortunately, chlorination of **13** in $PhCF_3$ at 100 °C provided **14** in 87% yield without the formation of byproducts. This is the first report of the ortho-selective chlorination of **13** to give **14**, which is usually prepared by formylation of 2-chlorophenol.[15] Chlorination of 2′-hydroxyacetophenone (**15**) in $PhCF_3$ at 100 °C was less selective, giving a mixture of **16** and **17** with some dichlorophenol **18**. Fortunately, *para*-chlorophenol **17** and dichlorophenol **18** are less polar than *ortho*-chlorophenol **16**, which can be easily isolated chromatographically in 53% yield. Chlorination of methyl salicylate under these conditions was unselective. Chlorination of 2-nitrophenol in toluene at 110 °C or $PhCF_3$ at 100 °C was completely ortho selective but because of the deactivating nitro group could not be pushed past 20% conversion even with additional TMP and $SO_2Cl_2$.

*ortho*-Chlorophenol **20** is an intermediate in the synthesis of lichen xanthones.[16] Although it has been prepared regioselectively by a multistep route starting with chlorination of the cyclohexane-1,3-dione precursor to **19**, chlorination of **19**[17] was useful for testing the scope of this reaction. The uncatalyzed chlorination of **19** with $SO_2Cl_2$ gave only **21**,[18] indicating that para-chlorination of **19** is inherently preferred. Chlorination with $SO_2Cl_2$ and 10% TMP in benzene-$d_6$ at 25 °C afforded only 10% of *ortho*-chlorophenol **20** as shown in Table 3. The

**Table 3. Chlorination of Methyl 2-Hydroxy-4-methoxy-6-methylbenzoate (19)**




| entry | solvent | temp (°C) | time (min) | conv[a] (%) | **20**[b] (%) |
|---|---|---|---|---|---|
| 1 | benzene-$d_6$ | 25 | 20 | 45 | 10 |
| 2 | toluene | 110 | 60 | 85 | 34[c] (17)[d] |

[a](**20** + **21** + dichlorophenol)/(**19** + **20** + **21** + dichlorophenol). [b]**20**/(**20** + **21**). [c]13% dichlorophenol. [d]Isolated yield.

selectivity for **20** increased to 34% in toluene at 110 °C, which clearly shows that ortho selectivity is enhanced at higher temperature even though the 17% isolated yield of **20** is not satisfactory.

In conclusion, we have found that 2,2,6,6-tetramethylpiperidine (TMP)-catalyzed (1−10%) chlorinations of phenols by $SO_2Cl_2$ in aromatic solvents are more ortho selective than with primary and less hindered secondary amine catalysts. Ortho-selective chlorination is successful even with electron deficient phenols such as 2-hydroxybenzaldehyde and 2′-hydroxyacetophenone. Notably, ortho selectivity increases with the reaction temperature. On the other hand, tetraalkylammonium chloride catalyzed chlorinations are moderately para selective.

## EXPERIMENTAL SECTION

**General Experimental Methods.** Reactions were conducted in flame- or oven-dried glassware under a nitrogen atmosphere and were stirred magnetically. The term concentrated refers to removal of solvents by means of a rotary evaporator attached to a diaphragm pump (15−60 Torr) followed by removal of residual solvents at <1 Torr with a vacuum pump. Flash chromatography was performed on silica gel 60 (230−400 mesh). Analytical thin layer chromatography (TLC) was performed using silica gel 60 F-254 precoated glass plates (0.25 mm). TLC plates were analyzed by short wave UV illumination or by use of a $KMnO_4$ stain. $^1H$ and $^{13}C$ NMR spectra were obtained on a 400 MHz spectrometer in $CDCl_3$ unless otherwise indicated. Chemical shifts are reported in $\delta$ (ppm downfield from tetramethylsi-


dx.doi.org/10.1021/jo402424h | J. Org. Chem. 2014, 79, 809−813

lane) and are referenced to the residual solvent peak of $CDCl_3$ at $\delta$ 7.26 and $\delta$ 77.00 in $^1H$ and $^{13}C$ NMR, respectively, or $C_6D_6$ at $\delta$ 7.15 and $\delta$ 128.00 in $^1H$ and $^{13}C$ NMR, respectively. Coupling constants are reported in Hz with multiplicities denoted as s (singlet), d (doublet), t (triplet), q (quartet), p (pentet), m (multiplet), and br (broad). IR spectra were acquired by ATR on an FT-IR spectrometer and are reported in wave numbers ($cm^{-1}$). Methyl 2-hydroxy-4-methoxy-6-methylbenzoate (**19**) was prepared according to the literature procedure.[17]

**Exploratory Experiments.** $SO_2Cl_2$ (18 $\mu$L, 0.22 mmol, 1.1 equiv) was added via a 50 $\mu$L syringe to a solution of phenol **5** or **8** (0.2 mmol) and the amine or ammonium chloride specified in Tables 1 or 2 in 0.4 mL of $C_6D_6$ in an NMR tube. The sample was monitored by $^1H$ NMR spectroscopy for the time indicated in Tables 1 and 2.

**Reaction of TMP and $SO_2Cl_2$ in $CDCl_3$.** $SO_2Cl_2$ (8 $\mu$L, 0.1 mmol, 0.5 equiv) was added to a solution of TMP (28 mg, 0.2 mmol) in 0.4 mL of $CDl_3$ in an NMR tube. The $^1H$ NMR spectrum showed an approximately 1:1 mixture of TMP·HCl (methyl singlet at $\delta$ 1.54) and TMPCl (methyl singlet at $\delta$ 1.19). The $^{13}C$ NMR spectrum showed an approximately 1:1 mixture of TMP·HCl ($\delta$ 57.0, 35.0, 27.5, 16.2) and TMPCl ($\delta$ 62.5, 40.5, 27.2, 17.1). The peaks at $\delta$ 62.5 ($C_2$ and $C_6$) and 27.2 (Me) were broadened by a slow exchange process.

A reference sample of TMP·HCl was prepared by treating TMP with 4.0 M HCl in dioxane. A reference sample of TMPCl was prepared by the literature procedure.[9]

*Data for TMP.* $^1H$ NMR ($CDCl_3$) 1.68−1.61 (m, 2), 1.32 (br t, 4, $J$ = 6.1 Hz), 1.11 (s, 12); $^1H$ NMR ($C_6D_6$) 1.57−1.48 (m, 2), 1.23 (br t, 4, $J$ = 5.4 Hz), 1.06 (s, 12); $^{13}C$ NMR ($CDCl_3$) 49.6, 38.5, 31.5, 18.3; $^{13}C$ NMR ($C_6D_6$) 49.6, 38.6, 32.0, 18.8.

*Data for TMP·HCl.* $^1H$ NMR ($CDCl_3$) 1.76−1.68 (m, 6), 1.59 (s, 12); $^{13}C$ NMR ($CDCl_3$) 56.9, 35.2, 27.7, 16.3. Lack of solubility precluded obtaining data in $C_6D_6$.

*Data for TMPCl.* $^1H$ NMR ($CDCl_3$) 1.65−1.58 (m, 4), 1.58−1.52 (m, 2), 1.23 (s, 12); $^1H$ NMR ($C_6D_6$) 1.38 (br t, 4, $J$ = 5.5 Hz), 1.26−1.20 (m, 2), 1.21 (s, 12); $^{13}C$ NMR ($CDCl_3$) 62.6, 40.7, 27.4, 17.2; $^{13}C$ NMR ($C_6D_6$) 62.5, 40.8, 27.4, 17.4.

**Reaction of TMP and $SO_2Cl_2$ in $C_6D_6$.** $SO_2Cl_2$ (8 $\mu$L, 0.1 mmol, 0.5 equiv) was added to a solution of TMP (28 mg, 0.2 mmol) in 0.4 mL of $C_6D_6$ in an NMR tube. TMP·HCl crystallized as colorless needles. The $^1H$ NMR spectrum showed mainly TMPCl (methyl singlet at $\delta$ 1.20). The $^{13}C$ NMR spectrum showed a little TMP·HCl ($\delta$ 56.9, 34.8, 27.4, 16.3) and mainly TMPCl ($\delta$ 62.5, 40.8, 27.3, 17.4). The peak at $\delta$ 27.3 (Me) was broadened by a slow exchange process.

**2-*tert*-Butyl-6-chlorophenol (6).** To a solution of 2-*tert*-butylphenol (**5**) (150.3 mg, 1.00 mmol) and 2,2,6,6-tetramethylpiperidine (0.4 M in toluene, 25 $\mu$L, 0.01 mmol) in toluene (10 mL) at 25 °C was added $SO_2Cl_2$ (90 $\mu$L, 1.1 mmol) slowly under $N_2$. After 24 h, the reaction was concentrated to give 179.6 mg of crude **6**. Flash chromatography (20:1 hexanes/EtOAc) gave 160.6 mg (87%) of **6** as a clear oil: $R_f$ 0.74 (7:1 hexanes/EtOAc); $^1H$ NMR ($CDCl_3$) 7.22 (dd, 1, $J$ = 7.8, 1.5), 7.20 (dd, 1, $J$ = 7.8, 1.5), 6.82 (dd, 1, $J$ = 7.8, 7.8), 5.87 (s, 1, OH), 1.44 (s, 9); $^{13}C$ NMR ($CDCl_3$) 149.7, 137.6, 126.4, 125.7, 120.9, 120.3, 35.2, 29.3 (3 C); IR (neat) 3524, 1434, 1242, 1186. The $^1H$ NMR and IR spectral data are identical to those previously reported.[19]

**3-Chloro-2-hydroxy-4-methoxybenzaldehyde (9).** To a solution of 2-hydroxy-4-methoxybenzaldehyde (**8**) (248 mg, 1.63 mmol) and 2,2,6,6-tetramethylpiperidine (28 $\mu$L, 0.16 mmol) in toluene (15 mL) at 110 °C was added $SO_2Cl_2$ (145 $\mu$L, 1.82 mmol) slowly under $N_2$. The reaction mixture was heated for 30 min, cooled, and concentrated. The residue was dissolved in $CH_2Cl_2$, which was washed with saturated NaCl solution and dried over $Na_2SO_4$ to give 415.1 mg of a 74:16:10 mixture of **9**, *para*-chlorophenol **10**, and recovered **8**. Flash chromatography (15:1 to 10:1 hexanes/EtOAc) gave 91.6 mg (30%) of a 2:1 mixture of **10** and **8** followed by 168.0 mg (56%) of **9** as a white solid: $R_f$ 0.28 (4:1 hexanes/EtOAc); mp 123−125 °C (lit.[20a] 125 °C, lit.[20b] 114−117 °C); $^1H$ NMR ($CDCl_3$) 11.77 (s, 1, OH), 9.75 (s, 1), 7.47 (d, 1, $J$ = 8.6), 6.65 (d, 1, $J$ = 8.6), 4.00 (s, 3); $^{13}C$ NMR ($CDCl_3$) 191.7, 161.7, 158.9, 133.4, 115.9, 107.3, 103.6, 56.7; IR (neat) 1633, 1503, 1294, 1073, 792, 754.

**2,6-Dichlorophenol (12).** To a solution of 2-chlorophenol (**11**) (128.6 mg, 1.00 mmol) and 2,2,6,6-tetramethylpiperidine (0.4 M in toluene, 25 $\mu$L, 0.01 mmol) in toluene (10 mL) at 25 °C was added $SO_2Cl_2$ (90 $\mu$L, 1.1 mmol) slowly under $N_2$. After 24 h, the reaction mixture was concentrated. The residue was dissolved in $CH_2Cl_2$, which was washed with saturated NaCl solution and dried over $Na_2SO_4$ to give 149.1 mg (91%) of analytically pure **12** as a white solid: $R_f$ 0.63 (7:1 hexanes/EtOAc); mp 64−66 °C (lit.[21] 67−70 °C); $^1H$ NMR ($CDCl_3$) $\delta$ 7.26 (d, 2, $J$ = 8.0), 6.83 (t, 1, $J$ = 8.0), 5.84 (s br, 1, OH); $^{13}C$ NMR ($CDCl_3$) $\delta$ 147.8, 128.3 (2 C), 121.15 (2 C), 121.12; IR (neat) 3451, 1578, 1464, 1338, 770, 573. The $^1H$ and $^{13}C$ NMR spectral data are identical to those previously reported.[22]

**3-Chloro-2-hydroxybenzaldehyde (14).** To a solution of 2-hydroxybenzaldehyde (**13**) (122.5 mg, 1.00 mmol) and 2,2,6,6-tetramethylpiperidine (14.0 mg, 0.10 mmol) in $PhCF_3$ (10 mL) at 100 °C was added $SO_2Cl_2$ (160 $\mu$L, 2.00 mmol) slowly under $N_2$. The reaction mixture was heated for 30 min, cooled, and concentrated. The residue was dissolved in $CH_2Cl_2$, which was washed with saturated NaCl solution and dried over $Na_2SO_4$ to give 158.0 mg of crude **14**. Flash chromatography (20:1 hexanes/EtOAc) gave 3.5 mg (2%) of a mixture of **13** and the *para*-chlorophenol, followed by 136.0 mg (87%) of **14** as an off-white solid: $R_f$ 0.32 (7:1 hexanes/EtOAc); mp 53−54 °C (lit.[15a] 56 °C); $^1H$ NMR ($CDCl_3$) 11.49 (s, 1, OH), 9.91 (s, 1), 7.63 (dd, 1, $J$ = 7.9, 1.2), 7.51 (dd, 1, $J$ = 7.9, 1.2), 7.00 (dd, 1, $J$ = 7.9, 7.9); $^{13}C$ NMR ($CDCl_3$) 196.0, 157.2, 136.9, 132.1, 122.2, 121.4, 120.2; IR (neat) 1645, 1446, 1293, 1223, 745, 677. The $^1H$ NMR, $^{13}C$ NMR, and IR spectral data are identical to those previously reported.[15a]

**3′-Chloro-2′-hydroxyacetophenone (16).** To a solution of 2′-hydroxyacetophenone (**15**) (136.3 mg, 1.00 mmol) and 2,2,6,6-tetramethylpiperidine (15.5 mg, 0.11 mmol) in $PhCF_3$ (10 mL) at 100 °C was added $SO_2Cl_2$ (160 $\mu$L, 2.00 mmol) slowly under $N_2$. The reaction mixture was heated for 45 min, cooled, and concentrated. The residue was dissolved in $CH_2Cl_2$, which was washed with saturated NaCl solution and dried over $Na_2SO_4$ to give 181.3 mg of a ∼55:15:30 mixture of **16**, *para*-chlorophenol **17**, and dichlorophenol **18**. Flash chromatography (20:1 hexanes/EtOAc) gave 76.8 mg (45%) of a mixture of **17** and **18** followed by 90.0 mg (53%) of **16** as an off-white solid: $R_f$ 0.43 (7:1 hexanes/EtOAc); mp 44−47 °C (lit.[23] 49.5−50 °C); $^1H$ NMR ($CDCl_3$) 12.84 (s, 1, OH), 7.68 (dd, 1, $J$ = 8.0, 1.7), 7.57 (dd, 1, $J$ = 8.0, 1.7), 6.87 (dd, 1, $J$ = 8.0, 8.0), 2.66 (s, 3); $^{13}C$ NMR ($CDCl_3$) 204.4, 158.0, 136.3, 129.1, 122.8, 120.5, 119.0, 26.7; IR (neat) 2363, 1641, 1430, 770, 735. The $^1H$ NMR spectral data are identical to those previously reported.[24]

**Methyl 3-Chloro-2-hydroxy-4-methoxy-6-methylbenzoate (20).** To a solution of methyl 2-hydroxy-4-methoxy-6-methylbenzoate (**19**) (137.0 mg, 0.70 mmol) and 2,2,6,6-tetramethylpiperidine (11.0 mg, 0.077 mmol) in toluene (10 mL) at 110 °C was added $SO_2Cl_2$ (62 $\mu$L, 0.77 mmol) slowly under $N_2$. The reaction mixture was heated for 60 min, cooled, and concentrated. The residue was dissolved in $CH_2Cl_2$, which was washed with saturated NaCl solution and dried over $Na_2SO_4$ to give 140.5 mg of a ∼1:1.9:0.6:0.6 mixture of **20**, **21**, dichlorophenol, and recovered **19**. Flash chromatography (20:1 hexanes/EtOAc) gave 27.3 mg (17%) of a 2:1:1 mixture of recovered **19**, **21**, and dichlorophenol followed by 76.6 mg (51%) of a 4:1 mixture of **21** and dichlorophenol. Lastly, 25.4 mg (17%) of **20** was isolated as a white solid: mp 163−166 °C, 167−169 °C after recrystallization from $CH_2Cl_2$/pentane (lit.[16b] 169−170 °C); $R_f$ 0.20 (7:1 hexanes/EtOAc); $^1H$ NMR ($CDCl_3$) 12.23 (s, 1, OH), 6.35 (s, 1), 3.96 (s, 3), 3.94 (s, 3), 2.55 (s, 3); $^{13}C$ NMR ($CDCl_3$) 171.9, 159.9, 158.8, 141.3, 107.3, 106.56, 106.52, 56.2, 52.2, 24.6; IR (neat) 2930, 2858, 1652, 1559, 1440, 1317, 1103. The $^1H$ NMR spectral data are identical to those previously reported.[16]

The data for **21** were determined from the mixture: $^1H$ NMR ($CDCl_3$) 11.55 (s, 1, OH), 6.43 (s, 1), 3.95 (s, 3), 3.90 (s, 3), 2.63 (s, 3). The $^1H$ NMR spectral data are identical to those previously reported.[18,25]

The data for the dichlorophenol were determined from the mixture: $^1H$ NMR ($CDCl_3$) 11.57 (s, 1, OH), 4.00 (s, 3), 3.93 (s, 3), 2.61 (s,


dx.doi.org/10.1021/jo402424h | J. Org. Chem. 2014, 79, 809−813

3). The $^{1}H$ NMR spectral data are identical to those previously reported.[18]

## ■ ASSOCIATED CONTENT

### Supporting Information

Copies of $^{1}H$ and $^{13}C$ NMR spectral data. 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.

## ■ ACKNOWLEDGMENTS

We thank Brandeis University for financial support and Dr. Xiao-Chuan Cai for experimental assistance.

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