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Unanticipated participation of HCl in nucleophilic chlorination reaction: expedient route to *meta* chlorophenols

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This communication is dedicated to Dr. Hsing-Pang Hsieh on the occasion of his 53rd birthday

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ABSTRACT

o-Quinone monoketals participated in a 1,4-addition reaction with HCl furnishing *m*-chlorophenols in high yields. Several readily available *o*-quinone monoketals were selected to display the generality of this serendipitous and unprecedented reaction and the results are presented herein.

For the past few years our research group has been involved in expanding the scope of masked *o*-benzoquinones (MOBs, *o*-quinone monoketals)[1,2] in organic synthesis.[3] During the course of our research programme employing MOBs as substrates, a variety of *meta* functionalized phenols have been synthesized.[2d,4] Interestingly, during the optimization process for the preparation of aryl glycine derivative **I** and *C*-aryl acetophenone **II**, we observed the formation of small quantities of *m*-chlorophenol derivative **3a-*m*** (Fig. 1). However, this was only noticed when MOB **2a** was not completely consumed in the first step (Michael addition). Therefore, we attributed the unexpected formation of 2,3-dimethoxy-5-chloro phenol (**3a-*m***) to the nucleophilic 1,4-addition of 'chloride' from HCl (utilized in the second step) to MOB **2a** followed by aromatization. We were intrigued by the fact that 'chloride' was able to undergo a smooth Michael addition to MOB **2a**. To the best of our knowledge, such an observation is unknown in *o*-quinone monoketal chemistry.[5] In general, phenols undergo electrophilic substitution producing *ortho* or *para* derivatized products. In the present reaction, starting from 2,3-dimethoxyphenol (**1a**, the precursor of MOB **2a**, Fig. 1), we ended-up with a *m*-chlorophenol derivative **3a-*m*** via a dearomatization–1,4-addition reaction–rearomatization sequence. As a result of this unprecedented outcome coupled with a novel procedure for *meta* chlorination of phenols in hand, it was contemplated that this serendipitous observation was worth pursuing further.

Our investigations for the envisaged protocol commenced by verifying the conversion of MOB **2a** to product **3a-*m***. To begin with, phenol **1a** was converted to MOB **2a** via oxidative dearomatization using $PhI(OAc)_2$ in methanol (Scheme 1).[2–4] The obtained MOB **2a** was subsequently treated with 4 N HCl in 1,4-dioxane (5 equiv) at room temperature. Almost instantaneous disappearance of the yellow colour of the reaction mixture indicated the complete consumption of MOB **2a**. However, the reaction was run for 2–3 min to ascertain that MOB **2a** was completely consumed. Simple aqueous work-up (saturated aqueous $NaHCO_3$/ethyl acetate) provided clean product in 95% yield (Table 1, entry 1) without the need for column chromatographic purification.[6] The coupling constants ($J_{H4-H6} = J_{H6-H4} = 2.4$ Hz) from the ^1H NMR spectra indicated the *meta* relationship of protons H4 and H6 in **3a-*m*** confirming the assigned regiochemistry. After some experimentation it was found that the reaction was high yielding and instantaneous even when 2.0 equiv of HCl was used, which represented the optimal conditions for subsequent reactions. Encouraged by this result several *o*-quinone monoketals **2b–j** (Scheme 1) were prepared from readily available 2-methoxyphenols.[2–4,7c] To our satisfaction MOBs

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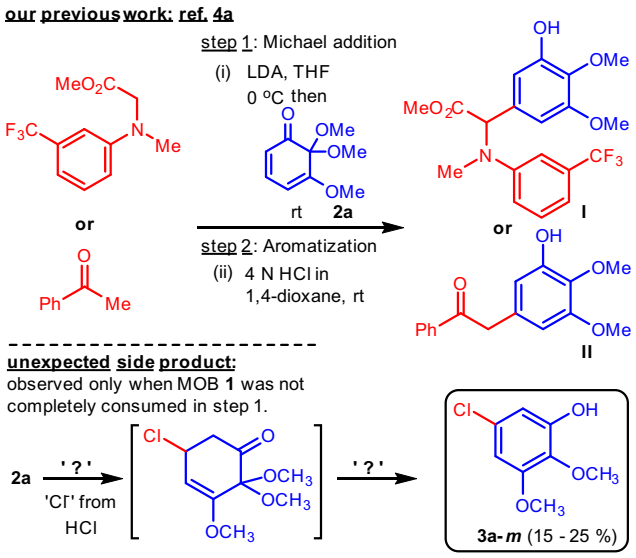
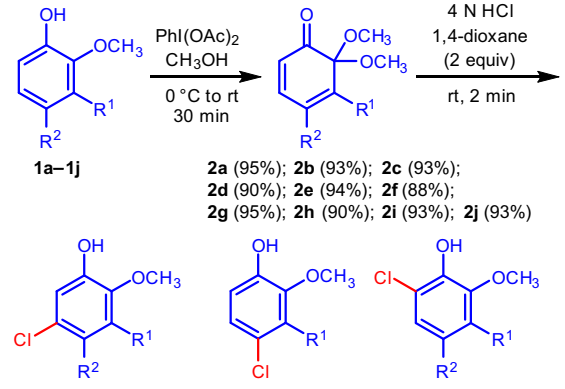


Figure 1. Unexpected formation of chlorophenol derivative **3a-*m*** via 'chloride' Michael addition to MOB **2a**.

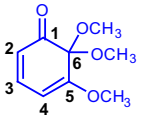
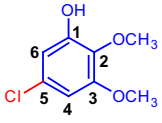
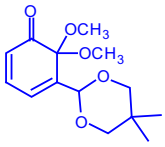
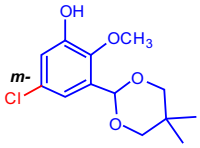
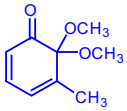
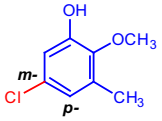
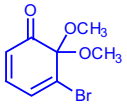
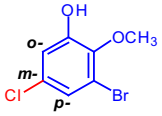
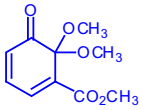
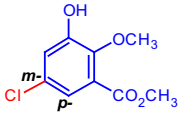
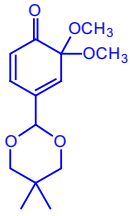
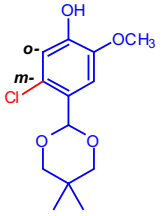
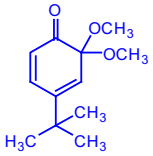
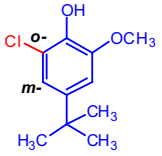
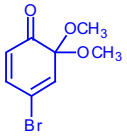
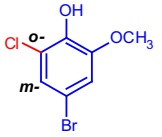
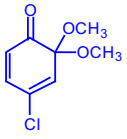
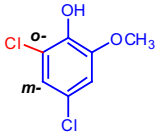
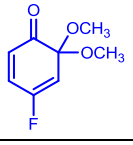
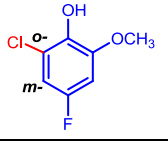
2b–**e** provided the expected *meta* chlorophenols **3b-*m*** to **3e-*m*** as major isomers along with small amounts of other regioisomers as indicated in Table 1, entries 2–5. A unique feature of MOBs is that all its carbon centres (C-1 to C-6) are potentially electrophilic in nature (Fig. 2).[7] As a consequence the possibility for the formation of other regioisomers is often inevitable. However, the exclusive formation of, or unequal amounts of regioisomers in the nucleophilic addition onto MOB can be attributed to (i) the nature of nucleophile (ii) electronic factors (i.e., substituents dictating the charge densities at the reaction centre) and (iii) sterically hindering groups near to the reaction site. The cumulative effect of the above factors influencing the regioselectivity also cannot be ruled-out. Thus, in the present study the formation of small amounts of regioisomers was not surprising. From the above results, it was evident that the carbonyl group strongly dictated 'chloride' addition to C-3, resulting in the observed *meta*-selectivity. Moreover, activation by the dimethoxy ketal moiety (Fig. 2, **B**) in MOB **2** could in principle provide **3-*o*** (*ortho*) or **3-*p*** (*para*) products. In MOBs **2c**–**e**, the C-4 position appeared to be the next preferred position for 'chloride' addition, subsequently providing **3c-*p*** to **3e-*p*** as the minor isomer. Similar *para* selectivity was observed during the synthesis of 3-arylindoles where MOBs were utilized as an aryl source.[2d]



a: R^1 = OCH_3; R^2 = H **b:** R^1 = ketal; R^2 = H **c:** R^1 = CH_3; R^2 = H
d: R^1 = Br; R^2 = H **e:** R^1 = CO_2CH_3; R^2 = H **f:** R^1 = H; R^2 = ketal
g: R^1 = H; R^2 = ^{t}Bu **h:** R^1 = H; R^2 = Br **i:** R^1 = H; R^2 = Cl **j:** R^1 = H; R^2 = F

Scheme 1. Preparation of masked *o*-benzoquinones (MOBs) and nucleophilic 'chloride' addition to MOBs.

Table 1
Tandem 1,4/1,6-nucleophilic 'chloride' addition followed by aromatization[a]

Entry	Substrate	Product/isolated yield	
1		**2a** 	**3a-*m***: 95%
2		**2b** 	**3b-*m***: 92%
3		**2c** 	**3c-*m***: 81% (***m***:***p*** = 90:10)[a]
4		**2d** 	**3d-*m***[b]: 82% **3d-*p***: 2% (***m***:***p***:***o*** = 91:6:3)[a]
5		**2e** 	**3e-*m***: 82% (***m***:***p*** = 90:10)[a]
6		**2f** 	**3f-*m***: 78% (***m***:***o*** = 87:13)[a]
7		**2g** 	**3g-*m***: 0% **3g-*o***: 90%
8[c]		**2h** 	**3h-*m* + 3h-*o*** ***o*** = 90% (***m***:***o*** = 25:75)[a]
9[c]		**2i** 	**3i-*m* + 3i-*o*** ***o*** = 90% (***m***:***o*** = 30:70)[a]
10[b]		**2j** 	**3j-*o***: 90%[d] (***m***:***o*** = 0:100)[d]

[a] Ratio of isomers was obtained by ^{1}H NMR integration of diagnostic peaks in the crude reaction mixture.
[b] Ref. 8.
[c] Chromatographically inseparable mixture of isomers was obtained.
[d] Small amount of an inseparable unknown impurity was also observed.

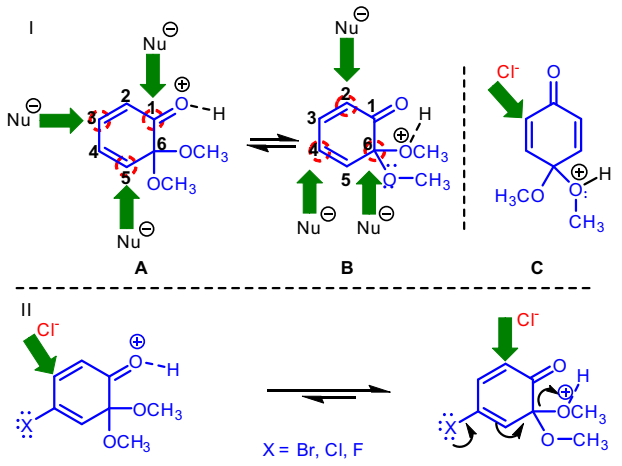
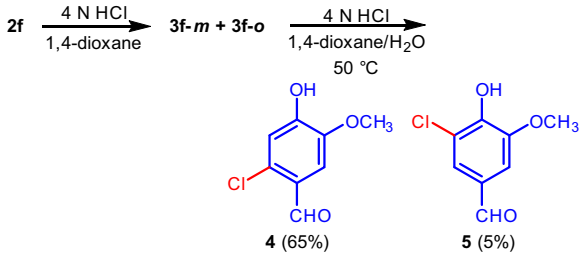


Figure 2. (I) **A** and **B**: All carbon centres in a MOB are electrophilic in nature; **C**: Rationale for the observed *ortho* selectivity in the case of *p*-quinone monoketals; (II) possible reason for *ortho* preference of the 'chloride' nucleophile for halogenated MOBs **2h**–**2j**.

Next, MOB **2f** (4-ketal substitution, Table 1, entry 6) was subjected to the optimized reaction conditions. As usual MOB **2f** provided **3f-*m*** as the major isomer (78% isolated yield) along with 13% of isomer **3f-*o*** as indicated by ^{1}H NMR analysis of the crude reaction mixture. Interestingly, the ketal group in the minor isomer **3f-*o*** was hydrolysed during column chromatography to give benzaldehyde derivative **5**. Alternatively, when the reaction mixture **3f-*m*** + **3f-*o*** was further treated with 15.0 equiv of 4 N aq HCl and heated to 50 °C for 6 h, the ketal groups of both isomers were hydrolysed providing separable benzaldehyde derivatives **4** and **5** in acceptable yields (Scheme 2).

To test the effect of steric hindrance near the reaction site on the regioisomeric ratio MOB **2g** was utilized which exclusively furnished isomer **3g-*o*** (Table 1, entry 7). This suggested that the bulky *t*-butyl group indeed completely blocked the β-position of the α,β-unsaturated ketone from 'chloride' attack. Subsequently, 4-halogenated MOBs **2h**–**j** were tested in the reaction. 4-Bromo (**2h**) and 4-chloro (**2i**), substituted MOBs provided inseparable mixtures of chlorophenol derivatives **3h/i-*m*** and **3h/i-*o***, where *meta* regioselectivity was the minor reaction pathway (Table 1, entries 8 and 9). The reversal of the regioselectivity in these cases could be due to halogens' ability to participate in mesomeric effect, thus changing the selectivity (Fig. 2-II). To further ascertain the presence of the halogen effect, we utilized MOB **2j** (with a fluoro substitution) in the reaction. On the basis that fluorine participates in strong electron-donating resonance[9] compared to chloro and bromo,[9] we anticipated a profound halogen effect in MOB **2j**. As expected, in the case of MOB **2j** the only product observed was **2j-*o*** (Table 1, entry 10) compared to *ortho*/*meta* products in ratio of 75:25 and 70:30 for MOBs **2h** and **2i** (as indicated by ^{1}H NMR



Scheme 2. One pot tandem nucleophilic 'chloride' addition–aromatization–ketal deprotection sequence.

analysis of the crude reaction mixture), respectively. However, a small role of sterics caused by halogens near to the reaction centre cannot be ruled-out for the observed reversal of regioselectivity.

The assignment of regioselectivity was straightforward in most cases. For example, in the cases of **3a-*m*** to **3e-*m*** both aromatic protons had coupling constants of 2.4 Hz indicating the *meta* relationship of these protons; similarly **3f-*o*** to **3j-*o*** and **5** showed coupling constants between 1.8 Hz and 2.8 Hz indicating the *meta* relationship of the protons on the aromatic ring. Subsequently, for products **3f-*m***, **3h-*m***, **3i-*m***, regioselectivity was assigned based on the observed singlets in the aromatic region. The minor isomer **3e-*p*** was assigned by comparing its ^{1}H NMR δ values with that of starting phenol **1e** as shown in Figure 3. In the cases of substrates **2c** and **2d** where the major isomers were unambiguously assigned based on *meta* coupling constants, regioselectivity assignment of the minor isomers seemed challenging. However, upon comparing δ values of the ^{1}H NMR spectra of **3d-*o*** and **3d-*p*** the minor isomers were tentatively assigned as shown in Figure 3.[10] The difference in δ ppm values of the aromatic protons was very small in **3d-*o*** indicating that both protons were experiencing a similar environment. In the case of **3g-*o***, *meta* coupling unambiguously supported the assigned regioselectivity. Moreover, 2D-NOESY experiments also indicated the same. In regioisomer **3c-*p***, the methyl group did not show any cross peaks with aromatic protons in a 2D-NOESY experiment indicating the assigned regioselectivity.[10]

To further evaluate the scope of the reaction we then subjected *o*-naphthoquinone monoketals **8**[11] and **9**[11] to the general reaction conditions. Both substrates underwent the tandem Michael-addition followed by the aromatization reaction sequence providing the expected *m*-chloronaphthol derivatives **10**[12] and **11** in high yields (Scheme 3).

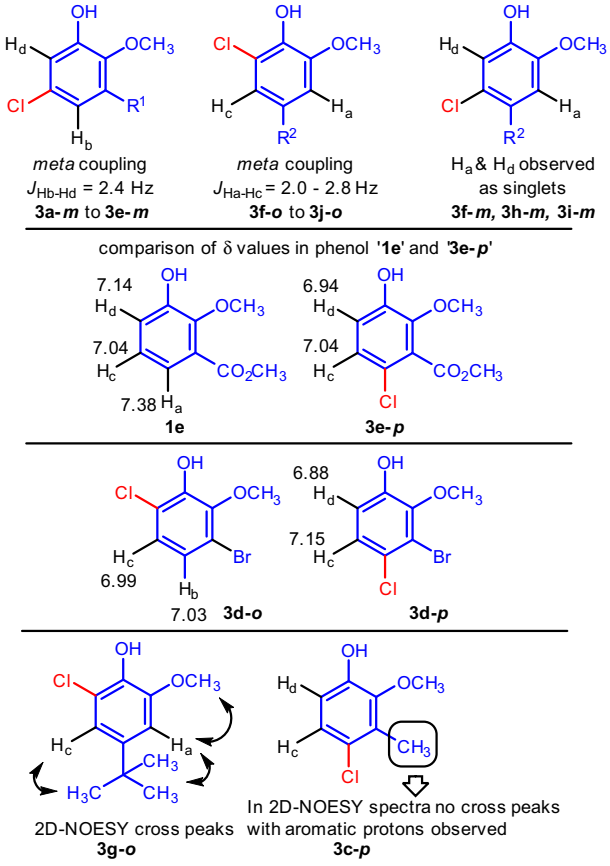
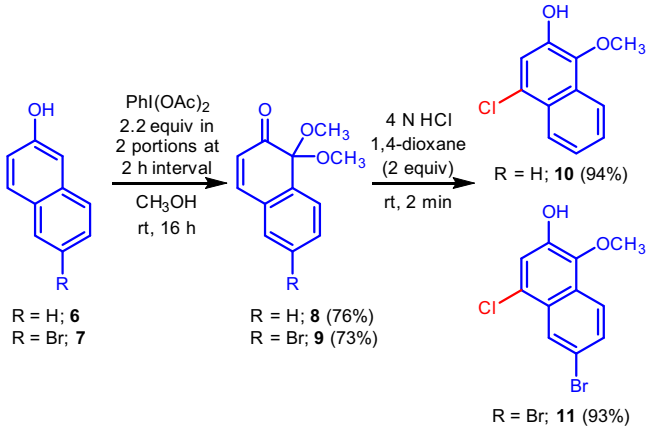
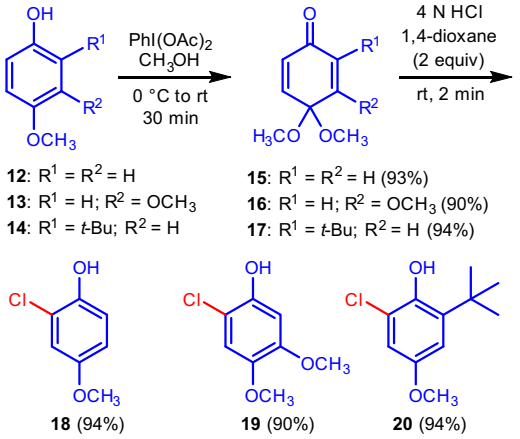


Figure 3. Regioselectivity assignment for the obtained products.



Scheme 3. *o*-Naphthoquinone monoketals **8**, **9** as substrates in a tandem 'chloride' Michael addition–aromatization sequence.



Scheme 4. *p*-Quinone monoketals as substrates in the nucleophilic 'chloride' addition–aromatization sequence.

Recently it was reported that *p*-quinone monoketals, upon reaction with *N*,*N*′-dimethylhydrazine dihydrochloride, provided *o*-chlorophenols.[5] It was also reported that 1 N HCl was successful in providing *o*-chlorophenol **15** in good yield, however substituted *p*-quinone monoketals provided lower yields under these conditions. To our delight, using our reaction procedure not only unsubstituted *p*-quinone monoketal **15**, but even substituted *p*-quinone monoketals **16** and **17** provided high yields of the *o*-chlorophenol products **19** and **20**, respectively (Scheme 4). In all cases the reaction was complete within 2 min and a simple aqueous work-up provided the clean product without the need for further purification. It appears that preferential activation of the methoxy group over the ketone moiety in *p*-quinone monoketals (**15**–**17**, Fig. 2C) by HCl results in the observed reversal of regioselectivity in the nucleophilic chloride addition. It should also be noted that acid mediated displacement of an allylic methoxy group in *p*-quinone monoketals was observed in several instances.[13]

In conclusion, a convenient and efficient method for the *meta*-chlorination of certain phenols has been developed. The reaction protocol relied on an arene oxidation–'chloride' Michael addition–aromatization sequence. It should be noted that the reaction conditions tolerated ester and ketal functionalities in substrates **2e**, **2b** and **2f** respectively. Moreover, this strategy could be extended to *o*-naphthoquinone derivatives which provided the corresponding chloronaphthols in high yields. In addition, it is evident from our study that commercial 4 N HCl in 1,4-dioxane is a highly reliable source of 'chloride' in the reaction and is distinct from that of a recent study which relied on *N*,*N*′-dimethylhydrazine dihydrochloride to furnish *o*-chlorophenols. Although regioisomers were obtained with several substrates, the observed regioselectivity was high and the isomers could be separated in some cases.

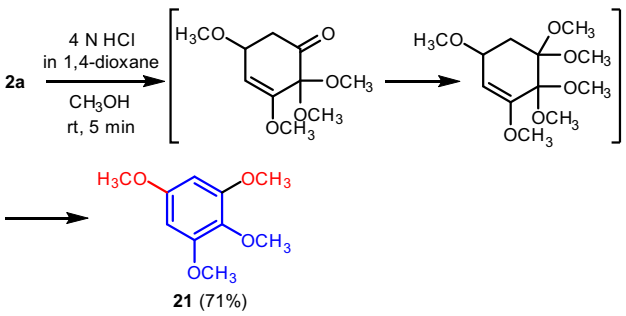


Figure 4. One pot tandem nucleophilic 'methoxy' addition–dimethoxy ketal formation–aromatization sequence.[6]

General procedure for the preparation of m-chlorophenols: To MOB **2a** (1.0 mmol) in a reaction vessel was added 4 N HCl in 1,4-dioxane (0.5 mL, 2 mmol) drop-wise. Disappearance of the yellow colour of MOB **2a** was instantaneous. The solvent was evaporated in vacuo. The residue was diluted with ethyl acetate (10 mL) and washed with saturated aqueous $NaHCO_3$ (5 mL). The organic fractions were dried over Na_2SO_4, filtered and concentrated to give *m*-chlorophenol **3a** in 95% yield. Whenever required column chromatographic purification was performed using ethyl acetate/hexanes gradient as eluent.

Acknowledgments

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Supplementary data

Supplementary data (copies of ^1H and ^{13}C NMR spectral data along with hydroxyl group ^1H NMR chemical shift trend table) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2015.11.012.

References and notes

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2. Synthetic protocols for the preparation of cyclohexadienones, see (a) Tamura, Y.; Yakura, T.; Haruta, J.; Kita, Y. *J. Org. Chem.* **1987**, *52*, 3927–3930; (b) Deffieux, D.; Fabre, I.; Titz, A.; Leger, J.-M.; Quideau, S. *J. Org. Chem.* **2004**, *69*, 8731–8738; (c) Pelter, A.; Elgendy, S. M. A. *J. Chem. Soc., Perkin Trans. 1* **1993**, 1891–1896; (d) Chittimalla, S. K.; Bandi, C.; Putturu, S.; Kuppusamy, R.; Boellaard, K. C.; Tan, D. C. T.; Lum, D. M. J. *Eur. J. Org. Chem.* **2014**, 2565–2575.
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5. While our project was in progress, nucleophilic addition of 'chloride' (*N*,*N*′-dimethylhydrazine dihydrochloride as a 'chloride' source) to *p*-quinone monoketals generating *o*-chlorophenol derivatives was reported: Yin, Z.; Zhang, J.; Wu, J.; Green, R.; Li, S.; Zheng, S. *Org. Biomol. Chem.* **2014**, *12*, 2854–2858.
6. When a methanolic solution of MOB **2a** was treated with 4 N HCl in 1,4-dioxane (2.0 equiv), we were surprised to isolate 1,2,3,5-tetramethoxybenzene

(**21**, 71% isolated yield, Fig. 4). However under the above reaction conditions, MOB **2g** and masked *p*-benzoquinone (MPB) **15** provided the corresponding chlorophenols **3g-*o*** and **18**, respectively. Currently, we are not sure what the driving force for the formation of **21** from **2a** might be. Work towards understanding this phenomenon is in progress. For analytical data for compound **21**, see Deodhar, M.; Black, D. StC.; Kumar, N*Tetrahedron* **2007**, *63*, 5227–5235.

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