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Interference of two adjacent methoxy groups as promoters of arene metallation

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Abstract

Two adjacent methoxy groups on a benzene ring reinforce each other as promoters of *ortho*-lithiation; the lower ease of metallation of veratrole with repect to anisole, observed in one special case, can be explained by the deactivation of the substrate upon formation of a chelate species with the lithium atom of the metallating agent. © 2000 Elsevier Science Ltd. All rights reserved.

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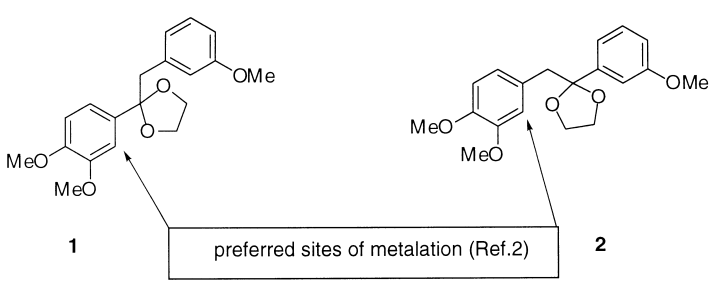
Based on the results of competitive lithiations of mono- to trimethoxy-substituted benzenes, Maggi and Schlosser have recently proposed as a general rule that two adjacent alkoxy groups interfere destructively as directors of *ortho*-metallation, because of the steric repulsion between the two methyl groups, which would disturb the coordination of the metallating agent prior to its interaction with the *ortho*-protons.[1] This is in contrast with what we have previously observed with other substituted benzenes and our conclusion that two adjacent methoxy groups actually reinforce each other in promoting the arene metallation to the extent that their combined effect can be exploited to bring about selective organic transformations, as it was demonstrated, for instance, by the selective metallation of the dimethoxy substituted ring of the two isomeric trimethoxysubstituted deoxybenzoin derivatives **1** and **2**.[2]



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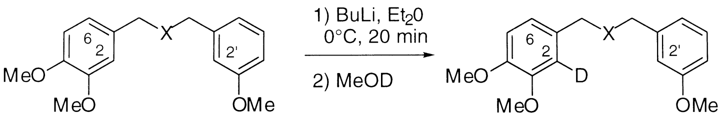
We wish to provide here the results of further experiments aimed at testing the generality of these conflicting statements and suggest a possible explanation for their apparent contrast.

When a slight excess of *n*-BuLi (as a 1.6 M solution in hexane) was added to a solution of dibenzyl amine **3a** in Et_2O under stirring in an ice bath, the precipitation of a solid occurred almost immediately; quenching of the reaction mixture with deuteriated methanol after 20 min led to a quantitative recovery of deuteriated amine **4a**. The site of deuterium incorporation was unambiguously determined from the ^1H NMR spectrum (benzene-d_6, 200 MHz), where the multiplets of the aromatic protons are sufficiently well separated; in particular, the doublet associated with proton 2-H disappeared upon deuteriation and the doublet of doublets associated to 6-H turned to a clean doublet. Deuteriation of this position was 100% within the error of the method. Parallel behaviour was exhibited by the dibenzyl ether **3b**, which gave **4b** with complete deuterium incorporation at the more substituted ring upon metallation and quenching with deuteriated methanol (Scheme 1).



3a X=NMe
3b X=O

4a X=NMe
4b X=O

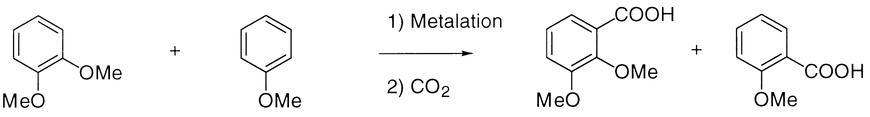
Scheme 1.

Also, the competitive metallations of veratrole (**5**) and anisole (**6**) turned out to be significantly influenced by the reaction conditions (see Table 1). Thus, when an equimolar mixture of the two aryl ethers (1 equiv. each) was allowed to react with *n*-BuLi (1 equiv.) at 0°C in Et_2O for 1 h and quenched with carbon dioxide, 2,3-dimethoxybenzoic (**7**) and 2-methoxybenzoic acid (**8**) were obtained in a ratio of 2:1, which reflect an inverted selectivity with respect to that obtained if the metallation is accomplished with *sec*-BuLi at –78°C in THF,[1] but still inferior to what could be expected on the basis of the metallation of **3**. Progressively higher values of the ratio **7**:**8** resulted by conducting the metallation with a deficiency of *n*-BuLi, whereas the highest preference for the metallation of **5** was obtained when the reaction was performed in the presence of tetramethylethylenediamine (TMEDA, 5 equiv.).

The above data seems to confirm the general view that the presence of a *meta*-methoxy group enhances the rate of metallation of an arene position and that two adjacent methoxy groups should be expected to be more powerful directors of the *ortho*-metallation than a single methoxy group. A *meta*-methoxy group might favour the metallation by enhancing the acidity of the C–H bond, through an inductive electron-withdrawing effect; also, as suggested by one of the referees of this paper, a *meta*-methoxy group might improve, through a conjugative effect, the ability of the *ortho*-methoxy group to coordinate the metallating agent. As to the lower reactivity of veratrole with respect to anisole observed by Maggi and Schlosser, a different effect should be taken into consideration.

The steric interaction between two vicinal methoxy groups on a benzene ring is probably not strong enough to prevent each single methoxy group from coordinating an alkyllithium and promoting the hydrogen–metal exchange of this reagent with the *ortho*-proton in a way which is

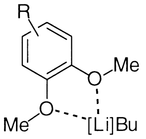
Table 1
Influence of reaction conditions on the competitive metallation of methoxy- and 1,2-dimethoxybenzene



5 **6** **7** **8**

Metallation conditions	**7/8 ratio**
sec-BuLi (1 eq.)/THF/-78 °C/2 h (Ref. 1)	1:2
n-BuLi (1 eq)/Et_2O/ 0 °C/1 h	2:1
n-BuLi (0.5 eq.)Et_2O/ 0 °C/1 h	3:1
n-BuLi (0.2 eq.)Et_2O/ 0 °C/1 h	4:1
n-BuLi/Et_2O (1 eq.)/TMEDA (5 eq.) / 0 °C/1 h	8:1

similar to the one in which anisole undergoes metallation, the differences between the two cases being dictated mainly by the different intrinsic acidities of the aromatic hydrogens and the different donor properties of the alkoxy groups. Unlike an isolated methoxy group, however, two vicinal methoxy groups can also behave as a chelating agent of the lithium atom of the metallating agent, giving rise to species like **9** (brackets around the Li atom mean that other species might be present in its coordination sphere), which can be expected to undergo *ortho*-metallation less easily than an unchelated species. In fact, the chelation of the lithium atom directs the oxygen lone pairs of the vicinal alkoxy groups toward each other, while pushing the methyl groups in the opposite direction, in such a way that they sterically hinder the approach of any metallating species to the *ortho* hydrogens; on the other end, the metallating agent trapped inside the chelate species **9** cannot abstract an *ortho* proton intramolecularly because it is too far away from it.



9

Depending on the reaction conditions (high temperature, presence of additives capable of strongly coordinating the lithium atom) and the substrate (presence of other heteroatoms capable of stabilizing the metallating agent in a situation more favourable for *ortho*-proton abstraction) the amount of chelate species related to **9** can be made progressively less important in retarding the metallation. As a matter of fact, the inhibition seems to be limited to an extreme situation. Confirmation of this view can be found also in Maggi and Schlosser's data: in fact 1,3,4-trimethoxybenzene undergoes lithiation more easily than 1,3-dimethoxybenzene.[1]

In conclusion, two adjacent methoxy groups can be expected to behave as better promoters of *ortho*-lithiation than an isolated methoxy group, except for the case in which the chelation of the metallating agent by the two methoxy groups is important. An interesting case of metallation inhibited by a strong complexation of the metallating agent by the substrate has possibly been found. Finally, attention should be paid when proposing acidity scales of carbon acids, because they can be influenced by the choice of metallation conditions.

Acknowledgements

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