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Metalation of *o*-methylanisole (*o*-MA); an optional-site selectivity reassessment

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ABSTRACT

'Deficiency catalysis' is the concept applied to metalation chemistry that increments of TMEDA or an equivalent or two of an ether activate alkyllithiums in hydrocarbon media. Amplification of this concept to conflicting reports of α- and *ortho*-metalation of *ortho*-methylanisole (*o*-MA) is explored. Both regioselective metalations were realized in selectivity ratios of >7:1 for the desired isomers. Some rationale is provided for the various selectivities. These results are at variance with prior results and interpretations thereof found in the literature.

1. Introduction

Directed *ortho*-metalation (DoM)[1] is a useful alternative to electrophilic aromatic substitution (EAS) for the preparation of specifically oriented multi-substituent aromatic compounds. A related reaction, directed α-metalation, affords regiospecific metalation at a benzylic position *ortho*- to a directing metalation group (DMG) situated on an aromatic nucleus. Directed α-metalation is the set of lateral metalations[2] at the benzylic positions of an arene ring that possesses the greater utility. Arene lateral metalations that are not directed, i.e., those where there is no *ortho*-DMG, are often a hindrance to regiospecific metalation in that they afford a secondary site for metalation and thereby provide mixtures of isomeric products upon addition of an electrophile.

Recently, a study of the optional-site selectivity of an oxazoline derivative of *o*-toluic acid revealed that careful manipulation of metalation conditions allowed optional site selective metalation at either the α-methyl group or the *ortho*-position of 4,4-dimethyl-2-(*o*-tolyl)oxazoline.[3] 'Optional-site selectivity' is a term attributable to Schlosser and co-workers,[4] which has primarily been used to indicate regiospecific metalation at a particular *ortho*-position of a benzene ring possessing *p*-oriented DMG's (Fig. 1). Its extension to *ortho*- versus α-metalation is useful and will be used throughout our discussion.

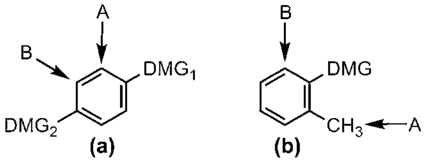

Figure 1. Optional-site selectivity: (a) two *p*-oriented DMG's on a benzene ring illustrating metalation at position A under conditions that allow $-$DMG$_1$ to control the site of metalation; a dissimilar set of metalating conditions will allow DMG$_2$ to control the site of metalation at position B. (b) Similarly, α-metalation is effected at position A under one set of conditions while under a dissimilar set of conditions *ortho*-lithiation is effected at position B.

Investigation of the atom-economical, hydrocarbon media supported regiospecific metalations of *o*-, *m*-, and *p*-methylanisoles was undertaken to understand the interplay among several conflicting factors involving α-lithiation, undirected lateral lithiation, and directed *ortho*-metalation (DoM). The goal was to find conditions to achieve regiospecific *ortho*- and, separately, α-metalation in all cases. Our intent was and still is to demonstrate the effectiveness of the concept of 'deficiency catalysis' in hydrocarbon media to bring about atom-economical metalations.[5a] As uncatalyzed hydrocarbon media do not normally provide sufficient alkyllithium activation[5b] to afford either *ortho*- or α-metalation, addition of increments of THF, TMEDA, etc., can be used to provide the necessary activation. That excellent metalation activation can be achieved by addition of modest amounts of these reagents is documented below.

The paper by Iwao and co-workers describes[3] two sets of metalation conditions that provide separately *ortho*-lithiation or α-lithiation. The dimethyloxazoline group is a relatively strong DMG[1b] with a reported pK_a of an *ortho*-H in 4,4-dimethyl-2-phenyloxazoline of 38.1.[6] Estimates of the pK_a of the methyl group in toluene ranges from 39 to 45.2 using a variety of media and

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measurement procedures.[7] If under metalation conditions the pK_a of the methyl group of 4,4-dimethyl-2-(*o*-tolyl)oxazoline is ≥40.1, then there is at least two orders of magnitude difference in the acidities of the two positions suggesting the possibility that selective *ortho*-lithiation can be achieved. Regioselective *ortho*-lithiation was realized under extraordinary aggressive conditions (10 equiv TMEDA, −78 °C), which the authors ascribe to being kinetic. Metalation of the putative less acidic α-methyl was achieved under less stringent conditions (ether, −78 °C).[3]

As the measured pK_a of the *ortho*-H in anisole is 39.0,[6] it was anticipated that greater difficulty would be encountered in discovering regioselective conditions for α- and, separately, for *ortho*-metalation of *o*-MA than for 4,4-dimethyl-2-(*o*-tolyl)oxazoline.[3] This preliminary analysis was based on the conjecture that the −OMe DMG would be at least as acidifying as the oxazoline DMG of their respective *ortho*-methyl groups. Hence the difference in the relative pK_a values of the *ortho*- versus α-protons would be less in *o*-MA than in the *ortho*-methyloxazoline thus making regioselective metalation conditions more difficult to discover. Moreover, we wished to provide less restrictive metalation conditions than those published by Iwao and co-workers.[3] Lastly, we wished to demonstrate the power of 'deficiency catalysis' in hydrocarbon solvents to bring about safe, relatively green, and atom-economical metalations.

Some success has already been achieved for *p*-methylanisole (*p*-MA). Use of a catalytic amount of TMEDA (0.2 equiv) and 2.0 equiv of *n*-BuLi afforded over a 90% extent of *ortho*-lithiation accompanied by 2–3% of the isomeric lateral metalated product as revealed by CITMS quench followed by GC/MS analysis.[8] Although this represented a considerable improvement in both regiospecificity and efficiency over previous reports, the metalation was not effected in hydrocarbon media and moreover was not atom-economical. An improved system was subsequently published using catalytic amounts of THF in *n*-hexane with a 1:1 ratio of substrate to *n*-BuLi.[9] This system allowed realization of about an 80% extent of metalation (EoM) at the *ortho*-position in 6 h with no detection of the laterally metalated product. Schlosser and co-workers[4] report a somewhat similar regiospecific *ortho*-lithiation of *p*-MA using more stringent conditions (*n*-BuLi/KOt-Bu, THF, 15 h, −50 °C, 78%) again with no evidence of the product of lateral metalation being found.[10] Earlier studies had reported low yields[11] and mixtures of products.[11b]

2. Results and discussion

In this article we report our detailed reinvestigation of the optional site selective metalations of *o*-MA. We were particularly interested in this project because of some conflicting past studies involving attempted optional site selective metalation of *o*-MA. Two early studies reported a mixture of α- and *ortho*-products ranging from a 1:1 ratio to one containing about a 3:1 mixture favoring the *ortho*-product.[11a,12] Further complicating these findings was the observation that anisoles, among them alkylanisoles, in refluxing superbase solution undergo a methyl migration from the oxygen atom to an adjacent ring position.[13] An authoritative review of lateral metalation, which examines this reaction in light of these earlier studies concludes that optional site selective metalation cannot be achieved at either the α- or the *ortho*-position of *o*-MA and therefore possesses no synthetic utility.[2] Furthermore, a computational treatment of the *o*-MA system concludes that 'in line with the experimental observations' optional site selective metalation of *o*-MA with alkyllithium reagents cannot be achieved.[14]

Our initial examination of the metalation of *o*-MA was with various *n*-BuLi/catalytic TMEDA (0.1 equiv, etc.,) systems in cyclohexane at 25 °C and at 60 °C followed by quenching with ClSiMe$_3$ (Table 1). An array of products was conjectured to be formed from these reactions (Fig. 2).

Table 1

Various conditions utilized in attempted regioselective metalation of *o*-MA[a]

Run	Time (h)	*T* (°C)	Equiv additive	% *o*-	% α-	% *o*-/α- Ratio
1	1	25	1.0 TMEDA	75.9	10.1	7.5
2[b]	1	60	1.0 TMEDA	82.5	11.3	7.3
3	18	25	0.1 TMEDA	66.2	20.3	3.3
4	1	60	0.1 TMEDA	71.8	13.2	5.4
5	4	25	0.5 TMEDA	73.0	11.2	6.5
6	28	25	1.0 THF/0.1 TMEDA	78.1	12.7	6.1
7	3	60	1.0 THF/0.1 TMEDA	69.6	16.6	4.2
8	4	25	3.0 THF/0.1 TMEDA	36.4	43.8	1/1.2
9	48	25	1.0 THF	50.7	8.8	5.7
10	24	25	2.0 THF	23.3	61.2	1/2.6
11	24	25	3.0 THF	19.8	62.9	1/3.2
12	24	0	1.0 THF/1.0 TMEDA	75.9	10.7	7.1
13	3	25	1.0 THF/0.1 TMEDA	71.7	10.1	7.1

[a] Conditions: 1:1 *o*-MA, *n*-BuLi in cyclohexane; analysis: GC of benzophenone quench product.

[b] Me$_2$S$_2$ quench afforded the −SMe derivatives in a mixture EoM of 75.4% *o*- and 10.4% α- for an *o*-/α- ratio of 7.2.

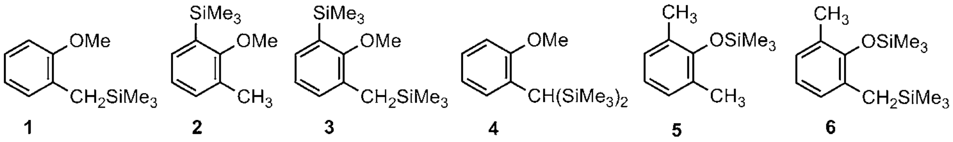


Figure 2. Possible TMS-derivatized products from the lithiation of *o*-MA: **1**, α-; **2**, *o*-; **3**, α-, *o*-; **4**, α-, α-; **5**, and **6**, Bates rearrangement products.[13]

It became apparent that both **1** and **2** were being generated but that they could not be satisfactorily resolved on our capillary GC column. Occasionally, a small amount of a bis-TMS product was detected by GC/MS, but the choice between the possible structures, **3** and **4**, could not be made. There is some literature precedent for the enhanced acidity of a methylene group attached to a −TMS moiety, which suggested to us the possibility of the structure **4**.[15] No evidence for Bates rearrangement products[13] were discerned, but cannot be ruled out.

Further attempts to successfully discover optional site selective conditions for the metalation of *o*-MA at either the α- or *o*- positions were made along with modification of our GC regimen. Derivatization of the lithio-intermediates with benzophenone produced readily resolvable derivatives for GC and GC/MS examination (Table 1). Use of our customary 'deficiency catalysis' systems, i.e., 1–3 equiv of THF or 0.1 or so equivalents of TMEDA at ambient temperature or 60 °C in hydrocarbon solvent, preferably cyclohexane, afforded mixtures of α- and *ortho*-metalated products with most sets of conditions affording mixtures that favored the *ortho*-isomer. Only equivalents of THF (runs 10 and 11) produced product ratios favoring the α-product.

Ultimately, extension of our concept of 'deficiency catalysis' provided a regioselective system for successful α-metalation of *o*-MA. It was reasoned that *t*-BuLi, because of its steric bulk, would be more selective in lithiating the α-position than the *ortho*-position. Likewise only mild activation of the *t*-BuLi was deemed necessary. Use of THF, even only 2 or 3 equiv, was not desirable due to THF's instability in the presence of *t*-BuLi.[16] Hence, activation was not attained with THF but rather with equivalents of MTBE. After repetitive studies of the metalation wherein only the equivalents of MTBE were varied, a maximized EoM of *o*-MA was realized using 1.5 equiv MTBE (Table 2). This *t*-BuLi effected metalation study was performed with analysis using $ClSiMe_3$ derivatization. The study only revealed the overall EoM, but sufficient GC separation of the α- and *ortho*-benzophenone derivatives could be achieved for determination that the product mixture was overwhelmingly α-.

Table 2
% Combined TMS products from the metalation of *o*-MA using various equivalents of MTBE

Equiv MTBE[a]	Metalation[b] (%)
0.5	58
0.75	71
1.0	76
1.5	81
2.0	74
3.0	63

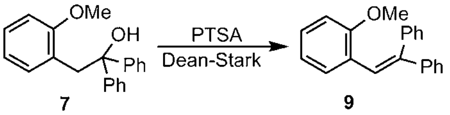
[a] 1:1 *o*-MA, *t*-BuLi in cyclohexane at 0 °C containing various equivalents of MTBE.
[b] $ClSiMe_3$ quench followed by uncorrected GC analysis.

Use of the maximizing equivalents of MTBE (1.5) at 0 °C and quenching with benzophenone brought about a satisfactory α-selectivity for the metalation of *o*-MA (Table 3).

Table 3
% Disposition of diphenylcarbinol derived products from the treatment of the α-metalated intermediates of *o*-MA with benzophenone[a,b]

Time (h)	% *o*-Product	% α-Product	α-/*o*- Ratio
1	8.7	66.9	7.7
2	9.9	74.0	7.5
3	10.9	76.1	7.0

[a] 1:1 *o*-MA, *t*-BuLi (each 1.1 M) and 1.5 equiv MTBE in cyclohexane at °0 C.
[b] Quenched with benzophenone after various times followed by uncorrected GC analysis.



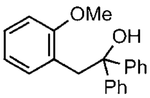
The question remained regarding the feasibility of a regioselective *ortho*-metalation of *o*-MA. This question was unexpectedly answered by a repetition of Shirley's original 1974 conditions[12a] (1 equiv TMEDA, 25 °C) (Runs 1 and 2, Table 1). After several attempts to impose our protocols (fractional equivalents TMEDA, 25 °C and, separately, at 60 °C) (Runs 3–8, 12, Table 1), as well as several involving equivalents of THF, (Runs 9–11, Table 1), a second procedure was found that provided enrichment similar to that of Shirley for regioselective production of the *ortho*-isomer (Run 13, Table 1). Interestingly, 2 and 3 equiv of THF provided enhanced metalation at the α-position (Runs 10 and 11, Table 1). Clearly an enhanced ratio of *ortho*- to α-product is produced over that reported by the original authors.[12a] More detail regarding the run (Run 1, Table 1) providing *ortho*-lithiation of *o*-MA is recorded in Table 4.

Table 4
Generation of the *o*-diphenylcarbinol derivative of *o*-MA[a,b]

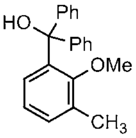
Time (h)	*o*-Metalation (%)	α-Metalation(%)	*o*-/α- Ratio
1	75.9	10.1	7.5
2	69.5	9.8	7.1
3	75.3	11.4	6.6
4	74.5	11.2	6.6
18	68.4	9.3	7.3

[a] 1:1:1 *o*-MA, *n*-BuLi, TMEDA (each 1.0 M) in cyclohexane at 25 °C.
[b] Benzophenone quench followed by uncorrected GC analysis.

Isolation of this benzophenone product, **8**, in 60% yield provided a new compound possessing a ^1H NMR spectrum containing a three-proton singlet at 2.28 ppm and a separate three-proton singlet at 3.04 ppm. This result, combined with the absence of a benzyl two-proton peak at 3.71 ppm, firmly supports the conclusion that *ortho*-derivatization of *o*-MA has been achieved.



2-(2-methoxyphenyl)-1,1-diphenylethanol
7



(2-methoxy-3-methylphenyl)diphenylmethanol
8

That the metalation had been successfully achieved at the α-position of *o*-MA was proven by isolation of the benzophenone derivative **7** in 61% yield. A ^1H NMR spectrum of this compound clearly exhibited a three-proton singlet at 3.79 ppm ($-OCH_3$) and a two-proton singlet at 3.71 ppm ($-CH_2-$). This is what one would anticipate for the product of α-substitution. Although the α-TMS derivative of *o*-MA has been previously reported, no spectral data have been provided. The unknown α-benzophenone derivative is surprisingly stable with no dehydration to the alkene detected upon work up.

To further amplify proof of structure of the α-product, **7** was subjected to dehydration conditions (equation below). Loss of water from **7** produced a triaryl substituted alkene, **9**, which has been reported in the literature.[17] The ^1H spectrum revealed the loss of the 2H benzylic protons at 3.71 ppm in the starting material with retention of the 3H methoxy group signal at 3.80 ppm. A broad unresolved envelope of signals integrating to 15H represents the total of 14 aromatic protons plus the single vinyl proton.

We conjecture that the way optional-site selectivity is manifested in *o*-MA is as follows. For α-metalation the combination of the steric effect of using *t*-BuLi plus the mildest of activation allows reasonable focus on the less hindered α-methyl group. *ortho*-Metalation, on the other hand, is accelerated by the complex-induced proximity effect (CIPE). An undetermined contribution to this acceleration must be an increase in acidity of the *ortho*-H. Thus the momentary pK_a of the *ortho*-H must be lower than the equilibrium value of 39 determined by Fraser and Monsour.[6] We speculate that this brings about a momentary two to three orders of magnitude lowering of the pK_a of the *ortho*-position of *o*-MA, which facilitates discriminating *ortho*-metalation.

3. Conclusion

In summary, separate conditions have been affirmed, which provide reasonable (>7:1 enhancement) yield of the product of either α- or *ortho*-metalation of *o*-MA. Although *ortho*-metalation of *o*-MA was accomplished using the conventional 1.0 equiv of TMEDA, the α-lithiation procedure elaborates our already articulated protocols for 'deficiency catalyzed' metalation. Some literature conjectures and conclusions have been modified by the observations contained herein. Furthermore, the protocols presented demonstrate that safe, relative green, and atom-economical conditions sufficient for scale up can be found to afford α- and *ortho*-optional-site selectivity in suitable arene substrates.

4. Experimental

4.1. General

All research chemicals were supplied by Aldrich Chemical Co. Solvents were ordered dry and used as received. GC analysis was performed on a Agilent 6850 equipped with a FID detector and GC/MS analysis was performed on an Agilent 5973 MSD instrument with 6890 N network system equipped with an FID detector. NMR's were performed on a JEOL Eclipse ECA 500 instrument.

*4.1.1. 2-(2-Methoxyphenyl)-1,1-diphenylethanol (**7**).* To a clean, dry round-bottom flask was added 2-methylanisole (2.5 mL; 20 mmol). Next *tert*-butyllithium (1.7 M in pentane) (11.8 mL; 20 mmol) was added slowly at 0 °C followed by slowly adding anhydrous MTBE (3.6 mL; 30 mmol). The reaction mixture was allowed to continue stirring at 0 °C for 3 h followed by the addition of benzophenone (3.04 g; 16.7 mmol, an amount estimated to only consume the metalated substrate) as a solid. After stirring overnight, the reaction was quenched with water and transferred to a separatory funnel with the aid of 30–40 mL MTBE. After the aqueous layer was separated and back extracted with an additional 30 mL MTBE, the combined organic layers were washed with brine, dried over sodium sulfate, and concentrated in vacuo to provide a crude white solid product, which was recrystallized with MTBE to afford (3.05 g; 60%), melting point 103.6–105.4 °C; R_f=0.60 (8:2, hexanes/ethyl acetate). ^{1}H NMR ($CDCl_3$) δ 3.71 (s, benzylic 2H), 3.79 (s, 3H), 3.99 (s, OH), 6.47–6.48, (d, J=7.5 Hz, 1H), 6.66–6.69 (t, J=7.5 Hz, 1H), 6.85–6.87 (d, J=8 Hz, 1H), 7.13–7.21 (m, 3H), 7.23–7.28 (m, 4H), 7.41–7.42 (m, 4H). ^{13}C NMR δ 42.4, 55.5, 78.8, 110.3, 120.6, 125.0, 126.5, 126.6, 127.8, 128.0, 132.7, 147.4, 157.7. Anal. Calcd for $C_{21}H_{20}O_2$ (304.38): C, 82.86; H, 6.62. Found: C, 83.25; H, 6.94.

*4.1.2. (2-Methoxy-3-methylphenyl)diphenylmethanol (**8**).* To a clean, dry round-bottom flask was added 2-methylanisole (1.87 mL; 15 mmol), anhydrous cyclohexane (3.4 mL), and TMEDA (2.25 mL; 15 mmol). Next *n*-butyllithium (2.0 M in cyclohexane) (7.5 mL; 15 mmol) was added slowly via syringe and the reaction was allowed to stir at room temperature for 1.5 h. The reaction was then cooled to 0 °C and benzophenone (2.5 g; 13.8 mmol, an amount estimated to only consume the metalated substrate) was added as a solid. After stirring overnight the reaction was quenched with water and transferred to a separatory funnel with the aid of 30–40 mL MTBE. After the aqueous layer was separated and back extracted with an additional 30 mL MTBE, the combined organic layers were washed with brine, dried over sodium sulfate, and concentrated in vacuo to provide a crude white solid product, which was recrystallized with MTBE to afford 2.55 g; 61% (three crops). Melting point 151.3–152.1 °C; R_f=0.69 (8:2, hexanes/ethyl acetate). ^{1}H NMR ($CDCl_3$) δ 2.28 (s, 3H), 3.04 (s, 3H), 5.80 (s, OH), 6.39–6.41 (dd, J=7.5, 1.2 Hz, 1H), 6.83–6.86 (t, J=7.5 Hz, 1H), 7.11–7.13 (d, J=6.9 Hz, 1H), 7.25–7.34 (complex m, 10H). ^{13}C NMR δ 16.6, 60.0, 82.3, 123.1, 127.2, 127.9, 128.0, 128.1, 131.5, 141.0, 147.0, 156.9. The above carbon spectrum is short one carbon peak. It was observed that the 127.9 peak is much larger than the other aromatic peaks. Anal. Calcd for $C_{21}H_{20}O_2$ (304.38): C, 82.86; H, 6.62. Found: C, 82.76; H, 6.85.

*4.1.3. (2-(2-Methoxyphenyl)ethene-1,1-diyl)dibenzene (**9**).* To a clean dry 100 mL two neck round-bottom flask equipped with a Dean–Stark tube was added 2-(2-methoxyphenyl)-1,1-diphenylethanol (1.7 g; 5.59 mmol), toluene (50 mL), and *p*-toluenesulfonic acid (spatula tip). Following reflux for 4 h the reaction mixture was washed with aqueous saturated sodium carbonate and brine, dried over sodium sulfate, and concentrated in vacuo to afford 1.1 g (69%) and analyzed crude. R_f=0.48 (9:1 hexanes/ethyl acetate) (GC purity >99%). ^{1}H NMR ($CDCl_3$) δ 3.80 (s, 3H), 6.61–7.31 (br m, 15H).

Acknowledgements

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