# New Construction of Ortho Ring-Alkylated Phenols via Generation and Reaction of Assorted *o*-Quinone Methides

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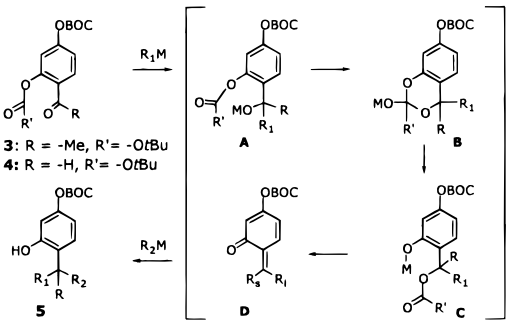
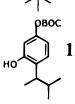
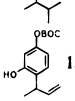
Ortho-functionalized phenols are ubiquitous among natural products. Often the riposte for their synthesis has been rearrangement,[1] electrophilic substitution,[2] lithiation,[3] or halogenation[4] followed by a metal-mediated coupling process.[5] However, these transformations alone cannot address all types of ring-alkylated phenols effectively.

McLoughlin,[6] Mitchell,[7] and Angle[8] have demonstrated that the reduction of ortho *O*-acylated phenones leads to phenols that display an ortho saturated alkyl substituent. We felt their observations might lead to a procedure that would permit a variety of type **1** and type **2** adducts (Scheme 1) to be prepared in a single flask. However, first a suitable *O*-acyl residue would have to be found that would permit the cascade to be easily governed. The factors controlling the formation of alkoxides **A**, **B**, and **C**, and the *o*-quinone methide **D** should depend on the reaction temperature, the strength of the various O−M bonds, the migratory aptitude of the acyl residue, the likelihood of *beta*-elimination, and the proclivity of **D** to undergo a subsequent 1,4-reaction. If the cascade could be successfully governed, then access to an assortment of transient *o*-quinone methide intermediates (cf. **D**)[9] would be achieved in a single procedural operation as well as a means to easily synthesize a wide range of ortho ring-alkylated phenols (**1** and **2**). These compounds are of interest as starting materials and as antioxidant, anticorrosive,[10] and anticancer agents.[11]

Despite the placement of other substituents on the aromatic ring system,[12] the cascade proposed in Table 1 can be regulated quite successfully for ketones (i.e., **3**) and aldehydes (i.e., **4**) with an ortho O-BOC substituent. The product, however, depends on the attributes of the nucleophiles as well as the reaction conditions.

**Table 1**




| # | SM | $R_1M$ 1.05 eq | $R_2M$ 1.05 –2.5 eq | Product isolated | Yield [%] |
|---|---|---|---|---|---|
| *1*[a, e] | **4** | $NaBH_4$[e] | $NaBH_4$[e] |  **6** | 84 |
| *2*[a, e] | **3** | $NaBH_4$[e] | $NaBH_4$[e] | **7** | 83 |
| *3*[b, h] | **3** | $NaBH_4$[e] | MeMgBr[c] | **10** | 61 |
| *4*[a, h] | **4** | MeLi[c] | $NaBH_4$[e] |  **7** | 88 |
| *5*[a, h] | **4** | PhLi[f] | $NaBH_4$[e] |  **8** | 83 |
| *6*[13, a, h] | **3** | MeLi[c] | ---- |  **9** | 98 |
| *7*[a, g] | **4** | MeMgCl[d] | MeMgCl[d] |  **10** | 97 |
| *8*[a, h] | **3** | MeMgBr[c] | MeMgBr[c] |  **11** | 82 |
| *9*[a, h] | **4** | MeLi[c] |  |  **12** | 72 |
| *10*[a, h] | **4** | MeLi[c] | $CH_2$=CHMgBr[d] |  **13** | 86 |
| *11*[a, g] | **4** |  |  |  **14** | 71[i] |
| *12*[b, h] | **4** | PhMgBr[d] | $NaBH_4$[e] | **8** | 81 |
| *13*[b, h] | **4** |  | $NaBH_4$[e] | **15** | 68[j] |
| *14*[b, h] | **4** | $NaBH_4$[e] |  |  **15** | 81 |

[a] One-pot protocol. [b] Two-pot protocol. Reagent added in [c] $Et_2O$. [d] THF. [e] 1/1 THF/$H_2O$. [f] Majority of the solvent is cyclohexane. [g] Majority of the solvent is $Et_2O$ [h] Majority of the solvent is THF. [i] <25% of the bis-isopropyl adduct was also observed. [j] A 4:1 mixture of the 1,4- and 1,6-reduction products was obtained.

Table 1 reveals the scope of this procedure. First, reductions of ketone **3** and aldehyde **4** were examined using $NaBH_4$. Implementing the standard conditions of McLoughlin for the addition of two hydrides to the ketone **3** or to the aldehyde **4** afforded the anticipated ring-alkylated phenols**.** Presumably with an excess of $NaBH_4$, the first hydride adds to either **3** or **4** and initiates the cascade. First, intermediate **A** is formed, then the acyl group is transferred via intermediate **B**, forming phenoxide **C**, which in turn, undergoes $\beta$-elimination producing **D**. Finally, **D** reacts with a second hydride in 1,4-fashion to restore aroma-

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(12) Generic products will be reported elsewhere.

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ticity and thereby affords **7** or **6** starting from **3** or **4** respectively (entries 1−2, Table 1).

It is noteworthy that the *o*-OBOC substituent permits the cascade to be stopped at intermediate **A** by introducing the $NaBH_4$ at low temperatures (0 °C) for short reaction times. Treatment of the corresponding alcohol **A** in a separate pot with an excess of the appropriate Grignard reagent reinitiates the cascade and produces the anticipated ring alkylated adducts in good yields [Table 1, entries 3, 14].

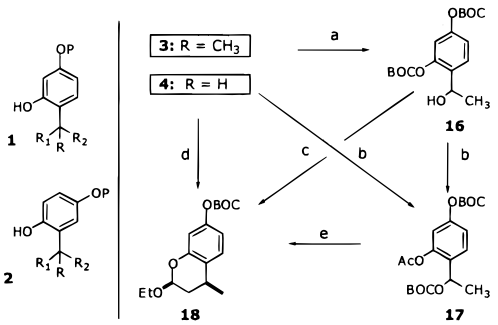
Next, the reactions of **3** and **4** with organolithium reagents were examined. It was found that in the case of aldehyde **4**, addition of an organolithium at −78 °C followed by the subsequent addition of a hydride slowly produced the corresponding alkylated materials **7**−**8** in 24 h [Table 1, entries 4, 5]. However, in the case of entry 6, addition of methyllithium (1.05 equiv, −78 °C) to ketone **3** did not lead to the anticipated product **10**, instead styrene **9** formed quite rapidly even at low temperature.[13]

Phenols ortho-substituted with α-branched chains (cf. **10**−**13**) were obtained either by adding 2 equiv of a Grignard reagent initially or by adding the first equivalent at low temperature, observing the disappearance of the starting material by TLC and then adding the second Grignard reagent [Table 1, entries 7−8]. Alternatively, α-branched phenols were prepared by adding a lithium species to the aldehyde **4**, warming to 0 °C, followed by addition of the appropriate organomagnesium reagent [Table 1, entries 9, 10]. However, in the case described by entry 9, 12% of **7** was also observed. Indeed, in cases where the second incoming nucleophile experienced significant nonbonded interactions, reduction of the quinone methide **D** often predominated. In entry 11 for example, only a small amount (<25%) of the bis-isopropyl adduct is observed, instead **14** is formed as the major product by reduction of **D** with *i*-PrMgCl.

If the intermediate that emerges from the addition of an organomagnesium reagent is to be subsequently reduced in 1,4-fashion with $NaBH_4$, then a two-pot procedure is required. The cascade can be stopped by protonation of the magnesium alkoxide at low temperature after a short reaction time. After separation and drying, treatment of the intermediate corresponding to **A** in a second pot with an excess of $NaBH_4$ reinitiates the cascade and produces the desired adducts [Table 1, entries 12, 13]. Both **8** and **15** were constructed in this manner; however, in the case of **15**, 20% of the product mixture was the regioisomer that had resulted from 1,6-hydride addition. A simple solution to this problem is to reverse the process. Thus, if **4** is first reduced with $NaBH_4$ and the cascade halted, then treatment of intermediate **A** with an excess of the vinyl Grignard reagent reinitiates the cascade and affords **15** cleanly [Table 1, entry 14].

Verification of the proposed intermediates **A**, **B**, **C**, and **D** required further experimentation (Scheme 1). All attempts to isolate **D** were unfruitful. However, the formation of products in good yield when RLi preceded RMgX and in moderate yield when RMgX preceded RLi seemed to indicate its presence. Curiously, all attempts to use organolithium reagents as both $R_1M$ and $R_2M$ failed. Upon further consideration the only indication that **D** had formed, when organolithium species were added, were the products described by entry 4 and entry 6. However, **7** in entry 4 could arise via intermediate **C** [M = Na] or [M = $BR_x$], while the styrene **9** in entry 6 could arise from several other pathways.[13] To further illuminate this issue, ketone **3** was submitted to $NaBH_4$. Quenching after a short interval led to alcohol **16** exclusively. Similarly treatment of the aldehyde **4** at −78 °C with MeLi (1.0 equiv) followed by a low-temperature addition of acetyl chloride yielded **17**. Treatment of either **16** or **17** at −78 °C with a Grignard, followed by the addition of ethyl vinyl ether (EVE) led to **18**, (>20:1/*endo:exo*). Compound **18** was also constructed in a single pot by treatment of **4** at −78 °C with MeMgBr (1.05 equiv) followed after a short interval by the addition of EVE (10 equiv). However, higher yields were obtained if EVE was used as the solvent for the reaction. Similar cycloaddition reactions could not be initiated from **4**, **16**, or **17** with organolithium reagents even at elevated temperatures. Instead, all of these reactions yielded complex mixtures of unidentified products. If, however, $MgBr_2 \cdot Et_2O$ were added soon after addition of the organolithium reagent, **18** formed smoothly. Thus, these experiments seem to indicate that the metal or its corresponding salt plays some role in the conversion of **C** → **D**.

**Scheme 1**[a]




[a] (a) 0 °C, 2.0 equiv of $NaBH_4$ 1 h. 88%. (b) −78 °C, MeLi (1.05 equiv) 30 min, AcCl (3.0 equiv) 75%. (c) −78 °C, *t*-BuMgBr (1.05 equiv), EVE (10 equiv) **18** (56%). (d) −78 °C, MeMgBr (1.05 equiv), EVE, **18** (77%). (e) −78 °C, MeMgBr (4.0 equiv), EVE, **18** (17%) + **17** (77%).

In summary, salient features of this new procedure include the use of *o*-OBOC substituted aryl ketones and aldehydes in combination with various organomagnesium reagents to generate *o*-quinone methides that undergo subsequent 1,4-conjugate addition as well as Diels Alder reactions to produce a wide range of ortho ring alkylated phenols and chromans. Several generalities have emerged. First, if a Grignard reagent is followed by $NaBH_4$, or if $NaBH_4$ is used to initiate the cascade, then the process requires protonation of intermediate **A** and a two-pot sequence. Second, the use of Grignard reagents or of an organolithium reagent followed by a Grignard reagent or $MgBr_2 \cdot Et_2O$ expedites the formation of **D** and possibly the subsequent reaction. In some cases, reduction occurs instead of 1,4-addition. However, this can be avoided by raising reaction temperature, by employing RMgCl, by using diethyl ether as the solvent, or by some combination of these tactics.

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**Supporting Information Available:** A general procedure, characterization, and $^1H$ NMR spectra for compounds **3**−**4**, **6**−**18** (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(13) Compound **9** was observed when adding MeLi to **3**, but **9** was not observed when adding MeMgBr to **3**. The two pathways shown below may explain the formation of **9**. One involves a 1,5-sigmatropic shift while the other one involves an intermolecular deprotonation of **E**, which could arise by a divergent collapse of intermediate **B** (Scheme 1).