A Detour Route for *meta* Functionalization of Phenols

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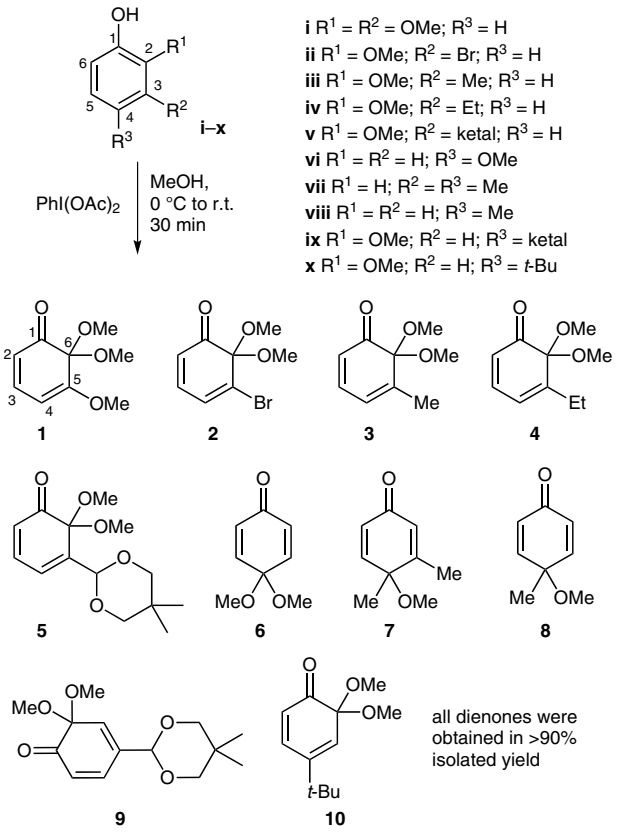
Abstract: Cyclohexadienones participate in a two-step procedure, a Michael addition followed by aromatization, providing hitherto difficult-to-synthesize *meta*-functionalized phenol derivatives in good yield. Application of the developed approach is exemplified by synthesizing *C*-aryl acetophenones, *C*-aryl glycines, and elemicin – an allylphenol natural product.

Key words: cyclohexadienones, aryl acetophenones, aryl glycines, aromatization, Michael addition

Appropriately substituted oxygenated benzene derivatives, both natural and unnatural products, are known to have several biological activities.[1] Classical procedures for the functionalization of oxygenated aryl systems generally involve electrophilic substitution via Friedel–Crafts reaction,[2a,b] formylation (such as the Duff reaction),[2c] Claisen rearrangement,[2d] halogenation, and nitration to name a few. The new functionality from these reactions is introduced at the *ortho* or/and *para* position with respect to the directing group present on the parent aryl substrate. Of late, C–H activation protocols are also employed for the *ortho* functionalization of suitably protected phenol derivatives.[3] On the other hand, *meta* functionalization of phenolic systems is uncommon. Nevertheless, *meta*-halogenated phenol derivatives can be subjected to metal-catalyzed cross-coupling reactions to install necessary substitutions in the place of halogen atoms.[4] Gaunt's research group reported a copper-catalyzed *meta*-selective arylation of aniline derivatives.[5] Recently, a straightforward route to the synthesis of 3-arylindoles in a tandem reaction using cyclohexadienones as the aryl source was reported by our group[6a] and others.[6b] During this study, we envisioned a detour protocol for *meta* functionalization of phenols. Consequently, it was expected that an appropriate Michael donor upon addition to a cyclohexadienone followed by aromatization would furnish hitherto difficult to achieve the synthesis of *meta*-substituted phenol products. Along similar lines, *meta*-functionalized aniline derivatives were reported.[7] Herein we wish to describe initial results on our above perception.

In order to attain the anticipated *meta*-substituted phenols, a variety of cyclohexadienone substrates were prepared in high yield upon treatment of a methanolic solution of the corresponding commercially or readily available phenol with diacetoxyiodobenzene (Scheme 1).[8] Initially, we investigated the possibility of installing various acetophenone units at C-5 (*meta* with respect to the hydroxyl group) of phenol **i**. The predicted reaction products are *C*-aryl acetophenones, which are known to serve as important precursors in the preparation of several biologically important compounds[9a,b] including isoflavanone natural products,[9c,d] combretastatin analogues,[10a–c] and combretastatin A-4 analogues.[10d]



Scheme 1 Preparation of cyclohexadienones **1**–**10**

At the outset, a THF solution of acetophenone (**a**) at 0 °C was treated with lithium diisopropylamide (LDA, 2.0 M solution in THF) and stirred for ten minutes at room temperature. To this reaction mixture was added cyclohexadienone **1** and stirred until thin-layer chromatography indicated the disappearance of dienone **1**. After extractive workup and column chromatographic purification, Michael adduct **1a-MA** was obtained in 93% yield. Expecting a facile acid-mediated aromatization, Michael adduct **1a-MA** was treated with 4 N HCl in dioxane (2 mL for 0.5 mmol). Aromatization did occur; however, contrary to our expectation a 1.2:1.0 mixture of chromatog-

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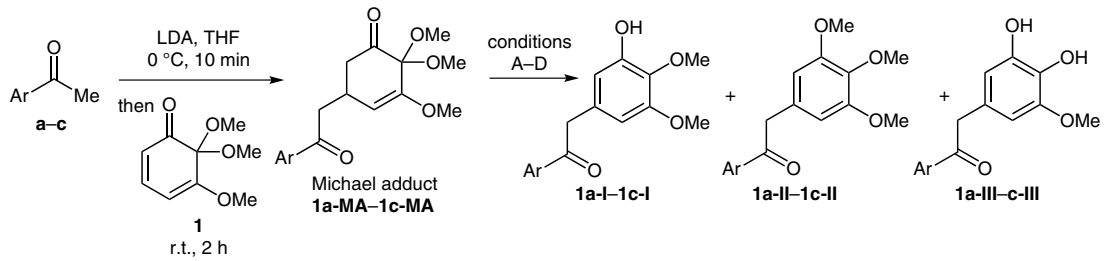
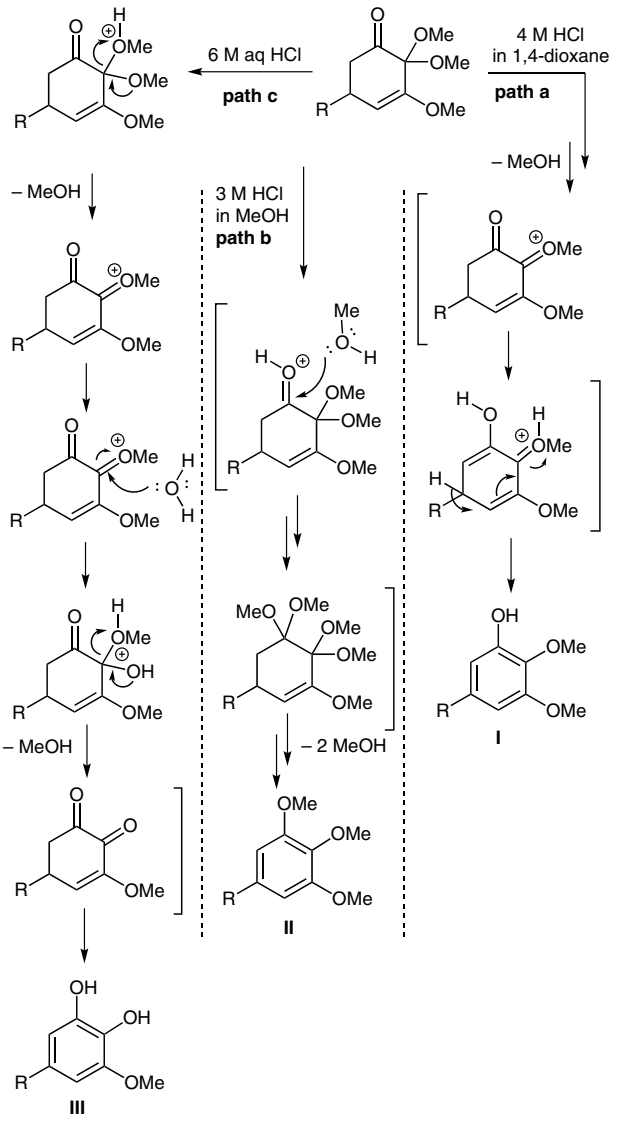
Table 1 Optimization of Reaction Conditions for the Synthesis of *C*-Aryl Acetophenones[a]



Entry	Ar	Conditions A,[b] yield (%)	Conditions B,[c] yield (%)	Conditions C,[d] yield (%)	Conditions D,[e] yield (%)
1	**a**	**1a-I** 47 **1a-II** 39	**1a-I** 77	**1a-II** 86	**1a-I** 40 **1a-III** 39
2	**b**	**1b-I** 45 **1b-II** 36	**1b-I** 80	**1b-II** 76	**1b-I** 42 **1b-III** 40
3	**c**	**1c-I** 52 **1c-II** 33	**1c-I** 92	**1c-II** 88	**1c-I** 39 **1c-III** 51

[a] Reaction conditions: **a**, **b**, or **c** (0.65 mmol), LDA (0.65 mmol), THF, 0 °C, 10 min; then dienone **1** (0.54 mmol) 0 °C to r.t., 2 h. Extractive workup gave a residue.
[b] To the residue obtained in step 1 was added 4 M HCl in 1,4-dioxane (2 mL), r.t., 2 h.
[c] To the residue obtained in step 1was added 1,4-dioxane (8 mL), 4 M HCl in 1,4-dioxane (2 mL), r.t., 4 h.
[d] To the residue obtained in step 1 was added MeOH (8 mL), 4 M HCl in 1,4-dioxane or 3 M HCl in MeOH (2 mL), r.t., 4 h.
[e] To the reaction mixture in step 1 without extractive workup was added aqueous 6 M HCl (10 mL), r.t., 4 h.

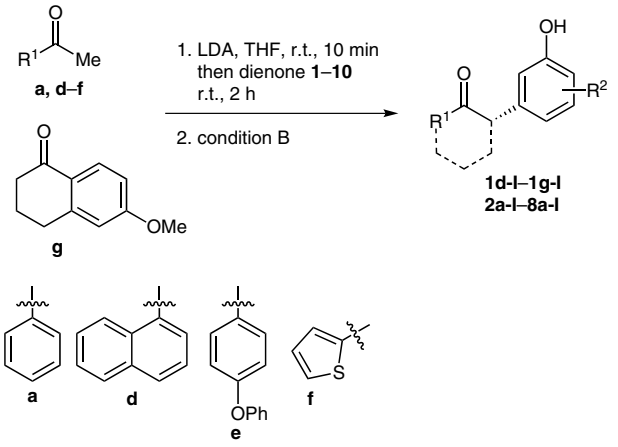
raphically separable **1a-I** (47%) and **1a-II** (39%) were produced (Table 1, entry 1, conditions A). Formation of trimethoxybenzene derivative **1a-II** can be reasoned to the participation of methanol in the reaction which is liberated during the formation of **1a-I** (Scheme 2, path a and b). Consequently, to improve the yield of **1a-I**, initially **1a-MA** was diluted with 1,4-dioxane (8 mL for 0.5 mmol) followed by treatment with 4 M HCl in 1,4-dioxane (2 mL for 0.5 mmol) at room temperature. After three hours reaction time, to our delight the only product isolated was **1a-I** in 77% yield (Table 1, entry 1, conditions B). Alternatively, when a methanolic solution of **1a-MA** was treated with 4 N HCl in 1,4-dioxane (or 3 M HCl in MeOH) at room temperature for three hours, the only product isolated was **1a-II** in 86% yield (Table 1, entry 1, conditions C). Next, when **1a-MA** was treated with aqueous 6 M HCl, a 1:1 ratio of **1a-I** and **1a-III** was obtained (Table 1, entry 1, conditions D). Interestingly, the ratio and total yield of products in all the above conditions did not vary much when unpurified crude **1a-MA** was used for the acid-catalyzed aromatization reaction. Subsequently, to test the generality, crude reaction mixtures of Michael adducts **1b-MA** and **1c-MA** obtained from the reaction of enolates generated from acetophenones **b** and **c**, respectively, with cyclohexadienone **1** were subjected to all the four different acid-catalyzed aromatization conditions discussed above. Gratifyingly, the total yield and ratio of products obtained did not alter much with the change in the acetophenone partner (Table 1, entries 2 and 3), demonstrating the conditions to be general. Based on these results, a plausible reaction pathway leading to the observed products is proposed. As indicated in Scheme 2, in aprotic solvent path a is preferred while path b and path c are also favored when the protic solvents methanol or water are used.



Scheme 2 Proposed pathway for the formation of products **I**, **II**, and **III**

Having established the optimal conditions for synthesizing products of type **I**, we next examined the scope of this method with regard to other aryl methyl ketones (Table 2). Thus, lithium enolates generated from ketones **d**–**g** on reaction with cyclohexadienone **1** followed by acid-mediated aromatization (conditions B) afforded the corresponding products **1d-I** to **1g-I** in up to 94% yield. Furthermore, the reaction of various selected dienones **2**–**8** with enolate generated from acetophenone furnished C-arylated acetophenones **2a-I** to **8a-I** in good yields after aromatization, indicating high substrate scope for this reaction sequence. It should be noted that, in the case of dienone **5**, under the standard reaction conditions the acid-sensitive ketal group was cleaved providing aldehyde derivative **5a-I** in 54% overall yield. Surprisingly, cyclohexadienones **9** and **10** on reaction with lithium enolate of **a** gave a complex reaction mixture. As of now, it is unclear why such unexpected results were observed with these substrates though steric crowding near to the reaction center may not be completely ruled out.

Table 2 Synthesis of *C*-Aryl Acetophenones Using Various Cyclohexadienones[a,b]



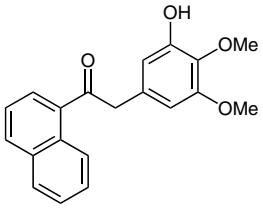
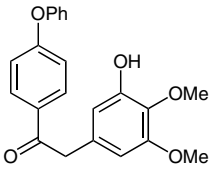
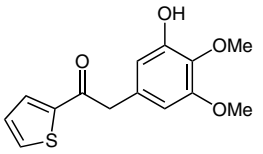
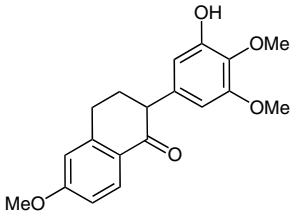
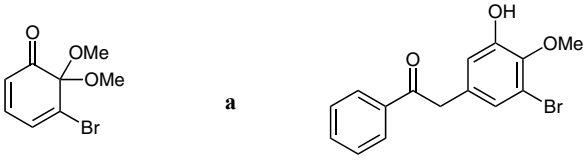
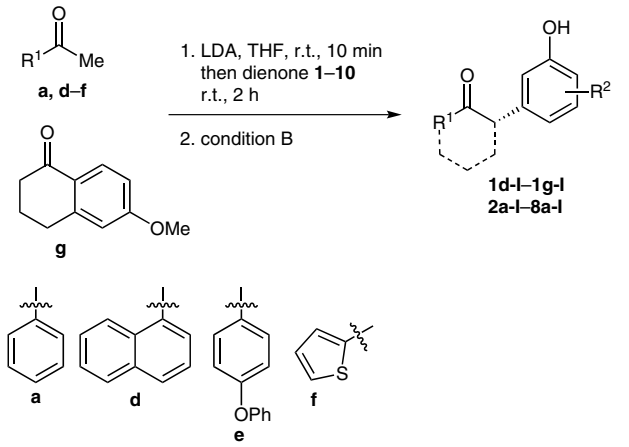
Dienone	Ketone	Product, yield (%)
1	**d**	 **1d-I** 90
1	**e**	 **1e-I** 94
1	**f**	 **1f-I** 84
1	**g**	 **1g-I** 86
2	**a**	 **2a-I** 71

Table 2 Synthesis of *C*-Aryl Acetophenones Using Various Cyclohexadienones[a,b] (continued)



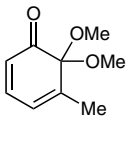
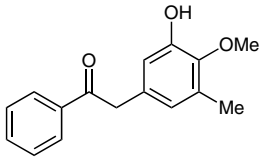
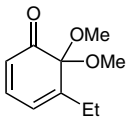
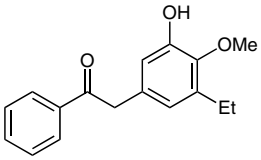
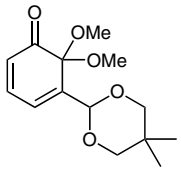
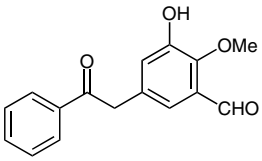
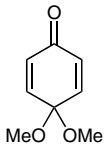
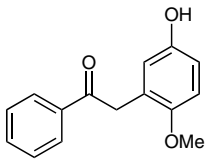
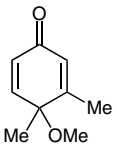
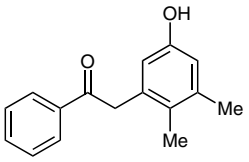
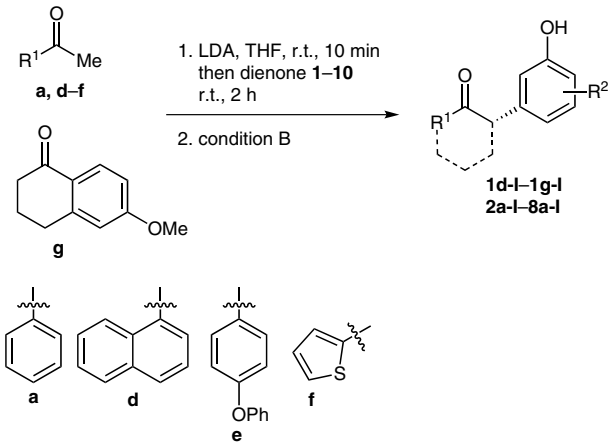
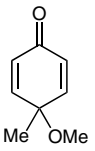
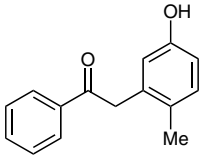
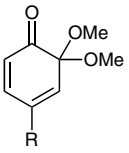
Dienone	Ketone	Product, yield (%)
 **3**	**a**	 **3a-I** 81
 **4**	**a**	 **4a-I** 88
 **5**	**a**	 **5a-I** 54
 **6**	**a**	 **6a-I** 92
 **7**	**a**	 **7a-I** 87

Table 2 Synthesis of *C*-Aryl Acetophenones Using Various Cyclohexadienones[a,b] (continued)

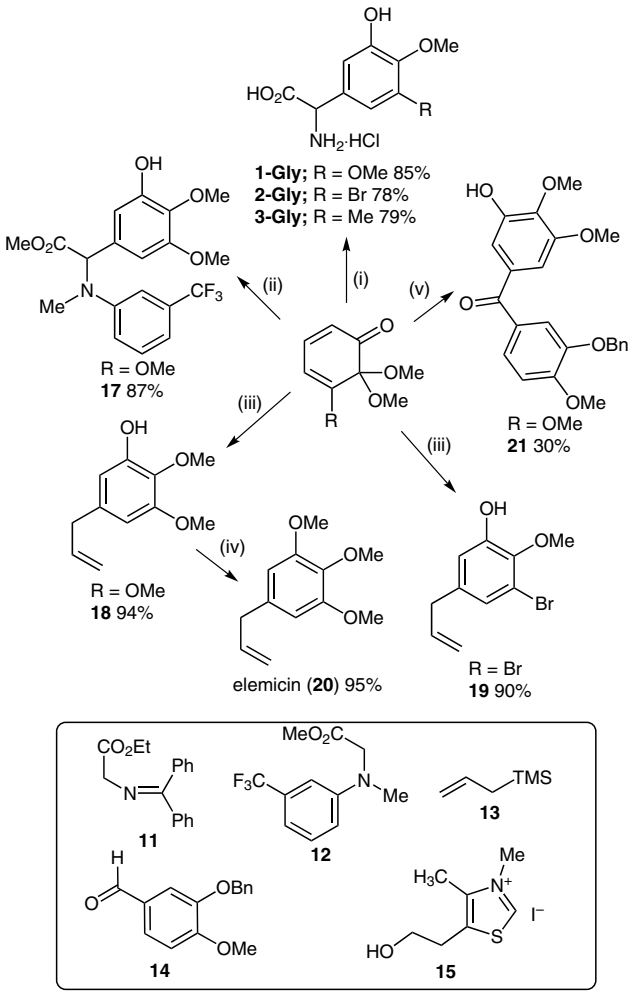


Dienone	Ketone	Product, yield (%)
 **8**	**a**	 **8a-I** 60[c]
 **9** R = ketal **10** R = *t*-Bu	**a** **a**	–[d] –[d]

[a] Reaction conditions: '**a**, **d**, **e**, **f** or **g**' (0.65 mmol), LDA (0.65 mmol), THF, 0 °C, 10 min; then dienone **1**–**10** (0.54 mmol) 0 °C–r.t., 2 h. Extractive workup gave a residue.
[b] To the residue obtained in step 1was added 1,4-dioxane (8 mL), 4 M HCl in 1,4-dioxane (2 mL), r.t., 4 h.
[c] 29% of **8a-II** was also isolated.
[d] Complex reaction mixture was obtained.

C-Aryl glycines are well-known synthetic intermediates for biologically important products[11] and are present in various natural products[12] due to which there has been continuous interest in developing novel methods for the synthesis of these compounds. Consequently, we envisioned the above developed protocol for the synthesis of *C*-aryl glycines. To this end, a THF solution of *N*-benzylidineglycinate (**11**) was treated with LDA at –30 °C for 30 minutes. To this was added a THF solution of cyclohexadienone **1**, and the reaction mixture was brought to room temperature and stirred for two hours. After usual workup, the crude reaction mixture was treated with 4 N HCl in dioxane for four hours followed by 6 M aqueous HCl for 16 hours to provide amino acid **1-Gly** in 85% yield (Scheme 3). Following the same procedure with dienones **2** and **3**, *C*-aryl amino acids **2-Gly** and **3-Gly** were

synthesized in 78% and 79% yield, respectively. Similarly, *N*-aryl glycine derivative **12** also participated in this reaction sequence furnishing *N*-aryl-*C*-arylglycine derivative **17** in 87% yield (Scheme 3).



Scheme 3 Application of the detour route for the synthesis of *meta*-functionalized phenols including aryl glycines, allylphenols, and a benzophenone analogue. *Reagents and conditions*: (i) **11** (1.2 equiv), LDA (1.5 equiv), THF, –30 °C, 30 min then dienone **1**, **2**, or **3** was added, r.t., 2 h, extractive workup provided a residue; to the residue was added 1,4-dioxane (8 mL), 4 M HCl in 1,4-dioxane (2 mL), r.t., 4 h; then solvent evaporated and 6 M aq HCl, THF, r.t., 24 h, then reverse-phase column chromatography; (ii) **12** (1.2 equiv), LDA (1.2 equiv), THF, 0 °C, 30 min then dienone **1** (1.0 equiv), r.t., 2 h then extractive workup; 1,4-dioxane (8 mL), 4 N HCl in 1,4-dioxane, r.t., 6 h; (iii) **13** (1.2 equiv), 1.0 M $TiCl_4$ in toluene (1.0 equiv), CH_2Cl_2, 0 °C, 30 min; (iv) MeI (1.5 equiv), K_2CO_3 (2.0 equiv), MeCN, r.t., 16 h; (v) **14** (0.8 equiv), 3-ethyl-5-(2-hydroxyethyl)-4-methyl thiazolium iodide (**15**, 0.15 equiv), Et_3N (1.5 equiv), EtOH, 80 °C, 16 h then extractive workup; 1,4-dioxane (8 mL), 4 M HCl in 1,4-dioxane, r.t., 6 h.

To demonstrate the broad applicability of the reaction sequence, Michael addition followed by aromatization, we were delighted to find the ease of cyclohexadienone **1** in participating in the Sakurai reaction[13] providing *meta*-allyl phenol derivative **18** (Figure 1) directly in 94% yield without the need of a separate aromatization step. Compound **18** was then quantitatively converted into the natural product elemicin[14] (**20**) by simple O-methylation of phenol **18** (Scheme 3). Under the Sakurai reaction conditions, allylphenol **19** with a bromo substitution was obtained in 90% yield. Benzophenone derivative **21**, a combretastatin analogue, was synthesized upon reacting dienone **1** in a Stetter reaction[15] sequence with aldehyde **14** catalyzed by commercially available thiazolium iodide **15** as catalyst followed by acid-catalyzed aromatization. In this reaction, 60% of ester **16** was also isolated along with 40% of 2,3-dimethoxyphenol (**i**).[16] Though the yield of the desired product is low for this reaction, we believe that judicious screening of N-heterocyclic carbene (NHC) catalysts would provide high yields. The work towards this end is in progress.

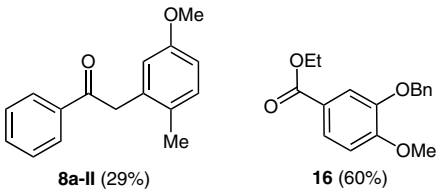


Figure 1 Structures of compound **8a-II** and **16**

In conclusion, we have demonstrated the ease of various cyclohexadienones to participate in a Michael addition–aromatization sequence to functionalize the *meta* position of phenols. Moreover, the flexibility and usefulness of this chemistry is demonstrated by synthesizing various aryl acetophenones, aryl glycines, benzophenone analogues, and elimicin – an allylphenol natural product. Further improvement of the protocols presented in this report along with the scope and limitations to access novel structural motifs with biological importance is being actively pursued.

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Supporting Information for this article is available online at http://www.thieme-connect.com/products/ejournals/journal/10.1055/s-00000083.

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