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# Exploring Morita−Baylis−Hillman Reactions of *p*-Quinols

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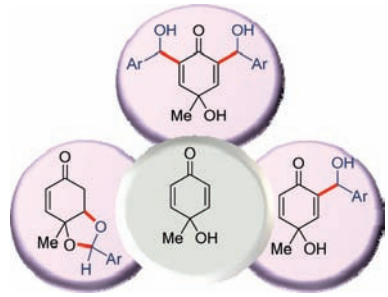
## ABSTRACT




**The Morita−Baylis−Hillman reaction of *p*-methylquinols with activated aromatic aldehydes has been studied. Depending on the reaction conditions (solvent and additives), three different products were formed. A mono or double Morita−Baylis−Hillman adduct and a fused 1,3-dioxolane could be obtained in good chemical yields. The use of non-nucleophilic bases to promote the reaction suggested an autocatalytic mechanism.**

The Morita−Baylis−Hillman reaction[1] (MBH) is a base-catalyzed carbon−carbon bond formation process which involves electron-deficient alkenes and aldehydes. Nucleophilic bases such as amines and phosphines[2,3] are necessary since the commonly accepted mechanism[4] involves an initial conjugate addition of the catalyst to the activated alkene leading to a zwitterionic enolate, whose reaction with the aldehyde is followed by a reversible elimination of the base to generate the product. Different types of activated alkenes such as cyclic and acyclic α,β-unsaturated ketones, aldehydes, esters, amides, nitriles, and alkenes substituted by nitro groups, sulfoxides, sulfones, sulfonic acids, or phosphonate derivatives have been used in the MBH reaction. In spite of the advances reached, reactions of 4-hydroxy-4-substituted cyclohexadienones (*p*-quinols) have not been reported to date. Such cyclohexadienone derivatives are of huge synthetic interest since these moieties are valuable starting materials

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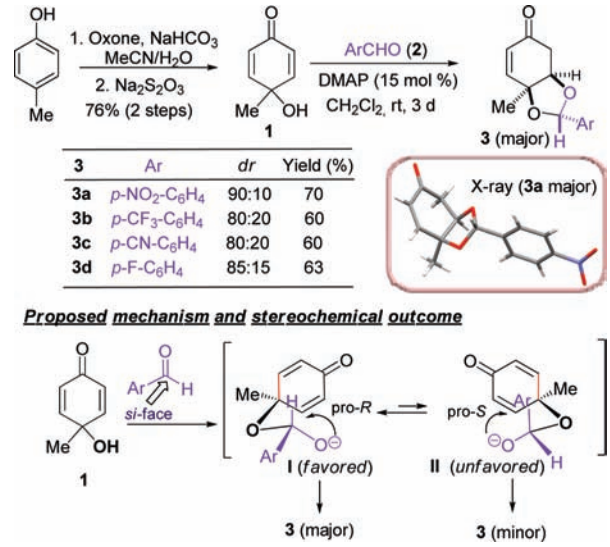
en route to a wide range of natural products,[5] and they are present in a group of novel therapeutic agents.[6] Further expansion of their reactivity will provide new tools for the rapid construction of more complex structures.

Following previous studies on the synthesis and applications of *p*-quinols,[7,8] we now report a study of the behavior of these cyclohexadienones under Morita−Baylis−Hillman conditions upon reaction with aromatic aldehydes. Our results suggest an essential role of the OH group of the *p*-quinol systems to initiate the MBH process.

The starting material, 4-hydroxy-4-methyl-2,5-cyclohexadienone **1**, was easily prepared in a one-pot/two step process from *p*-methylphenol. Thus, oxidative dearomatization of *p*-cresol with Oxone and $NaHCO_3$, as source of singlet oxygen,[9] led to the *p*-peroxyquinol intermediate that was reduced in situ with $Na_2S_2O_3$ to the *p*-quinol **1** in 76% isolated yield.[7a] Initial MBH experiments were carried out with different para-substituted benzaldehydes **2a**−**d** in the presence of a catalytic amount of DMAP at room temperature in $CH_2Cl_2$ as solvent. Under these conditions, *p*-quinol **1** did not lead to the desired MBH products. Instead, ketal derivatives **3a**−**d** were exclusively obtained in good yields (60−70%) (Scheme 1). Compounds **3** resulted as a mixture of epimers at the stereogenic benzylic carbon (dr 80:20 to 90:10). The unequivocal structure of the major diastereoisomer was confirmed by X-ray diffraction of **3a**.[10] Similar results were obtained using DABCO as base catalyst, though the reaction was not always completed. The formation of the cyclic ketal presumably involved a base-promoted 1,2-addition of the hydroxy group of the *p*-quinol to the carbonyl function of the aldehyde, followed by an intramolecular oxa-Michael *syn*-addition of the intermediate alkoxide to the cyclohexadienone moeity (Scheme 1).[11,12] The stereoselective oxa-Michael *syn*-addition from the face containing the OH group was expected on steric grounds.[13] When reaction of the *p*-quinol occurs from the *si*-face of the aldehyde, the subsequent intramolecular oxa-Michael addition can take place on either of the two prochiral $\beta$-carbons of the cyclohexadienone moiety. The attack at the pro-*R* $\beta$-carbon is favored due to the proposed transition structure **I**, with the aryl group at the equatorial position. Approach at the pro-*S* $\beta$-carbon (see **II**) shows a destabilizing 1,3-*syn* diaxial interaction, which would make such an attack less favorable.[14]

**Scheme 1.** Synthesis of *p*-Quinol **1** and Fused Ketal Derivatives **3**




| 3 | Ar | dr | Yield (%) |
|---|---|---|---|
| 3a | *p*-$NO_2$-$C_6H_4$ | 90:10 | 70 |
| 3b | *p*-$CF_3$-$C_6H_4$ | 80:20 | 60 |
| 3c | *p*-CN-$C_6H_4$ | 80:20 | 60 |
| 3d | *p*-F-$C_6H_4$ | 85:15 | 63 |

Similar results were obtained using THF or MeCN as solvents and the above-mentioned catalysts. In view of these results, we decided to carry out the reactions using protic solvents (e.g., MeOH or $H_2O$) that are known to enhance the rate of MBH processes.[15] Fortunately, the reaction of *p*-quinol **1** with different aromatic aldehydes **2** in the presence of a catalytic amount of DMAP in MeOH at room temperature led to the MBH products **4** in good yields (60−72%). In all cases, two benzyl diastereomers were formed in a 60:40 ratio that could be easily separated by column chroma-

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(10) CDCC 755300 (**3a**): $M_r$ $C_{14}H_{13}NO_5$, unit cell parameters $a$ = 7.58380(10) Å, $b$ = 17.6558(6) Å, $c$ = 9.6242(3) Å, $\beta$ = 98.371(2)°, space group *P*21/*c*. For details, see the Supporting Information.

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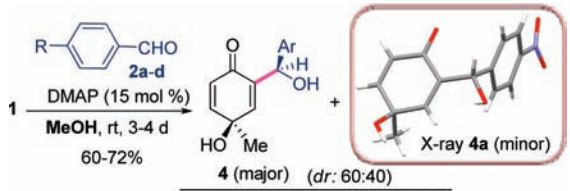
tography (Scheme 2). The formation of a mixture of diastereomers is a consequence of the prochiral character of cyclohexadienone moiety. The configuration of the most polar minor one was established by X-ray diffraction of the *p*-nitro derivative **4a**.[16]

**Scheme 2.** MBH Reactions of *p*-Quinol **1** with Aromatic Aldehydes and X-ray Diffraction of **4a** (Minor Diastereoisomer)




| 2 | R | *t* (d) | 4 (Yield %) |
|---|---|---|---|
| 2a | $NO_2$ | 3 | **4a** (64) |
| 2b | $CF_3$ | 3 | **4b** (70) |
| 2c | CN | 4 | **4c** (60) |
| 2d | F | 4 | **4d** (72) |

Other nitrogen bases such as DABCO gave similar results in the presence of the protic solvent. The use of metal salts, which are known to accelerate the MBH reaction[17] due to stabilization of the intermediate alkoxide, turned out to a be very useful. In particular, when we performed the reaction with DABCO (15 mol %) and $LiClO_4$ (70 mol %) as a cocatalyst[18] in THF, both α,β-unsaturated moieties of the cyclohexadienone participated in the MBH reaction giving rise, in a one-pot process, to the double MBH adducts (**5**−**7**) in 60−75% yield. The double MBH adducts were characterized as a mixture of three diastereoisomers that could be separated by column chromatography (Table 1).[19] The structure and stereochemistry of **5** (most unpolar spot-TLC) and **7** (most polar spot-TLC) could be unequivocally assigned by X-ray diffraction of the *p*-ciano derivatives (**5c** and **7c**)[20] (Figure 1). The relative configuration of the intermediate TLC spot isomer **6** was assigned to the *meso*-diastereoisomer shown in Figure 1.

When different phosphines, known catalysts for the Baylis−Hillman reaction, were used as base catalysts ($PPh_3$, $PBu_3$, $PCy_3$),[21] the starting *p*-quinol was recovered unaltered. This result induced us to consider the participation of the

(16) CDCC 755301 (**4a** minor): $M_r$ $C_{14}H_{13}NO_5$, unit cell parameters $a$ = 6.9945(3) Å, $b$ = 8.7663(6) Å, $c$ = 10.6230(6) Å, α = 101.662(3)°, $\beta$ = 98.586(3)°, $\gamma$ = 91.319(3)°, space group *P*-1. For details, see the Supporting Information.

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(19) Using MeOH as solvent reaction was sluggish, and double MBH adducts were obatined in low yields.

(20) (a) CCDC 753513 (**5c**): $M_r$ $C_{23}H_{18}NO_4$, unit cell parameters $a$ = 9.71730(10) Å, $b$ = 10.03110(10) Å, $c$ = 10.20860(10) Å, α = 87.6830(10)°, $\beta$ = 80.2460(10)°, $\gamma$ = 86.4870(10)°, space group P-1. (b) CCDC 755302 (**7c**): $M_r$ $C_{23}H_{18}NO_4$, $a$ = 8.3330(6) Å, $b$ = 22.7385(15) Å, $c$ = 10.3520(7) Å, $\beta$ = 105.193(4)°, space group *P*21/*n*. For details, see the Supporting Information.

**Table 1.** MBH Reactions of *p*-Quinol **1** with **2a**−**d** in the Presence of $LiClO_4$


| entry | R | time (d) | product (ratio)[a] | yield (%) |
|---|---|---|---|---|
| 1 | $NO_2$ | 3 | **5a/6a/7a** (50:10:40) | 65 |
| 2 | $CF_3$ | 2 | **5b/6b/7b** (50:10:40)[b] | 60 |
| 3 | CN | 4 | **5c/6c/7c** (46:12:42) | 60 |
| 4 | F | 4 | **5d/6d/7d** (53:13:34) | 73 |

[a] The ratio was obtained from the $^1$H NMR spectrum of the crude reaction mixture. [b] The ratio was obtained from HPLC Chiral Chromatography (Diacel Chiralpack OD chiral column, 95/5 hexane/2-propanol, 0.9 mL/min, 210 nm).

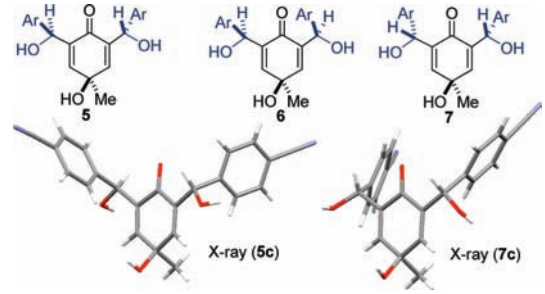



**Figure 1.** Structures of compounds **5**−**7** and X-ray structures of **5c** and **7c**.

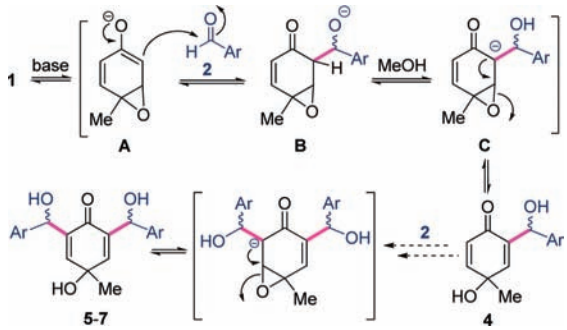
hydroxyl group of the *p*-quinol in the MBH process that could be inhibited due to the oxophilic nature of the phophorus. To test this hypothesis, *p*-quinol methyl ether (4-methoxy-4-methyl-2,5-cyclohexadienone), lacking the free OH, was used as substrate. Its reaction with *p*-nitrobenzaldehyde **2a**, using DABCO or DMPA as catalysts failed, and the starting materials were recovered unchanged. Moreover, the reaction of **1** with aldehyde **2a** using a non-nucleophilic base, such as $K_2CO_3$ or $Cs_2CO_3$ in a methanolic solution, was faster (18 h instead of 3 d) and gave a 70:30 mixture of **4a** and double MBH adducts (**5a**−**7a)** (Scheme 3).[22]

**Scheme 3.** Reaction of *p*-Quinol **1** with **2a** using $Cs_2CO_3$ as Base


The formation of MBH compounds from *p*-quinol **1** in the absence of a nucleophilic tertiary amine, and the lack of

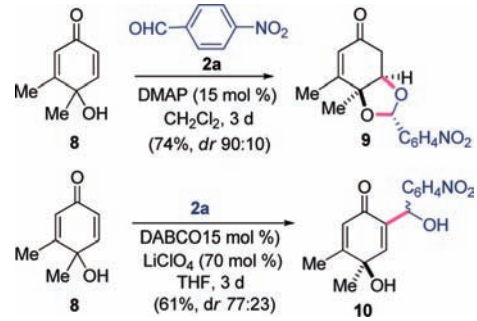
reaction of the *p*-quinol methyl ether suggest a domino intramolecular oxa-Michael/aldol condensation/elimination mechanistic pathway, instead of the commonly accepted MBH mechanism. As shown in Scheme 4, the cycle could start by an acid−base equilibrium reaction of **1** followed by an entropically favored oxa-Michael intramolecular addition, leading the enolate−epoxide intermediate **A**. Subsequent aldol reaction with **2** (**B**) and abstraction of the acidic α-proton, favored by the protic solvent, could explain the formation of a new enolate−epoxide **C**, which evolve to the Baylis−Hillman adduct **4** by epoxide ring-opening. The double-MBH adducts (**5**−**7**) could be formed through an analogous sequence from **4a**. Among the variety of bases explored as catalysts for MBH reactions in the literature, nucleophilic oxygenated bases have been scarcely used.[23,24] To our knowledge, an autocatalytic Morita−Baylis−Hillman process similar to the one proposed in the *p*-quinol system has never been reported.

**Scheme 4.** Proposed Mechanism for the Synthesis of MBH Adducts from *p*-Quinol **1**




Finally, we examined the behavior of 3-methyl-4-hydroxy-4-methylquinol **8**[7a] reacting with *p*-nitrobenzaldehyde **2a** under the reaction conditions previously used for **1** (Scheme 5). Thus, reaction of *p*-quinol **8** with *p*-nitrobenzaldehyde in the presence of DMAP in $CH_2Cl_2$ afforded the ketal **9** in good yield (74%) and diastereoselectivity (90:10). In this case, the formation of the ketal took place by the oxa-Michael intramolecular addition to the more electrophilic unsubstituted double bond of the cyclohexadienone moiety to give the *cis*-fused bicyclic structure **9**. When DMAP and MeOH were used, the starting *p*-quinol **8** was recovered unchanged. On the other hand, the use of DABCO/$LiClO_4$ in THF gave the desired adduct **10** as a 77:23 mixture of diastereoisomers, easily separable by column chromatography in 48% and 13% isolated yields, respectively. Compound **10** could also be obtained in a similar diastereomeric ratio and 60% yield using $Cs_2CO_3$ as base in MeOH. In this case, no double MBH products were detected, probably due to the diminished electrophilic character of the *β*-methyl-substituted double bond of *p*-quinol **8**.

**Scheme 5.** Reaction of Methyl *p*-Quinol **8** with *p*-Nitrobenzaldehyde **2a** with DMAP in $CH_2Cl_2$




In summary, the reactions of *p*-quinols with aromatic aldehydes under Morita−Baylis−Hillman conditions have been explored for the first time. Fused dioxolanes **3** and **9** or mono and double MBH adducts can be synthesized by choosing the reaction conditions. Highly functionalized *p*-quinol derivatives are directly available in a one-pot reaction. Our work evidenced an unprecedented autocatalysis in the MBH process of *p*-quinol systems. The C-4 hydroxy group of the *p*-quinol has the ability to act as an internal oxygenated nucleophilic catalyst essential to trigger the MBH reaction through an intramolecular oxa-Michael addition followed by the aldol-type reaction.

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**Supporting Information Available:** Experimental procedures, spectroscopic data, and copies of $^1H$ NMR and $^{13}C$ NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(21) Methot, J. L.; Roush, W. R. *Adv. Synth. Catal.* **2004**, *346*, 1035–1050.

(22) The use of the protic solvent methanol was shown to be essential since when $CH_2Cl_2$ was used, the heterogeneous mixture of *p*-quinol **1** and $Cs_2CO_3$, yielded the fused bicyclic ketal derivative **3a**.

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