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Diels–Alder reaction of 4-halogenated masked *o*-benzoquinones with electron-rich dienophiles

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ABSTRACT

Inverse-electron-demand Diels–Alder reaction of masked *o*-benzoquinones (MOBs) ensuing from the corresponding 4-halo-2-methoxyphenols with styrene, dihydrofuran and ethyl vinyl ether, butyl vinyl ether, phenyl vinyl sulfide and vinyl acetate to afford the highly functionalized halogen substituted bicyclo[2.2.2]octenones are described.

The electron-rich aromatic compounds such as 2-methoxy-phenols, which are nucleophilic in nature, can be transformed into electrophilic intermediates by oxidative dearomatization. Chemical or electrochemical oxidation of 2-alkoxyphenols in an alcoholic solvent generates 6,6-dialkoxycyclohexa-2,4-dienones known as orthobenzoquinone monoketals or masked *o*-benzoquinones (MOBs).[1] These transiently generated electrophilic quinonoid intermediates can be intercepted with nucleophiles in Michael addition and with dienophiles in [4+2] cycloaddition. The intermolecular Diels–Alder reaction of masked *o*-benzoquinones with either electron-deficient[2] or electron-rich[3] dienophiles proceeds in regio- and stereo-selective manner[1f] to produce highly functionalized bicyclo[2.2.2]octenones. Liao and co-workers have successfully utilized the cycloadducts derived from inter and intramolecular Diels–Alder reactions of masked *o*-benzoquinones for the efficient synthesis of structurally complex frameworks and natural products.[1c,f,4]

The reactivity of these conjugated cyclohexadienones can be harnessed by appropriately substituting the arene moiety. When there is no substitution on the aromatic ring (i.e., parent 2-methoxyphenol) or the presence of electron-withdrawing groups such as CO_2Me at position-4 enhances the reactivity. Any substitution (alkyl, alkoxy, ester, etc.) on the position-5 produces non-dimerizing MOBs[5] (Fig. 1). If the self-dimerization is an undesired event, the strategies generally used for diminishing this incident

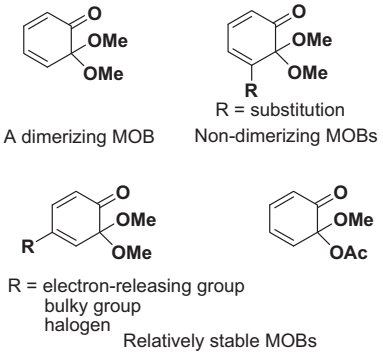

Figure 1. Reactivity of MOBs.

are (i) slow generation of masked *o*-benzoquinones by regulated addition of either 2-methoxyphenols or the oxidising agent in the presence of large excess of dienophile, (ii) introducing bulky/electron releasing groups[2a,5b,6] at position-4 and (iii) replacing one of the methoxy groups at position-6 with acetoxy group.[7] Diels–Alder dimerization of masked *o*-benzoquinones followed by retro Diels–Alder reaction in the presence of external dienophiles is a tactic generally adopted to achieve better yields for the reaction of dimerizable MOBs.[8] Introduction of a halo substitution at position-4 brings about the stability for the 4-halo masked *o*-benzoquinones and retard the Diels–Alder dimerization.[2b,6a,9,10] The bromo substituent present on the masked *o*-benzoquinones[11] and on the cycloadducts[12] can be employed as handles for further synthetic manipulations.

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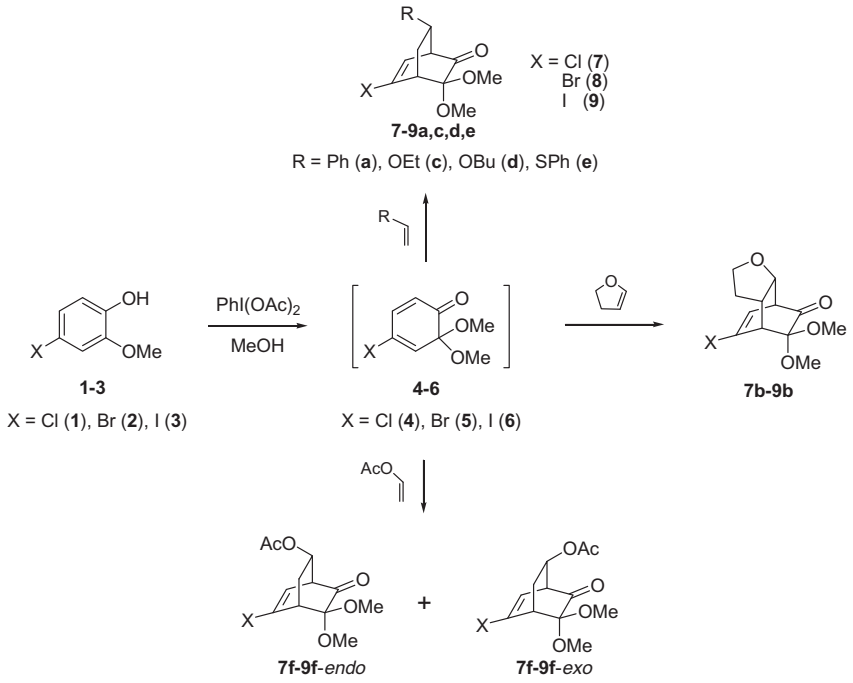
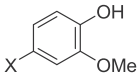
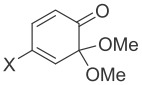
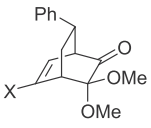
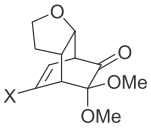
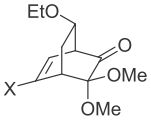
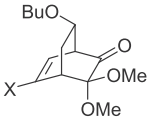
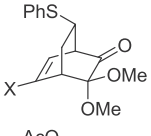
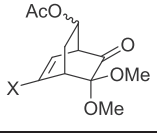


Scheme 1.

Table 1
Inverse-electron-demand Diels–Alder reaction of halo-MOBs **4**–**6** generated from 4-halo-guaiacols **1**–**3**[a]

Entry	4-Halo 2-methoxyphenol (X)		4-Halo MOB (X)		Dienophile	Time[b] (h)	Product		Yield[c] (%)
1		**1** (Cl)		**4** (Cl)		20		**7a**	89
2		**2** (Br)		**5** (Br)		20		**8a**	74
3		**3** (I)		**6** (I)		20		**9a**	75
4	**1**		**4**			20		**7b**	90
5	**2**		**5**			20		**8b**	95
6	**3**		**6**			20		**9b**	85
7	**1**		**4**			2		**7c**	75
8	**2**		**5**			2		**8c**	75
9	**3**		**6**			2		**9c**	87
10	**1**		**4**			5		**7d**	82
11	**2**		**5**			5		**8d**	85
12	**3**		**6**			5		**9d**	88
13	**1**		**4**			20		**7e**	83
14	**2**		**5**			20		**8e**	77
15	**3**		**6**			20		**9e**	91
16	**1**		**4**			24		**7f**	70[d]
17	**2**		**5**			24		**8f**	90[d]
18	**3**		**6**			24		**9f**	90[d]

[a] The reactions were carried out with 0.5 mM of halo-guaiacol, 10 mM of dienophile and 0.6 mM of DAIB in 5 mL of MeOH.

[b] Represents the reaction time after the addition of DAIB.

[c] Yields of pure and isolated products.

[d] Product was obtained as 1:1 mixture of *endo* and *exo* isomers.

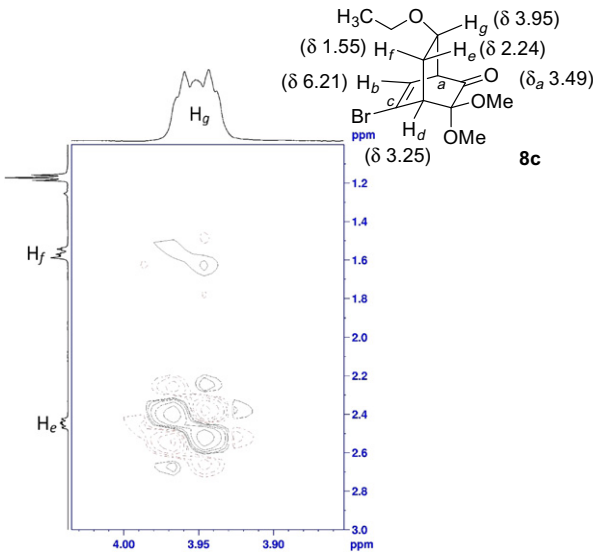


Figure 2. ROESY spectrum of cycloadduct **8c**.

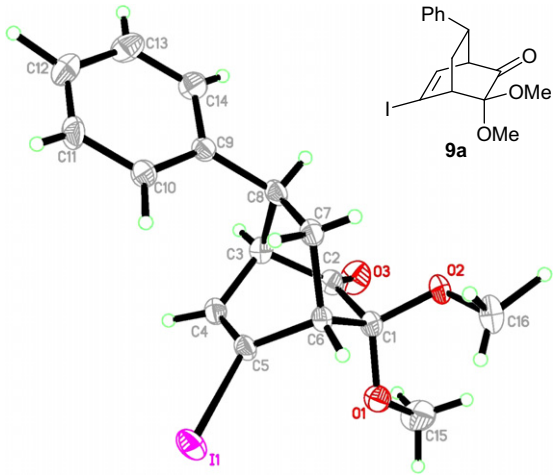


Figure 3. ORTEP plot of the crystal structure of adduct **9a** (numbering is arbitrary).

Recently we reported the Diels–Alder reaction between transiently generated 4-halo masked *o*-benzoquinones and electron-deficient dienophiles to afford the corresponding cycloadducts in very good yields.[10] We became interested to evaluate the reactivity of the relatively stable 4-halo MOBs with less reactive electron-rich dienophiles in inverse electron demand Diels–Alder reaction. Herein we report the results from these studies.

Environmentally benign and less expensive hypervalent iodine reagent diacetoxyiodobenzene (DAIB)[13] was used in methanol to oxidise guaiacol derivatives into the orthoquinone monoketals. Our initial studies on the oxidation of 4-fluoro-2-methoxyphenol in the presence of ethyl vinyl ether or butyl vinyl ether in methanol at room temperature resulted in the formation of the corresponding Diels–Alder cycloadducts in low yields. However, when we carried out the reaction of commercially available 4-chloro-2-methoxyphenol (**1**) under similar conditions[14] with dienophiles such as styrene, 2,3-dihydrofuran, ethyl vinyl ether and butyl vinyl ether, the corresponding adducts **7a–d** were obtained in high yields (Scheme 1). Similarly, the cycloaddition of in situ generated chloro MOB **4** with phenyl vinyl sulfide provided the cycloadduct **7e**. The oxidation of **1** with DAIB in the presence of vinyl acetate in methanol gave a mixture (^{1}H NMR) of two stereoisomers **7f**-*endo* and **7f**-*exo*. The results are presented in Table 1.

Encouraged by the results obtained from the reaction of phenol derivative **1**, we then investigated the reactions of 4-bromo-2-methoxyphenol (**2**)[15] and 4-iodo-2-methoxyphenol (**3**)[16] under oxidative dearomatization conditions. The in situ generated MOBs **5** and **6** were trapped with the dienophiles to furnish the Diels–Alder adducts **8a–e** and **9a–e**, respectively (Table 1). Again, the reactions of MOBs **5** and **6** with all the dienophiles, except with vinyl acetate, proceeded in highly regio- and stereo-selective manner.

The cycloadducts derived from vinyl acetate were obtained as mixtures of *endo* and *exo* isomers. The non-selective Diels–Alder reaction of vinyl acetate was documented in literature.[3a] While the reactions of MOBs with styrene, 2,3-dihydrofuran, phenyl vinyl sulfide and vinyl acetate reached completion in relatively longer times (20–24 h), the acyclic enol ethers – ethyl vinyl ether and butyl vinyl ether – reacted faster (2–5 h). The Diels–Alder reaction of 4-halo MOBs **4–6** with styrene, DHF, ethyl vinyl ether, butyl vinyl ether and phenyl vinyl sulfide afforded a single isomer in each case.

The assigned structures of halogen substituted bicyclo[2.2.2]octenones **7a–f**–**9a–f** were on the basis of their IR, ^{1}H (500 MHz) and ^{13}C (125 MHz) NMR, DEPT and GC–MS/ESI-MS spectral analysis.[17] The remarkable level of regio- and stereoselectivities observed in the products **7a–e**–**9a–e** was in accordance with the literature precedents.[2,3] Of the possible four isomers, only the one possessing *ortho* regiochemistry (ERG is adjacent to octenone carbonyl function) and *endo* stereochemistry (ERG is *anti* to octenone carbonyl function) is formed in **7a–e**-**9a–e**. The regiochemistry of these cycloadducts was deduced in each case from proton–proton decoupling experiments.

The *endo* stereochemistry of the products is corroborated from the coupling constants between H_e–H_g and H_f–H_g. For the adduct **8c** as shown in Figure 2, the larger J value for H_e–H_g (J = 8.5 Hz) reveals the *cis* orientation of the protons H_e and H_g over the less coupling constant (J = 6.0 Hz) of H_f–H_g; thus confirming the *endo* stereochemistry of the [4+2] cycloadduct. The two-dimensional rotational frame nuclear Overhauser effect spectroscopy (ROESY) measurements in selected examples indicated the proximity of H_e and H_g, further confirming the assigned *endo* stereochemistry. An expanded portion of the ROESY spectrum of compound **8c** is shown in Figure 2. The assigned *ortho* and *endo* selectivity of compound **9a** was confirmed from its single-crystal X-ray structure[18] (Fig. 3).

In summary, a practical chemical protocol for the synthesis of highly substituted bicyclo[2.2.2]octenone derivatives from 4-haloguaiacols is now available. This method demonstrates the synthesis of polyfunctionalized bicyclic systems from relatively less reactive dienophiles and stable 4-halo MOBs. The assigned regio- and stereo-selectivities are confirmed by 1-D and 2-D NMR experiments.

Acknowledgements

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14. *General procedure*: To a solution of a 2-methoxy-4-halophenol (0.5 mM) in anhydrous MeOH (5 mL) was added DAIB (0.6 mM) at 0 °C under nitrogen atmosphere. After 10 min stirring, a dienophile (10 mM) was added at the same temperature and the stirring was continued. Then the temperature was allowed to rise to RT, and the stirring was continued up to complete disappearance of MOB (the time specified in Table 1). After the reaction was complete, the reaction mixture was concentrated using rotary evaporator under reduced pressure and the residue was purified by silica gel column chromatography with 10% ethyl acetate in hexanes as eluent to furnish the cycloadduct.
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17. NMR spectral data for the representative examples.
    Compound **7a**: ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.32–7.21 (m, 3H), 7.16–7.13 (m, 2H), 6.04 (dd, J = 2.5, 7.0 Hz, 1H), 3.43 (s, 3H), 3.41 (s, 3H), 3.41–3.37 (m, 1H), 3.33–3.31 (m, 1H), 3.27 (dd, J = 2.0, 7.0 Hz, 1H), 2.58 (ddd, J = 3.0, 9.5, 13.0 Hz, 1H), 1.85 (ddd, J = 3.0, 6.5, 13.5 Hz, 1H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ 200.2, 143.2, 136.7, 128.7, 127.4, 127.0, 120.4, 93.5, 56.0, 50.7, 50.2, 48.2, 40.0, 30.1 ppm.
    Compound **7c**: ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.99 (dd, J = 1.5, 6.5 Hz, 1H), 3.98–3.95 (m, 1H), 3.57 (dd, J = 2.5, 6.5 Hz, 1H), 3.53–3.47 (m, 1H), 3.44–3.39 (m, 1H) 3.37 (s, 3H), 3.31 (s, 3H), 3.16 (q, J = 3.0 Hz, 1H), 2.46 (ddd, J = 2.5, 8.0, 13.5 Hz, 1H), 1.56 (ddd, J = 3.0, 3.0, 13.5 Hz, 1H), 1.17 (t, J = 7.0 Hz, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ 199.8, 136.0, 119.4, 93.4, 74.1, 64.4, 54.6, 50.8, 49.9, 46.9, 30.6, 15.3 ppm.
    Compound **8e**: ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.41–7.38 (m, 2H), 7.36–7.27 (m, 3H), 6.33 (dd, J = 2.0, 7.0 Hz, 1H), 3.64–3.59 (m, 1H), 3.38 (s, 3H), 3.33 (s, 3H), 3.32–3.29 (m, 1H), 3.26 (dd, J = 2.0, 6.5 Hz, 1H), 2.59 (ddd, J = 3.0, 9.5,14.0 Hz, 1H), 1.49 (ddd, J = 3.0, 5.5, 14.0 Hz, 1H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ 199.1, 133.9, 132.1, 129.3, 127.8, 125.6, 124.4 93.8, 54.7, 50.9, 50.2, 49.3, 41.9, 28.9 ppm.
    Compound **9b**: ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.61 (dd, J = 1.0, 6.5 Hz, 1H), 4.35 (dd, J = 3.0, 8.5 Hz, 1H), 3.95 (dt, J = 3.0, 8.0 Hz, 1H), 3.64–3.58 (m, 1H), 3.51 (dd, J = 3.0, 6.5 Hz, 1H), 3.49–3.46 (m, 1H), 3.38 (s, 3H), 3.34 (s, 3H), 3.13–3.06 (m, 1H), 2.17–2.09 (m, 1H), 1.92 (m, 1H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ 199.0, 134.5, 93.6, 93.1, 77.9, 69.3, 58.4, 54.7, 51.2, 50.0, 39.8, 29.4 ppm.
18. CCDC deposition No. 815225.