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1,3-Methoxy Rearrangement of Masked *o*-Benzoquinones: A Novel Synthesis of *p*-Quinol Ethers

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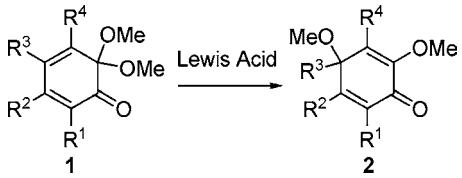
ABSTRACT



***p*-Quinol ethers are valuable synthons in synthetic organic chemistry. MOBs 1a–1i can be converted to *p*-quinol ethers 2a–2i in a highly efficient manner via 1,3-methoxy migration catalyzed by Lewis acids. The migration was found to be reversible and dependent on the electronic effect of substituent R^3 of MOBs.**

Ortho- and paraquinones and their quinol variants are potential synthons for the syntheses of a myriad of complex molecular ensembles which in turn are utilized in the syntheses of biologically active products.[1] These valuable intermediates are commonly encountered in Diels−Alder reactions[1,2] and in the preparation of various useful precursors including their asymmetric versions.[3] For the past few years, we have been exploiting masked *o*-benzoquinones (MOBs) **A** (Figure 1) for finding new synthetic methodologies based on their Diels−Alder reactions. MOBs are found to be excellent Diels−Alder partners with several dienophiles;[4] their cycloaddition reactions proceed in a regio- and stereoselective manner to provide highly functionalized systems of great synthetic value.[5] In our efforts to reduce the reactivity

Figure 1. Cyclohexadienones **A** and **B**.

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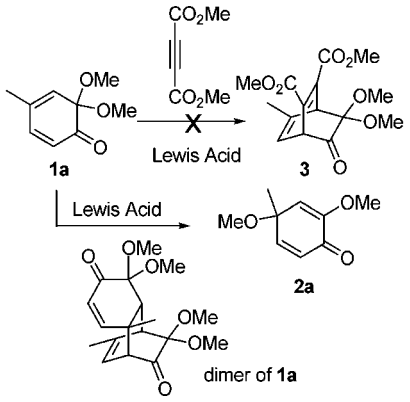
of some underutilized quinones which are prone toward dimerization and rearomatization, we were able to discover new protocols for stabilizing these MOBs.[1d] In continuation of our efforts to develop novel methodologies for organic synthesis, we became interested in Lewis acid catalyzed transformations of MOBs.

MOBs are structurally similar to cyclohexadienone **B**, the only difference being the presence of dialkoxy groups for **A** in the place of dialkyl groups for **B** (Figure 1). However, many rearrangements of cyclohexadienones **B** have been well-studied; for example, [1,2], [1,3],[1,4],[1,5], [3,3], [3,4], [3,5], and [5,5] rearrangements are observed under acidic conditions.[6]

Several Lewis acids bearing chiral ligands are known to both enhance the rate of Diels−Alder reactions and induce chirality in the obtained adduct.[7] With two possibilities in the presence of a Lewis acid, namely, Diels−Alder reaction and rearrangement process, we were curious to test the selectivity in the reaction pathway for MOB. Recently, Quideau prepared stable monoketal orthoquinone conveniently and found 1,3-acetoxy migration on silica gel via [3,3] and [3,5] sigmatropic rearrangements.[8]

Our initial study started with isolable MOB **1a** as a diene and dimethyl acetylene dicarboxylate (DMAD) as a dienophile in the presence of $Cu(OTf)_2$ as a catalyst (Scheme 1).

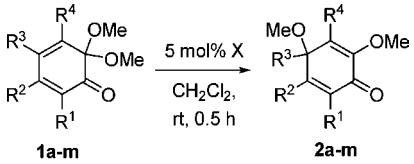
Scheme 1. An Effective Transformation of MOB **1a** to *p*-Quinol **2a**



We expected to obtain a cycloadduct such as **3** or the migration product **2a**, but no characterizable products were detected following ^{1}H NMR spectroscopy of the crude reaction mixture. When stronger Lewis acids $BF_3{\cdot}OEt_2$ and $AlEtCl_2$ were exploited, a similar result was obtained. We continued to test other milder Lewis acids $Sc(OTf)_3$, ZnI_2, $Pd(OAc)_2$, $Pd(PPh_3)_4$, $AuPPh_3Cl$, and PTSA with MOB and DMDA, only to observe dimerization product via homo-Diels−Alder reaction of two **1a** monomers. However, when $Rh(COD)_2BF_4$ was used as a catalyst,[9,10] we obtained the *p*-quinol ether **2a** via 1,3-methoxy migration. Neutral Rh complexes such as $[Rh(COD)Cl]_2$ and $RhPPh_3Cl$ failed to give the migration product. It is in the same group of the periodic table as Rh and so we expected that the 1,3-methoxy migration of MOB could also be catalyzed by the Ir complex. Accordingly, cationic $Ir(COD)_2BF_4$[9] was utilized to test this concept; in fact, the migration product **2a** was obtained in high yield. This interesting transformation of MOB to *p*-quinol ether is notable since the latter are molecules of unrealized potential in organic synthesis.[1g] This result inspired us to study in more detail the scope and limitation of 1,3-methoxy migration of MOBs.

With the use of $Rh(COD)_2BF_4$, we investigated the scope of this procedure using a series of isolable MOBs generated from the corresponding 2-methoxyphenols by oxidation with diacetoxyiodobenzene.[11] The results of this investigation are summarized in Table 1. All the rearrangement products were identified by means of ^{1}H NMR, ^{13}C NMR, and mass spectral analyses.

Table 1. 1,3-Methoxy Migration of MOBs **1a**−**m** to *p*-Quinol Ethers **2a**−**m**



MOB[a]	R^1	R^2	R^3	R^4	product/ yield (%)[b]
1a	H	H	Me	H	**2a** (80)
1b	ketal	H	*n*-Pr	H	**2b** (82)
1c	H	H	*i*-Pr	H	**2c** (60)
1d	*t*-Bu	H	*t*-Bu	H	**2d** (64)
1e	ketal	H	Me	H	**2e** (68)
1f	Me	H	*i*-Pr	H	**2f** (65)
1g	H	Me	Me	H	**2g** (70)
1h	H	ketal	Me	H	**2h** (58)
1i	H	H	Me	Me	**2i** (60)
1j	H	H	H	Me	**2j** (NR)[c]
1k	H	H	TMS	H	**2k** (NR)[c]
1l	H	H	Br	H	**2l** (NR)[c]
1m	H	H	H	CO_2Me	**2m** (NR)[c]

[a] Stable MOBs synthesized in our lab. [b] Isolated yields of *p*-quinol ethers. [c] No reaction, starting material was recovered even at reflux temperature.

In a general procedure, after 0.5 h of mixing MOBs **1a**−**m** in CH_2Cl_2 with $Rh(COD)_2BF_4$, at room temperature, the MOBs **1a**−**i** reacted to give *p*-quinol ethers **2a**−**i** with isolated yields 58−82%. Further analysis of the data in Table 1 reveals that the transformation is strikingly general and

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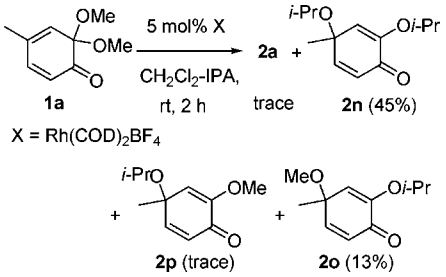
regioselective. MOBs with at least an electron-donating group (EDG) for R^3 such as **1a**−**h** undergo 1,3-methoxy migration, whereas MOBs with electron-withdrawing groups (EWGs) such as **1k**, **1l**, and **1m** are insensitive to undergoing migration. Various reaction temperatures were examined for providing the migration product in these cases, but no desired product was obtained, and the starting material was recovered.

From the results of **1a**−**1d**, the steric hindrance of R^3 has shown slight influence on the yield of the transformation. Even when the acid-sensitive ketal group was installed for MOBs **1b**, **1e**, and **1h**, migration occurred in good yields. Both R^3 and R^4 were installed with methyl groups, and the migration product was generated in good yield. The absence of a methyl group for R^3 as in **1j** led to the recovery of starting material. It may be noted that the energy of **1j** is more stable than **2j** by 6.6 kcal/mol from theoretical calculation (RHF/3-21G*).

The contrasting chemical behavior between electron-donating and electron-withdrawing MOBs toward 1,3-methoxy migration suggests the intermediate of the migration reaction is a carbocationic species which can be stabilized by the EDG.[12] To further justify our assumption, we determined the reactivity of **1a** in isopropanol (IPA)/CH_2Cl_2 (1:1) solvent system and obtained the transformation products **2a** and **2p** in trace amounts and the *p*-quinols **2n** and **2o** with a combined isolated yield of 58% (Scheme 2).

Scheme 2. Allylic Rearrangement of **1a** in the Presence of Isopropanol Solvent



Intervention of the nucleophilic solvent during the rearrangement process to yield the products **2n**−**p** is reminiscent of a cationic intermediate. The reaction mechanism is proposed as shown in Scheme 3.

The rhodium catalyst acting as a Lewis acid interacts with one of the methoxy groups to generate the oxonium intermediate **3**, which can be quenched with a nucleophilic solvent isopropanol to furnish the MOB **5** and the resonance form **3′**, which will pick up either nucleophilic isopropanol molecule to afford *p*-isopropoxy quinol **2p** or methanol to furnish *p*-methoxy quinol **2a**. The MOB **5** undergoes demethoxylation catalyzed by the cationic rhodium catalyst to generate the oxonium species **6**; its resonance form **6′** would pickup either the nucleophilic molecule isopropanol to afford *p*-quinol **2n** or methanol to furnish *p*-quinol **2o**.

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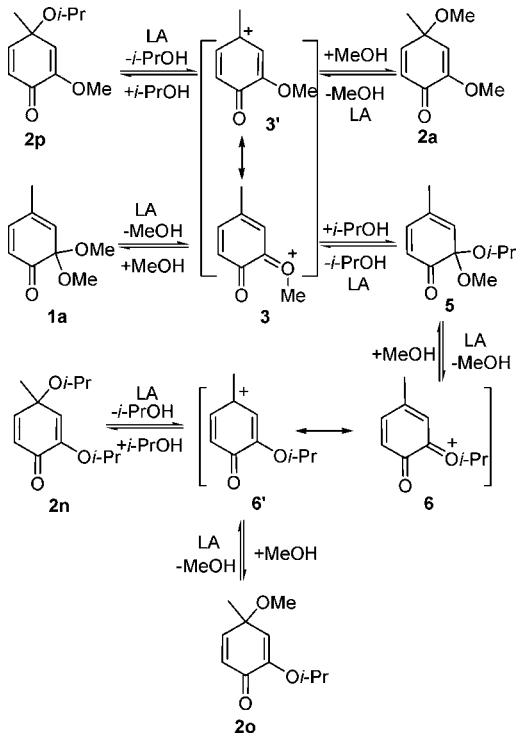
Scheme 3. Plausible Mechanism for the Rearrangement of **1a** in Isopropanol Solvent



The propensity of the reaction to proceed toward **2n** can be attributed to the higher concentration of isopropanol in the system and the greater interaction of the catalyst with the less bulky methoxy group, which is easily dislodged from MOB **5**.

The proposed mechanism that 1,3-methoxy rearrangement of **1a** is reversible and competes with the dimerization of **1a** can be proved by the following experiments monitored with ^{1}H NMR spectral method. We mixed **2a** with 5 mol % of $Rh(COD)_2BF_4$ in CH_2Cl_2 at room temperature. Thirty minutes later, the ratio of **2a** and the dimer of **1a** was 15:1; **2a** was not found from ^{1}H NMR after 2 h. We also examined **2a** with 5 mol % of $Rh(COD)_2BF_4$ at −20 °C, and only **2a** was recovered after 2 h.

This suggests the reversibility of *p*-quinol **2a** to MOB **1a** and that **1a** subsequently transformed to the corresponding dimer via Diels−Alder reaction of two MOB monomers. If we assume that **2a** and the dimer of **1a** are kinetically and thermodynamically controlled products, respectively (Scheme 4), then lowering the temperature would probably affect the

Scheme 4. Potential-Energy Diagram of **1a** in the Presence of Lewis Acids

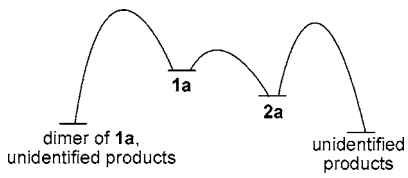
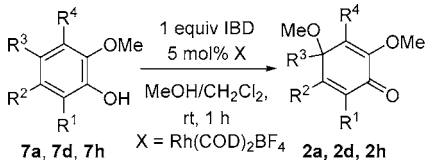


Table 2. One-Pot Preparation of *p*-Quinol Ethers



7a, **7d**, **7h** → **2a**, **2d**, **2h**

substrate	R^1	R^2	R^3	R^4	product/ yield (%)
7a	H	H	Me	H	**2a** (60)
7d	*t*-Bu	H	*t*-Bu	H	**2d** (55)
7h	H	ketal	Me	H	**2h** (57)

rate of the production of **2a** and the dimer of **1a** due to the higher energy barrier of the dimer of **1a**. To prove this assumption, we lowered the temperature of the reaction mixture of **1a** in CH_2Cl_2 to −20 °C for 1 h in the presence of the following catalysts: $Sc(OTf)_3$, $Eu(OTf)_3$, $Gd(OTf)_3$, $Nd(OTf)_3$, and $Rh(COD)_2BF_4$. Strikingly, we obtained the migration product **2a** in quantitative yield for all these catalysts.

Having established an efficient process of producing *p*-quinols in a two-step process, we extended the scope of this process by carrying out the reaction in one pot. The *o*-methoxyphenols **7a**, **7d**, and **7h**, which gave the corresponding MOBs **1a**, **1d**, and **1h**, were exposed to iodobenzenediacetate (IBD) and 5 mol % of $Rh(COD)_2BF_4$ at room temperature for 1 h (Table 2). Gratifyingly, we obtained the migration products **2a**, **2d**, and **2h**, respectively, in moderate isolated yields.

In conclusion, we found out that the selected Lewis acids successfully transformed MOBs to *p*-quinol methyl ethers through 1,3-methoxy migration. A one-pot domino process (sequential oxidation of *o*-methoxyphenol followed by the 1,3-methoxy migration) also proved to be efficient for the *p*-quinol methyl ether synthesis. The 1,3-migration of MOBs is not only reversible process but also dependent on the electronic effect of substituent at the attacking site.

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Supporting Information Available: ^{1}H NMR spectra of compounds **2a**−**2i**. This material is available free of charge via the Internet at http://pubs.acs.org.

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