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Chemoselective Reactions of 3-Benzyloxy-1,2-*o*-Quinone with Organometallic Reagents

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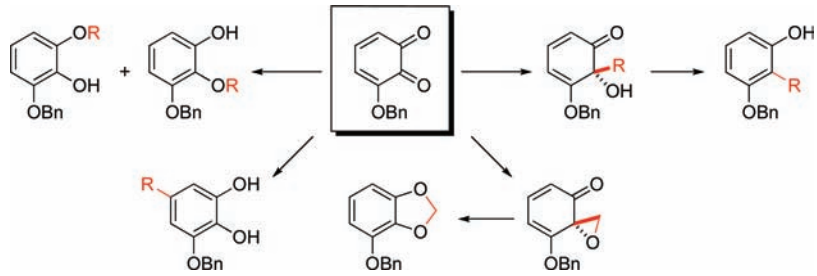
ABSTRACT



Chemoselective additions of organometallic reagents to 3-benzyloxy-1,2-*o*-quinone are described. Various nucleophiles are shown to undergo selective 1,2-addition, 1,4-addition, and etherification. Selective 1,2-additions provide stable, nondimerizing *o*-quinols as a novel alternative to oxidative dearomatization.

o-Quinones are useful synthetic building blocks. They are easily reduced to the corresponding catechol,[1] and they undergo oxidative ring-opening to the corresponding hexadienedioate skeleton.[2] Furthermore, their alkene and carbonyl components can be distinguished by [4 + 2][3] and [3 + 2][4] cycloadditions, as well as by oxidation with peracid[5] or bromine.[6] In addition, they react sparingly with organophosphorus[7] and organobismuth reagents,[8] nitroalkane anions,[9] and transition metals.[10] Sporadic reactions with alkyl,[11] alkynyl,[12] vinyl,[13] and allyl[14] organometallic reagents, as well

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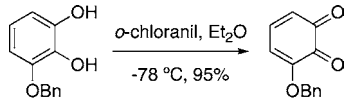
as enol ethers[15] and enamines,[16] have been reported for hindered systems.

o-Quinols, on the other hand, are highly reactive compounds. They are generally synthesized by the oxidative dearomatization of *o*-alkylphenols and resorcinols.[17] Lead (IV) and iodine (V) reagents facilitate this dearomatization via an ortho-delivery mechanism.[18] However, simple *o*-quinols which possess a cyclohexa-2,4-dienone skeleton display a propensity for dimerization. Their synthesis by oxidation has often proven capricious and substrate dependent.[19] These drawbacks, in addition to the troubling lack of experimental reports in this area, prompted us to examine an alternative for their construction: a chemoselective 1,2-addition of an organometallic nucleophile to a dissymmetric *o*-quinone.

3-Benzyloxy-1,2-*o*-quinone **2** was chosen as our focus for this model study (Scheme 1). We felt this compound was

Scheme 1. Synthesis of *o*-Quinone **2**



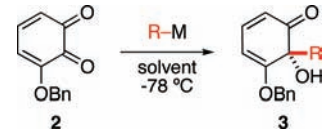
1 **2**

an attractive starting point because the carbonyls and alkene residues are electronically differentiated. Additionally, compound **2** was expected to be more stable than the parent 1,2-benzoquinone given its reduced hydride affinity. 4-Alkoxy-1,2-*o*-quinones, on the other hand, exhibit a greater proclivity toward electron transfer.

We began with the known 3-benzyloxy-catechol **1**, which is available in three steps from commercially available pyrogallol.[20] The catechol **1** readily oxidizes using Carlson's procedure to afford dissymmetric *o*-quinone **2** as a stable crystalline solid, which proves stable for months at 0 °C.[21]

With *o*-quinone **2** in hand, several 1,2-additions of Grignard reagents were investigated (Table 1). We observe addition of methylmagnesium chloride to give a very reproducible 60% yield of the corresponding quinol adduct **3a** (Table 1, entry 1). As we expected, other alkyl-Grignard reagents also chemoselectively participate in 1,2-addition reactions to afford moderate yields of the corresponding adducts (Table 1, entries 2, 4−6, 9). However, in the case of hexylmagnesium bromide and alkynylmagnesium bromide (Table 1, entries 3 and 7), precomplexation of the *o*-quinone **2** with BF_3•Et_2O prior to addition of the Grignard reagent greatly increases the yields of **3c** and **3g** to 50 and 66%

Table 1. Chemoselective 1,2-Additions to *o*-Quinone **2**



2 **3**

entry	reagent	conditions	product	yield
1	MeMgCl	THF	R = Me **3a**	60%
2	EtMgBr	THF	R = Et **3b**	53%
3	*n*-HexMgBr	DCM BF_3•Et_2O	R = Hex **3c**	50%
4	*i*-ButMgCl	THF	R = *i*-But **3d**	56%
5	H_2C=$CHCH_2CH_2MgBr$	THF	R = C_4H_9 **3e**	42%
6	BnMgCl	THF	R = Bn **3f**	50%
7	HCCMgBr	DCM BF_3•Et_2O	R = ethynyl **3g**	66%
8	PhMgBr	DCM BF_3•Et_2O	R = Ph **3h**	51%
9	PhMgBr	DCM $Al(OPh)_3$	**3h**	47%
10	MeLi CuI	THF	**3a**	45%
11	$AlMe_3$	THF	**3a**	45%
12	$ZnMe_2$	THF	**3a**	40%

respectively. Addition of phenylmagnesium bromide results in a mixture of etherification products (Table 4, entry 3). However, addition of BF_3•Et_2O to the *o*-quinone prior to Grignard addition leads exclusively to the 1,2-adduct (Table 1, entry 8).

The change in reaction selectivity observed in the presence of a Lewis acid prompted additional investigations. Complexation of the *o*-quinone **2** with bulky aluminum-derived Lewis acids followed by addition of phenyl Grignard and dimethylcuprate surprisingly results in 1,2-addition (Table 1, entries 9−10) instead of 1,4-addition. We speculate that the *o*-quinone **2** may be acting as a bidentate ligand, which may facilitate a directed 1,2-delivery of the nucleophile.

Much to our chagrin however, organolithiums were found to reduce the *o*-quinone **2** to the corresponding catechol **1**. Remarkably, addition of trimethylaluminum and dimethyl zinc to the *o*-quinone **2** results in the formation of the corresponding 1,2-adduct (Table 1, entries 11−12). Notably, all *o*-quinol products proved stable and do not undergo cyclodimerization.[22]

We subsequently found that treatment of these alkoxy *o*-quinols with hydrogen gas in the presence of rhodium on charcoal promotes reductive rearomatization with elimination of water to produce the corresponding dissymmetric resorcinol derivatives (Table 2). Rhodium on charcoal was chosen to ensure that the benzyl protecting group emerged unscathed from the reaction. Reduction of phenyl *o*-quinol **3h** to the biaryl **4h** (Table 2, entry 3) is a nice alternative for synthesizing electron rich biaryl compounds that prove difficult to obtain by standard metal mediated cross-coupling procedures.

While attempting other assorted 1,2-additions, we observed that allylmagnesium bromide by itself reduces the *o*-quinone

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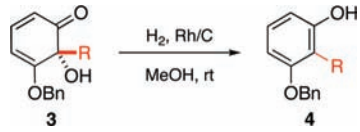
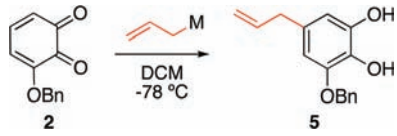
Table 2. Reductive Rearomatization of *o*-Quinols

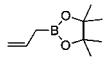


entry	quinol	product	yield
1	**3a**	R = Me **4a**	90%
2	**3f**	R = Bn **4f**	90%
3	**3h**	R = Ph **4h**	95%

2 to the catechol **1**, whereas precomplexation with BF_3•Et_2O, affords the unexpected 1,4-product (Table 3, entry 1). In an effort to obtain the 1,2-adduct, we also tested allyltributyltin and the allylboronic acid pinacol ester. Both reagents led to formation of the 1,4-adduct (Table 3, entry 2−3).

Table 3. Chemoselective 1,4-Allylation of *o*-Quinone **2**



entry	reagent	additive	product	yield
1	H_2C=$CHCH_2MgBr$	BF_3•Et_2O	**5a**	54%
2	H_2C=$CHCH_2SnBu_3$	BF_3•Et_2O	**5a**	55%
3		-	**5a**	50%

On the basis of these results, two possible mechanisms for allyl addition seemed plausible (Figure 1). In the first, the allyl group undergoes initial 1,2-addition via a six membered transition state (**A**) to afford the *o*-quinol (**B**). This intermediate then succumbs to a 1,2-sigmatropic shift to produce another *o*-quinol (**C**). Successive [3,3] rearrangement to (**D**) and rearomatization results in what would appear to be a 'net' 1,4-addition. The second potential mechanism involves 'reverse' 1,4-allylation of the *o*-quinone. To distinguish between these two possibilities, we submitted the *o*-quinone **2** to the crotylboronic acid pinacol ester shown. The reaction affords the 1,4-addition product **5b**, which would seem to corroborate mechanism 1. This supposition agrees with Soga's work,[23] where an allyl group adds 1,2 when the 1,4-position is blocked, and Castle's observation of a similar allyl migration.[24]

Table 4 shows the reagents and conditions that favor etherification of *o*-quinone **2**. Unlike dimethyl zinc, which affords only the 1,2-product, Et_2Zn and *i*-Pr_2Zn both produce mixtures of phenols (Table 4, entries 1−2). Likewise, phenylmagnesium bromide and *p*-methoxyphenylmagnesium

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(24) Nielsen, D. K.; Nielsen, L. L.; Jones, S. B.; Toll, L.; Asplund, M. C.; Castle, S. L. *J. Org. Chem.* **2009**, *74*, 1187.

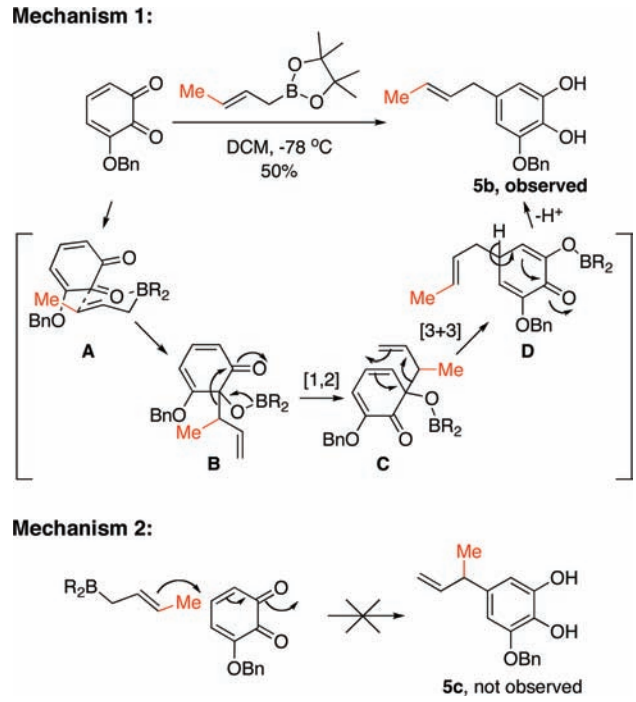
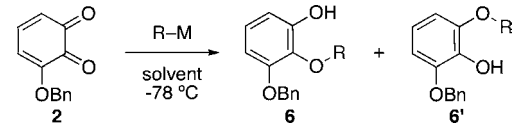
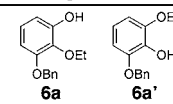
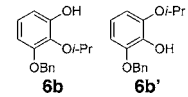
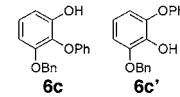
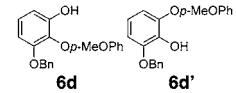


Figure 1. Mechanistic preference for formation of catechol **5b**.

bromide provide mixtures of phenols (Table 4, entries 3−4). Remarkably, addition of phenylmagnesium bromide to 3-methoxy-1,2-*o*-quinone leads to a single regioisomer (not

Table 4. Etherification of *o*-Quinone **2**

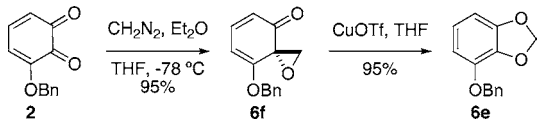


entry	reagent	conditions	product	yield
1	Et_2Zn	THF	 **6a** **6a'** 3:1	63%
2	*i*-Pr_2Zn	THF	 **6b** **6b'** 3:1	52%
3	PhMgBr	THF	 **6c** **6c'** 1:1	54%
4	*p*-MeOPhMgBr	THF	 **6d** **6d'** 1:1	55%
5	CH_2N_2	CuOTf THF	 **6e**	90%

shown). We believe these results reflect the greater electrophilicity of one of the carbonyls and the greater single electron character of the organometallic species (as compared to their corresponding dimethyl zinc and alkyl Grignard counterparts).[25] Precoordination with BF_3·Et_2O and other Lewis acids was not observed to influence formation of the corresponding ethers with these reagents.

Attempts to implement a Charette cylcopropanation[26] of compound **2** using copper triflate and diazomethane resulted in the benzodioxolane **6e** in a 90% yield (Table 4, entry 5). However, in the absence of copper triflate, diazomethane smoothly provides the *o*-quinol spiroepoxide **6f** (Scheme 2).[27]

Scheme 2. Synthesis of Benzodioxolane **6e** via Spiroepoxide **6f**



This product is then readily converted into the benzodioxolane **6e** by subsequent treatment with copper triflate or BF_3·Et_2O. Spiroepoxides resembling **6f** are most often produced by the corresponding Becker-Adler oxidation of hydroxymethyl phenols.[28] The utility of these highly functionalized spiroepoxide intermediates in diastereoselective syntheses is well documented.[29]

Several other reagents and conditions were also investigated in conjunction with the *o*-quinone **2** (Figure 2). Conditions were limited to low temperature because of the propensity of compound **2** to dimerize.[30] Most reagents

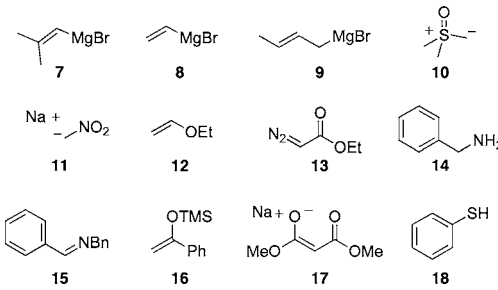


Figure 2. Other nucleophiles investigated with *o*-quinone **2**.

proved unreactive or resulted in either reduction or decomposition of the starting material. Organolithium, organocadmium, and organocerium reagents all led to catechol formation. Organomercury reagents failed to undergo reaction with **2**. Grignard reagents **7**−**9** and anions **10**−**11** all resulted in catechol formation, even when introduced in the presence of BF_3·Et_2O. Reagents **12**−**16** proved unreactive under forceful conditions. On the other hand, **2** undergoes reaction with **17** to afford the corresponding 1,4-addition product. Exposure of **2** to **18** results in 1,6-addition and provides the corresponding thioetherificated catechol.[31]

To summarize, several new modes of reactivity for **2** have been identified. 1,2-Addition followed by reductive rearomatization provides dissymmetric resorcinol derivatives. Allyl organometallic reagents undergo net 1,4-addition reactions. Organometallic reagents displaying single electron character favor 1,4-addition to an oxygen atom resulting in net etherification. Further expansion of the 1,2-addition technology may provide chiral *o*-quinol scaffolds in an enantioselective manner.

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Supporting Information Available: Full experimental procedures and data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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