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Reductive Aromatization of Quinols with B_2pin_2 as Deoxidizing Agent

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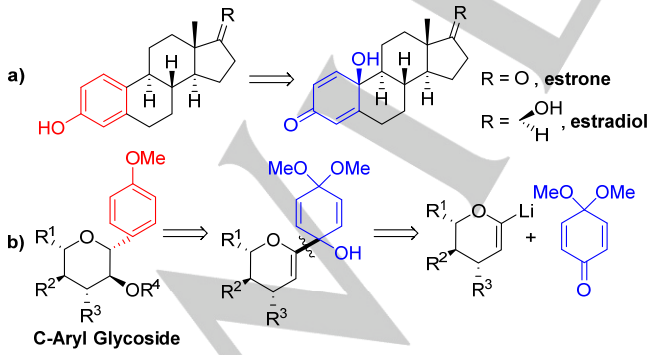
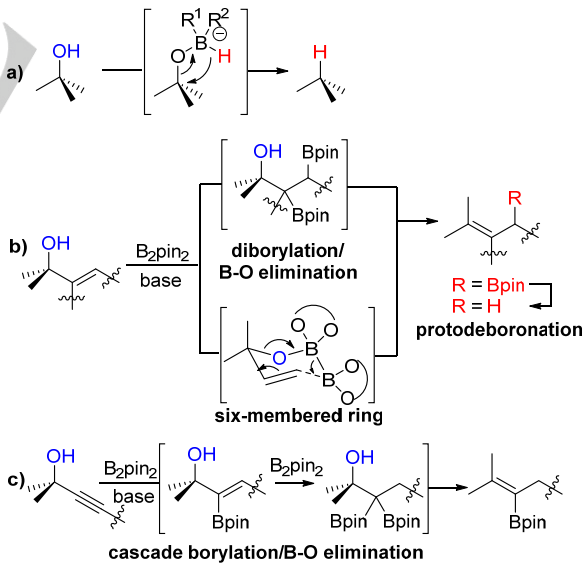
Abstract: We have demonstrated B_2pin_2 as superior deoxidizing agent for the reductive deoxygenation of quinol derivatives under basic conditions. A wide range of highly functionalized phenols were obtained in good yields including complex drug molecule which revealed the high functional group tolerance of this protocol.

Quinols usually emerge as key units in various natural products and drug molecules as exemplified by estrone or eatradiol in steroids. Meanwhile, quinols represent highly versatile intermediates in organic transformations like cycloaddition,[1] Michael addition[2] and reductive aromatization[3]. The nucleophilic addition to quinone followed by reductive aromatization provide an efficient protocol to introduce functionalized phenols wherein classical coupling methods might be hardly accessible. Indeed, such strategy had been employed in the synthesis of C-aryl glycosides as successively reported by Parker *et. al.*[3c, 3f, 3k] as shown in **Scheme 1b**. The successful reductive aromatization relied on the use of $Na_2S_2O_4$ as reductant while $NaBH_4$, Zn/AcOH, Al(Hg) would lead to undesired side product.[3c] In this consider, it is always of demand to develop straightforward and mild methods for the selective reductive aromatization of quinols.



Scheme 1. Reductive aromatization of quinols in natural product synthesis

Boron compounds are mostly known as reducing agent towards unsaturated C-C or C-heteroatom bonds. In case of deoxygenation,[4] borohydride is crucial to drive the cleavage of C-O bond, achieving nucleophilic substitution towards borate ester. Alternatively, deoxygenation process with diboron compounds is also available, requiring anchimeric assistance of alkene to undergo Fernádez-type diborylation/B-O elimation[5] or via six-membered ring[6] (followed by protodeboronation sometimes[7]) to complete deoxygenation process (Scheme 2b) wherein the olefin migration during this transformation is inevitable. Parallelly, Song-type cascade borylation/B-O elimation from propynols could also afford deoxygenated structures (Scheme 2c).[8] Inspired by these works, we envisaged that reductive aromatization of quinols could be realized with B_2pin_2 as deoxidizing agent under basic conditions.

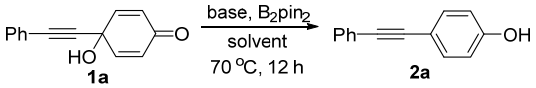


Scheme 2. Deoxygenation with organoboron compounds

The reaction was initially conducted with **1a** and B_2pin_2 following conditions from our previous work of borylation on propargylic alcohols,[5c] however, reductive deoxygenation of quinol led to the product **2a** in 65% yield in this case. Switching alkali metal hydroxides to NaH slightly increased the yield to 70% (Entry 4, Table 1). Solvent effect was thereafter examined and polar solvents like DMF and MeCN were verified to be

inferior to DMSO, affording the product in 55% and 58% yield, respectively. When conducted in THF, complex mixture was observed. Improvements was achieved in DCE providing **2a** in 80% yield. Further exploration of other typically employed alkali salts or organic bases failed to deliver better outcomes (entries 10-14) wherein **1a** were recovered.

Table 1. Optimization of conditions[a]

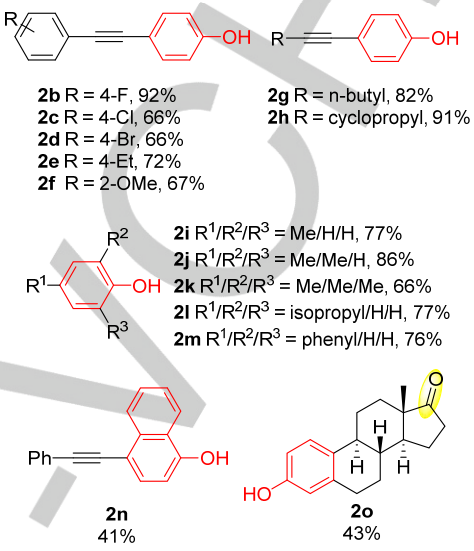


Entry	Base	Solvent	Yield(%)[b]
1	LiOH·H_2O	DMSO	65
2	NaOH	DMSO	60
3	KOH	DMSO	62
4	NaH	DMSO	70
5	NaH	DMF	55
6	NaH	MeCN	58
7	NaH	THF	complex
8	NaH	Toluene	65
9	NaH	DCE	80
10	t-BuOK	DCE	20
11	t-BuOLi	DCE	31
12	Cs_2CO_3	DCE	59
13	DABCO	DCE	60
14	DBU	DCE	35

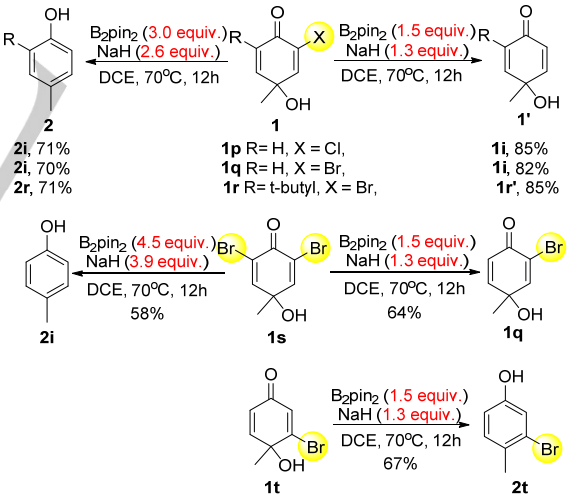
[a] The reaction of **1a** (0.2 mmol) and B_2pin_2 (0.3 mmol) was carried out in solvent (1 mL) at 70 °C in the presence of base (0.26 mmol) for 12 h. [b] Isolated yield.

Thereafter we assessed the substrate scope with the optimal conditions in hand (Scheme 3). Various arylethynyl substituted quinols bearing electron-donating (**2e-2f**) and electron-withdrawing (**2b-2d**) groups well participated in the reductive deoxygenation providing functionalized phenols in good yields ranging from 66% to 92%. Meanwhile, alkylethynyl substituted quinols reacted efficiently to give desired products (**2g-2h**) with intact triple bonds. The unsaturated bonds on substrates were found not necessary from the outcomes of **2i-2m**. It is notable that substitutions on quinol moiety do not obstruct this transformation although slightly lower yield was obtained (**2k**). The naphthoquinol substrate displayed lower reactivity, delivering the product **2n** in 41% yield with starting material recovered. We then investigated the reaction of complex molecules estrone quinol **2o**. To our delight, site-selective reduction on quinol generated estrogen in 43% wherein the carbonyl group remained silent during this process.

Some interesting results were observed as we screening halogen-substituted compounds (Scheme 4). When subjecting **1p-1r** to the standard conditions, dehalogenate quinols were produced in high yields instead of reductive aromatization. Moreover, if we doubled the amount of reductant and base, phenols eventually formed after the cascade dehalogenation/deoxygenation process. Similar trend was observed with dihalogeno substrate **1s**, treating with 1.5 equiv. of B_2pin_2 resulted in mono-dehalogenation while fully reduction to phenol **2i** required 4.5 equiv. of reductant. Comparatively, if switching halogen atom to C-3 position (**1t**), only reductive aromatization observed under the standard condition while bromine represents inert.



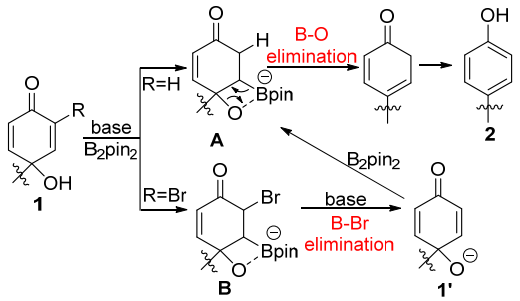
Scheme 3. Substrate scope (conditions: **1** (0.2 mmol) and B_2pin_2 (0.3 mmol) was carried out in solvent (1 mL) at 70 °C in the presence of base (0.26 mmol) for 12 h. Isolated yield.)



Scheme 4. Reaction with halogen-substituted compounds

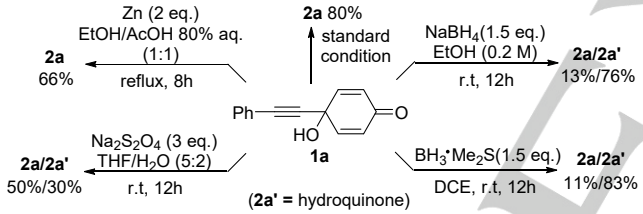
Based on the aforementioned observations and previous reports,[5-9] we propose a mechanism shown in **Scheme 3**. Non-halogen-substituted **1** would undergo borylation on *α,β*-unsaturated carbonyl moiety[10] assisted by neighboring hydroxyl group. Following B-O elimination and aromatization give product **2**. In case of halogen-substituted **1**, the initial borylation happened on the bromo-substituted double bond which is more electron-deficient. B-Br elimination which is triggered by the borate moeity[9] dominated the following step instead of B-O elimination, resulting dehalogenation product **1'**. In the presence

of extra B_2pin_2 and base, secondary borylation generated intermediate **A** and eventually continued to phenol **2**.



Scheme 5. Proposed mechanism

Several sets of know conditions for reductive aromatization of quinols were examined with **1a** to evaluate our apporach. Exposing **1a** to borane or borohydride resulted in the formation of **2a** in very low yields (<15%) along with hydroquinone **2a'** obtained as decomposited product (Figure 3). Under the conditions developed by Parker,[3c] phenol **2a** was generated in 50% yield while decomposition is still unavoidable. Better results were given when treated with Zn/AcOH affording the desired product in 66% yield without observation of hydroquinone but still inferior comparing to our conditions.



Scheme 6. Comparison experiments

Generally, we have developed a mild approach for the selective reductive aromatization of quinols using B_2pin_2 as deoxidizing reagents. Cascade borylation/B-O elimination process was suggested to furnish the formal deoxygenation process. Moreover, this protocol had been demonstrated highly efficient by comparison experiments.

Acknowledgements

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Keywords: reductive aromatization • boron • deoxygenation • quinols

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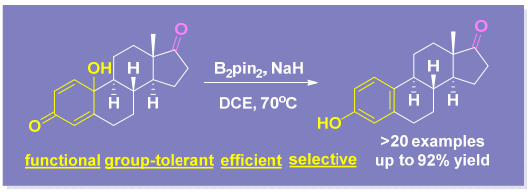

Reductive deoxygenation of quinols was achieved under B_2pin_2/NaH conditions affording functionalized phenols in good yields. This approach featured in high functional group tolerance and chemoselectivity comparing to well-established methods.