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Selective oxidation of benzylic or allylic hydroxyl group of *sec*-1,2-diols

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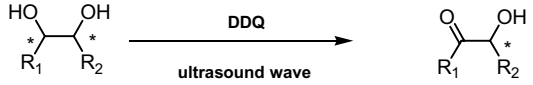
Abstract—A mild and efficient method to selectively oxidize chiral *sec*-1,2-diols has been developed, which demonstrates that 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) can selectively oxidize benzylic or allylic hydroxyl group of *sec*-1,2-diols under ultrasound wave promotion. The configuration of the adjacent chiral center is retained.

Enantiomerically pure α-hydroxy ketones are important synthons for the asymmetric synthesis of many natural products. This structure unit is commonly found in such biologically active natural products as sugar, pheromones, antibiotics, terpenes and alkaloids. Many methods of synthesis of this structure have been reported, for example, the reduction of diketones by yeast,[1] the asymmetric oxidation of ketone enolates[2,3] by enantiomerically pure aprotic oxidizing reagents. However, the reagents that they used are either expensive or difficult to prepare.

One of the simplest way to prepare chiral α-hydroxy ketone is selective oxidation of asymmetric *sec*-1,2-diols, which can be easily done by the Sharpless asymmetric dihydroxylation. Many reports on selective oxidation focus on primary hydroxyl group of diols[4] or one hydroxyl group of diols that have the same chemical environment.[5–7] A remarkable total synthesis work involves the selective oxidation of benzylic hydroxyl group, but the hydroxyl groups in this synthesis work are not at vicinal position, and the other hydroxyl groups have been protected before oxidation.[8] The Ganem' group and Ley's group reported selective oxidation of cyclohexenediol[9] and 1-(3,4,5-trimethoxy-phenyl)-propane-1,2-diol,[10] respectively. Under the condition of their experiments, the reaction needs heating, and the reaction times are longer than 12 h. The major reason that causes this difficulty of selective oxidation is that the two hydroxyl groups of *sec*-1,2-diols have little difference at chemical- and stereo-environment. To solve this problem, our efforts are aimed mainly at two sides, (1) selection of suitable oxidant, (2) seeking for suitable reaction condition to achieve the selective oxidation and decrease the byproducts (diketones and product of the cleavage of 1,2-diols).

After many trials, it is found that DDQ can not only efficiently oxidize the benzylic hydroxyl group as literature[11] reported, but can also work well in selective oxidation of *sec*-1,2-diols (Scheme 1). Some substrates (entry **5** and **10**) can react quickly at room temperature, which is as similar as Ferreira's group reported,[12] but most substrates react slowly at room temperature and some substrates cannot even react (entries 7 and 8). Under the reflux condition, the products were complicated due to overoxidation. Therefore, it is very valuable



R_1= Alkenyl, Phenyl

R_2= Alkyl

Scheme 1.

Keywords: Selective oxidation; DDQ; Ultrasound wave; Vicinal position.

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Table 1. Selective oxidation of diols to α-hydroxy ketones by using DDQ

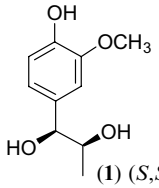
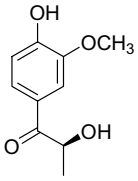
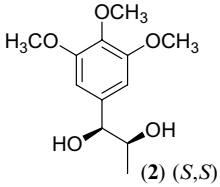
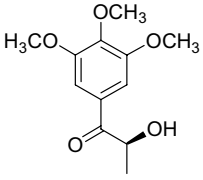
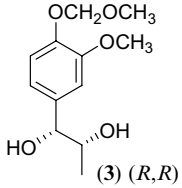
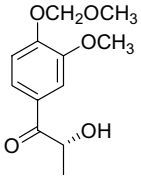
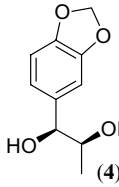
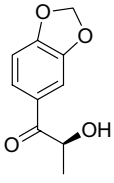
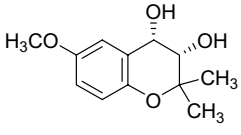
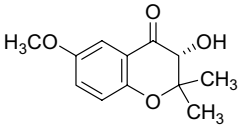
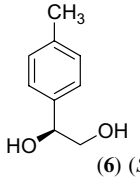
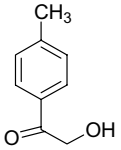
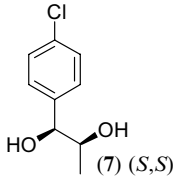
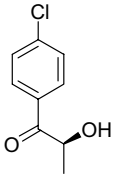
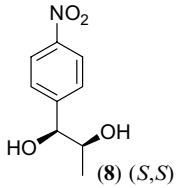
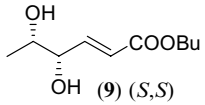
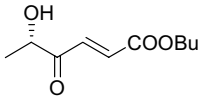
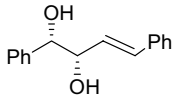
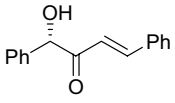
Entry	Diols[a]	Conditions[b]	Time (h)	Products	Yield[c] (%)	Ratio[d]	$[\alpha]_D^{22}$
1	 (**1**) (*S*,*S*)	(a)	5		72	>9:1	−31
2	 (**2**) (*S*,*S*)	(a)	5		82	>9:1	−32
3	 (**3**) (*R*,*R*)	(a)	5		84	>9:1	+24
4	 (**4**) (*S*,*S*)	(a)	5		79	>9:1	−25
5	 (**5**) (*S*,*R*)	(a)	5		79	>9:1	−19
6	 (**6**) (*S*)	(a)	5		67	>8:1	
7	 (**7**) (*S*,*S*)	(a)		No reaction			
		(b)	5		56	>9:1	−27

Table 1 (*continued*)

Entry	Diols[a]	Conditions[b]	Time (h)	Products	Yield[c] (%)	Ratio[d]	$[\alpha]_D^{22}$
8	 (**8**) (*S*,*S*)	(a) (b)	>5	No reaction Product complex			
9	 (**9**) (*S*,*S*)	(a)		No reaction			
		(b)	7		34	>6:1	−7
10	 (**10**) (*S*,*S*)	(a)	2		62	>8:1	+29

[a] The substrate was prepared by Sharpless asymmetric dihydroxylation with AD-mix α or with AD-mix β.
[b] (a) Anhydrous benzene, ultrasound wave, rt, 2 Mequiv of DDQ; (b) anhydrous benzene, reflux, 2 Mequiv of DDQ.
[c] The yields were determined by isolation.
[d] The ratio (α-hydroxy ketone/diketones) was calculated by isolation yields.

to find one general and mild reaction condition, which can be suitable for various substrates.

In recent years, the ultrasound wave promotion reactions have been widely applied in modern organic synthesis. It offers the potential tools for shorter reaction time. The influence of ultrasonic energy on chemical activities may involve any or all of the following, production of heat, facilitation of mixing, enhancement of intimate contact.[13] Under the promotion of ultrasound, it is found that selective oxidation reaction of *sec*-1,2-diols can proceed very well by using DDQ as an oxidation reagent in anhydrous benzene. Under this condition, several different diols were selectively oxidized to the corresponding α-hydroxy ketones (Table 1).

The above results revealed some important information. Firstly, most substrates with benzylic hydroxyl group react faster than those with allylic hydroxyl group. The substrates with benzylic hydroxyl group can be oxidized in mild condition (condition a) and the products were obtained in good yields (entries 1–5), but the substrates with allylic hydroxyl group were oxidized very slowly under the same condition (entry 9). Entry 9 was also tried under reflux condition (condition b) and the expected product was obtained, but yields were still low as we supposed. In our experiment, it was found that DDQ can also efficiently selectively oxidize secondary hydroxyl group of primary, secondary-1,2-diols (entry 6). Secondly, the electronic property of substituent can influence this reaction. If the substituent is an electron-donating group, the reaction react more quickly in mild condition a. Whereas entries 7 and 8 did not work in condition a. In entry 7, the expected product was obtained under condition b. Nitryl of entry 8 may be has a too strong electronegativity, so its product in condition b was very complex. The last substrate (entry 10) was designed to have both benzylic hydroxyl and allylic hydroxyl groups that are at vicinal position, but the result is against our expectation. It is very interesting that the allylic hydroxyl group was oxidized preferentially. As for this point, we will continue to study it in our future work. Thirdly, the transformation of the diols into α-hydroxy ketone occurs selectively with practically retention of configuration at the remained chiral center.[15] It will be very useful in organic synthesis.

In conclusion, a mild, economic and efficient way is found to selectively oxidize *sec*-1,2-diols in good yields by using easily obtained DDQ. The generality of this method has been proved, and this new approach shows the considerable practical value due to its efficiency and simplicity.

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References and notes

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15. The absolute configuration of α-hydroxy ketones are determined by Mosher's method. Typical procedures for preparation of (*R*)-and (*S*)-MTPA esters.[14] (*R*)-MTPA ester of 2-hydroxy-1-(3-methoxy-4-(methoxymethoxy)-phenyl)-propan-1-one (entry 3). To a solution of 2-hydroxy-1-(3-methoxy-4-(methoxymethoxy)phenyl)-propan-1-one (8 mg, 33.3 mmol) in CH_2Cl_2 (1 mL), was added (+)-MTPA chloride (66.7 mmol, 12 μL), TEA (0.05 mmol, 7 μL), DMAP (catalytic quantity) and the solution is allowed to stand at room temperature for 30 min. the residue was purified by column chromatography on silica gel. The results are very satisfactory according to our conclusion, and the ee% of products obtained form NMR are above 85%.