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Brønsted Acid-Catalyzed Dihydroxylation of Olefins in Aqueous Medium

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Abstract: The *trans*-dihydroxylation of olefins occurs efficiently by aqueous hydrogen peroxide catalyzed by *p*-toluenesulfonic acid at 50 °C, allowing the catalyst reuse and an outstanding substrate functional group tolerance such as *tert*-butoxycarbonylamino (BocNH), benzyloxycarbonylamino (CbzNH), benzyloxy (OBn), tosyloxy (OTs), hindered ketal, (2-trimethylsilyl)ethoxymethoxy (OSEM), benzylamino (NBz), benzyloxy (OBz) and free amino acid.

Keywords: dihydroxylation; 1,2-diols; hydrogen peroxide; olefins; water

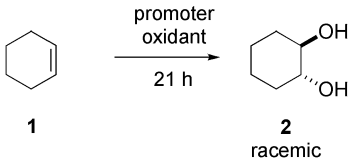
The 1,2-diol unit is a very useful synthetic building block precursor, and is present in many synthetic and natural important molecules.[1] The dihydroxylation of olefins is the most efficient approach and it has been very well established for the *syn*-dihydroxylation based mainly on metal catalysis such as OsO_4,[2] $KMnO_4$,[3] RuO_4,[4] and iron complexes,[5] among others. Que et al. have reported an iron catalyst with different ligands that mimics the facial N,N,O site of the mononuclear iron center of Rieske deoxygenases (responsible in nature for *cis*-dihydroxylation).[5a,6] The authors suggested the participation of an Fe(V) species as oxidant.[6] Although the main product obtained was the *cis*-1,2-diol, with electron-rich olefins, it was possible to obtain the epoxide as a secondary product. In spite of their high toxicity, osmium-based catalysts are among the most used methods for the *cis*-dihydroxylation of olefins due to their generality and high selectivity.[2,7] The mechanism involves the formation of cyclic esters that are further hydrolyzed to form the desired product. Several others metals, such as ruthenium[4a] and molybdenum,[8] were reported with similar postulated mechanisms as the osmium-based catalysts. Recently the use of palladium-based catalysts with hypervalent iodine as oxidant for the dioxygenation of olefins was reported.[9] Gade et al.[10] have also used this oxidant with different acids as catalysts, with triflic acid being the more efficient. The proposed mechanism involves the formation of an iodoso salt as intermediate.

trans-Dihydroxylation of olefins occurs mainly by epoxidation and hydrolysis by metal catalysis[11] or biocatalysis.[12] Recently a catalytic system was reported for the *trans*-dihydroxylation of olefins with selenium dioxide and hydrogen peroxide in 1,4-dioxane. The authors proposed that the olefin is epoxidized by the perseleninic acid formed *in situ*, followed by epoxide opening by water.[13] Other approaches have been developed that do not use any metal or biocatalyst: Adkins and Roebuck[14] reported in 1948 the use of formic acid as promoter and solvent with hydrogen peroxide as oxidant. This method uses a large excess of formic acid (13 equivalents) and since this is an exothermic reaction the olefin had to be added very slowly. In 2007 this reaction was reported in a microreactor[15] where the slow addition of olefin was eliminated, but the formate was still formed, and thus a second step of hydrolysis was needed. Sato et al.[16] reported the dihydroxylation of olefins in an aqueous medium with H_2O_2 as oxidant and NAFION® as a catalyst. However, NAFION® is a quite expensive sulfonic resin and the reaction works only above room temperature (70 °C). Another method was reported in 1991 by Zhu and Ford[17] and uses OXONE® as promoter and also as oxidant for the dihydroxylation reaction. OXONE® is a commercially available triple salt ($2KHSO_5 \cdot KHSO_4 \cdot K_2SO_4$) synthesized from H_2O_2 and H_2SO_4, followed by neutralization with K_2SO_3.[18] With this method is not possible to recycle OXONE® thus resulting in considerable waste material for the overall process. Although the dihydroxylation of the olefin can be achieved in water at room temperature, for some substrates an increase of temperature is

needed resulting in a faster decomposition of OXONE®. Here we described a method for the direct *trans*-dihydroxylation of olefins by aqueous hydrogen peroxide catalyzed by readily available sulfonic acids under mild conditions, which also tolerates a considerable range of functional groups.

Using cyclohexene **1** as a model substrate different promoters, oxidants and experimental conditions were tested, Table 1 (for more details see the Supporting Information). At room temperature, camphorsulfonic acid (CSA), *p*-toluenesulfonic acid (PTSA), and 4-dodecylbenzenesulfonic acid (DBSA) were efficient promoters for this reaction (Table 1, entries 1–3), providing the diol **2** in 34, 28 and 23%, respectively. The combination of CSA with the oxidant OXONE® (92%, Table 1, entry 11) was much more efficient than using H_2O_2 (34%, Table 1, entry 1). This result is in agreement with the reported use of OXONE® alone,[17] and a comparable experiment, using OXONE® in the absence of promoter accomplished by us (87%, Table 1, entry 10). Additionally H_2O_2 is much more desirable from the economic and environment point of view. In line with the reported method,[16] Nafion®, as well as Amberlyst®, was not efficient at room temperature (0 and 17% yield respectively, Table 1, entries 7 and 9), or even at 50 °C (40%, Table 1, entry 8). Formic acid was more efficient than the resins (34%, Table 1, entry 4), however as stated before,[15] at 20 °C formic acid gave rise to a mixture of diol and monoformate, and even at 50 °C was not an efficient catalyst for this transformation (40%, Table 1, entry 5). Since it has been observed that the occurrence of some CSA degradation *via* Baeyer–Villiger oxidation took place under the reaction conditions, PTSA was selected to be the promoter for this transformation. The use of a stoichiometric amount of PTSA at room temperature allowed the achievement of a high yield (88.2%, Table 2, entry 1). But when we raised the substrate quantity to 25 mmol, this biphasic reaction was not very efficient (50%, Table 2, entry 2), and then the temperature had to be raised to 50 °C resulting in 97.7% yield (Table 2, entry 3). Further optimization of the reaction condi-

Table 1. *trans*-Dihydroxylation of cyclohexene **1** under different reaction conditions.[a]

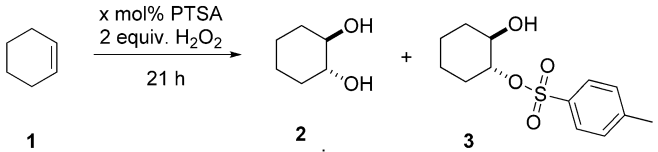


1 **2** racemic

Entry	Oxidant (equiv.)	Promoter (30 mol%)	Method[b]	Temp. [°C]	**2** Yield [%]
1	H_2O_2 (2)	CSA[c]	A	20	34
2	H_2O_2 (2)	PTSA[d]	A	20	28
3	H_2O_2 (2)	DBSA[e]	A	20	23
4	H_2O_2 (2)	HCOOH	A	20	34
5			B	50	40
6	H_2O_2 (2)	Oxone®	A	20	28
7	H_2O_2 (2)	Nafion®	A	20	0
8			B	50	40
9	H_2O_2 (2)	Amberlyst®	A	20	17
10	Oxone® (2)	–	A	20	87
11	Oxone® (2)	CSA	A	20	92[f]
12	Urea hydrogen peroxide (2)	CSA	A	20	2
13	H_2O_2 (1.2)	PTSA[g]	A	50	80.9[h]
14	H_2O_2 (2)	PTSA[g]	B	50	95.5

[a] Promoter (30 mol%), oxidant (1.2–2 equiv.) and cyclohexene (2.5–25 mmol) were stirred for 21 h.
[b] Method A: yield calculated by ^{1}H NMR using chloroacetic acid as internal standard. Method B: product isolated by extraction of crude reaction with diethyl ether.
[c] (*S*)-Camphorsulfonic acid.
[d] *p*-Toluenesulfonic acid.
[e] 4-Dodecylbenzenesulfonic acid.
[f] Reaction time: 48 h.
[g] Promoter amount: 20 mol%.
[h] At the end of the reaction the color was black.

Table 2. *trans*-Dihydroxylation of cyclohexene **1** using PTSA as catalyst.[a]

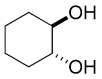
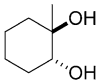
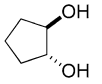
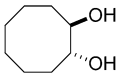
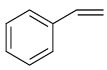
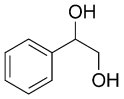
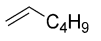
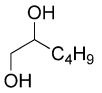
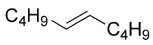
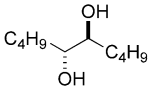
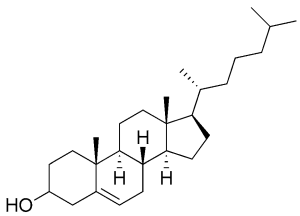
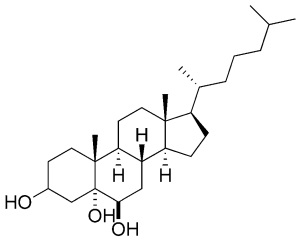
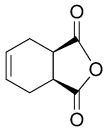
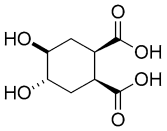


1 **2** racemic **3**

Entry	Temp [°C]	Scale of **1** [mmol]	PTSA [mol%]	**2** Yield [%][b]	**3** Yield [%]
1	20	2.5	100	88.2[c]	–[d]
2	20	25	100	50.0	50[e]
3	50	25	100	97.7	–[f]
4	50	2.5	20	85.8	–[f]
5	50	25	20	95.5	–[f]
6	50	250	20	93.5[g]	–[f]

[a] PTSA (20–100 mol%), H_2O_2 (30% aqueous solution, 2 equiv.) and cyclohexene (2.5–25 mmol) were stirred for 21 h.
[b] Method B: product isolated by extraction of crude reaction with diethyl ether.
[c] Method A: yield determined by ^{1}HNMR using chloroacetic acid as internal standard.
[d] It was not possible to quantify the yield of **3** due to the insolubility in D_2O, that was the solvent used to calculate the yield of diol **2** formed.
[e] Isolated yield of *trans*-2-hydroxycyclohexyl-*p*-toluenesulfonate **3** obtained by precipitation adding water to the reaction and filtration.
[f] Compound **3** was not detected by ^{1}H and ^{13}C NMR of the crude reaction.
[g] Reaction time: 72 h.

Table 3. *trans*-dihydroxylation of several olefins using PTSA as catalyst, at 50 °C.[a]

Entry	Substrate	Product	PTSA [mol%]	Yield [%][b]
1			20 100	95.5 97.7
2			20	82.9
3			20 100	95.7 55.7[c,d]
4			20 100	nr 75.5
5			20 100	86.4 91.6
6			20 20	62.4 86.8[e]
7			20	65.0
8			20	55.8
9			20	(89.6[d]), 80.9

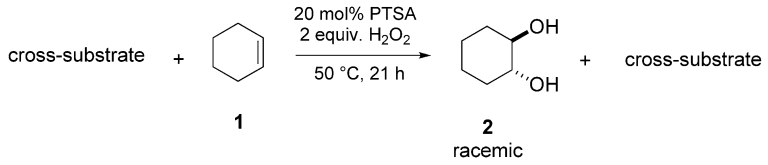
[a] PTSA (20 mol%), H_2O_2 (30% aqueous solution, 2 equiv.) and substrate (25 mmol) were stirred for 21 h.
[b] Method B: product isolated by extraction of crude reaction with diethyl ether.
[c] Temperature: 20 °C.
[d] Method A: yield determined by ^1H NMR using chloroacetic acid as internal standard.
[e] Temperature: 70 °C; nr: no reaction.

tions allowed the identification of efficient catalysis conditions: 20 mol% of PTSA at 50 °C using 2 equivalents of H_2O_2, providing the diol **2** in 95.5% yield (Table 1, entry 14).[19]

The substrate scope was tested (Table 3) and, in general, higher yields were obtained for cyclic olefins than for acyclic ones (Table 3, entries 1–4 *vs.* 5–7).

The substrate tolerance in the optimized conditions was explored by performing cross experiments using different substrates containing different functional groups plus cyclohexene (Table 4). Since some of these substrates are insoluble in water, we ensured the homogeneity of the reaction mixture by adding a co-solvent 1-propanol, that did not affect the reactivity of the experiment. Boc-protected amines were stable in the reaction conditions (Table 4, entry 1), and it was possible to recover *trans*-1,2-cyclohexanediol with 86% yield. The 1,2-Cbz-amino alcohol (entry 2) was also stable in the reaction conditions, although Fmoc-protected amino acid (entry 3) was only recovered in 40% yield. This group was partially stable in the reaction conditions despite the fact that it did not inhibit the *trans*-1,2-cyclohexanediol formation, which was obtained in 89% yield. Benzylamino alcohol (entry 4) was not stable in the reaction conditions, and inhibited the dihydroxylation reaction. Dimethylamide (entry 5) was stable in the reaction conditions, although it was not possible to separate the products by column chromatography. The hindered ketal TADDOL (entry 6) was stable in the reaction conditions, but the less hindered ketal (entry 12) was not, however the dihydroxylation reaction was con-

Table 4. Cross-experiments using different substrates containing different functional groups plus cyclohexene at 50 °C, with PTSA as catalyst (20 mol%).[a]



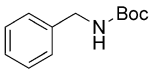
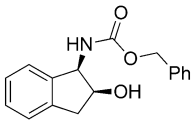
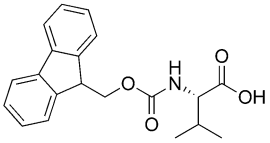
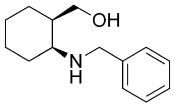
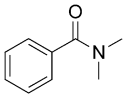
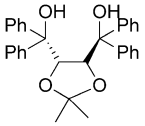
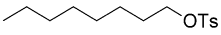
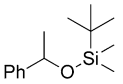
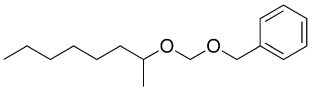
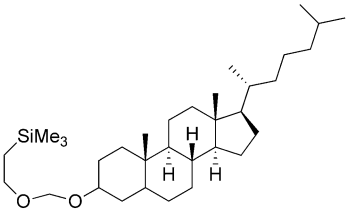
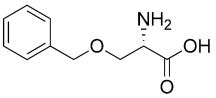
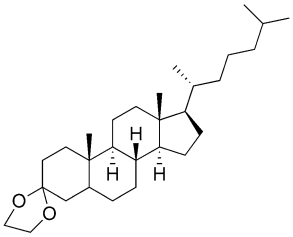
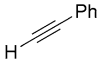
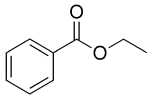
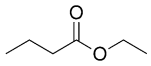
Entry	Cross-substrate	Stability (% recovered)[b]	**2** Yield [%][b]
1		yes (96%)	86
2		yes (85%)	87
3		yes/no (40%)	89
4		no	nr
5		yes[c]	nd
6		yes (94%)	87
7		yes (80%)	98.1
8		no[e]	61.0
9		no	72.3
10		yes (84.5%)	66.7
11		yes[c] yes[c,d]	nr nd
12		no	87.0

Table 4. (Continued)

Entry	Cross-substrate	Stability (% recovered)[b]	**2** Yield [%][b]
13		no	-
14		yes (76%)	98
15		no	75

[a] Method C: PTSA (20 mol%) and H_2O_2 (30% aqueous solution, 2 equiv.) were stirred for 5 min, then the cyclohexene (1–2.5 mmol) and the substrate (50 or 100 mol%) were added. After 21 h stirring at 50 °C, the reaction mixture was extracted with diethyl ether, and the mixture was separated by column chromatography on silica gel.

[b] The substrate stability was based on TLC, crude ^1H and ^{13}C NMR analysis and unless otherwise noted, recovery of the substrate was made by preparative TLC/column chromatography.

[c] Stability confirmed by ^1H and ^{13}C NMR, but the added substrate was not isolated.

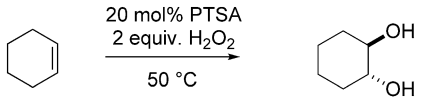
[d] 70 mol% of PTSA.

[e] 1-Phenylethanol was isolated. nr: no reaction, nd: not determined.

ducted and *trans*-1,2-cyclohexanediol was recovered with 87% yield. We also tested alcohol derivatives, such as *p*-toluenesulfonate (entry 7) and SEM-protected alcohol (entry 10) that were stable in the reaction conditions. TBDMS ether (entry 8) and BOM ether (entry 9) were unstable in the reaction conditions, although they did not inhibit the dihydroxylation reaction. *O*-Benzylserine (entry 11) was stable in the reaction conditions, although this amino acid could neutralize the 20 mol% of PTSA present in the reaction, inhibiting the dihydroxylation reaction. On increasing the PTSA amount to 70 mol% *versus* 50 mol% of amino acid, the dihydroxylation reaction occurred although it was not possible to separate the two compounds by column chromatography. Phenylacetylene (entry 13) was not stable in the reaction conditions and also inhibited the dihydroxylation reaction. The ester ethyl butyrate (entry 15) was not stable in the reaction conditions and did not inhibit the dihydroxylation reaction, although the more stable ester ethyl benzoate (entry 14) was stable in the reaction conditions. In a general overview there is a high compatibility for a considerable range of functional groups, demonstrating the milder conditions of this Brønsted acid-catalyzed methodology in aqueous medium.

The possibility to achieve catalyst reuse was explored by using cyclohexene as model substrate (Table 5). Just by extraction of the reaction mixture with diethyl ether, followed by new addition of H_2O_2 and the substrate, it was possible to recycle the catalyst at least seven times. In all cycles the reaction was complete and the diol **2** obtained was pure after solvent evaporation without the need of further purification by chromatography. The high efficiency of the reuse process is due to the preferential partition of the PTSA catalyst to the aqueous phase. The need of a higher reaction time to achieve completion of the reaction is probably due to loss of the catalyst during the extraction with diethyl ether.

Table 5. Reuse of the catalyst.[a]

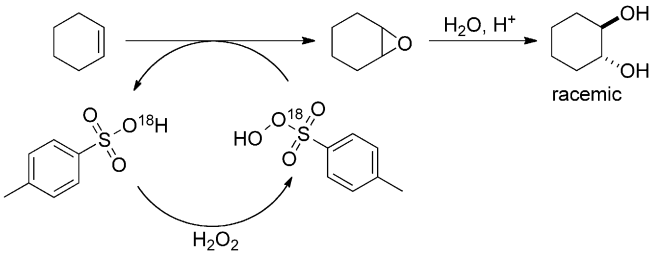


1 **2** racemic

Cycle	Yield [%]	Time
1	95.5	24 h
2	105.6	48 h
3	97.3	60 h
4	97.5	72 h
5	96.3	72 h
6	99.1	96 h
7	97.3	96 h
8	65.3	120 h

[a] Method D: PTSA (20 mol%, 951.1 mg), H_2O_2 (2 equiv., 30% aqueous solution, 5.66 g) were stirred for five minutes, and then the cyclohexene was added (25 mmol, 2.5 mL), at 50 °C. After the required reaction time the crude aqueous phase was extracted with diethyl ether (3 × 100 mL). The aqueous phase was concentrated by water evaporation, and the next cycle started by adding H_2O_2 (30% aqueous solution, 2 equiv., 5.66 g) and the substrate (25 mmol, 2.5 mL). Diethyl ether was removed from the organic layer, and the diol **2** was obtained in very high purity.

The observation of exclusive formation of *trans*-1,2-cyclohexandiol **2** (Table 2, entry 4) and, in some conditions, the formation of the corresponding *trans*-2-hydroxycyclohexyl *p*-toluenesulfonate **3** (Table 2, entry 2) supports a mechanism *via* epoxidation by the corresponding peroxysulfonic acid followed by acid-



Scheme 1. Proposed mechanism for the *trans*-dihydroxylation *via* epoxide formation.

catalyzed ring opening (Scheme 1). In addition, cyclohexene oxide afforded quantitatively the corresponding diol in only 5 min, at room temperature with 20 mol% of PTSA in H_2O. This result explains why cyclohexene oxide was never detected when following the cyclohexene dihydroxylation by ^1H and ^{13}C NMR spectroscopy under different experimental conditions. By using the catalyst PTSA enriched in ^{18}O under our optimized dihydroxylation conditions, it was observed by MS that ^{18}O was being retained exclusively in the recovered catalyst and not in the formed diol. The collected information supported an expected mechanism comprising epoxidation followed by fast ring opening by water in which both steps are catalyzed by PTSA.

In summary, we have described a simple, robust and mild Brønsted acid-catalyzed and metal-free dihydroxylation method of olefins in aqueous media that is also compatible with a considerable range of organic functional groups.

Experimental Section

Caution: *We have performed experiments with 30% hydrogen peroxide at 50 °C more than 50 times and no accident was observed, although performing reactions with this oxidant at this temperature always requires special attention, due to instability and the possibility of explosion.*

General Procedure A (Dihydroxylation of Cyclohexene using Different Promoters or Oxidants)

In a sealed flask was added the promoter and the oxidant that were stirred for 5 min, and then the cyclohexene (1–2.5 mmol) was added. After 21 h stirring at 20 °C (or 50 °C) chloroacetic acid (50 mol% approximately) was added. The mixture was analysed by ^1H NMR and the yield of 1,2-cyclohexenediol was calculated based on the amount of the internal standard (for more information see the Supporting Information).

General Procedure B (Dihydroxylation of Several Substrates)

In a sealed flask was added PTSA (20 or 100 mol%) and H_2O_2 (30% aqueous solution, 2 equiv.) that were stirred for 5 min, then the substrate (25 mmol) was added. After 21 h stirring at 50 °C, the reaction mixture was neutralized with sodium bicarbonate, and reduced with Na_2SO_3, and then extracted with diethyl ether.

General Procedure C (Dihydroxylation of Cyclohexene in the Presence of Substrates bearing Different Functional Groups)

In a sealed flask was added PTSA (20 mol%) and H_2O_2 (30% aqueous solution, 2 equiv.) that were stirred for 5 min, then the cyclohexene (1–2.5 mmol) and the substrate (50 or 100 mol%) were added. After 21 h stirring at 50 °C, the reaction mixture was extracted with diethyl ether, and the mixture was separated by column chromatography on silica gel. When the substrate was not soluble in the aqueous phase, or the olefin phase (cyclohexene), 1-propanol was added as co-solvent.

General Procedure D (Recycling the Catalyst)

In a sealed flask was added PTSA (20 mol%, 951.1 mg), H_2O_2 (2 equiv., 30% aqueous solution, 5.66 g) and the substrate (25 mmol, 2.5 mL), at 50 °C. After the required reaction time the crude aqueous phase was extracted with diethyl ether (3 × 100 mL). The aqueous phase was concentrated by water evaporation, and the next cycle started by adding H_2O_2 (2 equiv, 30% aqueous solution, 5.66 g) and the substrate (25 mmol, 2.5 mL). Diethyl ether was removed from the organic layer, affording the diol **2** in very high purity.

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[19] See Supporting Information.

