

A cost-effective and eco-friendly way to dihydroxylate terminal and internal alkenes using hydrogen peroxide/formic acid

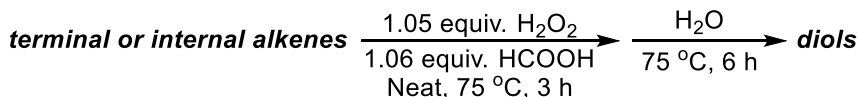
Chia-Wei Hsu^a
Trevor L. Dzwiniel^{*a}
Krzysztof Z. Pupek^a

^a Applied Materials Division, Argonne National Laboratory,
9700 S. Cass Ave, Lemont, Illinois 60439, U.S.A.

* indicates the corresponding author.

tdzwiniel@anl.gov

[Click here to insert a dedication.](#)



No catalyst or base is needed!

Received:
Accepted:
Published online:
DOI:

Abstract In this report, we present a modified dihydroxylation procedure for terminal and internal alkenes under neat conditions using formic acid and hydrogen peroxide. Upon the *in situ* formation of performic acid, followed by the hydrolysis of hydroxy-formoxy compounds with excess water, we can obtain a series of diols without catalysts and bases.

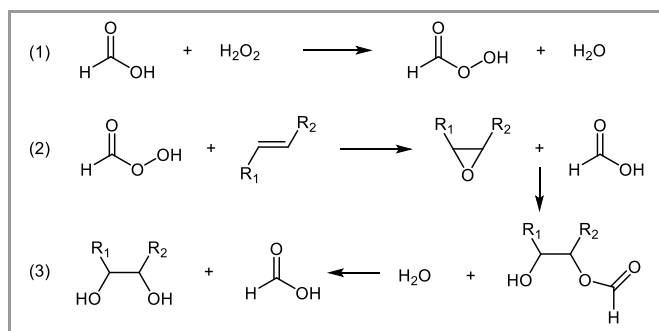
Key words catalyst-free dihydroxylation of alkene; formic acid; hydrogen peroxide

Vicinal diols are paramount building blocks in fine chemical syntheses and medicinal chemistry.¹ They are also common everyday substances such as ethylene glycol and propylene glycol, both well-known antifreeze chemicals. Propylene glycol is also applied in cosmetics², food and pharmaceutical industry.³ In battery chemistry, vicinal diols are precursors of cyclic carbonates forming battery electrolytes such as ethyl carbonate (EC)⁴ and propylene carbonate (PC).⁵ To obtain vicinal diols, the dihydroxylation of alkenes has been broadly studied using tungsten^{6a}, vanadium^{6a}, rhenium^{6b}, osmium^{6c}, etc. as the catalysts. However, the toxicity, cost and availability of these metals are highly concerned. Thus, a cost-effective and eco-friendly method will be valuable to the vicinal diol manufacture. Using a minimum amount of non-metal oxidizing agent is a plausible solution to provide a greener way to produce vicinal diols.

Organic peroxide compounds are commonly used to form epoxides from alkenes, followed by hydrolysis to produce diols with bases or acids—a two-step synthesis.^{6a} For instance, *meta*-chloroperoxybenzoic acid (*m*-CPBA)⁷, performic^{8,9} and peracetic acid⁸ are widely utilized. Storage and waste control of organic peroxides emerge from the dihydroxylation of alkene on a large scale. *In situ* production of organic peroxide has been reported and applied to the dihydroxylation of alkenes.^{8,9} For instance,

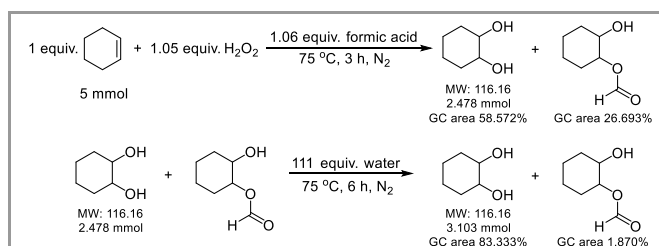
Swern and his coworkers utilized formic acid and hydrogen peroxide to produce performic acid and oxidize the unsaturated fatty acids. They used sodium hydroxide to hydrolyze epoxides and hydroxy-formoxy species to obtain diols (Scheme 1).⁸ The other representative example is cyclohexene dihydroxylation⁹ with a similar protocol to Swern's. Formic acid and hydrogen peroxide formed performic acid *in situ*, followed by epoxidation of cyclohexene, then the ring-open reaction to afford 1,2-cyclohexanediol.⁹

However, in both examples, excess formic acid (10 equiv.) was used as both reagent and solvent. Bases such as sodium hydroxide (3 *N* aqueous solution⁸; 2 equiv. of NaOH, 13 *N* aqueous solution⁹) were introduced to hydrolyze the epoxides and formate derivatives to form diols. Excessive use of caustic materials are hazardous and could negatively impact waste control. Interestingly, in Swern's report, "...during a period of several months exposure to the air the neutralization equivalent of hydroxy-formoxystearic acid diminished...These facts suggest the possibility of obtaining the free glycols from the formate esters by hydrolysis with water alone", they suggested that free diols can possibly be obtained by hydrolysis using water.⁸ Herein, we report the conversion of terminal and internal alkenes into diols using 1.06 equivalent of formic acid (5.3 mmol), 1.05 equivalent of hydrogen peroxide (5.2 mmol) and 1 equivalent of alkenes (5.0 mmol), followed by hydrolysis of epoxides using only water. This method reduces the amount of formic acid and avoids production of heat from adding sodium hydroxide to hydrolyze hydroxy-formoxy compounds.¹⁰



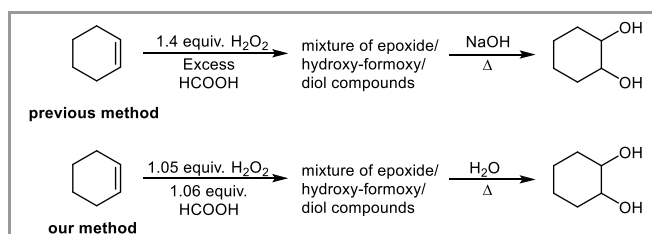
Scheme 1. Proposed reaction scheme by Swern's group.⁸

In this communication, we firstly carried out the dihydroxylation of cyclohexene under the following conditions: under nitrogen, cyclohexene (5.0 mmol, 0.413 g) and formic acid (5.3 mmol, 0.244 g) were mixed and hydrogen peroxide (5.2 mmol, 0.509 g, 35 wt.% H₂O₂ in water) was added dropwise into the same flask. After stirring for 5 minutes at room temperature, the reaction was gradually heated to 75 °C and stirred for 3 hours. Using GC-MS analysis, the epoxide species were detected along with the production of diols and hydroxy-formoxy compounds (See *Supporting Information*, Figure S1–S4 and Table S1). After the reaction was cooled to ambient temperature, an excess amount of water (10 g, 556 mmol) was added and the reaction was heated to 75 °C for 6 hours to hydrolyze the hydroxy-formoxy compounds. The diol was initially extracted by dichloromethane and later obtained as the residue after evaporating solvents from the aqueous solution under reduced pressure. The recrystallized yield of 1,2-cyclohexanediol is 22%. In order to assure that hydroxy-formoxy species gets involved in water-driven hydrolysis, we investigated the conversion of hydroxy-formoxy compounds to diols using GC-MS. After the oxidation of cyclohexene using 1.06 equivalent of formic acid and 1.05 equivalent of hydrogen peroxide, acid and water were distilled and the residue was examined by GC-MS (See *Supporting Information*, Figure S9). Diols and hydroxy-formoxy compounds are the major products (diols: 58.572%; hydroxy-formoxy compounds: 26.693%). Then the crude was reconstituted in 10 g of water and heated to 75 °C for 6 hours. Further GC-MS analysis of the hydrolyzed crude was taken after the complete removal of water and acid (See *Supporting Information*, Figure S10). The chromatogram displayed that the hydrolysis of hydroxy-formoxy compounds can be carried out with the presence of water (diols: 83.333%; hydroxy-formoxy compounds: 1.870%). According to the calibration curve, prior to water-driven hydrolysis, 2.478 mmol of 1,2-cyclohexanediol were present and after hydrolysis, a 25% increase was observed as 3.103 mmol of 1,2-cyclohexanediol (GC yield, 62%) were present. This result successfully reflects Swern's observation (Scheme 1, eq. 3) pertaining to the water-driven hydrolysis of hydroxy-formoxy compounds.



Scheme 2. Step-by-step GC-MS analysis of the dihydroxylation of cyclohexene.

In comparison with the previous report (Scheme 3)⁹, we simplify the procedure by using water as the hydrolyzing agent to avoid the use of excess bases. We further lower the usage of formic acid from 10 equivalent to 1.06 equivalent versus the alkene. Using this method, we can reduce cost and waste production at the same time. Indene is another internal alkene substrate that displays this efficient dihydroxylation under the same protocol with a decent recrystallized yield (53%) (Table 1).



Scheme 3. Representative dihydroxylation of alkene using different amount of formic acid and work-up procedure.

To broaden our scope, a series of terminal alkenes has been introduced to this report (Table 1.). Allylbenzene and styrene both led to diol derivatives **3** (43%) and **4** (31%).

Table 1. Dihydroxylation of terminal and internal alkenes.¹²

1 equiv. internal alkenes/ terminal alkenes	1.05 equiv. H ₂ O ₂ 1.06 equiv. HCOOH Neat, 75 °C, 3 h	excess H ₂ O 75 °C, 6 h	diols
Substrate	Product		Yield (%)
Cyclohexene	1,2-Cyclohexanediol 1		22% ^a (62%) ^b
Indene	1,2-Indanediol 2		53% ^a
Allylbenzene	Benzyl glycol 3		43% ^a
Styrene	Styrene glycol 4		31% ^a

^aIsolated yield after recrystallization; ^bGC yield.

This method not only demonstrates a metal-free and base-free dihydroxylation of alkenes that leads to a cost-effective and eco-friendly diol production, but also has potential applicability to continuous flow systems for the large scale synthesis of valuable diols in the battery materials market. The application of continuous flow systems using this method is in due course.

Funding Information

[Click here to insert sources of funding, grant numbers, etc. Do not repeat the same in the acknowledgment.](#)

Acknowledgment

Argonne National Laboratory is a U. S. Department of Energy Office of Science laboratory operated by UChicago Argonne, LLC, under contract DE-AC02-06CH11357. The work published is sponsored by DOE EERE Vehicle Technology Office.

Supporting Information

YES (this text will be updated with links prior to publication)

Primary Data

NO (this text will be deleted prior to publication)

References and Notes

- (1) (a) Muschallik, L.; Molinnus, D.; Jablonski, M.; Kipp, C. R.; Bongaerts, J.; Pohl, M.; Wagner, T.; Schöning, M. J.; Selmer, T.; Siegert, P. *RSC Adv.* **2020**, *10*, 12206. (b) Ray, A. M.; Barbour, J. D.; McElfresh, J. S.; Moreira, J. A.; Swift, I.; Wright, I. M.; Žunič, A.; Mitchell, R. F.; Graham, E. E.; Alten, R. L.; Millar, J. G.; Hanks, L. M. *J. Chem. Ecol.* **2012**, *38*, 1151. (c) Ji, X.-J.; Huang, H.; Ouyang, P. K. *Biotechnol. Adv.* **2011**, *29*, 351.
- (2) Fiume, M. M.; Bergfeld, W. F.; Belsito, D. V.; Hill, R. A.; Klaassen, C. D.; Liebler, D.; Marks, J. G.; Shank, R. C.; Slaga, T. J.; Snyder, P. W.; Andersen, F. A. *Int. J. Toxicol.* **2012**, *31*, 245S.
- (3) *Public Health Statement for Propylene Glycol*; Agency for Toxic Substances & Disease Registry, U.S. Department of Health and Human Services, Public Health Service: Atlanta, GA, **1997**.
- (4) Kitamura, T.; Inoue, Y.; Maeda, T.; Oyamada, J. *Synth. Commun.* **2016**, *46*, 39.
- (5) Pyo, S.-H.; Hatti-Kaul, R. *Adv. Synth. Catal.* **2016**, *358*, 834.
- (6) (a) Wang, C. *Asian J. Org. Chem.* **2018**, *7*, 509. (b) Plietker, B.; Niggemann, M.; Pollrich, A. *Org. Biomol. Chem.* **2004**, *2*, 1116. (c) Döbler, C.; Mehlretter, G. M.; Sundermeier, U.; Beller, M. *J. Am. Chem. Soc.* **2000**, *122*, 10289.
- (7) Fringuelli, F.; Germani, R.; Pizzo, F.; Savelli, G. *Synth. Commun.* **1989**, *19*, 1939.
- (8) Swern, D.; Billen, G. N.; Findley, T. W.; Scanlan, J. T. *J. Am. Chem. Soc.* **1945**, *67*, 1786.
- (9) Roebuck, A.; Adkins, H. *Org. Synth.* **1955**, *28*, 35.
- (10) In Ref. 8, the heat production was reported during the addition of sodium hydroxide into the mixture of the diol and hydroxy-formoxy species.
- (11) The experimental procedures and characterization data of 1,2-cyclohexanediol: under N₂ atmosphere, 5 mmol of cyclohexene (0.413 g) and 5.3 mmol (0.244 g) of formic acid were added, followed by dropwise addition of 5.2 mmol of hydrogen peroxide (0.509 g, 35 wt.% H₂O₂ in water) into a 3-necked, 50 mL round bottom flask with a stir bar. After stirring at ambient temperature for 5 minutes, the reaction was gradually heated to 75 °C for 3 hours (the reaction completion was monitored by GC-MS). After the reaction was cooled to ambient temperature, D.I. water (10 mL) was added into the flask and the reaction was stirred for 6 more hours at 75 °C. The crude 1,2-cyclohexanediol was extracted by 10 mL × 3 dichloromethane from the aqueous solution (the aqueous solution was kept for later use), followed by dehydration with MgSO₄ anhydrous. After removing the MgSO₄ and collecting the filtrate, the diol was obtained by evaporating solvent. To obtain more product, the aqueous solution was distilled to remove water and acid (50 mbar, 50 °C), and the diol was collected as the residue. Further purification was performed via recrystallization (hexane/ethyl acetate, hexane/dichloromethane at 6 °C). 127 mg of 1,2-cyclohexanediol was obtained after the recrystallization as white crystals (22% isolated yield). ¹H-NMR (80 MHz, CDCl₃): δ = 3.2–3.5 (m, 2H), 2.26 (br, 2H), 1.97 (m, 2H), 1.71 (m, 2H), 1.25 (m, 4H). ¹³C-NMR (20 MHz, CDCl₃): δ = 75.6, 32.8, 24.3. EI-MS: [M]⁺ = 116.1.
- (12) This series of reactions was not optimized and the oily crude diols resulted in low isolated yields.