An Effective Catalytic Epoxidation of Terpenes with Hydrogen Peroxide under Organic Solvent-Free Conditions

Yoshihiro Kon, Yutaka Ono, Tomohiro Matsumoto, Kazuhiko Sato*

National Institute of Advanced Industrial Science and Technology (AIST), Tsukuba Central 5 Higashi 1-1-1, Tsukuba, Ibaraki 305-8565, Japan

Fax +81(29)8614578; E-mail: k.sato@aist.go.jp Received 26 December 2008

Abstract: A catalytic system that operates well for the epoxidation of α -pinene, a very challenging substrate, at near-neutral pH and ambient temperature without organic solvent was developed. With hydrogen peroxide as a terminal oxidant, combination of Na₂WO₄, PhP(O)(OH)₂, and [Me(n-C₈H₁₇)₃N]HSO₄ successfully catalyzed the epoxidation of α -pinene to give α -pinene oxide in 95% selectivity at 91% conversion, while the previously published conditions that use NH₂CH₂P(O)(OH)₂ as a promoter provide no epoxide. The method is also well applicable to the epoxidation of the other acidsensitive terpenes.

Key words: oxidations, catalysis, epoxides, terpenoids, green chemistry

Terpenes are widely distributed in nature and are often key raw materials in organic chemistry.¹ Epoxidation of terpenes is recognized as a particularly significant procedure because the generated epoxides are important starting materials with a wide variety of uses such as in flavors, fragrances, and pharmaceuticals.^{1,2} Preparation of the oxidized terpenes under current industrial methods requires percarboxylic acids, which leave an equimolar waste product after the reaction.^{1a,2} As a part of the green concept, toxic oxidants are being replaced by alternative nontoxic reagents.³ Hydrogen peroxide (H_2O_2) is an ideal oxidant because water is the only side product and the atom efficiency is excellent.⁴ We have therefore developed various oxidation reactions with aqueous H₂O₂ under organic solvent-free conditions.⁵ Although a number of metal-catalyzed H₂O₂ epoxidation reactions have been reported thus far,^{6,7} the epoxidation of terpenes (especially, bicyclic terpenes) is still a challenging task due to their sensitivity toward acidic media.^{1b,8} Terpenes and their epoxides easily undergo ring opening, rearrangement, double-bond migration, and hydrolysis by acid catalysis or by application of heating.¹ These reactions are due to their isoprene units possessing trisubstituted alkenes and their epoxides are prone to generate a stable intermediate, namely, a tertiary carbocation through protonation or ring opening of the epoxides during the reaction. In the case of preparing α -pinene oxide, isomerization and/or hydrolysis of both the reactant and the product may lead to a complex mixture of β -pinene, 3-carene, camphene, campholenic aldehyde, α -terpineol, etc., as shown in Scheme 1.⁹ Few

SYNLETT 2009, No. 7, pp 1095–1098 Advanced online publication: 20.03.2009 DOI: 10.1055/s-0028-1088156; Art ID: U13208ST © Georg Thieme Verlag Stuttgart · New York successful examples that use an immobilized catalyst of polyoxometalates on mesoporous silica gel and methyltrioxorhenium catalysts have been shown to effectively catalyze terpene epoxidation.¹⁰ Additionally, these methods are not fully satisfactory because of the requirement of hazardous organic solvent and/or the complicated multistep preparation of catalysts using organic solvents. We have previously reported efficient methods for the epoxidation of alkenes¹¹ under organic solvent-free conditions, but unfortunately they did not work well for α-pinene epoxidation because of the highly acidic conditions and heating (the selectivity of α -pinene oxide was 0%).^{6b} A catalytic system applicable to nearly neutral conditions without loss of activity at ambient temperature is necessary for the epoxidation of terpenes under organic-solvent-free conditions. We report here a practical method for the syntheses of terpene oxides from the epoxidation of terpenes that can be carried out without organic solvent.



Scheme 1 Compounds obtained from α -pinene and α -pinene oxide via isomerization and/or hydolysis

 α -Pinene, a most challenging terpene, was chosen as a screening substrate. We found that at near-neutral pH screening of phosphonic acid additives shows big differences in the catalytic reactivity. These additives for improving the selectivity were tested under following conditions: using aqueous H₂O₂ (60% aq, 1.3 equiv) as an oxidant and NaOH (6 mol%) which adjust the pH to a nearly neutral condition. The solutions were mixed with a catalytic system consisting of Na₂WO₄ (8 mol% to

α-pinene) and [Me(n-C₈H₁₇)₃N]HSO₄ (phase-transfer catalyst, 8 mol%, Equation 1). The best choice of additive as a cocatalyst, which binds with the tungstate center to form a phosphonate complex,¹² was found to be PhP(O)(OH)₂ (4 mol%). The reaction of α-pinene with these catalytic conditions successfully gave α-pinene oxide in 87% yield (on the basis of the starting α-pinene) after stirring at 25 °C for 12 hours. Although the reaction preferred 60% H₂O₂ as the oxidant, an epoxidation with 30% H₂O₂ also gave satisfactory results (75% yield of α-pinene oxide).



Equation 1

Table 1 Effects of Additives on the Epoxidation of α-Pinene^a

Entry	Additive	Conversion (%) ^b	Yield (%) ^b	Selectivity (%) ^c
1	PhP(O)(OH) ₂	91	87	95
2	MeP(O)(OH) ₂	87	61	70
3	EtP(O)(OH) ₂	91	68	75
4	n-PrP(O)(OH) ₂	88	65	74
5	t-BuP(O)(OH) ₂	84	70	83
6	H ₃ PO ₄	86	66	77
7	NH ₂ CH ₂ P(O)(OH) ₂	74	35	47

^a Reaction conditions: α-pinene (3 mmol), 60% H_2O_2 (3.9 mmol), Na_2WO_4 (0.24 mmol), $[Me(n-C_8H_{17})_3N]HSO_4$ (0.24 mmol), additive (0.12 mmol), NaOH (0.18 mmol), 25 °C, 1000 rpm, 12 h.

 $^{\rm b}$ Yield on the basis of $\alpha\text{-pinene},$ determined by GC analysis with biphenyl as internal standard.

^c Yield/conversion (%)

The results with the other additives we examined are summarized in Table 1. Alkylphosphonic acids also worked as cocatalysts under the present reaction conditions, although their efficiencies were somewhat lower than that of $PhP(O)(OH)_2$, then the epoxidations using $MeP(O)(OH)_2$, $EtP(O)(OH)_2$, $n-PrP(O)(OH)_2$, and t-BuP(O)(OH)₂ resulted in the formation of α -pinene oxide in 61%, 68%, 65%, and 70% yield, respectively (Table 1, entries 2–5). As well as the alkylphosphonic acids, a reaction in the presence of H_3PO_4 gave a modest yield (66%, Table 1, entry 6). It is noteworthy that the catalytic ability of NH₂CH₂P(O)(OH)₂ (previously reported as the best cocatalyst under acidic conditions¹¹ and as a better cocatalyst than $PhP(O)(OH)_2^{11b}$) was found to be much inferior to that of $PhP(O)(OH)_2$. That is, the epoxidation using $NH_2CH_2P(O)(OH)_2$ gave the epoxide with less selectivity

(47%, Table 1, entry 7). The inefficiency of NH₂CH₂P(O)(OH)₂ could be attributed to its amino group. The yield of product was decreased to 54% when the epoxidation (the same conditions as entry 1) was carried out in the presence of n-BuNH₂ (4 mol%). Though the reason for this deterioration was unclear, these epoxidation experiments under nearly neutral pH conditions (adjusted by aq NaOH) eliminated the possibility for the amines of working just as a base that alters the pH. The addition of NaOH for weakening the Brønsted acid reactivity is important to protect the generated epoxide from hydrolysis. When the addition of NaOH was omitted (the other conditions as same as those of entry 1), 80% of the starting α -pinene was consumed, though the yield and selectivity of α -pinene oxide were low (13% and 16%, respectively).

This epoxidation system using PhP(O)(OH)₂ as cocatalyst can be adopted for the epoxidation of the other various terpenes to generate the corresponding terpene oxides. The results are shown in Table 2. As a model case of the simple cyclic trisubstituted alkene, 1-methyl-1-cyclohexene was successfully converted to the epoxide (92% yield, Table 2, entry 1). A reaction with bicyclic monoterpene, 3-carene, which is known to undergo an acid-catalyzed rearrangement upon treatment with peracid, ^{1b,10d,13} also provided an excellent yield of the corresponding epoxide (93%, Table 2, entry 4). A reaction with α -terpineol having a hydroxy group that causes intramolecular addition reactions in its product under acidic conditions¹⁴ also gave the corresponding epoxide in high yield (98%, Table 2, entry 6). A reaction with β -myrcene, with which it was difficult to achieve regioselective epoxidation by the former catalyst system,¹⁵ gave the 2,3-epoxide in 75% yield (entry 7). Epoxidation of limonene and β -caryophyllene, which have two alkene moieties in the molecule, was also successfully produced the corresponding monoepoxides in high yields (82%, entries 8 and 9).

The present method can be carried out on a hectogram scale of terpene epoxidation. That is, with 100 g of 3-carene as a starting material, 97.6 g of the corresponding epoxide was obtained after distillation of the crude product (87% yield, Equation 2 and Table 2, entry 5). Because the epoxidation of 3-carene is quite exothermic, careful reaction temperature control was found critical for a larger-scale preparation.



Equation 2

Table 2 H₂O₂ Epoxidation of Terpenes and Inner Olefin^a



^a Reaction conditions: alkene (3.0 mmol), 60% H₂O₂ (3.9 mmol), Na₂WO₄ (0.24 mmol), [Me(*n*-C₈H₁₇)₃N]HSO₄ (0.24 mmol), PhP(O)(OH)₂ (0.12 mmol), NaOH (0.18 mmol), 25 °C, 1000 rpm, 12 h. ^b Yield on the basis of alkene, determined by GC analysis with biphenyl as internal standard.

^c 30% H₂O₂ was used instead of 60% H₂O₂.

^d The reaction was run using 100 g of 3-carene, 1.3 equiv of 60% H_2O_2 , 4 mol% of Na_2WO_4 , 2 mol% of PhP(O)(OH)₂, 4 mol% of [Me(*n*-C₈H₁₇)₃N]HSO₄, 4 mol% of NaOH. ^e Isolated yield after distillation.

In summary, we have developed a green and practical method for terpene epoxidation using aqueous H_2O_2 as an oxidant under organic solvent-free conditions. The catalytic system, which consists of Na₂WO₄, PhP(O)(OH)₂, and [Me(n-C₈H₁₇)₃N]HSO₄, having high activity under nearly neutral pH conditions at ambient temperature, achieved the excellent yield and selectivity for epoxidation of very challenging acid-sensitive terpenes. The application of these conditions to the other challenging products, for example, styrene oxide derivatives, is now under investigation.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

Acknowledgment

This work was partially supported by a Grant-in-Aid for Scientific Research on Priority Areas 'Advanced Molecular Transformation of Carbon Resources' from the Ministry of Education, Culture, Sports, Science, and Technology, Japan. We are grateful to Prof. Dr. Akira Sekiguchi in Department of Chemistry, Graduate School of Pure and Applied Sciences, University of Tsukuba for the helpful cooperation.

References and Notes

- (a) Eggersdorfer, M. In Ullmann's Encyclopedia of Industrial Chemistry, 6th ed., Vol. 35; Wiley-VCH: Weinheim, 2003, 653. (b) Corma, A.; Iborra, S.; Velty, A. Chem. Rev. 2007, 107, 2411.
- (2) Sienel, G.; Rieth, R. In Ullmann's Encyclopedia of Industrial Chemistry, 6th ed., Vol. 12; Wiley-VCH: Weinheim, 2003, 279.
- (3) (a) Trost, B. M. Science 1991, 254, 1471. (b) Sheldon, R. A. Chem. Ind. 1992, 903.
- (4) Strukul, G. In *Catalytic Oxidations with Hydrogen Peroxide* as Oxidant; Kluwer Academic Publishers: The Netherlands, 1992.
- (5) (a) Sato, K.; Aoki, M.; Takagi, J.; Noyori, R. J. Am. Chem. Soc. 1997, 119, 12386. (b) Sato, K.; Aoki, M.; Noyori, R. Science 1998, 281, 1646. (c) Sato, K.; Takagi, J.; Aoki, M.; Noyori, R. Tetrahedron Lett. 1998, 39, 7549. (d) Sato, K.; Aoki, M.; Takagi, J.; Zimmermann, K.; Noyori, R. Bull. Chem. Soc. Jpn. 1999, 72, 2287. (e) Sato, K.; Hyodo, M.; Takagi, J.; Aoki, M.; Noyori, R. Tetrahedron Lett. 2000, 41, 1439. (f) Sato, K.; Hyodo, M.; Aoki, M.; Zheng, X.-Q.; Noyori, R. Tetrahedron 2001, 57, 2469. (g) Usui, Y.; Sato, K. Green Chem. 2003, 5, 373. (h) Usui, Y.; Sato, K.; Tanaka, M. Angew. Chem. Int. Ed. 2003, 42, 5623. (i) Kon, Y.; Usui, Y.; Sato, K. Chem. Commun. 2007, 4399. (j) Kon, Y.; Yazawa, H.; Usui, Y.; Sato, K. Chem. Asian J. 2008, 3, 1642. (k) Chishiro, T.; Kon, Y.; Sato, K. J. Synth. Org. Chem. Jpn. 2008, 66, 1085.
- (6) For recent examples, see: (a) Rüsch gen. Klaas, M.; Warwel, S. Org. Lett. 1999, 1, 1025. (b) Villa, A. L.; Sels, B. F.; De Vos, D. E.; Jacobs, P. A. J. Org. Chem. 1999, 64, 7267. (c) Salles, L.; Brégeault, J.-M.; Thouvenot, R. Surf. Chem. Catal. 2000, 3, 183. (d) Skrobot, F. C.; Valente, A. A.; Neves, G.; Rosa, I.; Rocha, J.; Cavaleiro, J. A. S. J. Mol. Catal. A: Chem. 2003, 201, 211. (e) Woitiski, C. B.; Kozlov, Y. N.; Mandelli, D.; Nizova, G. V.; Schuchardt, U.; Shul'pin, G. B. J. Mol. Catal. A: Chem. 2004, 222, 103. (f) Eimer, G. A.; Díaz, I.; Sastre, E.; Casuscelli, S. G.; Crivello, M. E.; Herrero, E. R.; Perez-Pariente, J. Appl. Catal., A 2008, 343, 77.
- (7) For recent reviews, see: (a) Applied Homogeneous Catalysis with Organometallic Compounds, 2nd ed.; Cornils, B.; Herrmann, W. A., Eds.; Wiley-VCH: Weinheim, 2002. (b) Lane, B. S.; Burgess, K. Chem. Rev. 2003, 103, 2457. (c) Modern Oxidation Methods; Bäckvall, J.-E., Ed.; Wiley-VCH: Weinheim, 2004.
- (8) Selective oxidation of monocyclic and noncyclic terpenes using PCWP-H₂O₂ system in CHCl₃ has been reported: Sakaguchi, S.; Nishiyama, Y.; Ishii, Y. J. Org. Chem. 1996, 61, 5307.

- (9) (a) Rudakov, G. A.; Ivanova, L. S.; Pisareva, T. N.; Borovskaya, A. G. *Gidroliz. Lesokhim. Promst* 1975, *4*, 7.
 (b) Kaminska, J.; Schwegler, M. A.; Hoefnagel, A. J.; Van Bekkum, H. *Recl. Trav. Chim. Pays-Bas* 1992, *111*, 432. (c) Carr, G.; Dosanjh, G.; Millar, A. P.; Whittaker, D. J. Chem. Soc., Perkin Trans. 2 1994, 1419.
- (10) (a) Villa, A. L.; De Vos, D. E.; Montes, C.; Jacobs, P. A. *Tetrahedron Lett.* **1998**, *39*, 8521. (b) Sakamoto, T.; Pac, C. *Tetrahedron Lett.* **2000**, *41*, 10009. (c) Saladino, R.; Neri, V.; Pelliccia, A. R.; Mincione, E. *Tetrahedron* **2003**, *59*, 7403. (d) Saladino, R.; Andreoni, A.; Neri, V.; Crestini, C. *Tetrahedron* **2005**, *61*, 1069.
- (11) (a) Sato, K.; Aoki, M.; Ogawa, M.; Hashimoto, T.; Noyori, R. J. Org. Chem. 1996, 61, 8310. (b) Sato, K.; Aoki, M.; Ogawa, M.; Hashimoto, T.; Panyella, D.; Noyori, R. Bull. Chem. Soc. Jpn. 1997, 70, 905. (c) Noyori, R.; Aoki, M.; Sato, K. Chem. Commun. 2003, 1977.
- (12) Duncan, D. C.; Chambers, R. C.; Hecht, E.; Hill, C. L. J. Am. Chem. Soc. **1995**, 117, 681.
- (13) Kolehmainen, E.; Laihia, K.; Heinänen, M.; Rissanen, K.; Fröhlich, R.; Korvola, J.; Mänttäri, P.; Kauppinen, R. *J. Chem. Soc., Perkin Trans.* 2 **1993**, 641.
- (14) Kopperman, H. L.; Hallcher, R. C.; Riehl, S. r. A.; Carlson, R. M.; Caple, R. *Tetrahedron* **1976**, *32*, 1621.
- (15) Pigulevskii, G. V.; Adrova, N. A. Zh. Obsbch. Khim. 1957, 27, 136; Chem. Abstr. 1957, 51, 12874i.

Copyright of Synlett is the property of Georg Thieme Verlag Stuttgart and its content may not be copied or emailed to multiple sites or posted to a listserv without the copyright holder's express written permission. However, users may print, download, or email articles for individual use.