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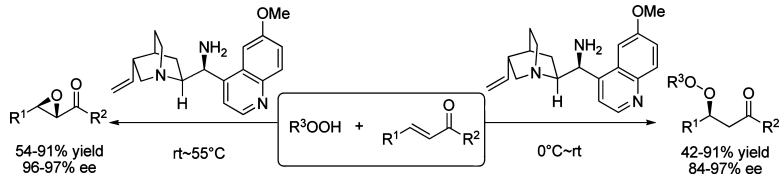


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# Catalytic Enantioselective Peroxidation of α,β-Unsaturated Ketones

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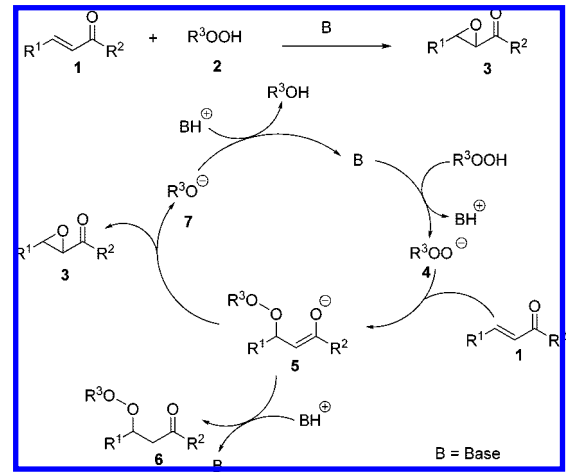
The number of biologically interesting natural products possessing peroxide structure motifs is substantial and still growing.[1] Many peroxy natural products display antitumor, anticancer, and antiparasite activities, which are attributed to the propensity of the peroxide to initiate radical reactions in an iron-rich environment.[2] Furthermore, peroxide natural products such as artemisinin are clinically important antimalaria drugs. Despite the potential of chiral peroxides as biologically interesting or even clinically important compounds, synthetic methods for the preparation of chiral peroxides are highly limited.[3–6] In particular efficient catalytic enantioselective peroxidations are urgently needed, yet none are available. In fact only a single example of a chiral auxiliary-directed peroxidation in high diastereoselectivity could be found in the literature.[7] Herein, we wish to report the development of a highly enantioselective peroxidation of α,β-unsaturated ketones with an easily accessible chiral organic catalyst.

The base-promoted reaction of α,β-unsaturated ketones **1** with hydroperoxides **2** represents a classic epoxidation reaction. Asymmetric variants of this epoxidation with both chiral metal and organic catalysts have also been reported.[8–13] It is well-established that the epoxide **3** is formed via a two-step mechanism (Scheme 1); nucleophilic addition of the hydroperoxide **2** to **1** followed by an intramolecular nucleophilic substitution of the resulting enolate (**5**) that breaks the weak peroxide bond. In principle this epoxidation pathway (**1** to **3**) could be converted into a peroxidation pathway (**1** to **6**) if **5** could be trapped by protonation, although the overwhelming preference of **5** for the intramolecular nucleophilic substitution is evident from the lack of reported peroxidation of α,β-unsaturated carbonyl compounds.

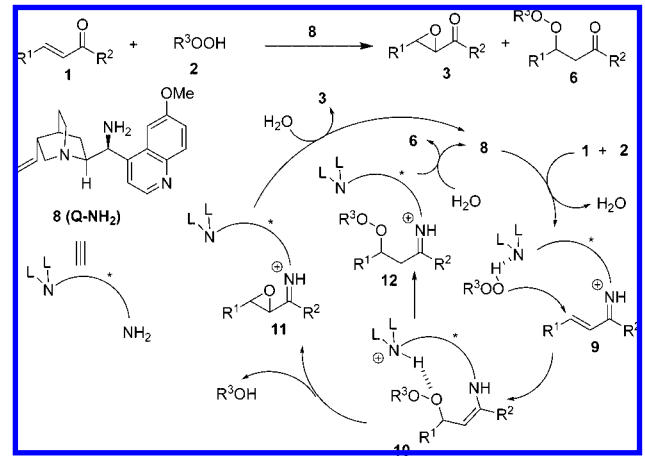
Although chiral amine-catalyzed nucleophilic epoxidations of α,β-unsaturated carbonyl compounds have already been reported,[13] we suspected that a cinchona alkaloid derivative such as **8**[14] could not only render the nucleophilic addition of the hydroperoxide **2** to the iminium intermediate **9** enantioselective, but also strongly influence the partitioning of the peroxyenamine intermediate **10** between the epoxidation (**10** to **11**) and the peroxidation (**10** to **12**) pathways (Scheme 2). Presumably, owing to steric crash and multipoint binding interactions between the peroxyenamine intermediate and the covalently linked cinchona alkaloid, the bond-rotational freedom of the peroxyenamine should be hampered, compared to that of the enolate **5** in Scheme 1. We expected that this conformational rigidity imposed by **8** on the peroxyenamine would diminish its ability to adopt the active conformation by which the nucleophilic enamine moiety is optimally aligned relative to the O−O bond for the nucleophilic attack. This in turn would decelerate the epoxidation. In contrast, with the protonated quinuclidine as a proton source nearby to facilitate the protonation of the peroxyenamine, the peroxidation might be accelerated.

We then investigated how α,β-unsaturated ketone **1A** reacted with TBHP (**2a**) in the presence of **8**. We found that, with TFA (20 mol %) as the additive, the reaction afforded the peroxide **6Aa** as the dominant product in 85% ee (entry 1, Table 1). When performed in toluene with 30 mol % TFA both the peroxide/epoxide (**6/3**) ratio and the enantioselectivity could be improved to an excellent level (entry 2, Table 1). Importantly, the reaction demonstrated considerable scope for both the α,β-unsaturated ketones **1** and the hydroperoxides **2**.

***Scheme 1.*** Mechanism of a Base-Catalyzed Nucleophilic Epoxidation of α,β-Unsaturated Ketones




***Scheme 2.*** A Proposed Catalytic Cycle for the Reaction of **1** and **2** with Cinchona Alkaloid **8**



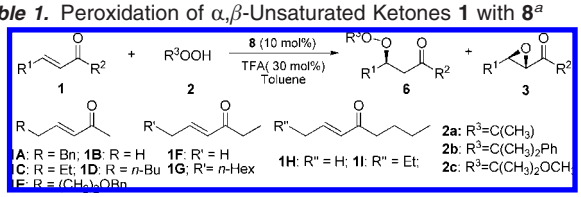

Particularly noteworthy are the highly enantioselective peroxidations of α,β-unsaturated ketones **1** with the α-methoxy isopropyl hydroperoxide **2c** (entries 18−23, Table 1). The ability to employ **2c** considerably increases the synthetic potential of this new catalytic asymmetric peroxidation, as the corresponding chiral peroxides could be readily converted to chiral hydroperoxides suitable for further elaborations (Scheme 3).[15] The catalytic asymmetric peroxidation also provides a new enantioselective route to the chiral β-hydroxy ketones as peroxides could be easily reduced to the corresponding alcohol (Scheme 3).[16]

Following our observation that the peroxide/epoxide ratio inversely correlated with the reaction temperature, we performed the reactions of various α,β-unsaturated ketones with cumene hydroperoxide (**2b**) at elevated temperature (23 or 55 vs 0 °C) to establish conditions for an asymmetric epoxidation of **1**.[17] As summarized in Table 2, highly



10.1021/ja802982h CCC: $40.75 

***Table 1.*** Peroxidation of α,β-Unsaturated Ketones **1** with **8**[a]




| entry | enone | peroxide | temp (°C) | time (h) | 6:3[b] | yield (%) **6** | ee (%)[c] **6** |
|---|---|---|---|---|---|---|---|
| 1[d] | **1A** | **2a** | 23 | 2 | 91:9 | nd | 85 |
| 2 | **1A** | **2a** | 23 | 4 | 92:8 | 85 | 91 |
| 3 | **1B** | **2a** | 23 | 4 | 94:6 | 88 | 84 |
| 4[e] | **1C** | **2a** | 23 | 4 | 94:5 | 91 | 90 |
| 5[f] | **1D** | **2a** | 23 | 4 | 93:7 (95:5) | 86 (90) | 93 (90) |
| 6 | **1E** | **2a** | 23 | 4 | 90:10 | 65 | 91 |
| 7 | **1F** | **2a** | 23 | 4 | 95:5 | 90 | 89 |
| 8 | **1H** | **2a** | 23 | 4 | 94:6 | 89 | 87 |
| 9[f] | **1I** | **2a** | 23 | 4 | 86:14 (93:7) | 64 (77) | 94 (88) |
| 10 | **1A** | **2b** | 0 | 16 | 86:14 | 74 | 94 |
| 11 | **1B** | **2b** | 0 | 12 | 77:23 | 70 | 92 |
| 12 | **1C** | **2b** | 0 | 12 | 88:12 | 75 | 92 |
| 13 | **1D** | **2b** | 0 | 16 | 87:13 | 77 | 95 |
| 14 | **1E** | **2b** | 0 | 12 | 90:10 | 82 | 96 |
| 15 | **1F** | **2b** | 0 | 24 | 89:11 | 75 | 94 |
| 16 | **1H** | **2b** | 0 | 24 | 85:15 | 66 | 96 |
| 17 | **1I** | **2b** | 0 | 24 | 65:35 | 55 | 97 |
| 18[g] | **1A** | **2c** | 0 | 19 | 77:23 | 60 | 92 |
| 19[g] | **1C** | **2c** | 0 | 24 | 86:14 | 70 | 95 |
| 20[g] | **1D** | **2c** | 0 | 24 | 88:12 | 62 | 95 |
| 21[g] | **1F** | **2c** | 0 | 17 | 95:5 | 63 | 95 |
| 22[g] | **1G** | **2c** | 0 | 24 | 78:22 | 42 | 94 |
| 23[g] | **1H** | **2c** | 0 | 24 | 95:5 | 60 | 94 |

[a] Unless noted, reactions were run with 0.3 mmol **1**, 0.36 mmol **2**. [b] Determined by $^1$H NMR. [c] See Supporting Information (SI). [d] Reaction was run with 0.1 mmol **1** and 20 mol % TFA. [e] Absolute configuration was established as *R* (see SI). [f] The results in parentheses were obtained with QD-$NH_2$. [g] Reaction was run with 20 mol % TFA.

***Scheme 3.*** Synthetic Transformations of Chiral Peroxides **6**

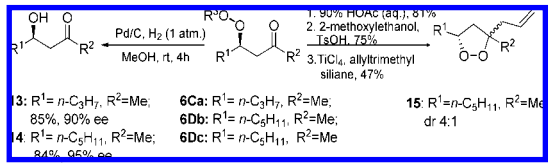
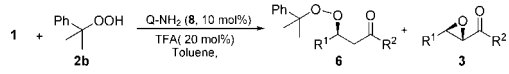



***Table 2.*** Epoxidation of α,β-Unsaturated Ketones **1** with **8**[a]




| entry | enone | temp (°C) | time (h) | 6:3[b] | yield (%) **3** | ee (%)[c] **3** |
|---|---|---|---|---|---|---|
| 1 | **1A** | 23 | 72 | 1:99 | 88 | 97 |
| 2 | **1C** | 23 | 72 | 1:99 | 91 | 97 |
| 3[d] | **1D** | 23 | 72 | 1:99 | 91 | 97 |
| 4 | **1F** | 55 | 24 | 32:68 | 55 | 97 |
| 5 | **1G** | 55 | 24 | 33:67 | 54 | 96 |
| 6 | **1H** | 55 | 24 | 13:87 | 71 | 97 |

[a] Unless noted, reactions were run with 0.3 mmol of **1**, 0.36 mmol **2b**. [b] Determined by $^1$H NMR analysis. [c] Entry 1 was determined by HPLC analysis, others are determined by GC analysis. [d] Absolute configuration was assigned as (3*R*,4*S*).

enantiomerically enriched epoxides were indeed obtained as the major product and in synthetically useful yields.[18]

In summary, by using a chiral catalyst to not only induce enantioselectivity but also to convert a well-established epoxidation pathway into a peroxidation pathway, we have developed the first highly enantioselective catalytic peroxidation reaction. Employing readily available reagents and catalyst, this novel reaction is expected to open new possibilities in the asymmetric synthesis of the biologically interesting chiral peroxides. Furthermore, with the same catalyst and reagents, a highly asymmetric epoxidations of acyclic enones could be achieved simply by performing the reaction at a higher temperature.

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**Supporting Information Available:** Experimental procedures and characterization of the products. This material is available free of charge via the Internet at http://pubs.acs.org.

## References

(1) For reviews, see: (a) Casteel, D. A. *Nat. Prod. Rep.* **1999**, *16*, 55. (b) Rahm, F.; Hayes, P. Y.; Kitching, W. *Heterocycles* **2004**, *64*, 523.
(2) (a) Posner, G. H.; O'Neill, P. M. *Acc. Chem. Res.* **2004**, *37*, 397. (b) Meshnick, S. R.; Thomas, A.; Ranz, A.; Xu, C. M.; Pan, H. Z. *Mol. Biochem. Parasitol.* **1991**, *49*, 181. (c) Posner, G. H.; Oh, C. H. *J. Am. Chem. Soc.* **1992**, *114*, 8328.
(3) For conversions of optically active oxetanes to peroxides, see : Dussault, P. H.; Trullinger, T. K.; Noor-e-Ain, F. *Org. Lett.* **2002**, *4*, 4591.
(4) For a kinetic resolution of racemic peroxide via oxidation of enantiopure phosphines, see : Driver, T. G.; Harris, J. R.; Woerpel, K. A. *J. Am. Chem. Soc.* **2007**, *129*, 3836.
(5) For allylic and benzylic peroxidations in modest ee, see : Schulz, M.; Kluge, R.; Gelalcha, F. G. *Tetrahedron: Asymmetry* **1998**, *9*, 4341.
(6) For select examples of constructions of chiral peroxide motifs via intramolecular conjugate additions of peroxides to α,β-unsaturated carbonyl compounds, see: (a) O'Neill, P. M.; Searle, N. L.; Raynes, K. J.; Maggs, J. L.; Ward, S. A.; Storr, R. C.; Park, B. K.; Posner, G. H. *Tetrahedron Lett.* **1998**, *39*, 6065. (b) Dussault, P. H.; Eary, C. T.; Woller, K. R. *J. Org. Chem.* **1999**, *64*, 1789. (c) Kawanishi, M.; Kotoku, N.; Itagaki, S.; Horii, T.; Kobayashi, M. *Bioorg. Med. Chem.* **2004**, *12*, 5297.
(7) Adam, W.; Güthlein, M.; Peters, E.-M.; Peters, K.; Wirth, T. *J. Am. Chem. Soc.* **2001**, *123*, 7228.
(8) For reviews of asymmetric nucleophilic epoxidations, see: (a) Porter, M. J.; Skidmore, J. *Chem. Commun.* **2000**, 1215. (b) Nemoto, T.; Ohshima, T.; Shibasaki, M. *J. Synth. Org. Chem. Jpn.* **2002**, *60*, 94.
(9) For asymmetric epoxidation of enones with chiral transition metal complexes, see: (a) Bougauchi, M.; Watanabe, S.; Arai, T.; Sasai, H.; Shibasaki, M. *J. Am. Chem. Soc.* **1997**, *119*, 2329. (b) Nemoto, T.; Ohshima, T.; Yamaguchi, K.; Shibasaki, M. *J. Am. Chem. Soc.* **2001**, *123*, 2725.
(10) For oligopeptide-catalyzed asymmetric epoxidation of enones, see: (a) Julià, S.; Masana, J.; Vega, J. C. *Angew. Chem., Int. Ed. Engl.* **1980**, *19*, 929. (b) Julià, S.; Guixer, J.; Masana, J.; Rocas, J.; Colonna, S.; Annunziata, R.; Molinari, H. *J. Chem. Soc., Perkin Trans. 1* **1982**, 1317. (c) Geller, T.; Roberts, S. M. *J. Chem. Soc., Perkin Trans. 1* **1999**, 1397.
(11) For chiral ketone-based asymmetric epoxidation, see : Wang, Z. X.; Shi, Y. *J. Org. Chem.* **1997**, *62*, 8622.
(12) Phase-transfer catalysis approach, for a review see: (a) Ooi, T.; Maruoka, K. *Angew. Chem., Int. Ed.* **2007**, *46*, 4222. Select examples, see: (b) Wynberg, H; Marsman, B. *J. Org. Chem.* **1980**, *45*, 158. (c) Lygo, B.; Wainwright, P. G. *Tetrahedron Lett.* **1998**, *39*, 1599. (d) Arai, S; Tsuge, H.; Shioiri, T. *Tetrahedron Lett.* **1998**, *39*, 7563. (e) Corey, E. J.; Zhang, F.-Y. *Org. Lett.* **1999**, *1*, 1287. (f) Ooi, T.; Ohara, D.; Tamura, M.; Maruoka, K. *J. Am. Chem. Soc.* **2004**, *126*, 6844.
(13) For chiral amine-catalyzed nucleophilic asymmetric epoxidations of carbonyls, see: (a) Marigo, M.; Franzén, J.; Poulsen, T. B.; Zhuang, W.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2005**, *127*, 6964. (b) Lattanzi, A. *Org. Lett.* **2005**, *7*, 2579. (c) Lee, S.; MacMillan, D. W. C. *Tetrahedron* **2006**, *62*, 11413. (d) Li, Y.; Liu, X.; Yang, Y.; Zhao, G. *J. Org. Chem.* **2007**, *72*, 288. (e) Wang, X.; List, B. *Angew. Chem., Int. Ed.* **2008**, *47*, 1119.
(14) For reports of **8**-catalyzed enantioselective reactions, see: (a) Xie, J.-W.; Chen, W.; Li, R.; Zeng, M.; Du, W.; Yue, L.; Chen, Y.-C.; Wu, Y.; Zhu, J.; Deng, J.-G. *Angew. Chem., Int. Ed.* **2007**, *46*, 389. (b) Xie, J.-W.; Yue, L.; Chen, W.; Du, W.; Zhu, J.; Deng, J.-G.; Chen, Y.-C. *Org. Lett.* **2007**, *9*, 413. (c) Bartoli, G.; Bosco, M.; Carlone, A.; Pesciaioli, F.; Sambri, L.; Melchiorre, P. *Org. Lett.* **2007**, *9*, 1403. (d) McCooey, S. H.; Connon, S. J. *Org. Lett.* **2007**, *9*, 599. (e) Singh, R. P.; Bartelson, K.; Wang, Y.; Su, H.; Lu, X.; Deng, L. *J. Am. Chem. Soc.* **2008**, *130*, 2422.
(15) (a) Dussault, P. H.; Sahli, A. S. *J. Org. Chem.* **1992**, *57*, 1009. (b) Ahmed, A.; Dussault, P. H. *Tetrahedron* **2005**, *61*, 4657. (c) Dussault, P. H.; Liu, X. *Org. Lett.* **1999**, *1*, 1391. (d) Dai, P.; Dussault, P. H. *Org. Lett.* **2005**, *7*, 4333. (e) Xu, C.; Raible, J. M.; Dussault, P. H. *Org. Lett.* **2005**, *7*, 2509. (f) Dai, P.; Trullinger, T. K.; Liu, X.; Dussault, P. H. *J. Org. Chem.* **2006**, *71*, 2283.
(16) For asymmetric approaches for the preparations of β-hydroxy carbonyls via enantioselective catalytic conjugate additions, see: (a) Vanderwal, C. D.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2004**, *126*, 14724. (b) Bertelsen, S.; Diner, P.; Johansen, R. L.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2007**, *129*, 1536. (c) Carlone, A.; Bartoli, G.; Bosco, M.; Pesciaioli, F.; Ricci, P.; Sambri, L.; Melchiorre, P. *Eur. J. Org. Chem.* **2007**, 5492.
(17) For an aspartate-catalyzed electrophilic epoxidation, see: Peris, G.; Jakobsche, C. E.; Miller, S. J. *J. Am. Chem. Soc.* **2007**, *129*, 8710.
(18) While this manuscript was in preparation, an **8**-catalyzed asymmetric epoxidation of cyclic enone with $H_2O_2$ was reported: Wang, X.; Reisinger, C. M.; List, B. *J. Am. Chem. Soc.* **2008**, *130*, 6070.

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