J|A|C|S
COMMUNICATIONS

Published on Web 04/22/2005

# Asymmetric Organocatalytic Epoxidation of α,β-Unsaturated Aldehydes with Hydrogen Peroxide

Mauro Marigo, Johan Franzén, Thomas B. Poulsen, Wei Zhuang, and Karl Anker Jørgensen*

*Danish National Research Foundation, Center for Catalysis, Department of Chemistry, Aarhus University, DK-8000 Aarhus C, Denmark*

Received March 22, 2005; E-mail: kaj@chem.au.dk

Catalytic asymmetric epoxidation holds a prominent place in asymmetric catalysis due to the fundamental importance of epoxides in organic chemistry.[1] The Sharpless epoxidation of allylic alcohols using catalytic amounts of titanium and tartrate represents a reaction of great importance.[2] Following this discovery, the asymmetric epoxidation of olefins catalyzed by the manganese−salen complexes developed by especially Jacobsen et al. provided an easy approach to, for example, unfunctionalized epoxides.[3] The asymmetric epoxidation of α,β-unsaturated carbonyl compounds is another important functionalization in organic chemistry[4] because of the usefulness of the corresponding α,β-epoxy carbonyl compounds. Shibasaki et al. have, by the use of chiral Lewis acid complexes, developed the catalytic asymmetric epoxidation of α,β-unsaturated ketones,[5a] esters, and amides[5b] applying *tert*-butyl hydroperoxide as the terminal oxidant. The catalytic asymmetric epoxidation of α,β-unsaturated ketones applying sodium hypochlorite has also been achieved using chiral phase-transfer catalysis, and the enantioenriched epoxides were generally obtained with high enantioselectivities.[6] Furthermore, the use of chiral ketones as catalysts for the asymmetric epoxidation of a broad range of olefins has also been demonstrated.[7]

The catalytic asymmetric epoxidation of α,β-unsaturated aldehydes remains a challenge to chemists, and according to our knowledge, there are no direct approaches for obtaining α,β-epoxy aldehydes. Chiral organic compounds, such as chiral amines, have recently been introduced as efficient catalysts for a variety of asymmetric transformations[8] of α,β-unsaturated aldehydes[9] and ketones.[10]

In this paper, we present the first asymmetric organocatalytic epoxidation of α,β-unsaturated aldehydes performed under simple and environmentally friendly reaction conditions using peroxides, such as $H_2O_2$, as the oxidant.

It was envisioned that we could use the properties of chiral amines to develop an efficient protocol for the catalytic asymmetric epoxidation of α,β-unsaturated aldehydes. In Scheme 1, our mechanistic proposal for the organocatalytic asymmetric epoxidation reaction is shown. The first step is the formation of the iminium ion intermediate by reaction of the α,β-unsaturated aldehyde with the chiral amine. In the next step, the peroxide adds as a nucleophile to the electrophilic β-carbon atom under formation of the carbon−oxygen bond leading to an enamine intermediate. The formation of the epoxide then takes place by attack of the nucleophilic enamine carbon atom to the electrophilic peroxygen atom, followed by hydrolysis of the iminium intermediate.

The development of the reactions started with the screening of conditions for the epoxidation of cinnamic aldehyde (**1a**) (eq 1). Various chiral amines can catalyze the epoxidation of α,β-unsaturated carbonyl compounds;[11] however, 2-[bis(3,5-bistrifluoromethylphenyl)trimethylsilanyloxymethyl]pyrrolidine (**3**) turned out

***Scheme 1.*** Mechanistic Proposal for the Organocatalytic Epoxidation of α,β-Unsaturated Aldehydes with Peroxides

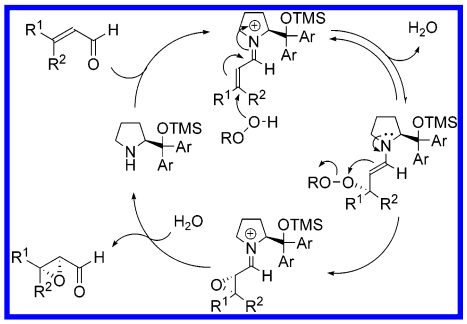
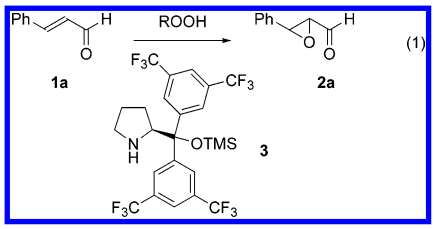



***Table 1.*** Screening of Oxidation Agents and Reaction Conditions for the Organocatalytic Epoxidation of Cinnamic Aldehyde (**1a**)[a]




| entry | oxidant | conversion (%) | dr[b] | ee (%)[c] |
|---|---|---|---|---|
| 1 | $H_2O_2$ (35% in $H_2O$) | >95 (2 h) | 94:6 | 96 |
| 2[d] | $H_2O_2$ (35% in $H_2O$) | 75 (7 h) | 93:7 | 95 |
| 3 | UHP[e] | >90 (5 h) | 93:7 | 96 |
| 4 | *t*-BuOOH | 30 (2 h) | 90:10 | 93 |
| 5 | cumene hydroperoxide | 40 (2 h) | 91:9 | 93 |
| 6 | *m*-CPBA | 3 (2 h) | | 53 |

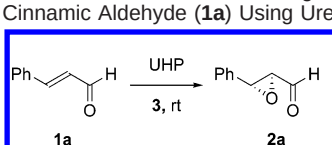
[a] Reaction performed at 1 mmol scale of the oxidant and 1.3 equiv of cinnamic aldehyde (**1a**) in 2 mL of $CH_2Cl_2$ as the solvent at room temperature. [b] The dr determined by chiral GC. [c] The ee determined by chiral GC. [d] With 5 mol % of catalyst **3**. [e] Urea hydrogen peroxide.

be an excellent catalyst for the reaction and in Table 1 are shown the results for the screening of different oxidants.

Hydrogen peroxide (35% w/w in $H_2O$) is an excellent oxidant for the epoxidation of cinnamic aldehyde (**1a**) using 10 mol % of **3** as the catalyst. The reaction proceeds to full conversion within a few hours at room temperature in $CH_2Cl_2$ as the solvent, and 3-phenyloxirane-2-carbaldehyde (**2a**) is formed with high dr (94:6) and, to our delight, with 96% ee (Table 1, entry 1). Reducing the catalyst loading leads to a decrease in conversion, while the diastereo- and enantioselectivity were unaffected (entry 2). Urea hydrogen peroxide (UHP) is also a suitable oxidation agent, and similar results as those found for $H_2O_2$ are obtained (entry 3). Organic peroxides are also useful for the epoxidation reaction (entries 4−6), but lower conversion is observed. *tert*-Butyl- and

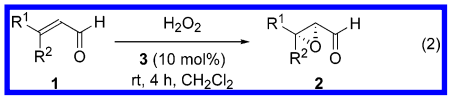

10.1021/ja051808s CCC: $30.25 

***Scheme 2.*** Solvents for the Organocatalyzed Epoxidation of Cinnamic Aldehyde (**1a**) Using Urea Hydrogen Peroxide (UHP)




| solvent | conv (%) | ee (%) and dr |
|---|---|---|
| $CH_2Cl_2$ | 94 (3 h) | 96 (93:7) |
| toluene | 77 (7 h) | 96 (95:5) |
| EtOH (95%) | 85 (7 h) | 92 (87:13) |
| MeOH (80%) | 36 (2 h) | 92 (87:13) |
| THF (90%) | 15 (2 h) | 94 (93:7) |
| TBME | 5 (2 h) | - (-) |

***Table 2.*** Scope of the Organocatalyzed Epoxidation of α,β-Unsaturated Aldehydes with Hydrogen Peroxide[a]




| entry | $R^1$ | $R^2$ | yield[b] (%) | dr[c] | ee[d] (%) |
|---|---|---|---|---|---|
| 1 | Ph − **1a** | H | **2a** − 80 | 93:7 | 96 |
| 2 | *o*-$NO_2$−Ph − **1b** | H | **2b** − 90 | 91:9 | 97 |
| 3 | *o*-Me-Ph − **1c** | H | **2c** − 65 | 90:10 | 96 |
| 4 | *p*-Cl−Ph − **1d** | H | **2d** − 63 | 95:5 | 98 |
| 5 | Et − **1e** | H | **2e** − >90[e] | 97:3 | 96 |
| 6 | *i*-Pr − **1f** | H | **2f** − 75 | 98:2 | 96 |
| 7 | $CH_2OBn$ − **1g** | H | **2g** − 84 | 96:4 | 94 |
| 8 | $CO_2Et$ -**1h** | H | **2h** − 60 | 90:10 | 96 |
| 9 | Me − **1i** | Me | **2i** − 65 | | 75 |

[a] 1.3 equiv of $H_2O_2$ used. [b] Isolated yield. [c] The dr was determined by chiral GC and NMR. [d] The ee was determined by chiral GC and HPLC. [e] More than 90% conversion was found; however, due to the volatility of the product, the α,β-epoxy aldehyde was transformed to the corresponding alcohol, which under nonoptimized conditions, was isolated in 43% yield.

cumene hydroperoxide gave the same results as $H_2O_2$ and UHP, while very low conversion was found using *m*-chloro perbenzoic acid.

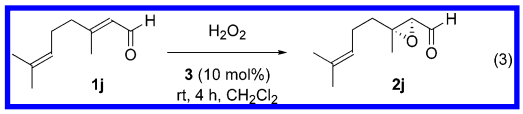
An important aspect of the organocatalytic asymmetric epoxidation catalyzed by **3** is that it proceeds in different solvents. In Scheme 2, some representative results are presented using UHP as the oxidant.

The results in Scheme 2 show that the asymmetric epoxidation proceeds well with high stereoselectivity in a variety of solvents, with the exception of TBME. Of particular interest is to note that in methanol (80%) and ethanol (90%), the enantiomeric excess of epoxide **2a** is 92% ee, showing that this process can take place under benign conditions.

To demonstrate the scope and potential for the organocatalytic epoxidation, a series of different substituted α,β-unsaturated aldehydes were reacted with $H_2O_2$ at room temperature in the presence of **3** (10 mol %) as the catalyst (eq 2). The results are summarized in Table 2.

α,β-Unsaturated aldehydes having aromatic substituents in the β-position, **1a**−**d**, are all converted to the corresponding optically active epoxides in good yields and diastereoselectivities and with excellent enantioselectivities (96−98% ee) (Table 1, entries 1−4). For the alkyl-substituted α,β-unsaturated aldehydes **1e**−**g**, a slight improvement in diastereoselectivity is found, and the high enantioselectivity is maintained (entries 5−7). 4-Oxo-but-2-enoic acid ethyl ester (**1h**) containing an ethyl ester functionality in the β-position gave 60% yield, 90:10 dr, and 96% ee of the corresponding epoxide **2h** (entry 8). The results in entries 7 and 8 show that heteroatom functionalities, a protected alcohol, and an ester are tolerated in the α,β-unsaturated aldehydes, giving the possibility for further transformations of this part of the optically active α,β-epoxy aldehyde.

The β-disubstituted α,β-unsaturated aldehyde, 4-methyl butenal (**1i**), is also epoxidized smoothly (entry 9); however, a slight decrease in enantioselectivity is observed compared to the monosubstituted substrates. This might be due to the fact that there is no stereocenter formed in the first step, which influences the formation of the second stereocenter (see Scheme 1). The possibility for an asymmetric epoxidation of these substrates is an important new development compared to existing methods.[4] We have taken in advantage this protocol for the direct formation of the sex pheromone from an acaric mite.[12] Epoxidation of citral **1j** (3:2 *E*:*Z* ratio was used) under the standard conditions gave the sex pheromone **2j** in 73% yield and 85% ee of the major diastereomer[13] (eq 3).




In summary, we have developed the first organocatalytic asymmetric epoxidation of α,β-unsaturated aldehydes using a sterically encumbered chiral pyrrolidine derivative, which is easily accessible in four steps from L-proline as the catalyst and hydrogen peroxide as the oxidant. The reactions can take place under environmentally friendly conditions, and for a series of different substituted α,β-unsaturated aldehydes, good to high yields and diastereoselectivities and excellent enantioselectivities of the corresponding α,β-epoxy aldehydes were obtained. Furthermore, the formation of the optically active female sex pheromone from an acaric mite in one step was presented.

**Acknowledgment.** This work was made possible by a grant from The Danish National Research Foundation. J.F. thanks The Wenner-Gren Foundation for a grant.

**Supporting Information Available:** Complete experimental procedures and characterization (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

## References

(1) (a) Johnson, R. S.; Sharpless, K. B. In *Comprehensive Organic Synthesis*; Trost, B. M., Flemming, I., Eds.; Pergamon Press: New York, 1991; Vol. 7, p 389. (b) *Catalytic Asymmetric Synthesis*, 2nd ed.; Ojima, I., Ed.; Wiley: New York, 2000. (c) *Comprehensive Asymmetric Catalysis*; Jacobsen E. N., Pfaltz, A., Yamamoto, H., Eds; Springer: New York, 1999. (d) Noyori, R. *Asymmetric Catalysis in Organic Synthesis*; John Wiley & Sons: New York, 1994.
(2) (a) Katsuki, K.; Sharpless, K. B. *J. Am. Chem. Soc.* **1980**, *102*, 5974. (b) Hanson, R. M.; Sharpless, K. B. *J. Org. Chem.* **1986**, *51*, 1992.
(3) Zhang, W.; Loebach, J. L.; Wilson, S. R.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1990**, *112*, 2801. See also: Aggarwal, V. K.; Lopin, C.; Sandrinelli, F. *J. Am. Chem. Soc.* **2003**, *125*, 7596.
(4) For a review, see: Porter, M. J.; Skidmore, J. *Chem. Commun.* **2000**, 1215. See also: Juliá, S.; Masana, J.; Vega, J. C. *Angew. Chem., Int. Ed. Engl.* **1980**, *19*, 929.
(5) (a) Bougauchi, M.; Watanabe, S.; Arai, T.; Sasai, H.; Shibasaki, M. *J. Am. Chem. Soc.* **1997**, *119*, 2329. (b) Nemoto, T.; Ohshima, T.; Shibasaki, M. *J. Am. Chem. Soc.* **2001**, *123*, 9474.
(6) Ooi, T.; Ohara, D.; Tamura, M.; Maruoka, K. *J. Am. Chem. Soc.* **2004**, *126*, 6844.
(7) Shi, Y. *Acc. Chem. Res.* **2004**, *37*, 488.
(8) For recent review dealing with organocatalysis, see: (a) Dalko, P. I.; Moisan, L. *Angew. Chem., Int. Ed.* **2004**, *43*, 5138. (b) Berkessel, A.; Gröger, H. *Asymmetric Organocatalysis*; VCH: Weinheim, Germany, 2004. (c) Seayad, J.; List, B. *Org. Biomol. Chem.* **2005**, *3*, 719.
(9) (a) Brown, S. P.; Nicole, C. G.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2003**, *125*, 2092. (b) Austin, J. F.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2002**, *124*, 1172. (c) Ouellet, S. G.; Tuttle, J. B.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2005**, *127*, 32. (d) Kunz, R. K.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2005**, *127*, 3240. (e) Yang, J. W.; Fonseca, M. T. H.; Vignola, N.; List, B. *Angew. Chem., Int. Ed.* **2005**, *44*, 108.
(10) (a) Halland, N.; Aburel, P. S.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2004**, *43*, 1272. (b) Halland, N.; Aburel, P. S.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2003**, *42*, 661. (c) Halland, N.; Hansen, T.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2003**, *42*, 4955.
(11) The use of L-proline and other chiral pyrrolidine derivatives as the catalyst gave poor or low conversion, and the epoxide **2a** was formed as a racemate, or with low enantiomeric excess.
(12) Mori, N.; Kuwahara, Y.; Kurosa, K. *Bioorg. Med. Chem* **1996**, *4*, 289.
(13) The dr (75:25) is higher than the *E*:*Z* ratio of **1j**.

JA051808S