Asymmetric Epoxidation

DOI: 10.1002/anie.200803238

Catalytic Asymmetric Hydroperoxidation of α,β-Unsaturated Ketones: An Approach to Enantiopure Peroxyhemiketals, Epoxides, and Aldols**

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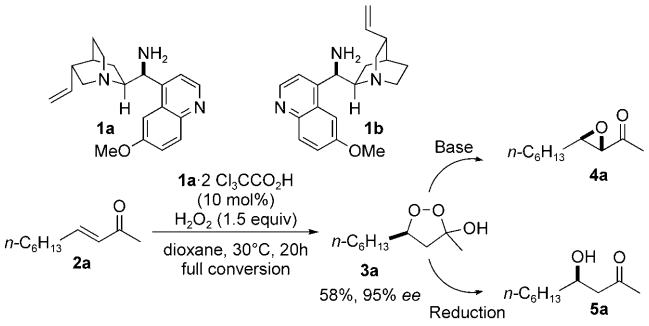
Despite the wealth of enantioselective and catalytic epoxidations of olefins—including those associated with the names of Juliá and Colonna, Wynberg, Jackson, Sharpless, Jacobsen, Katsuki, Enders, Shi, and Shibasaki—there is still no general method for the epoxidation of simple α,β-unsaturated ketones.[1] Previously described methods often lack scope, reactivity, and selectivity. Very recently, we introduced a highly enantioselective epoxidation of cyclic enones using amines such as **1a** and **1b** as catalysts and hydrogen peroxide as the oxidant.[2] Subsequent to our publication and during the preparation of this manuscript, Deng et al. described a catalytic asymmetric *tert*-alkyl peroxidation of enones using the same catalysts.[3] Here we report our independent studies leading to a highly enantioselective catalytic hydroperoxidation of simple aliphatic enones with hydrogen peroxide. Our process delivers enantiopure cyclic peroxyhemiketals, which are readily converted into either epoxides or aldols.

Iminium catalysis has been introduced recently as a powerful strategy for the enantioselective epoxidation of α,β-unsaturated carbonyl compounds. After pioneering contributions by Jørgensen et al., MacMillan's group and we have also reported secondary amine catalysts for the epoxidation of enals.[4] Continuing our studies on the use of primary amine catalysts for reactions of α,β-unsaturated ketones,[5] we have discovered a highly efficient, general, and enantioselective epoxidation of cyclic enones with hydrogen peroxide using cinchona alkaloid derived primary amine catalysts **1a** and **1b**.[2] These powerful and readily made catalysts have previously found utility in other selected transformations.[6] In an effort to expand the scope of our epoxidation, we turned our attention to acyclic aliphatic α,β-unsaturated ketones. Previously, few asymmetric epoxidation methodologies gave satisfactory results with this substrate class.[7] Remarkably, when 2-decenone (**2a**) was subjected to aqueous hydrogen peroxide (50 wt%) and the primary amine salt catalyst **1a**·2 Cl_3CCO_2H (10 mol%) at 30°C in dioxane for 20 h, peroxyhemiketal **3a** was formed in 58% yield (Scheme 1). Along with this cyclic peroxide, which is an intermediate and common a byproduct in Weitz–Scheffer-type epoxidations,[8] the expected epoxide **4a** was also formed in roughly 30% yield. Since cyclic peroxyhemiketals are known to be transformed into the corresponding epoxides under basic conditions,[9] basic workup of the product mixture will always enable quantitative epoxide formation independent of the initially observed ratio of peroxyhemiketal **3a** to epoxide **4a** (see below). Furthermore, reduction of peroxides such as **3a** should provide 3-hydroxy ketones (e.g. **5a**).



Scheme 1. Catalytic asymmetric hydroperoxidation.

In preliminary studies we evaluated the scope of the amine **1a**-catalyzed hydroperoxidation. Treating both linear and branched α,β-unsaturated ketones **2a–e** with three equivalents of aqueous hydrogen peroxide (30 wt%) in the presence of catalyst **1a**·2 Cl_3CCO_2H (10 mol%) at 32°C in dioxane for 36–48 h directly resulted in the formation of peroxyhemiketals **3a–e** in reasonable yields and with high enantioselectivities (Table 1). In general, the only detected by-products were the corresponding epoxides **4**, which are easily separated from peroxides **3**. Substrates with an aromatic residue at the double bond and trisubstituted olefins turned out to be unreactive under our reaction conditions. The 1,2-dioxolane subunit is present in many natural products and bioactive molecules, and peroxyhemiketals related to **3** are key intermediates in the synthesis of this structural motif.[10]

We also optimized the reaction conditions for epoxide formation. Indeed, subjecting linear and branched α,β-unsaturated ketones to a slightly modified version of the hydroperoxidation conditions [1.5 equiv aqueous hydrogen peroxide (50 wt%), **1a**·2 F_3CCO_2H (10–20 mol%), 50°C, dioxane, 12–48 h], followed by basic workup of the crude

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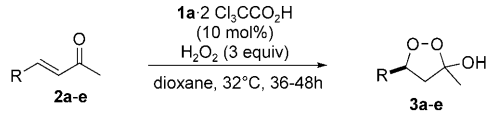
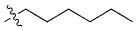
[**] This work was supported by the Max Planck Society, the DFG (SPP 1179, Organocatalysis), and the Fonds der Chemischen Industrie (Kekulé fellowship to C.M.R. and Award in Silver to B.L.). We thank our GC and HPLC departments for their support.

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.200803238.

Table 1: Catalytic asymmetric hydroperoxidation of enones.



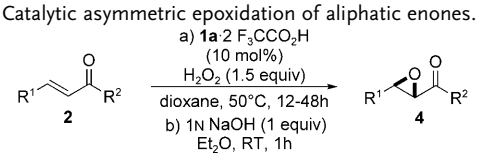
Entry[a]	R	Product[b]	Yield [%][c]	e.r.[d] (*ee* [%])
1		**3a**	65	39.5 (95)
2		**3b**	68	32.9 (94)
3		**3c**	69	31.9 (94)
4		**3d**	61	35.8 (95)
5		**3e**	54	44.9 (95)

[a] Enone **2a–e** (1.0 mmol) in dioxane (4 mL). [b] Mixtures of hemiketal diastereomers (d.r. ≈1:1). [c] Yield of isolated product. [d] Determined by GC analysis on a chiral stationary phase after derivatization of **3a–e** into the corresponding epoxides.

product with 1N NaOH, provided epoxides **4a–j** in good to high yields and in outstanding enantioselectivities of up to e.r. 237.1 (>99% *ee*) (Table 2). As expected, when the pseudoenantiomeric quinidine-derived primary amine **1b** was employed, the opposite enantiomer of epoxide **4b** was obtained, although in slightly lower enantioselectivity of e.r. 19.3 (Table 2, entry 3). Once again, only aliphatic substituents were tolerated on the double bond of enones **2**; aromatic and trisubstituted enones proved to be unreactive.

We became intrigued by the idea of also developing a one-pot synthesis of β-hydroxy ketones by a hydroperoxidation–reduction sequence. Indeed, this was accomplished by adding $P(OEt)_3$ as the reducing agent to the hydroperoxidation reaction mixture at 0°C after complete conversion of the

Table 2: Catalytic asymmetric epoxidation of aliphatic enones.

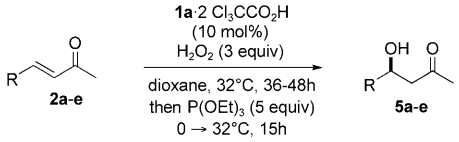


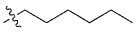
Entry[a]	R^1	R^2	Product	Yield [%][b]	e.r.[c] (*ee* [%])
1	*n*-C_6H_{13}	Me	**4a**	72	69.0 (97)
2		Me	**4b**	85	60.7 (97)
3[d]		Me	*ent*-**4b**	90	19.3 (90)
4		Me	**4c**	76	66.1 (97)
5	*i*Bu	Me	**4d**	77	62.3 (97)
6[e]	Cy	Me	**4e**	83	71.4 (97)
7		Me	**4f**	81	237.1 (99)
8[f]	Me	Et	**4g**	55	57.5 (97)
9[g]	*n*-C_9H_{19}	Et	**4h**	82	98.0 (98)
10[g]	*n*-C_5H_{11}	*n*-C_5H_{11}	**4i**	76	94.3 (98)
11[e,g]	*n*-C_5H_{11}	*i*Bu	**4j**	81	67.0 (97)

[a] Enone **2** (1.0 mmol) in dioxane (4 mL). [b] Yield of isolated product. [c] Determined by GC analysis on a chiral stationary phase. [d] Amine **1b** was used. [e] **1a**·2 F_3CCO_2H (20 mol%) was used. Cy = cyclohexyl. [f] Reduced yield as a result of the high volatility of **4g**. [g] THF was used instead of Et_2O.

starting material.[11] Aldol-like products **5a–e** were obtained in good yields along with high enantioselectivities (Table 3). Our sequence represents an attractive and simple solution to

Table 3: One-pot synthesis of aldol products.

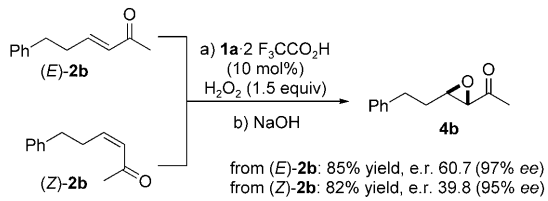


Entry[a]	R	Product	Yield [%][b]	e.r.[c] (*ee* [%])
1		**5a**	59	31.9 (94)
2[d]		**5b**	53	26.9 (93)
3		**5c**	55	25.1 (92)
4		**5d**	56	28.8 (93)
5		**5e**	46	22.6 (92)

[a] Enone **2a–e** (1.0 mmol) in dioxane (4 mL). [b] Yield of isolated product. [c] Determined by GC or HPLC analysis on a chiral stationary phase. [d] Absolute configuration (*R*) was determined from its known optical rotation.[6l]

the long-standing challenge of enantioselectively adding water to α,β-unsaturated ketones.[12] Employing comparatively simple starting materials (α,β-unsaturated ketones and hydrogen peroxide), our approach nicely complements proline-catalyzed aldol reactions since α-unsubstituted aldehydes are still challenging substrates in this transformation (Table 3, entries 1–4).[13]

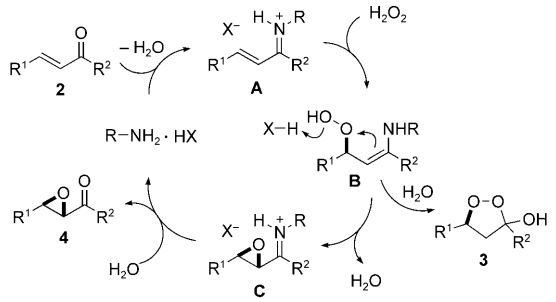
We also investigated the influence of the olefin geometry on the enantioselectivity of our reaction. Remarkably, enones (*E*)-**2b** and (*Z*)-**2b** both furnished the same enantiomer of *trans*-epoxide **4b** in very high enantioselectivity (Scheme 2).



Scheme 2. Illustration of the stereoconvergency.

Presumably, the *Z* isomer rapidly isomerizes to the corresponding *E* isomer under the reaction conditions, perhaps via a dienamine intermediate. This behavior has also been observed in our Hantzsch ester mediated transfer hydrogenation of enals[14] and to a lesser degree in the corresponding reductions of enones.[5]

The factors influencing the peroxyhemiketal/epoxide ratio are reflected in the proposed catalytic cycle shown in Scheme 3, which accounts for the formation of both peroxyhemiketal **3** and epoxide **4**. The activation of enone **2** as iminium ion **A** is followed by the nucleophilic conjugate



Scheme 3. Plausible catalytic cycle. The arrows in **B** refer to the reaction yielding **C**.

addition of hydrogen peroxide to give β-peroxyenamine intermediate **B**. The second basic amine site of catalyst **1a** may organize the transition state by activating hydrogen peroxide through general base catalysis and directing its attack toward one enantioface of the double bond (omitted for clarity in Scheme 3).[2] Enamine intermediate **B** can either undergo ring closure to give epoxide **4** or hydrolysis to provide peroxyhemiketal **3**. Additional water accelerates the hydrolysis step, whereas a stronger acid promotes the intramolecular nucleophilic ring closure by generating a suitable leaving group through protonation.

In conclusion, we have reported a highly enantioselective hydroperoxidation catalyzed by a primary amine salt to furnish stable and isolable cyclic peroxyhemiketals. The versatility of these intermediates, which for the first time can be prepared directly in enantiopure form, has been illustrated with the syntheses of epoxides and aldols from inexpensive and readily available starting materials: α,β-unsaturated ketones and hydrogen peroxide. Our current studies focus on understanding the detailed reaction mechanism and on extending the scope of these versatile processes.

Experimental Section

Amine **1a** (32.3 mg, 0.1 mmol) was added to a solution of Cl_3CCO_2H (32.6 mg, 0.2 mmol) in dioxane (4 mL). Enone **2a–e** (1 mmol) was added, and 20 min later aqueous hydrogen peroxide (3 equiv, 3 mmol, 30 wt %) was added at ambient temperature. After 36–48 h at 32 °C, the reaction mixture was extracted with diethyl ether (2 × 25 mL) and the combined organic phases were washed with brine, dried (Na_2SO_4), and filtered. Crude products were purified by silica gel column chromatography using pentane/diethyl ether as eluent to obtain pure peroxyhemiketals **3a–e**.

Received: July 4, 2008
Published online: September 22, 2008

Keywords: asymmetric catalysis · epoxidation · hydrogen peroxide · ketones · organocatalysis

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