Asymmetric Epoxidation

DOI: 10.1002/anie.200705326

Asymmetric Epoxidation of Olefins with Hydrogen Peroxide—Catalysis by an Aspartate-Containing Tripeptide

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epoxidation · hydrogen bonds · hydrogen peroxide · organocatalysis · peptides

Method development for the preparation of enantiomerically pure epoxides continues to be one of the most exciting fields of asymmetric catalysis.[1] Current methodology for the catalytic asymmetric epoxidation of olefins hinges largely on the use of chiral metal complexes[2,3] or on the use of organocatalysts such as chiral ketones.[4] Alternative methods for the preparation of enantiomerically pure epoxides include, inter alia, enzymatic transformations,[5] the addition of chiral sulfur ylides to aldehydes,[6] or the peptide-catalyzed asymmetric epoxidation of enones (Juliá-Colonna epoxidation).[7] Attempts to use chiral percarboxylic acids, even as stoichiometric epoxidation agents, have been met with little success thus far; the degree of asymmetric induction in the product epoxides is usually low, presumably because of the unfavorable orientation of chiral residue of the acid relative to the approaching substrate olefin.

The group of Scott Miller has shown, in a number of instances, that highly (enantio)selective organocatalysts can result from the proper combination of short oligopeptides with catalytically active functional groups.[8] Some of the most impressive examples are acyl-transfer reactions (including phosphorylations) that employ nucleophilic catalysis by *N*-methyl histidine(s), which rival the performance of transferase enzymes.[8,9] In one of their recent publications, Miller and co-workers presented the first highly enantioselective peptide catalysts for the electrophilic epoxidation of olefins by using hydrogen peroxide as the terminal oxidant in combination with carbodiimide compounds as stoichiomeric activators.[10] The method hinges on the generation of a percarboxylic acid from a carboxylic acid (Figure 1 a).

In the current example epoxidation catalysis is effected by the γ-carboxylic acid function of L-aspartate. Incorporation of this catalytically active residue into tripeptide **1** (Figure 1 b) provides the chiral environment necessary for an asymmetric transformation. Notably, the sequence L-Pro-D-Val induces a turn that is stabilized by an intramolecular hydrogen bond. In this arrangement, the "chiral information" of the C-terminal phenethylamide residue folds back in the direction of the catalytically active carboxylate group.

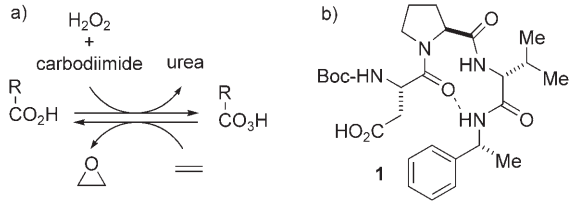
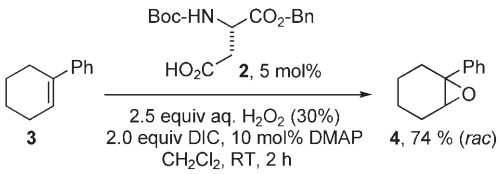


Figure 1. a) Epoxidation catalysis by an acid/peracid pair. b) Peptide catalyst **1** for the asymmetric electrophilic epoxidation of olefins.

In the first part of their study, Miller and co-workers employed *N*-Boc-protected L-aspartate benzyl ester **2** (Boc = *tert*-butyloxycarbonyl) to establish optimal conditions for epoxidation catalysis based on multiple carboxylic acid–peracid interconversions (Scheme 1). As it turned out, a combination of aqueous hydrogen peroxide, diisopropylcarbodiimide (DIC, stoichiometric activator) and dimethylaminopyridine (DMAP, acyl transfer catalyst) afforded almost 15 turnovers. Fortunately, DMAP-*N*-oxide, which forms under the oxidative conditions, appears to be just as suitable for acyl transfer catalysis as DMAP itself (in this case). The resulting epoxide (**4**) from 1-phenylcyclohexene (**3**) under these conditions was racemic, indicating that per-aspartate itself did not effect any significant asymmetric induction. Control experiments established that the epoxidation actually proceeded through the acid/peracid pair as intended.[11]



Scheme 1. Epoxidation of 1-phenylcyclohexene (**3**) with hydrogen peroxide in the presence of *N*-Boc-protected L-aspartate benzyl ester (**2**) as the catalyst.

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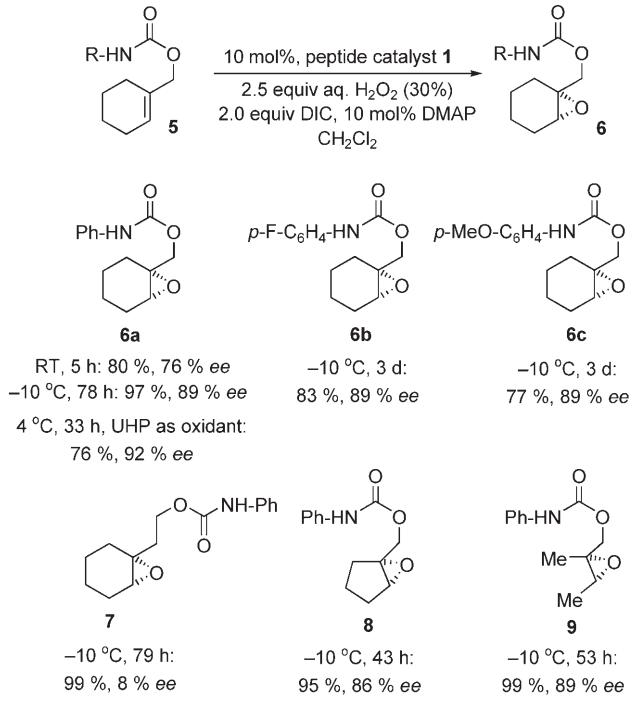
Catalytically active aspartate was then incorporated into a turn-forming tripeptide, resulting in structure **1**. With 1-phenylcyclohexene (**3**) as the substrate, asymmetric induction was observed, albeit low (10% *ee* of epoxide **4**). On the basis of earlier work in which hydrogen bonding between the substrate and catalysts of type **1** improved selectivity, Miller et al. switched to carbamate substrates **5**. Good epoxide yields and remarkable enantioselectivities were achieved with this type of substrate (Scheme 2); and lower reaction temperatures generally led to increased enantioselectivity. Additional improvements resulted from the use of hydrogen peroxide/urea clathrathe (UHP) instead of aqueous H_2O_2. The highest enantiomeric excess (92% for epoxide **6a**) was obtained with this oxidant, and it was revealed that the pendant phenyl carbamate rendered the epoxidation of a cyclopentene and a butene derivative enantioselective (epoxides **8** and **9**). *Para*-fluoro- or *para*-methoxy-substituted phenyl rings did not lead to a significant change in the efficiency of the reaction (epoxides **6b** and **c**). In contrast, elongation of the tether by only one methylene group is deleterious for stereoselectivity; in the case of the epoxide **7**, only 8% *ee* were observed.



Scheme 2. Asymmetric epoxidation of olefins in the presence of the peptide catalyst **1**.

The need for a hydrogen-bonding substituent (such as the tethered carbamate) and the high sensitivity of the enantioselectivity to the distance between the hydrogen-bonding moiety and the double bond to be epoxidized, point to hydrogen bonding as the crucial feature of catalyst–substrate interaction. Numerous arrangements can be envisaged in which the carbamate tether of the substrate may act as a hydrogen-bond donor or acceptor with the amide functional group of the peptide catalyst. Currently, there are no data available that might indicate a clear preference for one of the possible arrangements. A hypothetical hydrogen-bonded transition state (Figure 2; **A**) proposed by Miller et al. shows

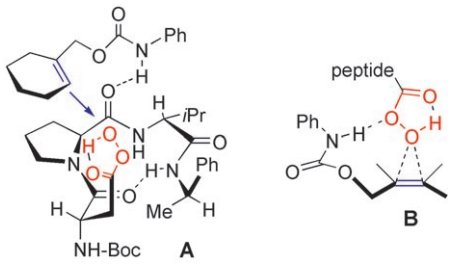


Figure 2. Hypothetical transition states for the peptide-catalyzed epoxidation of carbamate-tethered olefins.

that the carbamate group of the substrate is the hydrogen-bond donor and the proline carboxamide group of the catalyst is the acceptor. Alternative arrangements may be envisaged in which intermolecular hydrogen bonding involves the peracid moiety (e.g. Figure 2; **B**). The latter mode of substrate–oxidant interaction is reminiscent of what is usually assumed to result in the "Henbest effect", that is, the *cis* selectivity in the hydroxy-directed epoxidation of cyclic allylic alcohols with peracids.[13]

In summary, Miller and co-workers have reported enantioselective epoxidation catalysis that includes the formation of a peptide-derived peracid. Currently, the method is limited to olefin substrates having a pendant carbamate group that is important for hydrogen bonding to the peptide catalyst. However, Miller and co-workers have also shown that high selectivities can also be achieved for non-hydrogen-bonding substrates by the proper choice of the peptide template (enantiospecific acylation of alcohols).[14] This perspective clearly exists for the current work on peptide-derived epoxidation catalysis.

In the final paragraph of their publication, Miller and co-workers raise the intriguing point that, in principle, all components necessary for Asp-based epoxidation are available to biological systems (aspartate/glutamate, hydrogen peroxide, activator).[10] Yet, no such mode of biocatalysis appears to be known. In the future it will be interesting to see if the epoxidation catalysis observed here will be discovered in the biological context as well.

Published online: April 2, 2008

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