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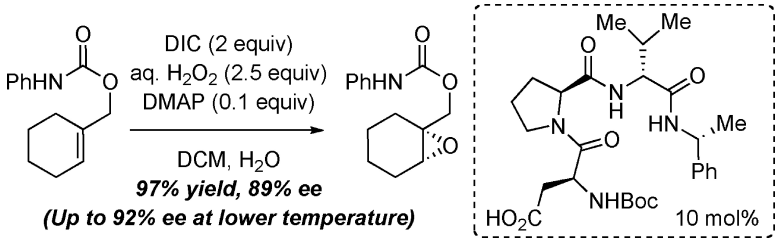

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Aspartate-Catalyzed Asymmetric Epoxidation Reactions

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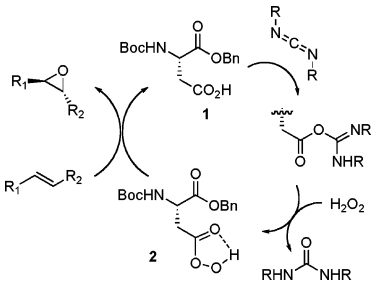
Asymmetric epoxidation reactions comprise a venerable method in organic synthesis and just as storied a testing ground for new concepts in asymmetric catalysis.[1] Among many highlights of this history are potent metal-catalyzed methods,[2] powerful ketone catalysts,[3,4] sulfide-catalyzed processes,[5] and also the Juliá−Colonna reaction of chalcones catalyzed by oligoamides such as poly(ala)$_n$.[6] Our own interest in this area stemmed from the hypothesis that tunable, peptide-based catalysts could be developed that could provide either enantioselectivity or regioselectivity for a range of alkenes or polyenes. In contrast to the classical nucleophilic epoxidation of enones, as exemplified in the Juliá−Colonna epoxidation, we sought to develop a system involving well-defined peptide-based catalysts that could operate by an alternative, potentially generalizable electrophilic mechanism.

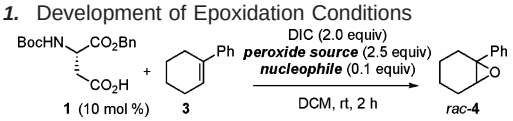
The key issue to be established initially was the nature of the catalytic moiety to reside within the peptide. As we wished to use only readily available amino acids as the catalytic residue, we were drawn to the carboxylic acid functionality of aspartic acid (Asp) and glutamic acid (Glu). The plan then emerged to develop a catalytic cycle based on Asp-derived peracids, as illustrated by the shuttle between **1** and **2** (Scheme 1). Our plan was to capitalize on concepts developed for carboxyl activation in peptide synthesis to generate and regenerate the aspartic peracid **2**.[7] As such, we found that carbodiimide activation of **1**, in the presence of 30% aqueous H_2O_2 or, less efficiently, urea−hydrogen peroxide (UHP), led to oxygen transfer to olefin **3** (Table 1, entries 2 and 3). The presence of an acyl transfer cocatalyst such as DMAP accelerates the entire process, so that catalytic epoxidation occurs to deliver epoxide *rac*-**4**, with up to nearly 15 catalytic turnovers (5 mol % of **1** leading to 74% yield of epoxide *rac*-**4** within 3.5 h; Table 1, entry 5). To our knowledge, these results constitute a unique demonstration of catalytic epoxidation employing acid−peracid shuttles that exhibit turnover.[8]

Scheme 1



Several additional experiments suggest a number of competing pathways that may operate alongside the productive catalytic cycle shown in Scheme 1. For example, control experiments aimed at establishing the role of each component of the reaction mixture show that, as expected from literature precedent,[9] the known[9b] Asp-derived diacyl peroxide **5** is formed under the reaction conditions (Scheme 2); this event has been shown to occur by reaction of peracid with *O*-acyl urea or with carbodiimide.[9a] The formation of

Table 1. Development of Epoxidation Conditions

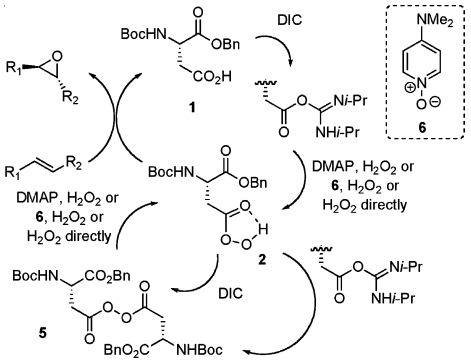


entry	peroxide source	nucleophile	equiv of **1**	yield[a]
1	aq H_2O_2		0.1	10%
2	aq H_2O_2	DMAP	0.1	83%
3	UHP	DMAP	0.1	19%
4	aq H_2O_2	NMO	0.1	25%
5[b]	aq H_2O_2	DMAP	0.05	74%

[a] Yield was measured by comparison to an internal NMR standard. [b] Reaction time was 3.5 h.

5 retards the oxygen transfer process, as **5** only slowly undergoes perhydrolysis (i.e., **5** to **2** in Scheme 2).[10] Fortunately, the addition of DMAP accelerates the oxygen transfer event (Table 1, entries 1 and 2), presumably by making the formation of **5** a reversible process and promoting the productive catalytic cycle. Although DMAP may undergo fast in situ oxidation to the DMAP-*N*-oxide **6**,[11] either DMAP or DMAP-*N*-oxide may function as a nucleophilic catalyst, promoting the generation of **2**. Indeed, NMO may be used in the place of DMAP, albeit with reduced efficiency (Table 1, entry 4). In any case, independent control experiments demonstrated the critical role of each component for efficient reactions. In particular, no reaction occurs in the absence of **1**, and all the components may coexist with essentially no conversion of **3** to **4** until Asp derivative **1** is introduced.[12]

Scheme 2



With a robust catalytic cycle in hand, we turned our attention to the critical issue of asymmetric induction. For this objective, we wished to introduce Asp into a peptide sequence that would be favorable for asymmetric catalyst−substrate interactions. We chose peptide **7** as an initial scaffold, as this array of residues was known to adopt β-turn-type structures that support enantioselectivity for other processes.[13] Although we expected that epoxidation would have its own nuanced requirements for enantioselective catalysis, β-turns have emerged as a reasonable starting place for catalyst development. We then looked at the proficiency of catalyst **7** for the asymmetric epoxidation of **8** to give **9** (eq 1). Carbamate functionality was incorporated to facilitate potential catalyst−substrate interactions through hydrogen bonding.

‡ Portions of this work were conducted in the Chemistry Department at Boston College, Chestnut Hill, Massachusetts 02467.

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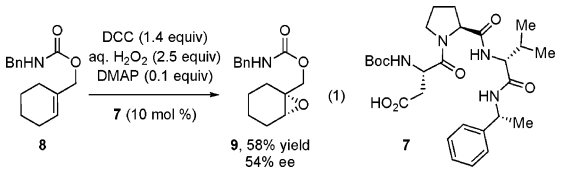
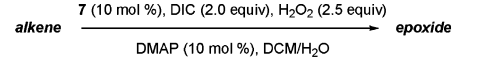
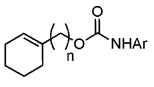
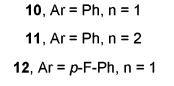
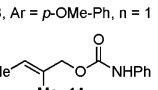


The initial epoxidations of **8** were encouraging, with **9** exhibiting 54% ee after isolation, when 10 mol % of catalyst was employed (eq 1). An initial survey of the nature of the carbamate revealed that enantioselectivity could be amplified to 76% ee if the benzyl carbamate were exchanged for the phenyl-substituted substrate **10** (Table 2, entry 1). The efficiency of the catalytic cycle allowed 17 catalytic turnovers at 25 °C, without appreciable loss in ee or yield (full conversion of alkene **10** with 5 mol % of catalyst, Table 2, entry 2). Simple optimization of the reaction conditions led to further increases in ee. For example, by performing the reaction at −10 °C, the product derived from **10** could be isolated in 97% yield with 89% ee (Table 2, entry 3). Further improvement in enantioselectivity (92% ee) was accomplished by running the reaction in toluene with UHP (Table 2, entry 4).

Homologation of the carbamate function (substrate **11**) results in near total loss of enantiocontrol (Table 2, entry 5). However, catalyst **7** exhibits excellent selectivities for a family of *N*-aryl-substituted substrates. For example, *p*-substitution with either electron-donating or electron-withdrawing groups does not lead to a significant change in the efficiency. *p*-Fluoro-substituted compound **12**, for example, is processed under the reaction conditions with 89% ee (Table 2, entry 6). *p*-Methoxy carbamate **13** is also epoxidized with comparable results (Table 2, entry 7), as is acyclic substrate **14** which delivers the corresponding epoxide with 89% ee (Table 2, entry 8). Cyclopentene derivative **15** is also a reasonable substrate for catalyst **7**, with the corresponding epoxide formed with 86% ee (Table 2, entry 9). Although electronic substitution does not significantly perturb selectivity, despite the possible modulation of H-bonding capacity of substrates, we do believe that these are H-bond-directed epoxidations.[14] For example, while phenylcyclohexene **3** is a substrate for catalytic epoxidation with **7**, epoxide **4** is formed with 10% ee, possibly due to the lack of a catalyst−substrate H-bond in the transition state (Table 2, entry 10). Nonetheless, carbamates (like **10**) do lead to efficient reactions.

Table 2. Scope of Asp-Catalyzed Asymmetric Epoxidation



entry	alkene	time/ temperature	isolated yield epoxide[a]	% ee
				
1	**10**, Ar = Ph, n = 1	5 h / rt	80%[b]	76%
2[c]	**10**, Ar = Ph, n = 1	4 h / rt	85%	76%
3	**10**, Ar = Ph, n = 1	78 h / -10 °C	97%	89%
4[d]	**10**, Ar = Ph, n = 1	33 h / 4 °C	76%[b]	92%
5	**11**, Ar = Ph, n = 2	79 h / -10 °C	99%	8%
6	**12**, Ar = *p*-F-Ph, n = 1	3 d / -10 °C	83%	89%
7	**13**, Ar = *p*-OMe-Ph, n = 1	3 d / -10 °C	77%	89%
8	 **14**	53 h / -10 °C	99%	89%
9	 **15**	43 h / -10 °C	95%	86%
10	**3**	3.5 h / rt	73%[b]	10%

[a] After SiO_2 chromatography. [b] Yield was measured by comparison to an internal NMR standard. [c] 5 mol % catalyst loading. [d] Reaction performed in toluene with UHP as the peroxide source.

The basis of enantioselectivity is difficult to describe at this time. However, our current thinking is that one or several catalyst−substrate ensembles may operate. One limiting case involves transition state **A**.[15] Yet, it is difficult to exclude alternatives such as transition state **B** or **C**. Ensembles **B**/**C** are consistent with ideas advanced to explain the "Henbest" directed epoxidation of functionalized alkenes.[16,17] The experimental evaluation of modes of asymmetric induction is currently underway.

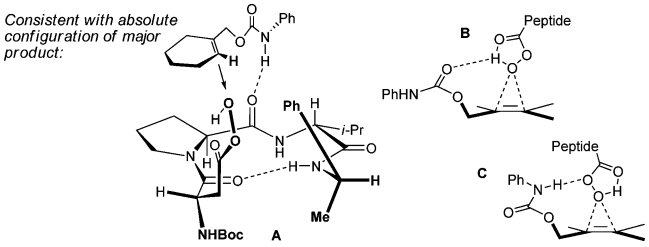


Figure 1. Limiting, hypothetical transition structures indicating potential catalyst−substrate contacts.

In summary, we have reported nonenzymatic, enantioselective epoxidation catalysts based on transient generation of peptide-based peracids in a catalytic mode with turnover. We note with some curiosity that, to our knowledge, the Asp-catalyzed epoxidations are not biomimetic with respect to "epoxidase" enzymes in biosynthesis.[18] Yet, given the presence of Asp and Glu in nature, ample biochemical mechanism for carboxyl activation, and reasonable biological concentrations of hydrogen peroxide, we wonder if analogous epoxidations might be relevant in natural biosynthesis in some way.

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

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