Published in final edited form as:

J Am Chem Soc. 2007 July 18; 129(28): 8710–8711. doi:10.1021/ja073055a.

Aspartate-Catalyzed Asymmetric Epoxidation Reactions

Gorka Peris U., Charles E. Jakobsche, and Scott J. Miller*

‡ Department of Chemistry, Yale University, P.O. Box 208107, New Haven, CT 106520-8107

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 processes⁵ 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 Julia-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 *per*-acid **2**.⁷ As such, we found that carbodiimide activation of **1**, in the presence of 30% aqueous H₂O₂ 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 co-catalyst 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 % **1** leading to 74% yield of epoxide *rac*-**4** within 3.5 h; Table 1, entry 5). To our knowledge, these results constitute the first demonstration of catalytic epoxidation employing acid-peracid shuttles that exhibit turnover.⁸

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 **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

E-mail: E-mail: scott.miller@yale.edu.

*Portions of this work were conducted in the Chemistry Department at Boston College, Chestnut Hill, MA 02467, USA.

the components may coexist with essentially no conversion of **3** to **4** until Asp-derivative **1** is introduced.¹²

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.

The initial epoxidations of **8** were encouraging, with **9** exhibiting 54% ee after isolation, when 10 mol % 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 % 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); unfortunately, these conditions lead to slow reactions.

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 related to **10** do lead to efficient reactions that proceed with substantial enantioselectivity.

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. Ensemble B is 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.

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.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

We thank the NIH (NIGMS), Merck & Co. and Yale University, each for partial support of this work.

References

1. Xia QH, Ge HQ, Liu ZM, Su KX. Chem Rev 2005;105:1603. [PubMed: 15884785]
2. Johnson, RA.; Sharpless, KB. Comprehensive Organic Synthesis. Trost, BM., editor. Vol. 7. Pergamon; New York: 1991. p. 389 Jacobsen, EN.; Wu, MH. Comprehensive Asymmetric Catalysis II. Jacobsen, EN.; Pfaltz, A.; Yamamoto, H., editors. Springer-Verlag; Berlin: 1999. p. 649
3. (a) Denmark SE, Wu ZC. Synlett 1999:847. (b) Yang D. Acc Chem Res 2004;37:497. [PubMed: 15311948]
4. Shi Y. Acc Chem Res 2004;37:488. [PubMed: 15311947]and references therein
5. Aggarwal VK, Winn CL. Acc Chem Res 2004;37:611. [PubMed: 15311960]
6. (a) Kelly DR, Roberts SM. Biopolymers 2006;84:74. [PubMed: 16167327] (b) Berkessel A, Koch B, Toniolo C, Rainaldi M, Broxterman QB, Kaptein B. Biopolymers 2006;84:90. [PubMed: 16283656]
7. Jain RP, Vederas JC. Org Lett 2003;5:4669. [PubMed: 14627411]
8. Rebek J, McCready R, Wolf S, Mossman A. J Org Chem 1979;44:1485.
9. (a) Greene FD, Kazan J. J Org Chem 1963;28:2168. (b) Spantulescu MD, Jain RP, Derksen DJ, Vederas JC. Org Lett 2003;5:2963. [PubMed: 12889919]
10. Exposure of a solution of alkene 3 (0.1 M in DCM) and benzoyl peroxide (2 equiv) to 30% H₂O₂ in H₂O (2.5 equiv) does not produce detectable amounts of epoxide 4 unless DMAP is introduced.
11. Vidal S, Court J, Bonnier JM. J Chem Soc Perkin Trans 2 1982:663.
12. For the direct activation of H₂O₂ with carbodiimides, see: (a) Majetich G, Hicks R, Sun GR, McGill P. J Org Chem 1998;63:2564. [PubMed: 11672120] (b) Murray RW, Iyanar K. J Org Chem 1998;63:1730.
13. Miller S. J Acc Chem Res 2004;37:601.and references therein
14. Hoveyda AH, Evans DA, Fu GC. Chem Rev 1993;93:1307.
15. Vasbinder MM, Jarvo ER, Miller SJ. Angew Chem, Int Ed 2001;40:2824.
16. Henbest HB, Wilson RAL. Chem Ind 1956;26:659.
17. Kocovsky P, Stry I. J Org Chem 1990;55:3236.
18. Gröschow, S.; Sherman, DH. Aziridines and Epoxides in Organic Synthesis. Yudin, AK., editor. Wiley-VCH; Weinheim: 2006. p. 349

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

Scheme 1.

Scheme 2.

Table 1

Development of epoxidation conditions.

Entry	Peroxide Source	Nucleophile	Equiv of 1	Yield ^a
1	aq. H ₂ O ₂	-	0.1	10%
2	aq. H ₂ O ₂	DMAP	0.1	83%
3	UHP	DMAP	0.1	19%
4	aq. H ₂ O ₂	NMO	0.1	25%
5 ^b	aq. H ₂ O ₂	DMAP	0.05	74%

^aYield was measured by comparison to an internal NMR standard.^bReaction time was 3.5 h.

Table 2

Substrate scope of Asp-catalyzed asymmetric epoxidation.

Entry	$\text{alkene} \xrightarrow[\text{DMAP (10 mol \%), DCM/H}_2\text{O}]{\text{7 (10 mol \%), DIC (2.0 equiv), H}_2\text{O}_2 \text{ (2.5 equiv)}} \text{epoxide}$	
	Alkene	Time/Temperature

1	10 , Ar = Ph, n = 1	5h / rt
2 ^c	10 , Ar = Ph, n = 1	4h / rt
3	10 , Ar = Ph, n = 1	78h / -10 °C
4 ^d	10 , Ar = Ph, n = 1	33h / 4 °C
5	11 , Ar=Ph, n = 2	79h / -10 °C
6	12 , Ar = p-F-Ph, n = 1	3d / -10 °C
7	13 , Ar = p-OMe-Ph, n= 1	3d / -10 °C
8		53h / -10 °C
9		43h / -10 °C
10	3	3.5h / rt

^a After SiO₂ 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.