

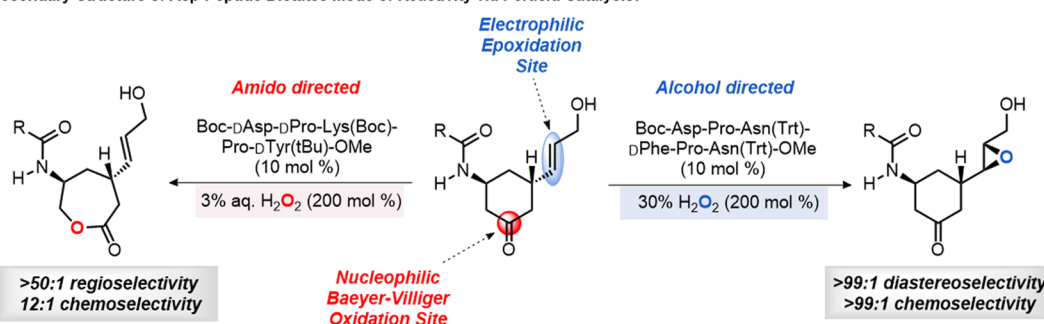
Aspartyl Oxidation Catalysts That Dial In Functional Group Selectivity, along with Regio- and Stereoselectivity

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S Supporting Information

Secondary Structure of Asp-Peptide Dictates Mode of Reactivity via Peroxid Catalysis:



ABSTRACT: A remarkable aspect of enzyme evolution is the portability of catalytic mechanisms for fundamentally different chemical reactions. For example, aspartyl proteases, which contain two active site carboxylic acid groups, catalyze the hydrolysis of amide bonds, while glycosyltransferases (and glycosyl hydrolases), which often also contain two active site carboxylates, have evolved to form (or break) glycosidic bonds. However, neither catalyst exhibits cross-reactivity in the intracellular environment. The large, macromolecular architectures of these biocatalysts tailor their active sites to their precise, divergent functions. The analogous portability of a small-molecule catalyst for truly orthogonal chemical reactivity is rare. Herein, we report aspartic acid containing peptides that can be directed to different sectors of a substrate for which the danger of cross-reactivity looms large. A transiently formed aspartyl peracid catalyst can participate either as an electrophilic oxidant to catalyze alkene epoxidation or as a nucleophilic oxidant to mediate the Baeyer–Villiger oxidation (BVO) of ketones. We show in this study that an appended peptide sequence can dictate the mode of reactivity for this conserved catalytic functional group within a substrate that has the potential to undergo both alkene epoxidation and BVO; in both cases the additional aspects of chemical selectivity (regio- and stereoselectivity) are high. This sequence-dependent tuning of a common catalytic moiety for functional group selective reactions constitutes a biomimetic strategy that may impact late-stage diversification of complex polyfunctional molecules.

INTRODUCTION

The management of competing chemical reactivity is a fundamental marvel of biochemistry.^{1–8} For synthetic chemists, however, it is a major challenge in complex molecular environments. Most chemical reactions target a unique mechanistic paradigm such that the pairing of one reactant's potential complements the reactivity of another.^{9,10} Enzymes generally abide by these rules, but in many cases they have evolved to exhibit a higher level of selectivity, such that specific reactions can occur in the presence of many competing reaction pathways involving functional groups of similar reactivity. We posited that small-molecule catalysts might also exhibit orthogonal reactivity as a result of rational modification of the scaffolding in the vicinity of a catalytic moiety that would dominate the reactive, bond-forming function of the catalyst.¹¹

We explored scenarios with the catalytic potential presented by the transient conversion of a terminal aspartyl residue to the corresponding aspartyl peracid by reaction of an activated acid with hydrogen peroxide (Figure 1a).¹² The ambiphilic aspartyl

peracid can deliver an O atom by one of two reaction pathways. In an epoxidation pathway, the peracid moiety is electrophilic (Figure 1a, path A); in the BVO pathway, the peracid is nucleophilic (Figure 1a, path B). Thus, the peracid moiety provides an opportunity to probe how the molecular environment surrounding a transiently generated reactive intermediate might fundamentally dictate a divergent chemical outcome. Recent studies from our laboratory have demonstrated the feasibility of each independent pathway (epoxidation and BVO). For example, utilizing combinatorial techniques, we discovered that peptide 1, Boc-Asp-Pro-Asn(Trt)-DPhen-Pro-Asn(Trt)-OMe, could catalyze the asymmetric epoxidation of many allylic alcohols, with enantioselectivities as high as 99:1 or (Figure 1a, path A).^{13,14} In a separate study, peptide 2, Boc-Asp-Pro-DLys(Boc)-DPro-Tyr(tBu)-OMe, was discovered to be an effective catalyst for

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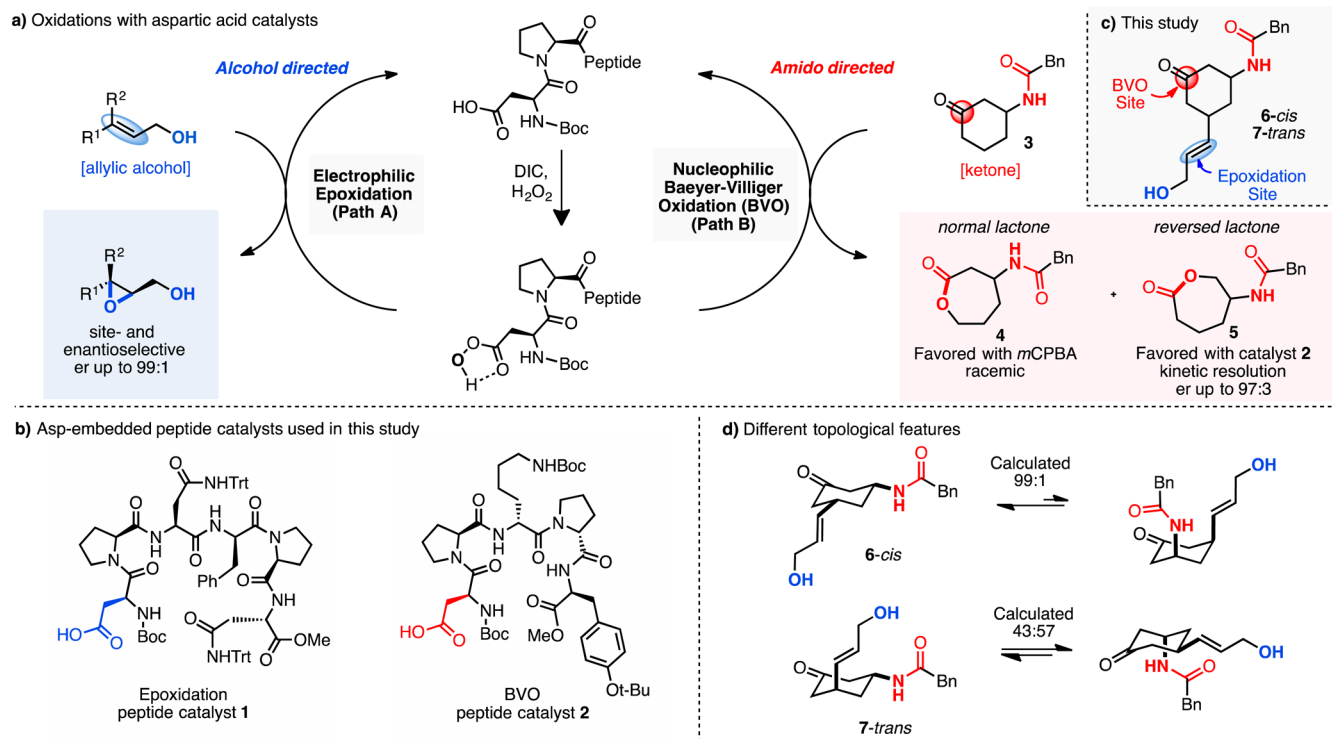


Figure 1. Aspartyl oxidation catalysts with different functional group reaction pathways: (a) catalytic cycles possible with aspartyl peptides under similar reaction conditions; (b) aspartyl peptide catalysts used in this study; (c) our proposed study featuring both a site of directed epoxidation and Baeyer–Villiger oxidation; (d) computations demonstrate the possibility of also examining the topological features of the proposed substrates **6** and **7**; DIC = *N,N'*-diisopropylcarbodiimide, H_2O_2 = hydrogen peroxide, Bn = benzyl, Boc = *tert*-butoxycarbonyl, Trt = trityl, *m*CPBA = *meta*-chloroperoxybenzoic acid.

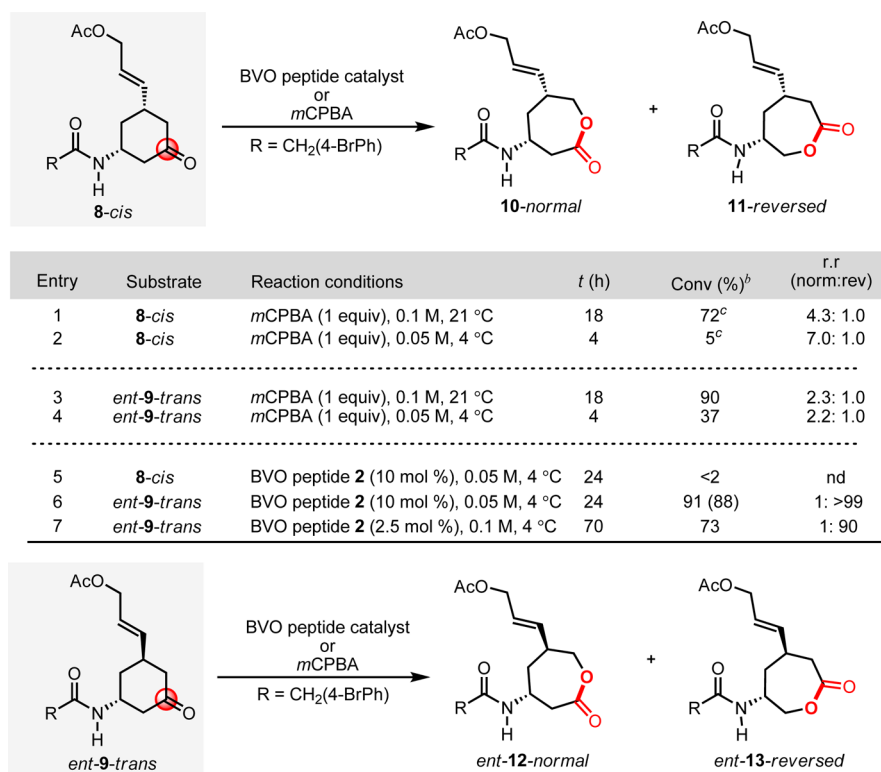
certain BVO reactions.¹⁵ Perhaps most notably, catalyst **2** not only proved effective for the ring expansion of cyclic ketones but also favored the product of reversed migratory aptitude in a number of cases. For example, with phenylacetamide **3** the conventional, stoichiometric oxidant *m*-chloroperoxybenzoic acid (*m*CPBA) produces “normal” lactone **4** as the major product (2.5:1), while catalyst **2** delivers lactone **5** (1:28 in the stereochemically matched series; Figure 1a, path B). These BVO reactions also exhibit high levels of enantioselectivity and the hallmarks of kinetic resolution when racemic starting materials are employed (e.g., lactone **5** observed with 97:3 er).¹⁶

These results, while providing a certain set of chemical validations for these as yet unknown roles of aspartic acid in biochemistry, encouraged us to investigate whether the specific function of the aspartyl catalysts (epoxidation versus BVO) could be preserved, and in fact dictated by the peptide sequence in the situation of an intramolecular competition between multiple reactive sites in a single substrate.¹⁷ Therefore, we designed substrates (**6-cis** and **7-trans**; Figure 1c) to test the ideas.¹⁸ These compounds were appealing since each (1) possesses attributes for both independent oxidation reactions; (2) could be compared as individual diastereomers; (3) could be obtained in its corresponding enantiopure form, in anticipation of the high degree of enantiospecificity exhibited in the reactions catalyzed by **1** and **2**.^{19,20} Keto-olefins **6-cis** and **7-trans** are also intriguing in that each presents different topological features in their oxidation reactions, in addition to different conformational equilibria. Computations provided a quantitative description of these geometrical features (Figure 1d), showing that **6-cis** exhibits an overwhelming preference for

the mutually bis-equatorial conformation (99:1). On the contrary, **7-trans** was found to display a 43:57 equilibrium distribution of conformers, suggesting that both conformations are amply populated under the reaction conditions, which adds an additional challenge for catalyst selectivity.²¹ The intrinsic reactivity of these compounds and their behavior in catalytic reactions are described below.

RESULTS AND DISCUSSION

Our initial studies focused on benchmarking the intrinsic reactivity of compounds like **6** and **7** toward the generic oxidation reagent, *m*-chloroperoxybenzoic acid. To probe the fundamental BVO tendencies, acetate analogues **8-cis** and **9-trans** were examined (Scheme 1), expecting that acetylation of the hydroxyl group of **8/9** would effectively dampen the epoxidation pathway, on the basis of well-known electronic effects in olefin epoxidation.²² Under standard *m*CPBA conditions,¹⁵ substrate **8-cis** proceeds to partial conversion furnishing lactones **10-normal** and **11-reversed**, albeit in a modest 4.3:1 ratio (Scheme 1, entry 1), along with some degree of unselective epoxidation. Under the same conditions, compound *ent*-**9-trans** was found to undergo a more efficient BVO with 90% conversion, with *ent*-**12-normal** and *ent*-**13-reversed** formed in an attenuated ratio of 2.3:1 (Scheme 1, entry 3).^{23,24} In this case, epoxide formation is not observed to an appreciable extent. Importantly, these findings suggest that the bis(equatorial)-substituted ketone (**8-cis**) is substantially less reactive than the axial/equatorial-substituted ketone (**9-trans**), likely due to intrinsic ground state destabilization in **9-trans**. When the reaction is catalyzed by previously discovered BVO catalyst **2**, minimal reactivity is observed with ketone **8-cis**

Scheme 1. Examination of Substituent Orientation and Baeyer–Villiger Oxidation Tendencies^a

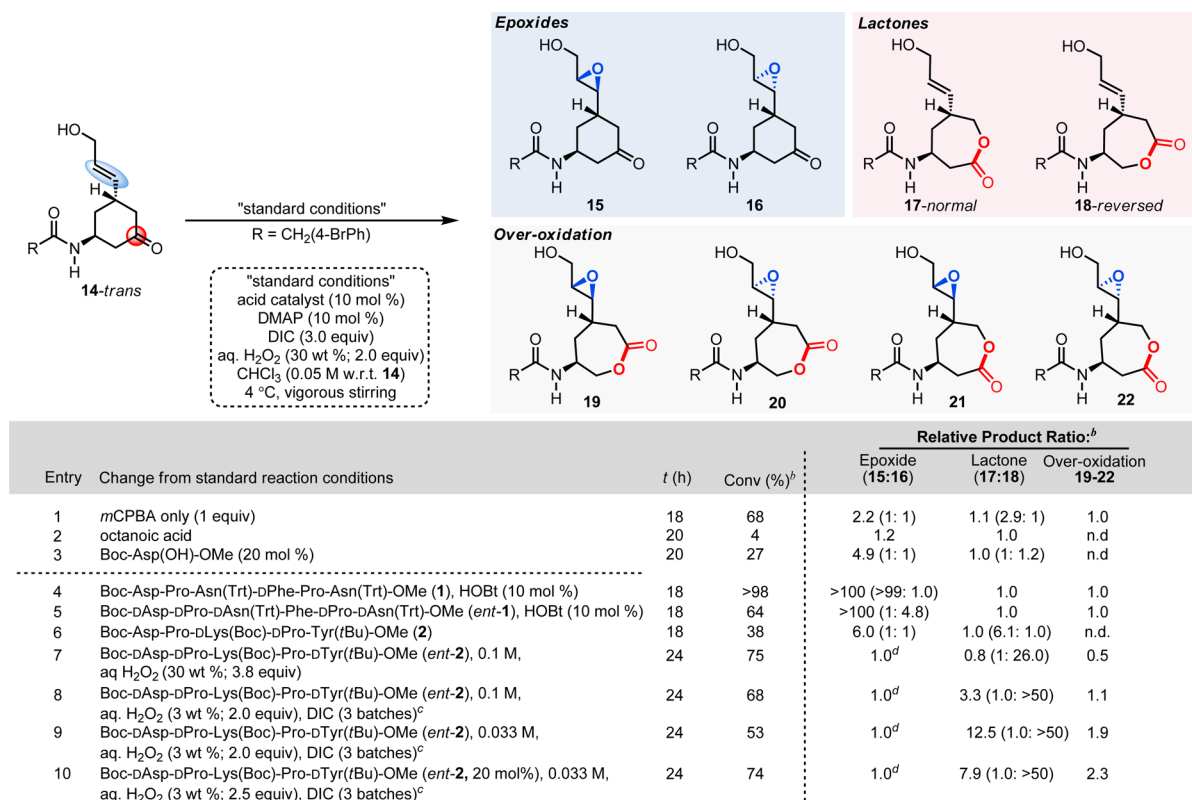
^aStandard conditions with *m*CPBA: substrate (1.0 equiv), *m*CPBA (1.0 equiv), chloroform, magnetic stirring. Standard conditions with peptide 2: substrate (1 equiv), 2 (10 mol %), 4-dimethylaminopyridine (DMAP; 10 mol %), aqueous H₂O₂ (30 wt %; 2.0 equiv), *N,N'*-diisopropylcarbodiimide (DIC; 3.0 equiv), chloroform, 4 °C, 24 h, magnetic stirring. ^bAverage from two trials; determined by uncalibrated HPLC integrations; value in parentheses refers to isolated yield (see Supporting Information for details). ^cOther oxidation products were detected.

(Scheme 1, entry 5). However, ketone *ent*-9-*trans* undergoes highly efficient BVO with enhanced regioselectivity for *ent*-13-*reversed* over *ent*-12-*normal*, at a ratio of >99:1 (Scheme 1, entry 6). This excellent chemo- and regioselectivity persists when the catalyst loading is reduced (Scheme 1, entry 7). These results reveal a high level of reactivity between catalyst 2 and the ketone *ent*-9-*trans*, echoing the previously observed high level of stereochemical matching between 2 and ketone 3, the topology of which is stereochemically complementary. With these observations in hand, we thus proceeded with the *trans* series (e.g., 7-*trans*-like compounds) for the critical assessment of functional group selectivity under the influence of peptides 1 and 2.

To benchmark the intrinsic reactivity of keto-olefins with the requisite allylic alcohol 14-*trans* (with no artificially introduced attenuation of epoxidation reactivity), we once again examined reactions with *m*CPBA as a preamble to reactions with peptides 1 and 2 (Scheme 2, entry 1).²⁵ When a stoichiometric amount of *m*CPBA is used, the reaction proceeds unselectively with respect to both functional group selectivity and regioselectivity, producing a myriad of products (15–22). Notably, with octanoic acid as a catalyst under conditions analogous to those employed for catalysts 1 and 2, only trace reactivity is observed. Furthermore, the use of protected aspartic acid as a catalyst (Boc-Asp(OH)-OMe) also resulted in low catalytic activity, favoring primarily epoxide products 15 and 16 (Scheme 2, entry 3). Collectively, these results demonstrate the ineffectiveness of the above catalysts in controlling the complex reaction coordinate that substrate 14-*trans* presents.

However, when peptide 1 is used as a catalyst in the reaction, a strikingly different outcome is obtained. Under these conditions, substrate 14-*trans* is consumed quantitatively, and the major product is monoepoxide 15, formed with >99:1 diastereoselectivity over 16 (Scheme 2, entry 4). Thus, peptide 1, as a function of its secondary structure, has exerted near total control of the complex reaction coordinate potential presented by multifunctional substrate 14, showcasing highly unique functional group selectivity. Examination of substrate 14-*trans* with the enantiomer of this peptide, *ent*-1, reveals a configuration mismatch of the olefinic side arm, resulting in lower levels of conversion and erosion of the diastereoselectivity being observed (1:4.8; 15:16; Scheme 2, entry 5); interestingly, as with catalyst 1, products derived from the BVO reaction are not detected.

We then turned our attention to the question of whether or not the previously discovered BVO catalyst 2 might exhibit orthogonal reactivity. The first experiment provided a cautionary tale. When substrate 14-*trans* is exposed to peptide 2 under the original catalytic conditions, the reaction proceeds to 38% conversion; however, instead of the anticipated preference for BVO products, we observe 6:1 preference for epoxides 15 and 16 over lactones 17 and 18. The diastereoselectivity for the epoxidation is also poor (1:1), and the regioisomeric preference among the lactones is discouraging, at a level of 6:1 favoring the normal over the reversed isomers (Scheme 2, entry 6). Based on these results, we speculated that the originally studied enantiomer of peptide 2 was stereochemically mismatched with bifunctional substrate 14-*trans*.¹⁸ Therefore, we prepared *ent*-2 and re-examined its performance under the same conditions,

Scheme 2. Chemoselectivity Evaluation and Optimization^a

^aStandard conditions with *m*CPBA: substrate (1.0 equiv), *m*CPBA (1.0 equiv), chloroform (0.05 M), 4 °C, magnetic stirring. Standard conditions with peptide 1: substrate (1 equiv), 1 (10 mol %), 4-dimethylaminopyridine (10 mol %), 1-hydroxybenzotriazole (10 mol %), aqueous H₂O₂ (30 wt %; 2.0 equiv), *N,N'*-diisopropylcarbodiimide (3.0 equiv), chloroform (0.05 M), 4 °C, magnetic stirring. Standard conditions with peptide 2: substrate (1 equiv), 2 (10 mol %), 4-dimethylaminopyridine (10 mol %), H₂O₂ (30 wt %; 2.0 equiv), *N,N'*-diisopropylcarbodiimide (3.0 equiv), chloroform (0.1 M), 4 °C, magnetic stirring. ^bAverage from two trials; determined by uncalibrated HPLC integrations of the crude reaction media (see Supporting Information for details). ^cMixing @ 30 rpm. ^d15 + 16 only.

and striking differences were observed (Scheme 2, entries 7–10).

Under these previously established reaction conditions,¹⁵ we now observed an improvement in BVO selectivity such that near parity between the epoxidation versus BVO pathways was observed (Scheme 2, entry 7), with a 1.0:0.8 preference for epoxides 15 and 16 over lactones 17 and 18. Of particular note, the preference for the lactone derived from reversed migratory aptitude was restored (1:26). Optimization of this result was guided by analysis of ¹H-¹H NMR derived structures of peptides 1 and 2 that rationalized the observations in our initial studies of enantioselective epoxidation and regio- and enantioselective BVO in our initial studies (Figure 2). In the case of 1-catalyzed epoxidation, hydroxyl-directed epoxidation through hydrogen bonding is consistent with previously reported enantioselectivity in epoxidation reactions (Figure 2a).¹⁴ In the case of 2-catalyzed BVO, a favorable interaction of the amido group with catalyst 2 is consistent with our recent observations (Figure 2b). This hypothesis was stimulated by analysis of an experimentally derived (ROESY) solution structure of 2,²⁶ along with our study of catalyst analogues.¹⁵ A critical role for the lysine side chain, along with the schematic secondary structure shown, contributes to a view of competing hydrogen bonding networks as catalyst *ent*-2 operates on substrate 14-*trans* (Figure 2c). One network promotes hydroxyl-directed epoxidation (the blue arrow); the second network promotes amide-directed BVO (the red arrow).

Critically, the blue arrow implies an electrophilic peracid; the red arrow implies a nucleophilic peracid. Our analysis culminated in the hypothesis that disruption of the hydroxyl-directed epoxidation pathway in blue might amplify selectivity for the BVO pathway with catalyst *ent*-2, if the red network could be preserved.

To disrupt putative hydrogen bonds to the substrate hydroxyl group, we hypothesized that an increased concentration of H₂O might effectively compete with hydroxyl-directed epoxidation to a greater extent than it would perturb the amide-directed BVO (Figure 2d). This speculation is in keeping with theories about hydrogen bond strength that point to the importance of complementarity of hydrogen bond donors and acceptors.²⁷ A systematic study with additional H₂O content supports these notions (Figure 3). Our findings reveal a linear relationship between the overall water content of the reaction medium and BVO/epoxide selectivity when using the BVO peptide catalyst *ent*-2: the more H₂O relative to H₂O₂, the higher the lactone/epoxide ratio. Unambiguously, H₂O plays an important role in these reactions, and the outcome is consistent with our hypothesis. With modest increases in H₂O content (15–100 extra equivalents of H₂O, relative to standard 30 wt % H₂O₂), overall conversion of substrate 14-*trans* remains high (70–75%) with a slight increase (2–3-fold, relative to Scheme 2, entry 7) in selectivity increase toward BVO. Strikingly, further increasing of the equivalents of H₂O leads to even greater selectivity for BVO (4–5-fold), albeit at

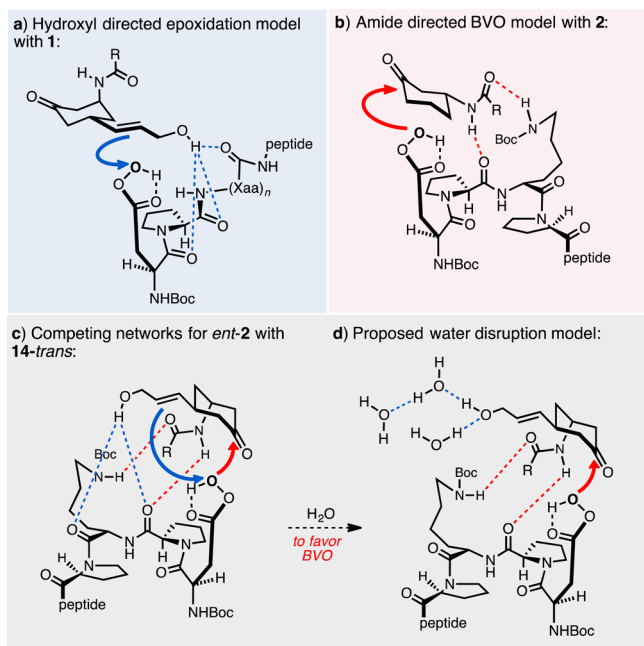


Figure 2. Representative models for the competing reaction pathways: (a) hypothetical model for hydroxyl-directed epoxidation; (b) hypothetical model for amide-directed Baeyer–Villiger oxidation; (c) presentation of a competing H-bonding network; (d) proposed water disruption of the H-bonding network.

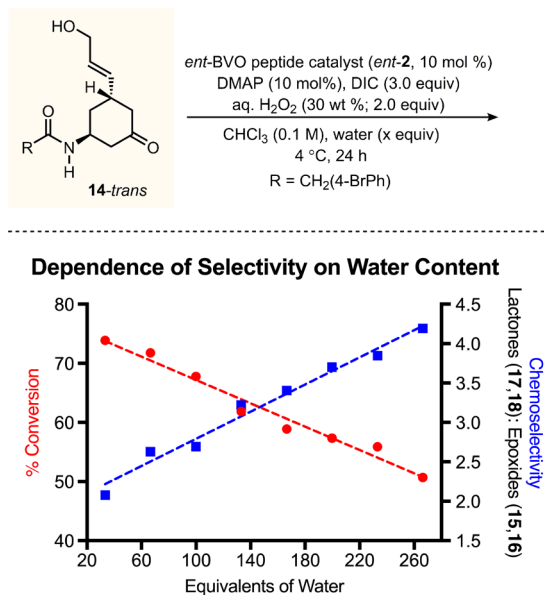


Figure 3. Systematic study with additional H_2O added to the reaction media. Standard conditions with peptide **2**: **14** (1 equiv), **2** (10 mol %), 4-dimethylaminopyridine (10 mol %), H_2O_2 (30 wt %; 2.0 equiv), N,N' -diisopropylcarbodiimide (3.0 equiv total; 1 equiv @ 0 h, 4 h, 8 h), chloroform (0.1 M wrt **14**), water ($n + 15$ equiv starting at 30 equiv), 4°C , mixing @ 30 rpm, 24 h. Conversion and selectivity were determined by uncalibrated HPLC integrations of the crude reaction media (see Supporting Information for details).

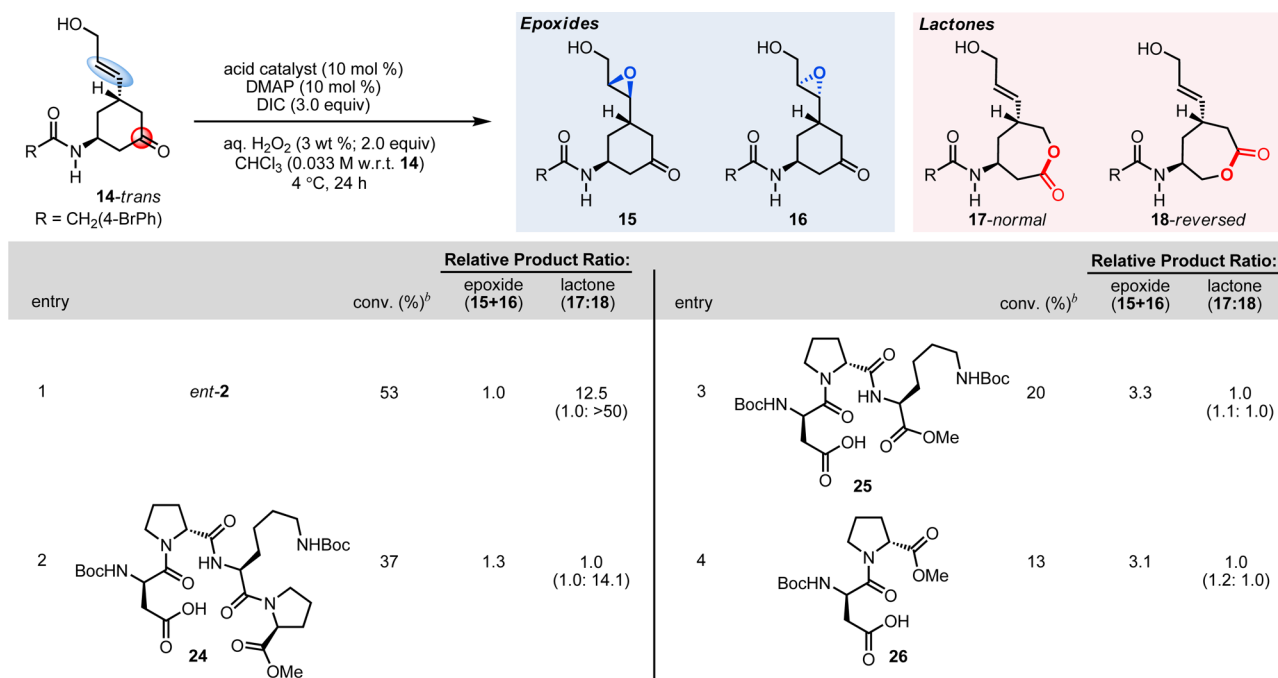
some expense of overall conversion (50–58%).²⁸ The erosion of conversion may be due to consumption of the carbodiimide reagent, DIC, and its adducts leading to a buildup of urea byproduct, 1,3-diisopropylurea, a competent H-bond donor/acceptor group.²⁹

These observations enabled further optimization for the BVO pathway. Thus, a transition from aqueous solutions of 30 wt % H_2O_2 to 3 wt % H_2O_2 in H_2O , ensuring optimum mixing of the biphasic reaction mixture, lead to rather dramatic results, such that substrate **14-trans** is converted to the corresponding oxidation products with total control over migratory aptitude (1:>50; Scheme 2, entry 8). Further dilution of the reaction mixture further increases the functional group selectivity leading to enhanced results, such that 53% conversion is observed, with a 1:12.5 ratio of epoxide to BVO products, again with total reversal of migratory aptitude (Scheme 2, entry 9). Finally, execution of these conditions with an increase in catalyst loading provides a high converting reaction with the desired functional group selectivity (Scheme 2, entry 10; see Supporting Information for complete screening of conditions). Under these conditions, the BVO products **17** and **18** are also observed to participate in overoxidation to a somewhat greater extent (**19–22**), modifying the ratios observed at lower conversion.³⁰ Overall, the BVO selectivity reversal observed using catalyst *ent-2* for the oxidation of **14-trans**, under high- H_2O conditions, appears to be due to a combination of both the catalyst's unique secondary structure and medium effects where the epoxidation and BVO pathways are differentially modulated by the demands of H_2O in this situation of competing hydrogen bond networks.

The critical role of the secondary structure, in light of the optimized high- H_2O reaction conditions, prompted us to evaluate several truncated peptide-based analogues of catalyst *ent-2* under the optimized reaction conditions. The sequential deletion of amino acids from the C-terminal end of the catalyst *ent-2* delivers incrementally inferior chemo- and regioselectivity along with reduced reaction efficiency. As shown in Scheme 3, catalyst **24** wherein the C-terminal dTyr(*t*Bu)-OMe of *ent-2* is replaced with a methyl ester (Scheme 3, entry 2) results in both a significant loss of functional group selectivity (1.3:1.0, epoxide:lactone) and a decrease in control of the migratory aptitude of the BVO products (1.0:14.1; **17:18**) in addition to lower levels of conversion. Reminiscent of an observation that emerged in our earlier work that the dPro-Xaa-Pro motif is a crucial sequence element for BVO, truncated peptide **25**, which lacks the $i + 3$ Pro, leads to a further erosion in conversion and chemoselectivity with epoxides **15** and **16** being favored over lactones **17** and **18** (3.3:1.0) and a total loss of control in migratory aptitude with a slight preference toward the “normal” lactone **17** (1.1:1.0; **17:18**; Scheme 3, entry 3). Moreover, deletion of the $i + 2$ Lys(Boc) residue, where Boc = *tert*-butoxycarbonyl, results in further reduced reaction efficiency (Scheme 3, entry 4) on par with the results of the monomer Boc-Asp(OH)-OMe (Scheme 2, entry 3). Collectively, these results demonstrate that the selectivity for the BVO reaction and attendant regio- and stereoselectivity are the unambiguous results of interaction of **14** with the peptide catalyst and its complete secondary structure.

CONCLUSION

It is thus established that aspartyl peptides can catalyze either epoxidation reactions as electrophilic oxidants or BV oxidations as nucleophilic oxidants, with accompanying diastereo- and regioselectivity, when presented with an intramolecular choice. The molecular context in which the aspartyl residue is placed—the peptide sequence that defines the catalyst secondary structure—provides the capacity to control orthogonal functional group selectivity in an intramolecular competition

Scheme 3. Selectivities Observed with Truncated Peptides^a

^aStandard conditions with peptide **2**: substrate (1 equiv), **2** (10 mol %), 4-dimethylaminopyridine (10 mol %), aqueous H₂O₂ (3 wt %; 2.0 equiv), *N,N'*-diisopropylcarbodiimide (3.0 equiv), chloroform (0.033 M), 4 °C, mixing @ 30 rpm, 24 h. ^bAverage from two trials; determined by uncalibrated HPLC integrations of the crude reaction media (see Supporting Information for details).

experiment. The ability to dial in functional group selectivity, while controlling attendant stereoselectivity issues, is a dimension that may create new possibilities for orchestrating the assembly of complex molecules, and for complex scaffold diversification. Perhaps more fundamentally, the peptide-regulated selectivity for specific functional groups within a multifunctional substrate signals control over the mechanistic behavior of common catalytic machinery, which at present seems to be known primarily only in the context of enzymes.³¹

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acscentsci.6b00237.

Synthetic procedures, descriptions of compounds, analytical methods, computational methods, and crystallographic data (PDF)

Crystallographic data are deposited with the Cambridge Crystallographic Data Centre under the accession numbers CCDC 1480519 and 1480521.

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Notes

The authors declare no competing financial interest.

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- (24) The term “*ent*” refers to the corresponding enantiomer.
- (25) For practical reasons, we elected to proceed in the study with the enantiomer of **14** that was derived from commercially available (S)-3-cyclohexenecarboxylic acid.
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