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Catalyst Control over Regio- and Enantioselectivity in Baeyer–Villiger Oxidations of Functionalized Ketones

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Supporting Information

ABSTRACT: We report a peptide-based catalyst that can strongly influence the regio- and enantioselectivity of the Baeyer–Villiger (BV) oxidation of cyclic ketones bearing amide, urea, or sulfonamide functional groups. Both types of selectivity are thought to arise from a catalyst–substrate hydrogen-bonding interaction. Furthermore, in selected cases, the reactions exhibit the hallmarks of parallel kinetic resolution. The capacity to use catalysis to select between BV products during an asymmetric process may have broad utility for both the synthesis and diversification of complex molecules, including natural products.

The oxidation of ketones to esters, known as the Baeyer–Villiger (BV) reaction,[1] has long been regarded as a powerful tool for organic synthesis. As such, there have been many attempts to render the process catalytic and enantioselective, which have seen the use of both enzymes[2] and small-molecule catalysts.[3] However, despite this storied history, the reaction still presents numerous challenges, such as the issue of regioselectivity, which can be difficult to predict, let alone control. For cyclic ketones, the effects of ring strain are an added complication; if the reaction forms a more strained lactone from a less strained ketone, then overcoming the energy barrier to C–C bond migration can be difficult without substantial activation. Finally, if complex molecule substrates are to be used, then the catalyst must also be sufficiently chemoselective to tolerate functionality in addition to the reacting ketone. Ideal catalysts must therefore be able to oxidize relatively unstrained ketones to deliver products with both regio- and enantioselectivity, while also tolerating the presence of additional functional groups.

We have been studying a catalytic cycle for oxidation in which the side-chain of a peptide-embedded aspartic acid shuttles between the carboxylic acid and the corresponding peracid *in situ*.[4] This system, which has proven particularly effective for electrophilic oxidation, is well suited to a variety of substrate and reaction types, such as the oxidation of allylic carbamate **1** to its epoxide (**2**, Figure 1a). The selectivity of the reaction is controlled by the peptide sequence, which may be tuned for the regio- and enantioselective oxidation of various substrates.[5] Notably, this approach may also be applied to cases where the reversal of a substrate's intrinsic reactivity is desired. For example, indole **3** has a strong proclivity to form diastereomer **4** when treated with various electrophilic oxidants; yet, it is converted to **5** in high yield in the presence of peptide catalyst **6** (Figure 1b).[6] In the context of the BV oxidation, a peracid functions as a nucleophile, not as an electrophile (Figure 1c). We thus wondered whether the aspartic acid system might be portable to the BV reaction, meeting the analogous requirements for selective oxidation in functional group-rich molecular environments, despite the fundamentally different role of the peracid intermediate.

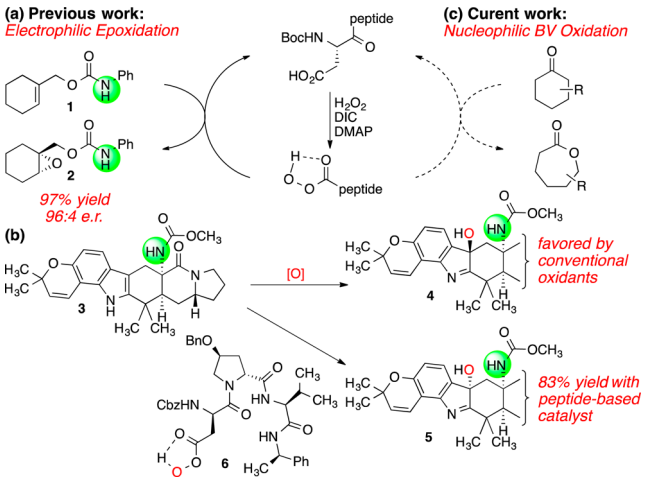

Figure 1. (a) Previous electrophilic epoxidation of alkenes. (b) Diastereoselective oxidation of an advanced intermediate. (c) Proposed nucleophilic oxidation of ketones. Cbz = benzyloxycarbonyl.

In earlier work, we demonstrated the viability of the acid/peracid catalytic cycle for the BV reaction.[7] However, despite exploration of many peptide sequences that had given high enantioselectivity for epoxidation reactions in the intervening years, we were unable to achieve comparable levels of selectivity for the fundamentally different BV reaction. We therefore turned our attention to combinatorial screening.[8]

For our initial screen, we synthesized an on-bead library of catalysts, as depicted in Figure 2a. We evaluated each catalyst in the kinetic resolution (KR)[9] of ketone **7** via oxidation to lactone **8** (Figure 2b), due to this reaction's facile analysis. After screening 245 beads, we identified several "hit" catalysts that exhibited a modicum of selectivity (e.g., catalyst **9a**, k_{rel} = 1.7; see SI). Intriguingly, the "Pro-DXaa-Pro" motif was conserved in the i + 1 to i + 3 positions, suggesting that this sequence might be especially suited to the BV reaction manifold.

While the initial threshold of selectivity for these hits was low, our experience dictated that stronger catalyst control could

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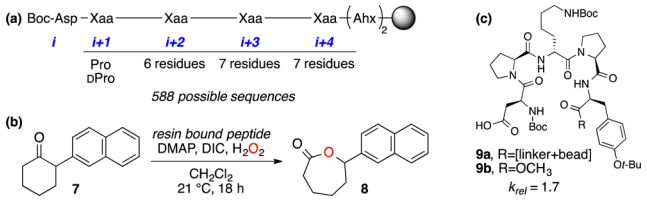


Figure 2. Combinatorial screening of BV catalysts. (a) Library composition. (b) Test reaction for on-bead screening. (c) Best performing catalyst from screen.

be achieved if the substrates possessed additional functional groups that could engage the peptide through H-bonding.[10] We thus turned our attention to the application of catalyst **9b** (the soluble methyl ester analog of **9a**) to the BV oxidation of **10a** (Figure 3a). Ketone **10a** presents an excellent test substrate in

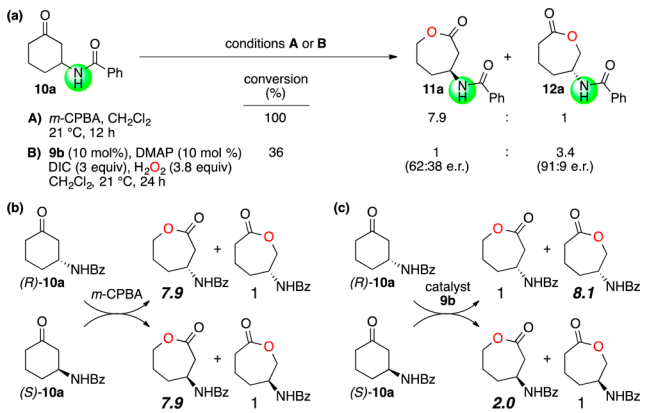


Figure 3. (a) BV oxidation of **10a**. (b) Tracking the regiochemistry of O atom insertion for each enantiomer of **10a** with *m*-CPBA, and (c) catalyst **9b**. See SI for absolute stereochemical assignment.

that both isomeric lactones **11a** and **12a** are formed upon exposure to 3-chloroperoxybenzoic acid (*m*-CPBA). When this stoichiometric oxidant is used, lactone **11a** dominates, in a ratio of 7.9 to 1. However, with catalyst **9b** (10 mol %), we observed notable catalyst control, including *reversal of intrinsic migratory aptitude*, with lactone **12a** being favored 3.4 to 1 at 36% conversion. Moreover, all three species (unreacted substrate and both lactones) were enantioenriched (Table 1, entry 1), with **12a** being formed in 91:9 enantiomeric ratio (er).

This reaction exhibits characteristics of a parallel kinetic resolution (PKR),[11] in that each enantiomer of substrate is converted preferentially to a different product. However, unlike an archetypical PKR, the enantiomers exhibit an ~5-fold rate

Table 1. Effect of Peptide Sequence on Selectivity[a]

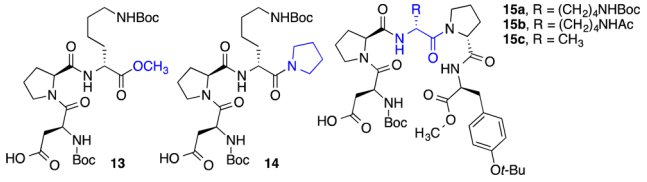
				er[c]		
entry	catalyst	conv. (%)[b]	ratio of 11:12[c]	10a	11a	12a
1	**9b**	36	1:**3.4**	66:34	62:38	91:9
2	**13**	12	**1.6**:1	51:49	58:42	72:28
3	**14**	31	1:**3.7**	64:36	61:39	92:8
4	**15a**	32	1:**3.1**	64:36	67:33	94:6
5	**15b**	27	1:**2.8**	61:39	64:36	94:6
6	**15c**	19	1:**1.6**	55:45	61:39	90:10

[a]Reaction conditions depicted in Figure 3, conditions **B**. [b]Conversion = $ee_{10}/(ee_{10} + ee_{pdt})$, where ee_{pdt} is the aggregate enantiomeric excess (ee) of both lactone products. [c]Determined by HPLC.

difference.[12] This situation creates the opportunity to track the degree to which catalyst-controlled reversal of intrinsic migratory aptitude occurs. Of course, with the achiral oxidant, each enantiomer of ketone **10a** delivers an equivalent ratio of lactones (**11a**/**12a**, 7.9:1; Figure 3b). Yet, with the chiral catalyst **9b**, one sees that the regioselectivity is more pronounced for (*R*)-**10a** (**11a**/**12a**, 1:8.1; Figure 3c) than for (*S*)-**10a**, which forms a less selective mixture of lactone isomers (**11a**/**12a**, 2.0:1). Thus, catalyst **9b** exhibits the hallmarks of a stereochemically "matched" case for reaction with (*R*)-**10a**; catalyst **9b** may be considered "mismatched" in reactions with (*S*)-**10a**.[13]

Fascinated by this catalyst-controlled regioselectivity, as well as the encouraging enantioselectivity, we wished to explore the role of the peptide sequence, with an eye toward optimization and identification of mechanistic roles for the different regions of the catalyst (Chart 1). One hypothesis emerging from the

Chart 1. Sample Peptides from Sequence Screen



initial on-bead catalyst screen was that the Pro-DXaa-Pro motif is a crucial sequence element. Indeed, truncated peptide **13**, which lacked the *i* + 3 Pro, led to a plummet in both conversion and selectivity, with "normal" lactone **11a** being favored (**11a**/**12a**, 1.6:1; residual **10a** nearly racemic; Table 1, entry 2). Conversely, when the two C-terminal residues were replaced with a simple pyrrolidine (**14**), the conversion and selectivity for the "abnormal" lactone were restored to levels comparable to catalyst **9b** (**11a**/**12a**, 1:3.7; **12a** with 92:8 er; Table 1, entry 3). Given the performance of catalyst **14**, the role of the *i* + 4 position is unclear, but a brief survey revealed DPro-Tyr(*t*-Bu)-OCH_3 as an optimal C-terminal sequence (**15a**), leading to lactone **12a** with as high as 94:6 er (**11a**/**12a**, 1:3.1; Table 1, entry 4). The role of the DLys(Boc), where Boc = *tert*-butyloxycarbonyl, side-chain in the *i* + 2 position is not definitively clear. Replacement of the Boc carbamate with an acetamide (**15b**) produces a minimal change in behavior (**11a**/**12a**, 1:2.8; **12a** with 94:6 er; Table 1, entry 5). However, substitution with DAla in this position (**15c**) leads to a drop in both conversion and selectivity (**11a**/**12a**, 1:1.6; **12a** with 90:10 er; Table 1, entry 6). We thus chose **15a** as our catalyst for further study.

A brief survey of reaction solvents showed halogenated solvents to be superior, with chloroform giving the best results in terms of both conversion and selectivity (**11a**/**12a**, 1:3.7; **12a** with 96:4 er; Table 2, entry 1). We next wished to test our hypothesis that the benzamide was acting mainly as an H-bonding handle, but that modifications that preserved this capability should be tolerated. Indeed, we find that when a CH_2 is inserted between the phenyl ring and the amide, as in **10b**, the selectivity not only remains but in fact improves, with **12b** forming in as high as 97:3 er at similar conversion (**11b**/**12b**, 1:4.5; Table 2, entry 2). Intriguingly, when the CH_2 is replaced with a NH (urea **10c**), the reaction shows a pronounced increase in conversion, seeming to reflect an accelerated reaction rate for the "mismatched" enantiomer. Importantly,

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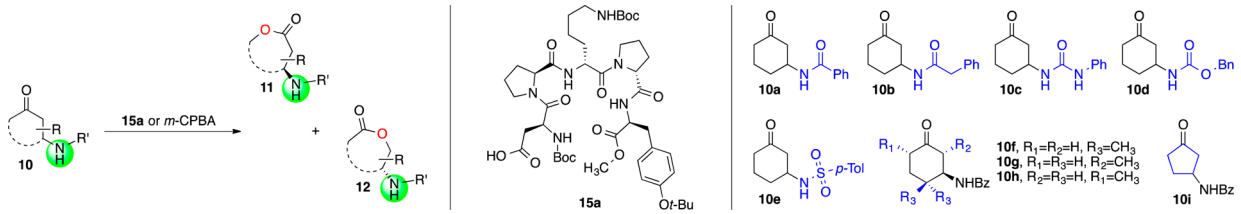
Table 2. Effect of Substituents and Ring Size on Selectivity[a]



			reversal of regioselectivity: regioisomer ratio (**11**:**12**)[b]			er[b]		
entry	substrate	conv. (%)[c]	*m*-CPBA[d]	(**15a**, total)	**15a**, matched[e]	**10**	**11**	**12**
1	**10a**	41	**7.9**:1	(1:3.7)	1:**12**	73:27	70:30	96:4
2	**10b**	45	**2.5**:1	(1:4.5)	1:**28**	76:24	85:15	97:3
3	**10c**	64	**1.4**:1	(1:1.8)	1:**24**	71:29	93:7	92:8
4	**10d**	20[f]	**3.0**:1	(1:3.1)	1:**8.2**	ND[g]	64:36	95:5
5	**10e**	20	**6.1**:1[h]	(1:1.8)	1:**4.4**	56:44	64:36	91:9
6	**10f**	44	**5.2**:1	(1:7.3)	1:**23**	80:20	71:29	93:7
7[i]	**10g**	51	1:**2.3**	(1:38)	<1:**100**	85:15	78:22	85:15
8	**10h**	52[f]	>**100**:1	(5.2:1)	**2.3**:1	54:46	56:44	99:1
9	**10i**	44[f]	**3.3**:1	(1.2:1)	1:**4.3**	53:47	83:17	88:12

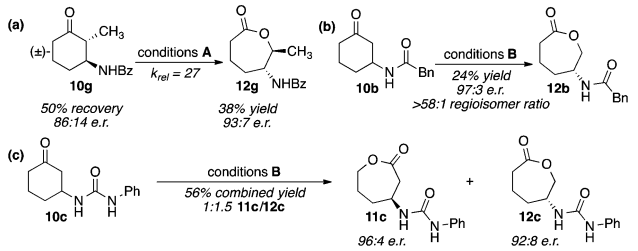
[a]Conditions: **15a** (10 mol %), 4-dimethylaminopyridine (DMAP, 10 mol %), *N*,*N*′-diisopropylcarbodiimide (DIC, 3.0 equiv), H_2O_2 (3.8 equiv), $CHCl_3$ (0.1 M), 21 °C, 24 h. [b]Determined by HPLC. [c]See Table 1, footnote b. [d]*m*-CPBA (1.1 equiv), $CHCl_3$ (0.1 M), 21 °C, 12 h. [e]Product ratio for the enantiomer that reacts more rapidly with the catalyst. [f]Conversion approximated from comparison of HPLC peak integrations of the products to the substrate. [g]ND = not determined. [h]*m*-CPBA (2.0 equiv) used. [i]DIC (1.5 equiv), H_2O_2 (1.9 equiv) used.

the rate acceleration in the mismatched series does not come at the expense of enantioselectivity. Instead, this reaction is more similar to an ideal PKR, with **11c** and **12c** forming in 93:7 and 92:8 er, respectively (**11c**/**12c**, 1:1.8; Table 2, entry 3). On the other hand, the reaction performs poorly with substrate **10d**, wherein the directing group is a carbamate. Decreases in both conversion and selectivity (**11d**/**12d**, 1:3.1; **12d** with 95:5 er; Table 2, entry 4) are observed in this case, possibly indicating that, in contrast to **10c**, the introduction of an oxygen, which is a nominal H-bond acceptor, creates Coulombic repulsion that weakens the catalyst−substrate interaction. Finally, tosylamide **10e** is also a competent substrate, exhibiting similar trends in both enantio- and regioselectivity (**11e**/**12e**, 1:1.8; **12e** with 91:9 er; Table 2, entry 5). Taken together, these data suggest an H-bonding interaction between the NH of the substrate and an as yet unidentified H-bond acceptor on the catalyst.

Having evaluated the catalyst's performance with a variety of H-bonding handles, we next wished to investigate the effect of modification to the ring. The catalyst tolerates substitution adjacent to the directing group, with 4,4-dimethyl substrate **10f** giving selectivity comparable to parent benzamide **10a** (**11f**/**12f**, 1:7.3; **12f** with 93:7 er; Table 2, entry 6). The introduction of a 2-methyl group adjacent to the amide (**10g**) creates a slight preference for the formation of lactone **12g** when *m*-CPBA is used (**11g**/**12g**, 1:2.3; Table 2, entry 7). This is strongly amplified by catalyst **15a**, leading to an almost undetectable level of **11g** (**11g**/**12g**, 1:38; Table 2, entry 7). This reaction, which is now similar to a classical KR, proceeds with good enantioselectivity, corresponding to a k_{rel} of 11. Conversely, isomeric substrate **10h** exhibits a strong preference for lactone **11h** (**11h**/**12h**, >100:1 with *m*-CPBA; Table 2, entry 8). Even so, catalyst **15a** forms an appreciable quantity of **12h** in almost enantiopure form (**11h**/**12h**, 5.2:1; **12h** with 99:1 er). Finally, we find that cyclopentanone **10i** also undergoes clean oxidation with "PKR-like" behavior, in which products **11i** and **12i** are formed in near equal quantities, with similar levels of enantioenrichment (**11i**/**12i**, 1.2:1; **12i** with 88:12 er, Table 2, entry 9).

Since the catalyst mediates a range of substrate-dependent reaction paradigms, from classical KR to PKR, we selected three substrates that exemplify distinct modes of reactivity and subjected them to minimally optimized BV conditions in order to demonstrate the isolation of enantioenriched products in each of these scenarios. Ketone **10g**, which undergoes a KR with catalyst **15a**, can be oxidized at −8 °C, to give 38% yield of **12g** in 93:7 er and 50% recovery of **10g** with 86:14 er (k_{rel} of 27, Scheme 1a). The oxidation of **10b**, which represents an "in between" form of KR/PKR since each substrate enantiomer leads to a different regioisomer but at different rates, allows for the isolation of "*m*-CPBA-disfavored" lactone **12b** in 24% yield (>58:1, **12b**/**11b**) with 97:3 er (Scheme 1b). Finally, ketone **10c**, which leads to a more "PKR-like" reaction, may be converted to lactones **11c** and **12c** in 56% combined yield, with 96:4 and 92:8 er respectively (Scheme 1c).

Scheme 1[a]



[a]Conditions: **15a** (10 mol %), DMAP (10 mol %), $CHCl_3$. **A**: DIC (1.5 equiv over 8 h), H_2O_2 (1.9 equiv), −8 °C, 58 h. **B**: DIC (4 equiv over 12 h), H_2O_2 (5 equiv), 21 °C, 32 h.

In summary, we have described catalysts that influence both the regio- and enantioselectivity of BV reactions involving functionalized ketones. The catalysts show the capacity to overturn the regioselectivity exhibited by *m*-CPBA, suggesting

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more generally that intrinsically disfavored BV products may be accessed with peptide catalysis. Furthermore, the mechanism underlying the selectivity, which likely stems from interactions between the peptide and H-bonding functionality of the substrate, constitutes a distinct approach to selective BV oxidation, relative to known small molecule catalysts. Further interrogation of this mechanism as well as applications to both enantioselective synthesis and natural product modification are ongoing objectives in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

Additional figures, experimental details and characterization. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(12) As conversion increases, the er of starting material and "mismatched" lactone should increase, whereas the er of the "matched" lactone should decrease. The ratio of matched to mismatched lactone should also decrease (see SI for details).

(13) The situation is reminiscent of double diastereoselection, as codified previously, but pertains to regio- and enantioselectivity in these cases. See: Masamune, S.; Choy, W.; Petersen, J. S.; Sita, L. R. *Angew. Chem., Int. Ed.* **1985**, *24*, 1.