Stereoselective Baeyer–Villiger oxidation of 3-substituted cyclobutanones promoted by flavinium-cinchona alkaloid ion-pair catalyst

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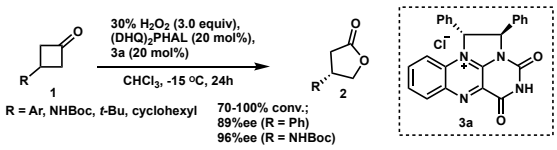
KEYWORDS. Baeyer-Villiger oxidation, Flavin co-factor, Stereoselective reaction, Organocatalyst, Ion-pair catalyst

ABSTRACT: The previously reported asymmetric Baeyer–Villiger (BV) oxidation of 3-substituted cyclobutanones promoted by a co-factor flavin derivative was revisited to broaden its scope. The correlation between the stereochemical outcome and the catalyst structure was examined, and only one stereocenter was found to be critical for achieving high stereoselectivity. This observation led to the identification of a new, simpler catalyst with improved selectivity. By positioning a lone pair donor on the substrate, the selectivity was further enhanced to 95% ee using the original catalyst or >99% ee with the new catalyst, among the highest selectivities achieved for the BV reaction using a small-molecule catalyst. This observation supports our hypothesis that the H-bonding network is central to the catalyst. This study demonstrates the power of mechanistic investigation to broaden the scope of catalytic systems and aid in catalyst design. We are currently exploring methods to expand the applicability of this catalyst and demonstrate its use.

Introduction

Since its discovery in 1899, the Baeyer–Villiger (BV) reaction has been an essential and versatile tool for accessing esters and lactones.[1,2] As chiral β- and γ-lactones are frequently used as synthetic building blocks,[3] catalytic, stereoselective versions of BV reactions have been actively sought and developed.[4–10] In contrast to enzymatic methods that have advanced significantly recently,[11–13] complementary methods using small-molecule catalysts are still in their infancy. The enantioselective BV reaction of symmetric cyclobutanones is particularly appealing because of its ease of synthesis, enhanced reactivity, and the growing number of subsequent transformations of the γ-lactone product, thus enabling rapid access to structurally diverse products.[14]

We have previously reported asymmetric BV oxidation using a self-assembled ion-pair catalyst, comprised of cationic co-factor flavin derivative, flavinium **Fl-1**, and cinchona alkaloid dimer, $(DHQ)_2PHAL$ (see Scheme 1).[15] Our method showed good-to-excellent conversion and enantioselectivity for 3-substituted cyclobutanones with up to 96% ee.

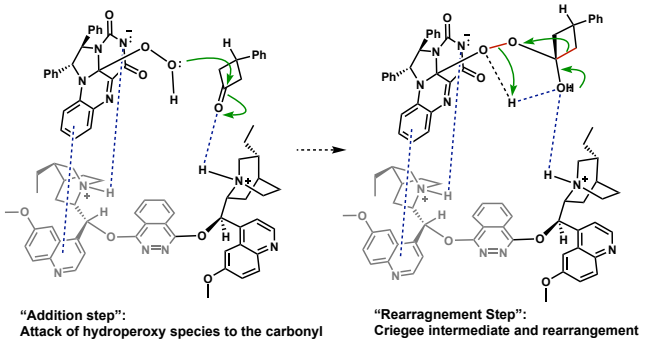


Scheme 1. Asymmetric Baeyer-Villiger reaction.

As a continuation of this study, we aimed to improve the catalytic reactivity, substrate scope, and enantioselectivity of this system. One proven method for achieving these goals is to investigate the mechanistic pathway of the reaction. Determining a correlation between the structures of the substrate and catalyst with respect to enantioselectivity could aid in redesigning the catalysts with desirable properties. Identifying the rate-determining step (RDS) can provide insights into improving the rate or selectivity. With these practices, we aim to broaden the scope of the catalysts. Herein, we report the development of a new and improved system to achieve this goal.

Results and Discussion

To initiate our study, we established the kinetic profile of the reaction. The accepted mechanism of the flavin-catalyzed BV reaction has been discussed in the literature,[16] in which the initial attack of hydrogen peroxide on flavinium forms an active peroxide. The flavin-attached peroxide then attacks the carbonyl group, leading to the Criegee intermediate, which rearranges to form lactone (Figure 2). The migrating C–C and breaking O–O bonds must have an antiperiplanar relationship.[17,18] With this principle, we proposed a mechanistic hypothesis that involved 1:1 ion-pair formation between the flavinium species and $(DHQ)_2PHAL$,[19] with a network of weak interactions, as illustrated in Scheme 2.[20]



Scheme 2. Final two steps of the investigated BV reaction.

For the BV reaction, the RDS is either the addition of peroxide to the carbonyl group or the subsequent rearrangement (Figure 2). In the original non-catalyzed BV reaction using peracid, the

RDS appeared to be the rearrangement step. However, the factors that determine the RDS and migratory aptitude are under debate and depend upon individual reaction conditions.[21] To determine the RDS, we adopted Hammett analysis, a frequently used method, as the electronic influence on these two steps would be opposite to one another.

We selected 3-phenylcyclobutanone as the benchmark substrate, used by us and other researchers, for this investigation. Several substrates with electron-donating and -accepting substituents at the *para*-position of the phenyl ring were used in this study. Prior to analysis, 3-phenylcyclobutanone was subjected to the previously determined optimal reaction conditions, and the concentration of the substrate was monitored using an external standard. Standard kinetic analysis showed that the reaction followed first-order kinetics, as a clear linear relationship was observed between the logarithm of the substrate concentration and the reaction time. The rate constant (k_H) was then obtained from the regression line.[20]

After determining the order of the reaction, the rate constants for the other substrates were calculated using the same method. Finally, the Hammett correlation was established by plotting $\log(k_x/k_H)$ versus the *para*-substituent constant, σ_x (Figure 1). The slightly positive slope of this linear correlation ($\rho = 1.27$) indicates a decrease in the electron density at the rate limit, suggesting that peroxide addition to the carbonyl group is the RDS.

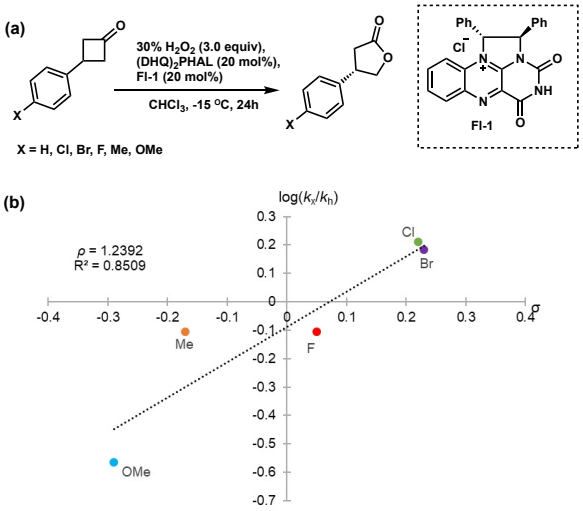


Figure 1. (a) BV reaction used for Hammett analysis. (b) Hammett plot with $\log(k_x/k_H)$ versus substituent constant σ_x.

To obtain further evidence for this result, the deuterium isotope effect at the 2-position of 3-phenylcyclobutanone was investigated.[20] The secondary isotope effect should be observed if the RDS is the rearrangement step, which involves bond cleavage adjacent to the carbonyl group. The experiments were carried out using a method for NMR analysis developed by Singleton.[22,23] The kinetic isotope effect (k_H/k_D) obtained by this method was 1.002,[20] showing no apparent secondary isotope effect, indicating that the rearrangement step is not the RDS (Figure 2). This result is consistent with the Hammett analysis.

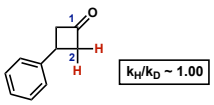
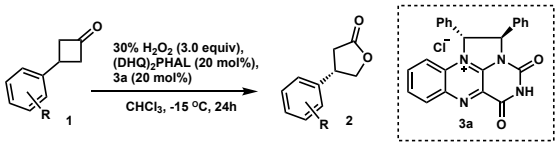


Figure 2. Kinetic isotope effect at the 2-position of 3-phenylcyclobutanone.

Next, we established the correlation between the substrate/catalyst structure and enantioselectivity (Table 1). Substrates with various substituents at the *para*-position of 3-phenylcyclobutanone were prepared and tested (Table 1, entries 2–7). In general, when electron-withdrawing substituents were added, a slight increase in the conversion and selectivity was observed (entries 2 and 3), whereas the introduction of electron-donating groups led to a decrease at both ends (entries 5 and 6).

Interestingly, when substituents were introduced at the *ortho*-position (entries 8–11), placing Br-, vinyl-, and Boc-protected amino groups significantly increased the enantioselectivity. In particular, *ortho*-NHBoc substrate showed the highest selectivity of 95.3% ee (entry 11). However, the introduction of an ethyl group at the same position resulted in a slight decrease in selectivity (entry 9).

Table 1. Influence of the substrate structure on selectivity



Entry	R	1	2	Conv.[a] (%)	ee[b] (%)
1	H	1a	2a	96.8	88.6[c]
2	4-Br	1b	2b	99.8	91.7[c]
3	4-Cl	1c	2c	99.5	91.6[d]
4	4-F	1d	2d	100.0	75.4
5	4-Me	1e	2e	94.9	86.2[d]
6	4-OMe	1f[e]	2f	54.4	47.7
7	4-NHBoc	1g	2g	79.6	81.7[d]
8	2-Br	1h	2h	96.7	94.6
9	2-ethyl	1i	2i	90.4	88.7
10	2-vinyl	1j	2j	99.8	95.2
11	2-NHBoc	1k	2k	97.8	95.3

[a]Determined by GC analysis using styrene as an internal standard. [b]Determined by chiral HPLC analysis. [c]The average of three experiments. [d]Determined after lactone ring-opening with benzyl amine. [e]The purity of cyclobutanone **1f** was 72.4%. The lower ee may be reflecting the impurities in this substrate.

The foregoing substituent effect that emerged from the structure–selectivity studies can be explained by the H-bonding interactions between the catalyst and the substrate (Figure 3). Thus, the enantioselectivity improved only when the lone pair donors were placed at this position (Table 1, entries 8–11). We previously proposed[15] that the H-bonding network plays an important role in creating the chiral environment in this system.[6,24] Mechanistically, the enantioselection step for the BV reaction is the rearrangement step of the Criegee intermediate, in which the stereoelectronic requirement is that the HOMO of the migrating C–C bond and the LUMO of the breaking O–O bond be

antiperiplanar.[17,18] Although our assumption was that the substrate carbonyl group may be activated by the protonated quinuclidine, after the formation of the Criegee intermediate, the peroxide proton should also be captured by the carbonyl group. The regenerated ammonium may interact with an electron-donating substituent at this position and further stabilize the conformation. In contrast, a substituent at the *para*-position was unlikely to reach this position, which is consistent with the results showing no apparent trend.

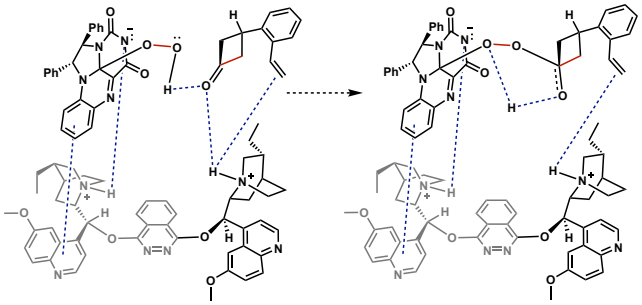
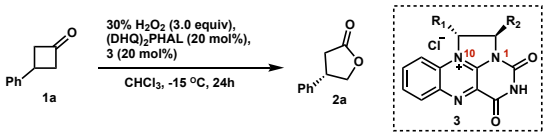


Figure 3. H-bonding interactions between the substrate and catalyst as a possible explanation for the *ortho*-substituent effect of 3-phenylcyclobutanone.

Next, the correlation between the enantioselectivity and the structure of flavin derivatives was studied (Table 2).[25] We were most interested in the effect of the two stereocenters on the chiral bridge since removing both substituents would diminish selectivity and substantially decrease the reactivity (entries 1 and 2).[26]

We found that removing one substituent next to N^1 had a slight effect on the conversion and was sufficient to retain the benchmark selectivity (entries 1 and 3). Based on this finding, we focused on introducing various substituents to the remaining stereocenter next to N^{10} (entries 3–11). Excluding the thiobenzyl group (entry 11), most substituents showed increased selectivity (entries 3–10). Catalysts bearing benzyloxy and *tert*-butoxymethyl substituents showed particularly high selectivity (entries 8 and 9).

Table 2. Influence of the catalyst structure on selectivity using 3-phenylcyclobutanone

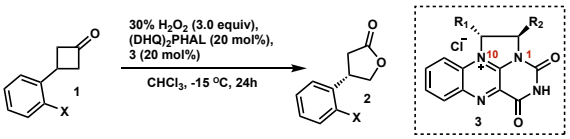


Entry	3	R^1	R^2	Conv.[a] (%)	ee[b] (%)
1	3a	Ph	Ph	96.8	88.6[c]
2	3b	H	H	29.1	70.1
3	3c	Ph	H	86.1	88.8
4	3d	Bn	H	99.7	90.8
5	3e	^{i}Pr	H	92.3	90.5
6	3f	1-NpCH$_2$	H	97.2	91.3
7	3g	2-NpCH$_2$	H	89.3	88.4
8	3h	^{t}BuOCH$_2$	H	97.5	93.0
9	3i	BnOCH$_2$	H	97.8	92.2
10	3j	BnOMeCH	H	94.9	88.5
11	3k	BnSCH$_2$	H	59.1	45.7

[a]Determined by GC analysis using internal standard. [b]Determined by chiral HPLC analysis. [c]The average of three experiments.

Because higher selectivity was achieved using mono-substituted catalysts, some of these catalysts were tested using *ortho*-substituted 3-arylcyclobutanones to determine whether their selectivity could be further improved (Table 3). As expected, most flavin catalysts consistently provided better selectivity when using these substrates (entries 1–6), except for flavin **3d**, for which the results were comparable. Notably, the reaction using a combination of catalyst **3h**, which showed the best selectivity using the benchmark substrate **1a**, and substrate **1k** which showed the highest selectivity using catalyst **3a**, demonstrated a selectivity of >99% ee (entry 6). This result is among the highest selectivities achieved for BV reactions using small-molecule catalysts.[4]

Table 3. Influence of the catalyst structure on selectivity using ortho-substituted 3-aryl cyclobutanones

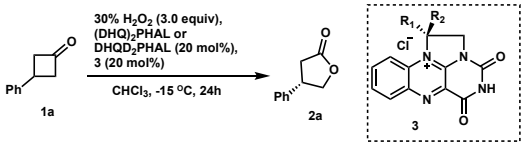


Entry	3	X	R^1	R^2	Conv.[a] (%)	ee.[b] (%)
1	3a	Br	Ph	Ph	99.2	94.5
2	3b	Br	H	H	32.5	73.2
3	3c	Br	Ph	H	99.6	94.4
4	3d	Br	Bn	H	99.8	90.5
5	3e	Br	*i*Pr	H	98.8	94.2
6	3h	NHBoc	*t*BuO	H	98.8	>99

[a]Determined by GC analysis using an internal standard. [b]Determined by chiral HPLC analysis.

A matched/mismatched relationship between the flavin derivative and the alkaloid dimer was confirmed by testing the reaction with **3c** and its enantiomer **3l** as well as $(DHQ)_2PHAL$ and its pseudo-enantiomer $(DHQD)_2PHAL$ in all four combinations (Table 4). As observed previously, **3c** and $(DHQ)_2PHAL$ was the matched combination, and the pseudo-enantiomer combination yielded the antipode product with comparable conversion and opposite selectivity (entries 1 and 4). The mismatched combination showed a slight decrease in the conversion and selectivity for the same antipode delivered by the same alkaloid enantiomer. Thus, chirality induction mostly arose from the chirality of the alkaloid dimer and not from the flavin derivatives. This observation is consistent with our previous study using a flavin catalyst and a cinchona alkaloid.[15]

Table 4. Matched/mis-Matched combination of the flavinium and alkaloid dimer.

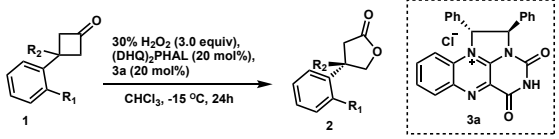


Entry	Alkaloid	3	R^1	R^2	Conv.[a] (%)	ee[b] (%)
1	$(DHQ)_2PHAL$	3c	Ph	H	86.1	88.8
2	$(DHQ)_2PHAL$	3l	H	Ph	69.1	68.2
3	$(DHQD)_2PHA$	3c	Ph	H	63.0	–45.2[c]
4	$(DHQD)_2PHA$	3l	H	Ph	82.4	–74.6[c]

[a]Determined by GC analysis using an internal standard. [b]Determined by HPLC analysis. [c]*R* configuration.

After establishing the optimal reaction conditions for 3-aryl cyclobutanones, we examined their applicability to 3,3-disubstituted cyclobutanones bearing prochiral quaternary carbons (Table 5). A significant decrease in enantioselectivity and conversion was observed when a methyl group was introduced at the γ position of cyclobutanone (entries 1 and 2). To improve the selectivity, the corresponding cyclobutanones with *ortho*-substituents were tested (entries 3–5). Interestingly, a reversal in selectivity was observed in all cases, even when a group with no lone-pair donor was introduced (entry 5). A matched/mismatched correlation was also examined for substrate **1m** and was confirmed to be the matched case for this substrate.[20]

Table 5. Substrates with quaternary stereocenters



Entry	R^1	R^2	1	2	Conv.[a] (%)	ee[b] (%)
1	H	H	1a	2a	96.8	88.6[c]
2	H	Me	1l	2l	30.2	56.4
3	Br	Me	1m	2m[c]	34.0	–43.4[d]
4	vinyl	Me	1n	2n[c]	27.7	–51.8[d]
5	ethyl	Me	1o	2o[c]	27.5	–20.4[d]

[a]Determined by GC analysis using an internal standard. [b]Determined by chiral HPLC analysis. [c]The average of three experiments. [d]*R* configuration.

The lack of reactivity for this series of substrates presumably reflects either or both the electronic and steric effects of the methyl group, which slows down the peroxide addition to the carbonyl step, which was confirmed as the RDS.

The reversal of selectivity in this reaction could proceed in two different ways. The first involves peroxide addition from the face opposite to the original substrate. If all elements are identical, bond migration happens with the opposite bond. However, this contradicts the fact that this reversal occurs only in substrates with *ortho*-substituents. Alternatively, it could take place when the breaking O–O bond is twisted by 90°, such that this bond (or the LUMO of the bond) is lined up with the opposite C–C bond. We believe that the steric repulsion between the *ortho*-substituent and the quinicline portion of the alkaloid may be the cause.

Conclusion

In summary, the previously reported asymmetric BV reaction was revisited to broaden its scope. First, kinetic analysis showed that the RDS was the peroxy addition to the carbonyl group rather than the more common rearrangement step. Next, by examining the correlation between the enantioselectivity and the catalyst structure, only one stereocenter was found to be critical for achieving high stereoselectivity. This observation led to the discovery of a new, simpler catalyst with improved selectivity. By positioning a lone pair donor on the substrate, the selectivity was further enhanced to 95% ee using the original catalyst or >99% ee with the new catalyst, which is among the highest selectivities achieved for the BV reaction using a small-molecule catalyst. However, this system was applicable only to monosubstituted cyclobutanone substrates.

Our results show the power of mechanistic investigations to broaden the scope of catalytic systems and aid in catalyst design. We are currently exploring methods to further expand the applicability of our catalyst and demonstrate its use.

Supporting Information

Experimental procedures and spectral data for new compounds. This material is available free of charge on the ACS Publications website as Electronic Supporting Information (PDF).

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Author Contributions

J.F. performed most of the experiments and prepared the ESI; E.S. performed part of the experiments and ESI. K.Y. supervised and directed the study. The manuscript was written with contributions from all the authors. All the authors approved the final version of the manuscript.

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(19) This 1:1 interaction was further confirmed in this study with Jobs plot analysis, see the ESI.

(20) See the ESI.

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(24) In the study by Miller and coworkers, H-bonding network played a cruicial role in their stereoselective BV oxidation using chiral phosphothreonine embedded peptide catalyst. See reference (6).

(25) The structure of the dimeric cinchona alkaloid was also re-examined, however no improvement of selectivity was seen. See the ESI.

(26) We think the decrease in selectivity was caused by, at least partially, the poor solubility of **3b**.

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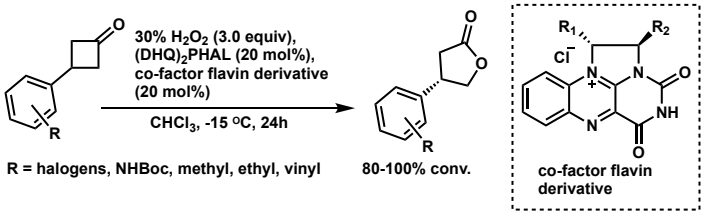

89%ee ($R_1 = R_2$ = Ph; R = H)
93%ee ($R_1 = CH_2OtBu$, R_2 = H; R = H)
95%ee ($R_1 = R_2$ = Ph; R = *o*-NHBoc)
>99%ee ($R_1 = CH_2OtBu$, R_2 = H; R = *o*-NHBoc)