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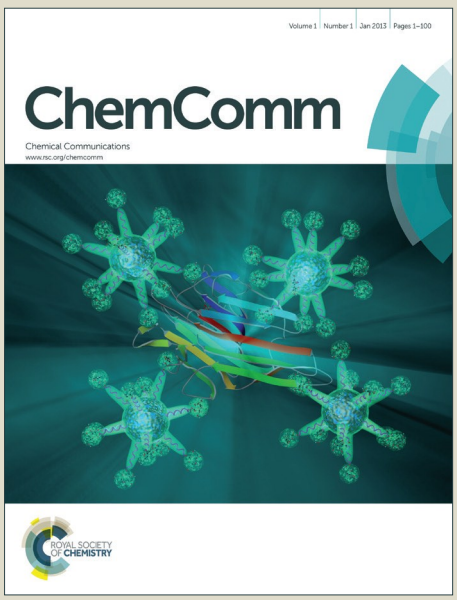

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Self-Assembled Ion–pair Organocatalysis – Asymmetric Baeyer-Villiger Oxidation Mediated by Flavinium-Cinchona Alkaloid Dimer

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Abstract: An ion–pair catalyst generated by assembly of a chiral flavinium and a cinchona alkaloid dimer for use in asymmetric Baeyer–Villiger oxidation is presented. Ion–pair formation is essential for enhancing the catalytic activity and stereoselectivity. The catalyst is applicable to structurally diverse 3-substituted cyclobutanones, providing good to excellent enantioselectivities (up to 98:2 e.r.). This study provides the first example of self-assembly of a flavin derivative and a base to form a chiral reaction site that enables a highly stereoselective reaction to occur.

Recently, there has been emerging interest in the use of supramolecular catalysts, i.e., catalysts formed by self-assembly of small molecules through non-covalent interactions, in asymmetric synthesis.[1] This modular system has the advantage of facile catalyst preparation, which enables rapid access to compound libraries. It is particularly useful for asymmetric reactions in which a chiral component and a catalytically active module can be assembled together. Here, we present our study in which a catalytically active flavinium species was paired with a chiral base through ionic assembly,[2] and successfully used to achieve high stereocontrol in Baeyer–Villiger (BV) oxidation.

Riboflavin (Figure 1) is a central component of a family of major cofactors that are involved in many flavoenzymes that mediate redox transformations.[3] Its simpler synthetic derivatives have been studied in recent decades, providing new catalysts for diverse oxidation reactions.[4, 5] These catalysts use molecular oxygen or hydrogen peroxide as an end-oxidant, making them attractive leads for atom-economical and environmentally benign oxidation catalysts.

The BV oxidation is one such oxidation reaction that is mediated by flavin derivatives.[6] These derivatives show high catalytic activities and unusual chemoselectivities,[7] but limited stereoselectivities.[4] With the exception of biocatalyzed reactions,[8] catalytic BV oxidations using sustainable oxidants and reaching high regio- and stereoselectivities are still challenging, and are extensively researched.[9]

The difficulty in attaining asymmetric control using flavin derivatives stems from their conformational changes; they cycle between a "bent (chiral)" form and a "planar" form during the redox cycle.[10] Previously developed catalysts were designed to block one face of the heterocycle with a covalently bound chiral component. The substrate therefore approaches and reacts on the opposite face from the chiral component, resulting in little chirality transfer. These catalysts still induce a modest level of stereoselectivity for some aromatic substrates, because of inherent π–π interactions between the catalyst and the substrates that control their binding orientation.[11]

We[12] and others[13] have designed and prepared a series of chiral flavinium salts **1**–**5**, in optically pure forms (Figure 1). These catalysts show high catalytic activities but marginal stereoselectivities in the BV reaction. We hypothesized that addition of a basic co-catalyst that interacts with these molecules through acid–base reactions could aid the transfer of chiral information to the substrate. Our initial attempts showed that addition of a tertiary amine to the reaction mixture significantly enhanced both the reaction conversion and stereoselectivity, leading us to embark on a full screening program.

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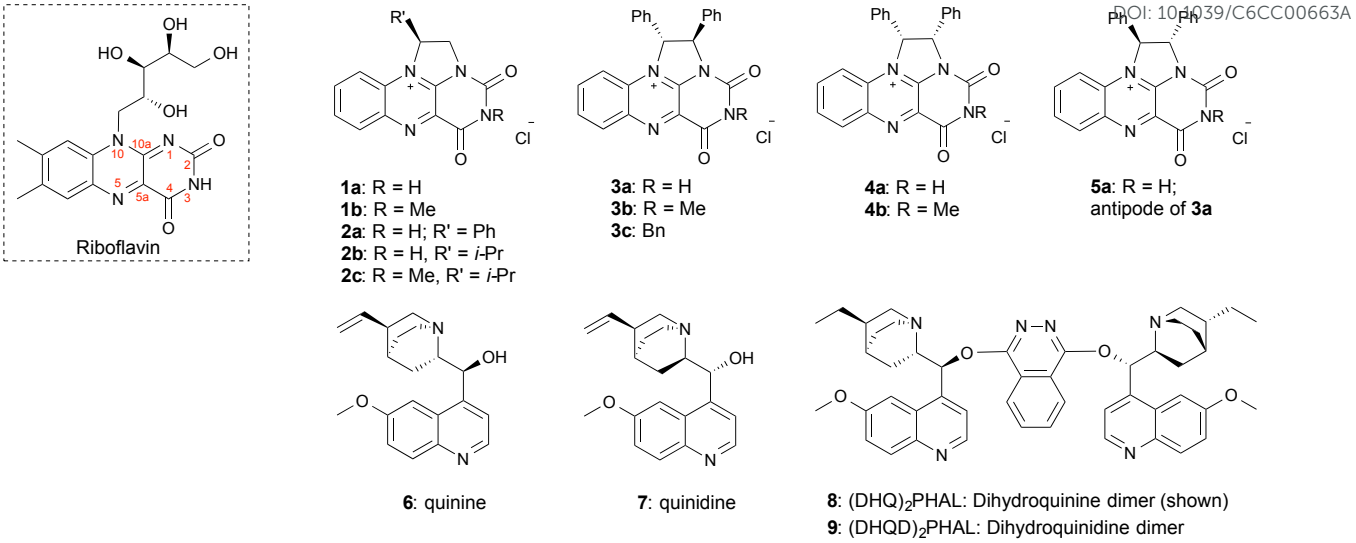
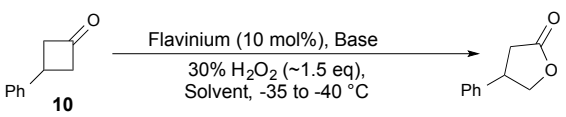


Figure 1. The structures of synthetic flavinium species, cinchona alkaloids and their derivatives.

The co-catalyst screening was performed by simply mixing flavinium **3a** with various commercially available amine bases (Table 1). A cinchona alkaloid, namely quinine (**6**) or quinidine (**7**), (Figure 1) provided the best selectivity among the examined bases (Table 1, entries 1–5),[12] therefore our early studies were performed using these bases. Neither the flavinium catalyst nor the base alone gave high conversion or enantioselectivity (entries 1 and 2). Although **6** and **7** are considered to be quasi-enantiomeric, each of them in combination with **3a** gave rise to (*S*)-γ-lactones (entries 4 and 5). Similarly, replacing **3a** with its *cis* diastereomer **4a** or with achiral flavinium **1a** also favored formation of the same (*S*) enantiomer when used with **7** (entries 9 and 10). However, a combination of **5a** (antipode of **3a**) and **6** or **7** produced (*R*)-γ-lactones with low selectivities (entries 9 and 10). The combined effect of the flavinium and the base therefore contributes to the observed chirality transfer. Further studies indicated that as little as 2 equiv of base relative to the flavinium catalyst was sufficient to produce the optimal effect (entries 4 and 6). Screening was performed at –35 to –40 °C showing a reasonable reaction rate. A survey of solvents indicated that ethyl acetate, acetonitrile, and chlorinated solvents performed best, providing similar selectivities in most cases, whereas polar alcoholic solvents enhanced the reaction rate but decreased the selectivity (entries 4, 11 and 12).[12] This solvent effect differs from those reported in previous studies of flavinium–catalyzed asymmetric oxidations, in which (polar) alcoholic solvents alone or in mixtures with other solvents were often favored, suggesting that the reaction in our system is mechanistically distinct from those in other systems in which π–π interactions play a major role.[11, 14]

Table 1. Asymmetric BV oxidation of 3-phenylcyclobutanone



catalyzed by a flavin derivative and a base[a]

Entry	Cat.	Base [mol%]	Solvent	Conv. [%]	e.r. [*S*/*R*][e]
1	**3a**	–	MeCN	na	51:49
2	–	**7** (100)	MeCN	12.4	52:48
3	**3a**	Et_3N (100)	MeCN	60.5	62:38
4	**3a**	**7** (100)	MeCN	49.2[b]	74:26
5	**3a**	**6** (100)	MeCN	16.9	77:23
6	**3a**	**7** (20)	MeCN	21.3	74:26
7	**4a**	**7** (20)	MeCN	3.1	53:47
8	**1a**	**7** (20)	MeCN	13.6	59:41
9	**5a**	**7** (20)	MeCN	12.0	43:57
10	**5a**	**6** (20)	MeCN	13.3	39:61
11	**3a**	**7** (100)	DCM	22.7	67:33
12	**3a**	**7** (20)	TFE[d]	94.6	51:49
13	**3c**	**7** (20)	MeCN	6.8	48:52
14	**5a**	**7**[c] (20)	MeCN	1.7	48:52

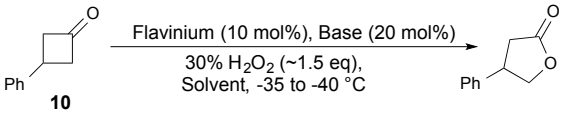
[a] Conditions: 0.1 mmol scale; [**10**] = 100 mM; [flavinium] = 10 mM; [base] = 20–110 mM; solvent (1 mL); 30% H_2O_2 (1.1–1.5 equiv.); –35 to –40 °C; 15–24 h; [b] 83% conversion after 50 h. [c] *N*-benzylquinidinium salt. [d] Use of MeOH led to low conversion and selectivity as well as acetal by-product formation. [e] Determined by chiral HPLC analysis.

Ion–pair formation between flavinium and the base was confirmed by the following observations: use of N^3-protected **3c** (Table 1, entry 13) or *N*-benzylquinidinium (Table 1, entry 14) decreased both the enantioselectivity and reaction conversion; Job plots based on a UV-vis spectroscopic study of **3a** and **7** showed clear 1:1 interactions;[12] on mixing, a downfield shift of all the signals and disappearance of the N^3 proton of **3a** and an upfield shift of the base were seen in the ^{1}H-NMR spectra. Presumably, the role of the second equivalent of base with respect to the catalyst is to deprotonate hydrogen peroxide, which promotes the rate-limiting hydroperoxyflavin formation.[15]

We speculated that use of a dimeric base might further promote this reaction through the proximity effect. Commercially available dihydroquinidine (DHQD) and dihydroquinine (DHQ) dimers were

examined in combination with either flavinium **3a** or **5a** (Table 2). Among the commercial dimers examined, phthalimide (PHAL) dimers (Figure 1) have shown the best selectivity.[12] There are clear indications of "matched" dimers for **3a** being DHQ dimers and that of antipode **5a** being DHQD dimers. Unlike the flavinium catalysts with a monomeric alkaloid, a combination of **3a** or **5a** with the respective "matched" dimer behaved similarly to enantiomers and gave rise to the opposite antipode, with comparable selectivity (entries 2 vs 8; 10 vs 11), whereas combination with the "mismatched" dimer resulted in lower selectivity (entries 1 vs 5; 6 vs 7)). In addition, the use of $CHCl_3$ as the solvent greatly improved the selectivity (entry 4 vs 1–3). Finally, by raising the reaction temperature to –15 °C, the reaction conversion increased to >90% after 24 h (entry 9). As expected, the stoichiometry of the dimer could be reduced to 1 equiv relative to the base without sacrificing the reaction selectivity (entry 10).

Table 2. Asymmetric BV oxidation of 3-phenylcyclobutanone catalyzed by a flavin derivative and a base[a]



Entry	cat.	Base	Solvent	Temp. [°C]	Conv. [%]	e.r. [*S*/*R*][e]
1	**3a**	**8**	MeCN	–38	33.7	72:28
2	**3a**	**8**	EtOAc	–38	27.6	74:26
3	**3a**	**8**	DCM	–38	21.5	80:20
4	**3a**	**8**	$CHCl_3$	–38	16.6	92:8
5	**3a**	**9**	MeCN	–40	28.5	53:47
6	**5a**	**8**	DCM	–38	7.4	49:51
7	**5a**	**9**	DCM	–38	18	24:76
8	**5a**	**9**	EtOAc	–35	9.4	25:75
9	**3a**	**8**	$CHCl_3$	–15	92	94:6
10	**3a**	**8**[b]	$CHCl_3$	–15	86.2[c]	94:6
11	**5a**	**9**	$CHCl_3$	–15	78[d]	10:90

[a] Conditions: 0.1 mmol scale; [**10**] = 100 mM; [flavinium] = 10 mM; [base] = 20 mM; solvent (1 mL); 30% H_2O_2 (1.1–1.5 equiv.); 24 h. [b] 10 mol% of the base was used. [c] 42 h (70% conversion after 24 h). [d] 72% isolated yield. [e] Determined by chiral HPLC analysis.

Our working model of the transition state that explains the selectivity is illustrated in Figure 2. Initially, **3a** binds to either side of the dimer with a selective orientation set by π–π and ionic interactions. This binding mode also explains the matched combination of **3a** and **8**, where no steric interference occurs between the phenyl group next to N^1 and the ethyl group of DHQ. Subsequently, the other base deprotonates hydrogen peroxide, which attacks the iminium of **3a** to form hydroperoxy species.[16] Hydroperoxide then attacks the less-hindered side of the substrate (possibly activated by hydrogen bonding with ammonium), which leads to formation of a Criegee intermediate (shown) that undergoes rearrangement.

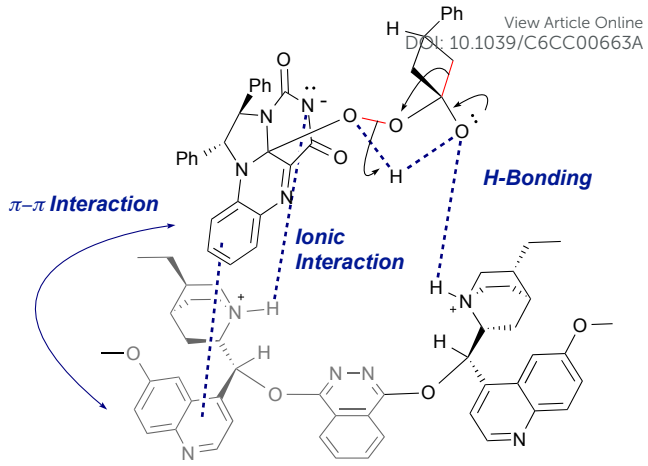
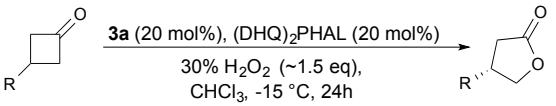


Figure 2. Proposed transition state of BV oxidation of 3-phenylcyclobutanone catalyzed by **3a** and $(DHQ)_2PHAL$ (**8**).

Next, the scope and limitation of the optimized conditions were explored using a series of 3-substituted cyclobutanones (Table 3).[17] As expected, 3-naphthylcyclobutanone (**11**) provided comparable selectivity to that of 3-phenylcyclobutanone (**10**) (entries 1 vs 2). Gratifyingly, substrates with no aromatic components proximal to the reaction center gave good to excellent selectivities (entries 3–6), except for 3-*tert*-butylcyclobutanone (**16**) that gave fair selectivity (entry 7). In particular, *N*-Boc-aminocyclobutanone (**14**) provided excellent selectivity (entry 5, 98:2 e.r.), the best of all the previously developed flavinium catalysts. It is of note that the product of this substrate, a β-amino acid derivative, is an important intermediate in a number of pharmaceutical and natural product syntheses.[18] The utility of the method was demonstrated by conducting the oxidation with **10** on a 0.3 g scale; the reaction provided the γ-lactone in 98.5:1.5 e.r. and 52% yield after a single recrystallization.[12, 19] This product and the related 3-aryl-γ-butyrolactones are precursors of clinically important $GABA_B$ receptor agonists.[20]

Table 3. Scope and Limitation of **3a**-Catalyzed Asymmetric Baeyer–Villiger oxidation of cyclobutanones[a]



Entry	R =	Conv. (%)	Yield (%)[b]	e.r. [*S*/*R*][c]
1[i]	Phenyl (**10**)	97	87	95:5
2	1-Naphthyl (**11**)	92	92	97:3
3	$BnOCH_2$- (**12**)	89	85	82:18
4	BnOOC- (**13**)	70	58	11:89[f]
5	BocNH- (**14**)	100	92	2:98[d], [f]
6[j]	Cyclohexyl (**15**)	86	85	67:33[e], [g]
7	*tert*-Butyl (**16**)	–	80	57:43[h]

[a] Conditions: 0.1 mmol scale; [substrate] = 100 mM; [**3a**] = 20 mM; [**8**] = 20 mM; $CHCl_3$ (1 mL); –15 °C; 24 h. [b] Isolated yield. [c] Determined by chiral HPLC analysis. [d] Determined by optical rotation. [e] Determined after

conversion to hydroxyl benzylamide derivative.[12] [f] Note the change in substituent priorities in the Cahn-Ingold-Prelog system. [g] Ratio: (–/+). [h] The configuration was not determined. [i] Also conducted on 0.3 g scale using 10 mol% **3a** that gave rise to 87% yield after 64 h (92:8 e.r.).[12] [j] 88 h.

Conclusions

We have developed an ion–pair catalyst derived by in situ assembly of a chiral flavinium and a cinchona alkaloid dimer for use in asymmetric BV reactions. Our observations confirmed acid–base interactions between the flavinium and the dimer by ion–pairing, presumably leading to formation of an artificial chiral reaction site, and enabling the reaction to proceed with high stereoselectivity. Our study represents the first example of use of a supramolecular assembly for controlling the stereoselectivity of a flavinium-catalyzed reaction. We believe that this approach can be extended to other reactions catalyzed by cofactors or redox-active small molecules, and widen the scope of their applications.

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