Organocatalysis

An Aerobic, Organocatalytic, and Chemoselective Method for Baeyer–Villiger Oxidation**

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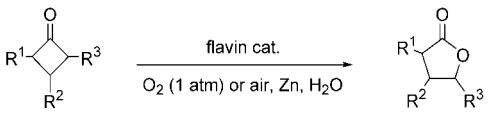
Direct incorporation of molecular oxygen into organic substrates has recently attained widespread interest as a forward-looking technology for mild and green molecular transformations.[1] One subject of great urgency is the development of organocatalytic methods.[2] These methods should facilitate new strategies that provide an alternative to the conventional unsustainable processes, which use oxygenated transition-metal complexes.[3] A limited number of organocatalytic aerobic oxidations has been reported. These reactions involve a multistep radical-transfer process from O_2 by using semistable organic radicals[4] and photoinduced electron-transfer systems.[5]

A new method for organocatalytic aerobic oxidation of heteroatomic organic compounds[6] was recently developed by simulating the enzymatic function of microsomal FAD-containing monooxygenase.[7] As this new system includes the direct conversion of molecular oxygen into synthetic flavin hydroperoxides, which are highly reactive towards various organic substrates,[8,9] the principle of the reaction should enable sustainable aerobic oxidation chemistry with high selectivity and controllability. As a variation on this system, we describe herein the first organocatalytic aerobic method of the Baeyer–Villiger oxidation, which exhibits rare and high chemoselectivity for this nucleophilic oxidation [Eq. (1)].

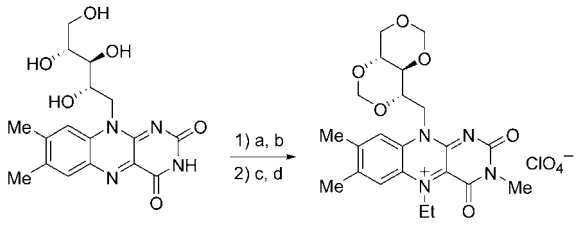
The Baeyer–Villiger oxidation is a special class of nucleophilic oxidative transformation that proceeds specifically with peroxides and peracids through noncatalytic[10] and



(1)

catalytic reactions.[9a,b,11,12] The aerobic method for Baeyer–Villiger oxidations is limited to reactions that involve the in situ generation of peracids from aldehydes by a transition-metal-mediated radical-chain process with molecular oxygen.[12] Thus, there has been no exploitation of organocatalytic methods and no molecular design of the catalysts. Furthermore, one of the unsolved problems of catalytic Baeyer–Villiger oxidations is the lack of chemoselectivity for nucleophilic oxidations over electrophilic oxidations. There is no report of a chemoselective catalytic method in the presence of heteroatomic moieties. This omission is due to the strong electrophilic character of their peroxo intermediates. Although catalytic methods that resist epoxidation have been reported,[13] the strength of the oxidant usually results in electrophilic oxidation of heteroatomic compounds.[14] The application of our new strategy has meant that we can overcome these long-unsolved problems to produce a selective, sustainable, and highly practical method.

The catalytic activity of a series of flavin compounds was examined for the aerobic oxidation of 3-(2-naphthyl)cyclobutanone (**1**) with zinc dust (1.5 equiv) in CH_3CN/EtOAc/H_2O (8:1:1, v/v) under oxygen (1 atm). Unlike electrophilic oxidations that need specific flavins,[6] the present nucleophilic oxidation exhibits high catalytic activities for a variety of 5-ethylisoalloxazinium perchlorates that bear 3,10-dimethyl, 3,7,8,10-tetramethyl, or 3-methyl-10-phenyl functionalities. A new type of flavin catalyst—5-ethyl-3-methyl-2′,4′:3′,5′-di-*O*-methyleneriboflavinium perchlorate ([DMRFlEt]$^+$[ClO_4]$^-$), which can be readily derived from commercially available vitamin B_2 (Scheme 1)—also shows



Scheme 1. Synthesis of [DMRFlEt]$^+$[ClO_4]$^-$: a) HCHO, HCl, 60 °C, 3 days; b) CH_3I, K_2CO_3, DMF, RT, overnight; c) CH_3CHO, $NaBH_3CN$, $Na_2S_2O_4$, DMF, 60 °C, 2 h; d) $NaNO_2$, $HClO_4$, $NaClO_4$, 0 °C.

high catalytic activity, comparable with that of 3,7,8,10-tetramethyl flavins. The preparation is quite easy compared with the multistep methods that are required for conventional flavin catalysts.[15] Zinc dust acts as an efficient reductant for the activation of the flavin catalysts. Water is an essential proton source for this system, and the use of water-containing solvent mixtures, such as CH_3CN/EtOAc/H_2O, results in the production of the corresponding lactones.

Representative results for the aerobic Baeyer–Villiger oxidation catalyzed with [DMRFlEt]$^+$[ClO_4]$^-$ are summar-

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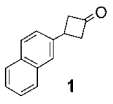
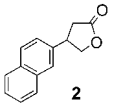
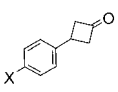
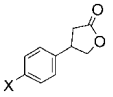
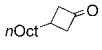
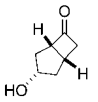
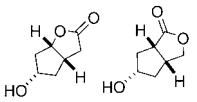
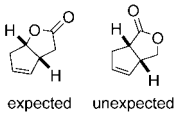
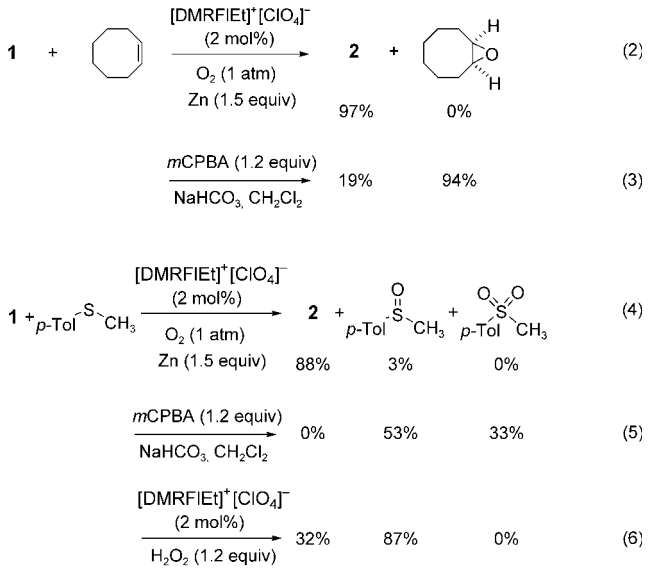
Table 1: Aerobic Baeyer–Villiger oxidation of ketones with $[DMRFlEt]^+[ClO_4]^-$.

Entry	Substrate	Product	*t* [h]	Yield [%]
1			7	94
2			7	91[a]
3	**1**	**2**	12	88[b]
4 (X = H)			4	78
5 (X = F)			4	80
6 (X = Cl)			6	84
7			4	95[c]
8			8	86 (72:28)[d]
9		 expected unexpected	4	83[e] (57:43)[e]

[a] 5-Ethyl-3,7,8,10-tetramethylisoalloxazinium perchlorate (2 mol%) was used instead of $[DMRFlEt]^+[ClO_4]^-$. [b] The reaction was performed in air. [c] Zinc dust (2.0 equiv) was used. [d] $[DMRFlEt]^+[ClO_4]^-$ (4 mol%) was used. [e] Regioselectivities of the expected and unexpected lactones were determined by ^{1}H NMR spectroscopy.

ized in Table 1. Various substituted cyclobutanones can be converted into the corresponding lactones efficiently when a 1.0 M solution of the substrate is stirred in a mixture of $CH_3CN/EtOAc/H_2O$ (8:1:1 v/v) at 60 °C in the presence of the catalyst (2 mol%), zinc dust (1.5 equiv), and oxygen (1 atm). The products can be isolated simply by filtration and extraction because the reactions are generally clean and are accompanied only by the formation of insoluble $Zn(OH)_2$. The reaction can be also conveniently performed in air (Table 1, entry 3). Similar treatment of bicyclic ketones gave a mixture of expected and unexpected lactones (Table 1, entries 8 and 9), both of which are important synthetic intermediates for various biologically active compounds such as prostaglandins and pheromones.[16b] Baeyer–Villiger monooxygenase, which is also an important class of flavoenzyme, also exhibits similar selectivity,[16] whereas conventional synthetic methods generally give an expected lactone by the ordinary electronic limitations of the Criegee rearrangement.[10,11]

One important feature of the new method is the chemoselective oxidation of ketones in the presence of other reactive functionalities. Indeed, the flavin-catalyzed reaction of an equimolar mixture of **1** and cyclooctene gave exclusively the Baeyer–Villiger product **2**, without the formation of cyclooctene oxide [Eq. (2); Scheme 2]. Similar treatment with methyl *p*-tolyl sulfide also afforded **2** with extraordinarily high selectivity [Eq. (4)]. The intramolecular version of such a preference is also exhibited in entries 8 and 9 of Table 1, in which highly reactive cyclopentanol and cyclopentene moieties are completely tolerated under the stated conditions, as they are with an enzymatic oxidation.[16b] This selectivity is rare under artificial oxidative conditions,[14] and this is the first



Scheme 2. Performance of $[DMRFlEt]^+[ClO_4]^-$ in Baeyer–Villiger reactions of **1**. *m*CPBA = *meta*-chloroperbenzoic acid.

chemoselective catalytic method for nucleophilic oxidation in preference to oxidation at the heteroatom. Even the use of *m*CPBA, a specific oxidant for the Baeyer–Villiger oxidation, shows unsatisfactory results, as exemplified in Equations (3) and (5) (Scheme 2). Furthermore, the flavin-catalyzed Baeyer–Villiger oxidation with H_2O_2[9a,b] does not exhibit chemoselectivity for nucleophilic oxidations, as shown in the preferential formation of the sulfoxide [Eq. (6)].

The reaction can be rationalized by the formation and subsequent oxidative transformation of the reactive 4a-peroxyflavin intermediate, as already described for the aerobic oxidation of heteroatomic compounds.[6] The flavin cation, $FlEt^+$, undergoes a two-electron reduction with zinc to afford the reduced flavin, $FlEt^-$.[17] The $FlEt^-$ intermediate and its semiquinone radical precursor, FlEt•, have been confirmed by the UV/Vis analysis of the control experiments of $[DMRFlEt]^+[ClO_4]^-$ with zinc dust.[18] Incorporation of molecular oxygen into $FlEt^-$ affords the flavin 4a-peroxy anion $FlEtOO^-$,[19] which effects nucleophilic oxidation of ketones to afford the corresponding lactones. Dehydrogenation of the resulting FlEtOH regenerates $FlEt^+$ to complete the catalytic cycle. Chemoselective Baeyer–Villiger oxidations in this process can be ascribed to the neutrality of the reaction media and the highly nucleophilic character of the anionic peroxy intermediate,[20] which forms under the influence of the zinc counterion. Indeed, dramatic loss of the chemoselectivity has been observed when acidic CF_3CH_2OH was employed as one component of the solvent mixture. Research is currently underway to elucidate the mechanism and to apply the reaction to other systems.

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