Biomimetic flavin-catalysed reactions for organic synthesis

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Organic & Biomolecular Chemistry

REVIEW

Biomimetic flavin-catalysed reactions for organic synthesis

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Using simple riboflavin related compounds as catalysts biomimetic, catalytic oxidation of various substrates with hydrogen peroxide or molecular oxygen can be performed selectively under mild conditions. The principle of these reactions is fundamental and will provide wide-scope for environmentally benign future practical methods.

Introduction

Oxidation is one of the most fundamental reactions in organic synthesis.[1] Owing to the current need to develop technology that is environmentally benign with respect to efficient, highly selective formation of products, many aspects must be considered in the search for new catalytic oxidation reactions. Simulation of the functions of enzymes such as flavoenzymes and Cytochrome P-450 using simple organocatalysts and transition metal catalysts may lead to the discovery of biomimetic, catalytic oxidation reactions.[2] Flavin-catalysed oxidation is one of the attractive approaches for designing environmentally benign catalytic oxidation reactions with organocatalysts.[2a,3] The important flavins in nature are riboflavin, flavin mononucleotide (FMN), and flavin adenine dinucleotide (FAD) (Scheme 1), whose functions are unique.[4] Flavin-containing enzymes have three major functions; as a member of the monooxygenase family, as a member of the oxidase family, and as a member of the electron-transferase family. Flavin-dependent monooxygenases are biological agents responsible for the oxidation of substrates by the activation of molecular oxygen to transfer oxygen atoms to the substrates from molecular oxygen, while oxidases are dehydrogenating agents (Scheme 2).[4a]

By simulation of the functions of flavoenzymes, environmentally benign catalytic methods for oxidation of various substrates with H_2O_2 or molecular oxygen under mild

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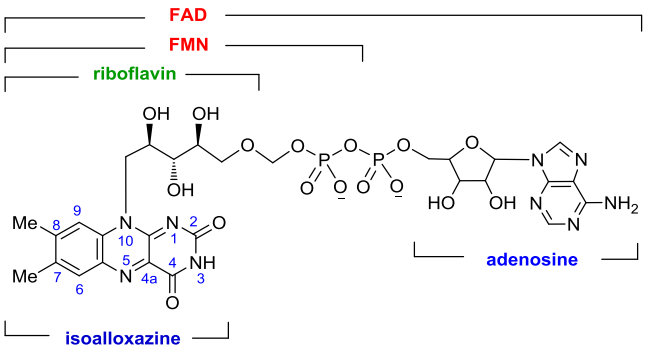
Hiroki Iida

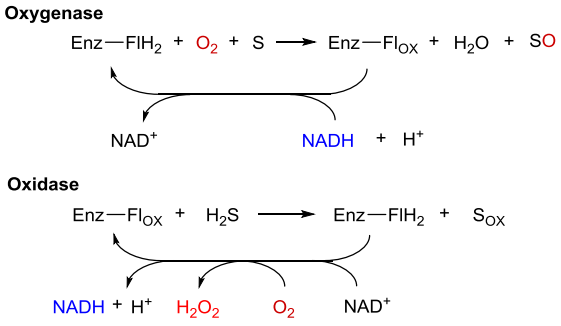
Hiroki Iida received his BSc (2000), MSc (2002) and PhD (2005) degrees from Osaka University under the supervision of Prof. Shun-Ichi Murahashi, Yasushi Imada and Takeshi Naota. After postdoctoral studies with Prof. Michael J. Krische at the University of Texas at Austin, he joined the faculty at Nagoya University as an assistant professor in 2007, working with Prof. Eiji Yashima. Since 2014, he has been an associate professor at Shimane University, where his group is developing biomimetic organocatalysts and chiral functional polymers and supramolecules.

Yasushi Imada

Yasushi Imada received his BSc (1981), MSc (1983) and Ph D (1991) degrees from Osaka University under the supervision of Prof. Shun-Ichi Murahashi. He joined Osaka University as a research associate in 1985, and spent one year (1995–1996) with Prof. Howard Alper at the University of Ottawa as a postdoctoral fellow. In 1997, he was promoted to associate professor at Osaka University. Since 2012, he has been a professor at Tokushima University. His research interests involve the development of novel synthetic methods, in particular those focused on organocatalytic oxidation and asymmetric synthesis.



Scheme 1 Flavin coenzyme.



Scheme 2 Oxidation with flavoenzymes.

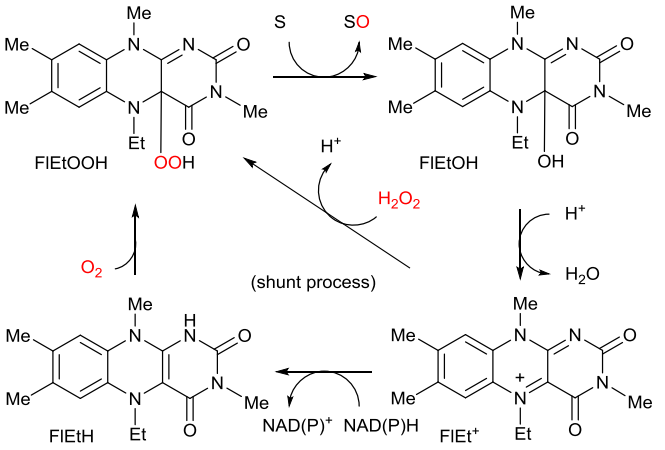
conditions have been explored. The background, principle, mechanism of the oxidative transformation, and application to organic synthesis will be discussed.

Simulation of the function of oxygenase

The catalytic cycle of the key structure of FAD-containing monooxygenase (FADMO) can be shown using its simple analogue 5-ethyl-3-methyllumiflavin (Scheme 3).

Shun-Ichi Murahashi

Shun-Ichi Murahashi received his PhD degree in 1967 from Osaka University under the supervision of Prof. Ichiro Moritani. He worked as a postdoctoral fellow with Prof. Ronald Breslow at Columbia University (1968-1970). He joined the faculty of Osaka University in 1963 and was appointed as a full professor in 1979. He moved to Okayama University of Science in 2001. He is the recipient of many prizes, including Chemical Society of Japan Award, Humboldt Research Award, Special Award in Synthetic Organic Chemistry, Japan Academy Prize, and The Order of the Sacred Treasure Gold Rays with Neck-Ribbon. His research interests are in the area of OMCOS chemistry, biomimetic oxidation, ruthenium and palladium chemistry, and C-H functionalization.



Scheme 3 Catalytic cycle of FADMO-catalysed oxidation using its simple analogue 5-ethyl-3-methyllumiflavin.

4a-Hydroperoxyflavin (FlEtOOH) participates in the monooxygenation of a substrate (S), to give an oxidized product (SO) and 4a-hydroxyflavin (FlEtOH), which undergoes dehydration to give oxidized flavin ($FlEt^+$). $FlEt^+$ is reduced by the hydrogen donor ZH (NAD(P)H) to give reduced flavin (FlEtH), which undergoes a reaction with molecular oxygen to generate FlEtOOH, to complete the catalytic cycle.[4]

In 1976, Bruice and co-workers succeeded in the isolation of FlEtOOH for the first time by treatment of the flavinium salt with H_2O_2[5a] or treatment of reduced FlEtH with molecular oxygen.[5b] They also demonstrated that the first electrophilic, stoichiometric oxygen transfer from the hydroperoxyflavin to a substrate.[6a] Thus, the 5-ethyl-3-methyllumiflavinium cation undergoes reaction with hydrogen peroxide to give 4a-hydroperoxylumiflavin, which shows powerful oxidation of sulfides and amines. The oxidation ability is very strong and 10^4 times stronger than H_2O_2.[6b] However, the catalytic recycling steps, that is, the conversion of 4a-hydroxyflavin FlEtOH to FlEtOOH were ambiguous.

In order to determine the reactivity of the 4a-hydroxyflavin FlEtOH a kinetic study of its reactivity was performed using the stopped-flow technique. It was shown that 4a-hydroxyflavin FlEtOH undergoes very fast pseudo-first-order ionization to generate a unique flavinium cation.[7] FlEtOH is readily transformed into FlEtOOH upon treatment with H_2O_2. Thus, the treatment of FlEtOH with 30% aqueous hydrogen peroxide in methanol gave FlEtOOH (82%). Considering the facile formation of FlEtOOH from FlEtOH, the oxidation of a substrate with H_2O_2 in the presence of a catalytic amount of FlEtOH should occur. The catalytic oxidation of a secondary amine was examined, because this reaction is closely related to the metabolism of amines. Indeed, the catalytic oxidation of dibutylamine with aqueous H_2O_2 in methanol gave *N*-butylidenebutylamine *N*-oxide. The catalyst is not limited to FlEtOH; FlEtOOH, FlEtH, $FlEt^+$ and 5-ethyl-1,5-dihydrotetraacetylriboflavin TAcFlEtH can be used as an active catalyst, although flavins that have no substituent at the 5(*N*) position such as 3-methyllumiflavin, riboflavin, and FMN are ineffective. It is noteworthy that FADMO, which has no substituent at the 5-*N* position, undergoes oxidation. This is

because complexation of Enz(4a-FlHOOH) with NAD(P)$^+$ retards the elimination of H_2O_2.[8]

Flavin-catalysed oxidation with H_2O_2

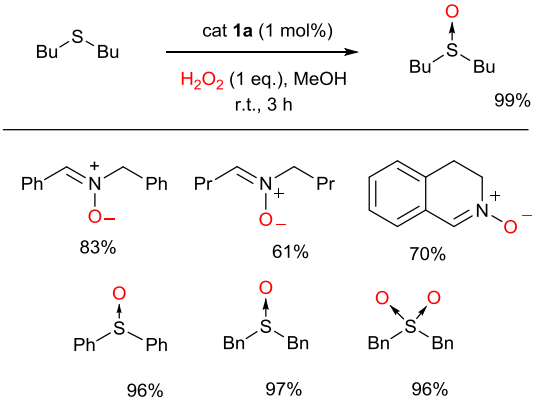
Flavin-catalysed oxidation of amines and sulfides

5-Ethyl-3,7,8,10-tetramethylisoalloxazinium perchlorate $FlEt^+ClO_4^-$ (**1a**) has been used as a robust organocatalyst because of its efficiency and stability. When oxidations of amines and sulfides with H_2O_2 using a catalytic amount of flavinium perchlorate **1a** were reported by Murahashi et al. in 1989,[7] this was received as a milestone in flavin chemistry[3a] that was as significant as the previous works of Bruice et al.[6]

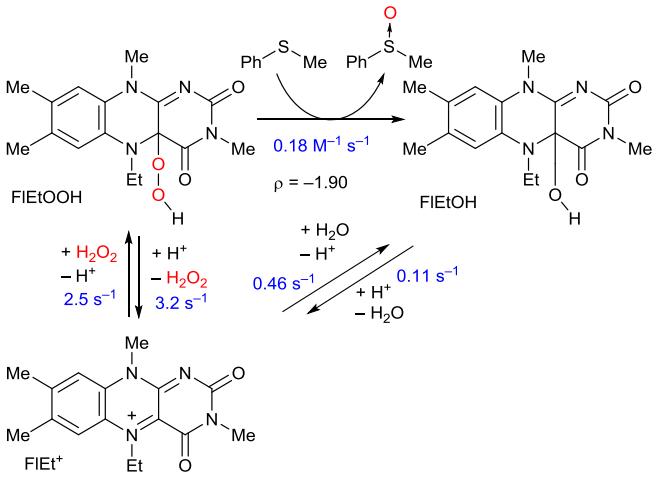
Flavin-catalysed oxidation of secondary amines gives nitrones, which are valuable synthetic intermediates. This finding is extremely important in view of synthetic organic chemistry, because it was the first example of direct oxidative transformation of secondary amines to nitrones, and the nitrones thus obtained are highly useful key intermediates. This method is compatible with transition-metal catalysed direct oxidative transformation of secondary amines to nitrones.[9]

Flavinium salt **1a**-catalysed oxidation of aryl and alkyl sulfides with hydrogen peroxide gave the corresponding sulfoxides in excellent yields (Scheme 4).[7] Sulfoxides are important intermediates in the synthesis of biologically important compounds. Environmentally benign catalytic oxidation of sulfides proceeds chemoselectively under mild conditions without overoxidation and without using transition metal catalysts.

The kinetics of the oxidation of methyl phenyl sulfide to its sulfoxide was studied in detail using GLC and stopped-flow spectrophotometry in methanol at 30 °C. The rate-determining step is the ionization of the FlEtOH to the flavinium cation $FlEt^+$ (k_1 = 0.11 s^{-1}), while the pseudo-first-order rate constant for addition of H_2O_2 to $FlEt^+$ to form FlEtOOH is 0.7 s^{-1}, whereas the second-order rate constant ($k_{5'}$) and the rate of oxidation (v) were 0.18 $M^{-1}s^{-1}$ and 3.9 mM h^{-1}, respectively (Scheme 5). Decomposition of 4a-hydroperoxyflavin FlEtOOH was observed



Scheme 4 Flavin-**1a**-catalysed oxidations of amines and sulphides.

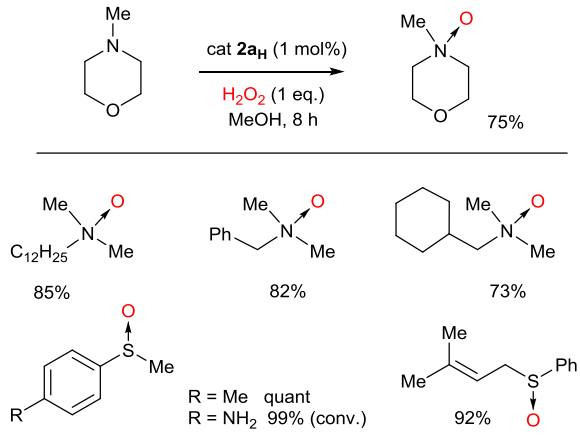


Scheme 5 Catalytic cycle and kinetic data for the oxidation of methyl phenyl sulfide with H_2O_2 in the presence of $FlEt^+ClO_4^-$ catalyst (**1a**).

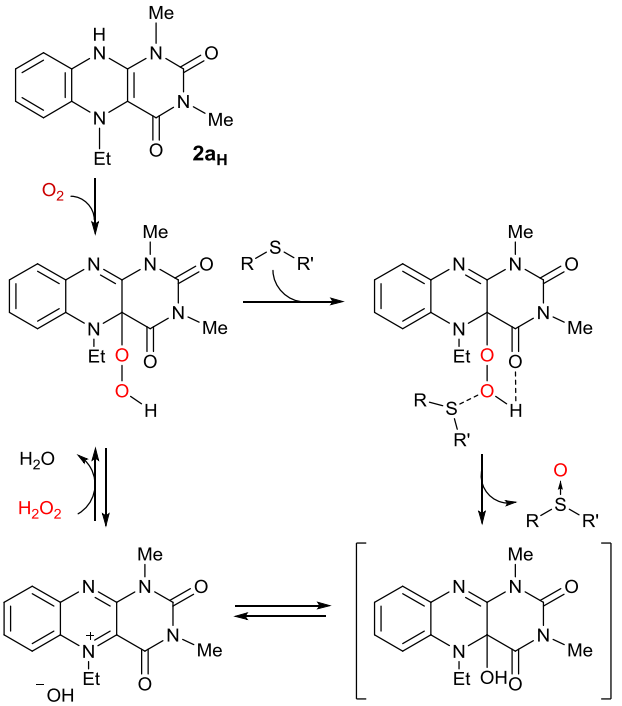
to give 10a-spirohydantoin, but this step is very slow. Competitive catalytic oxidations of *p*-substituted phenyl methyl sulfides show a good free-energy relationship between σ and relative reactivity. The ρ-value was –1.90, indicating that the flavin hydroperoxide FlEtOOH undergoes electrophilic attack on sulfides.[7] The catalytic cycle shown in Scheme 5 corresponds to the shunt process shown in Scheme 3.

Bäckvall and co-workers reported that chemoselective oxidations of tertiary amines to *N*-oxides[10a] and sulfides to sulfoxides[10b] with H_2O_2 occurred in the presence of neutral 1,3-dimethyl-5-ethyl-5,10-dihydroalloxazine catalyst (**2a$_H$**) highly efficiently (Scheme 6). The reaction can be extended to allylic and vinylic sulfides. Selective oxidation of allyl sulfides is highly useful for organic synthesis.

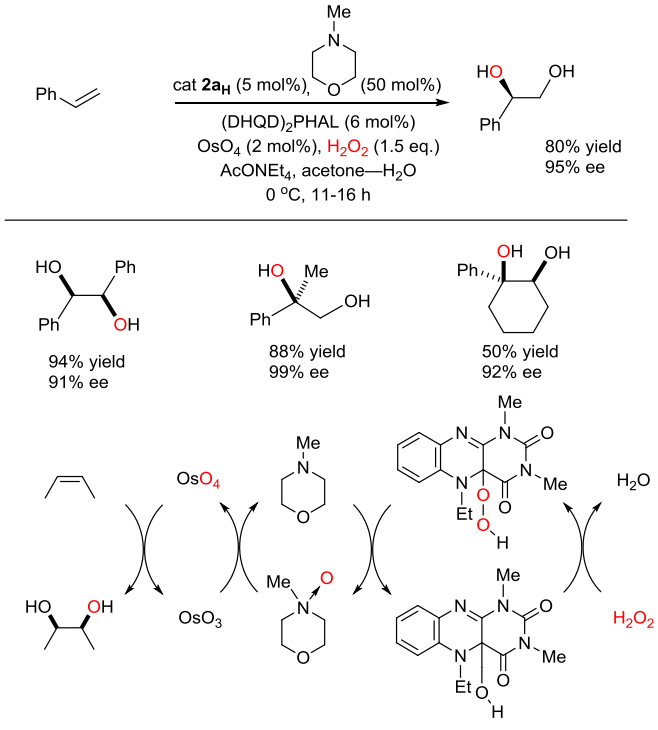
The reaction is initiated by the reaction of catalyst **2a$_H$** with molecular oxygen to give flavin hydroperoxide, which can be regenerated by H_2O_2 in the catalytic cycle (Scheme 7). The flavin hydroperoxide transfers an oxygen atom to the sulfide via a hydrogen-bonded transition state to give sulfoxide and hydroxyflavin. Elimination of OH^- from hydroxyflavin produces the aromatic 1,4-diazine, which undergoes reaction with H_2O_2 to regenerate flavin hydroperoxide.[10]



Scheme 6 Flavin-**2a$_H$**-catalysed oxidation of tertiary amines and sulphides.



Scheme 7 Catalytic cycle of the Flavin-$\mathbf{2a_H}$-catalysed reaction.



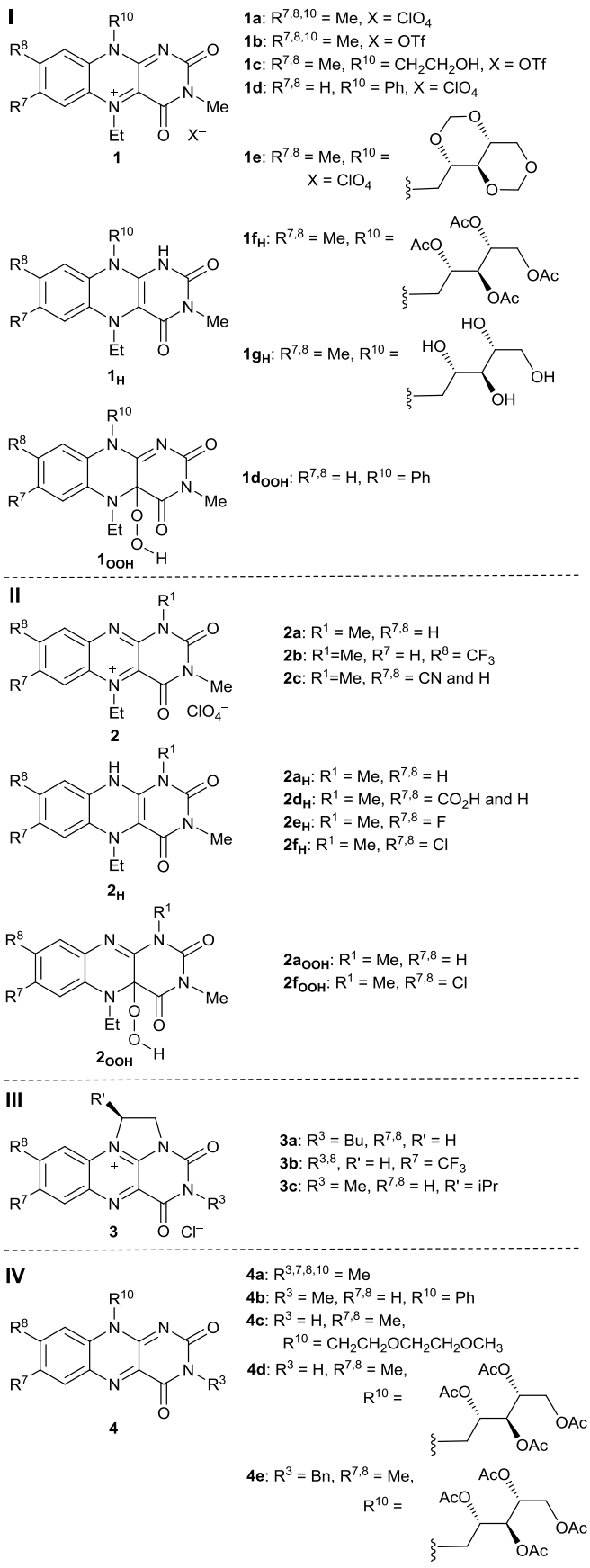
Scheme 8 Triple catalytic system for the Os-catalysed dihydroxylation of olefins with the amine *N*-oxide catalytically generated by the flavin catalysis.

The above flavin-$\mathbf{2a_H}$-catalysed oxidation of tertiary amines to *N*-oxide can be applied to the osmium-catalysed dihydroxylation of olefins with *N*-oxide (Scheme 8).[11] Thus, the dihydroxylation of olefins with H_2O_2 *via* coupled electron transfer can be carried out in the presence of catalytic amounts of OsO_4, *N*-methylmorpholine, and flavin catalyst $\mathbf{2a_H}$. Using the Sharpless chiral ligand, asymmetric dihydroxylation of olefins proceeds with high enantioselectivity.[12]

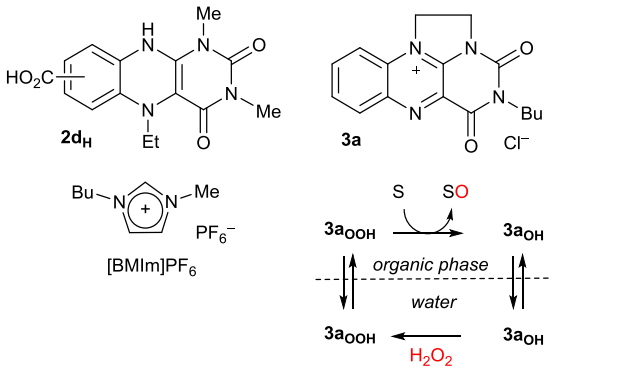
After the breakthrough for the flavin-catalysed oxidation with **1a**,[7] various organocatalytic oxidations mediated by flavin catalysts have been reported. Many efficient and readily available flavin catalysts have been designed, of which there are four types; I, isoalloxazinium catalysts **1** such as **1a**[7], their 1,5-dihydro derivatives $\mathbf{1_H}$ and their 4a-hydroperoxides $\mathbf{1_{OOH}}$, II, alloxazinium catalysts **2** such as **2a**[10], their 5,10-dihydro derivatives $\mathbf{2_H}$ and their 4a-hydroperoxides $\mathbf{2_{OOH}}$, III, 1,10-bridged flavinium catalysts **3**[13] and IV, 5-unsubstituted neutral isoalloxazine catalysts **4** (Scheme 9).

The flavinium perchlorate catalyst ($FlEt^+ClO_4^-$) (**1a**)[7] is an excellent catalyst, so the ClO_4^- anion has been used as a counter ion. The flavinium ion bearing a safer counter ion of OTf^- such as **1b** and **1c** is a useful catalyst for large-scale preparation. 5-Ethyl-10-(2-hydroxyethyl)-3,7,8-trimethylisoalloxazinium triflate (**1c**), which is prepared simply and easily from commercially available riboflavin (vitamin B_2), is a stable and excellent catalyst. The hydroxyl group did not retard any catalytic activity. The other flavin catalysts, which are readily derived from vitamin B_2, are **1e**, $\mathbf{1f_H}$ and $\mathbf{1g_H}$. The different behavior of the isoalloxazinium **1** and alloxazinium catalysts **2** is a consequence of a change in the rate-determining step in the catalytic cycle, resulting from their significantly different abilities to react with nucleophiles. Isoalloxazinium salts **1** are electrophilic and have been used for the oxidation of various substrates. The rate-determining step for the oxidation of sulfides with H_2O_2 is dehydration of water from hydroxyflavin,[7,14c] and hence electron-rich isoalloxazinium salts such as 7,8-dimethyl substituted isoalloxazinium salts, which are close to flavoenzyme are very active catalysts. Alloxazinium catalysts **1** are very weak electrophiles**,** and formation of alloxazine hydroperoxide is a crucial step in the catalytic cycle.[14] Therefore, alloxazinium catalysts bearing electron withdrawing substituents such as **2b**, **2c** and their analoguos such as $\mathbf{2e_H}$, $\mathbf{2f_H}$ are active catalysts for oxidation of sulfides. The oxidation of tertiary amines can be carried out highly efficiently because of the high basicity of tertiary amines.[14c,d] Non-substituted, reduced alloxazine catalyst $\mathbf{2a_H}$ has been used as an excellent catalyst for the oxidation of tertiary amines.[10a] 1,10-Bridged flavinium catalysts **3**[13] are similar to alloxazinium catalysts, and the catalysts bearing an electron-withdrawing group such as **3b** are more active for the oxidation of sulfides with H_2O_2. The 5-non-substituted natural flavins **4** are employed as organocatalysts for the oxidase-mimicked transformations and aerobic hydrogenation of alkenes as described later.

In order to use the flavin-catalysed sulfoxidation with H_2O_2 practically the catalytic system has been modified. Bäckvall et al. used a mixture of 1,3,5-trialkylated reduced alloxazines bearing a carboxylate group in either the 7 or 8 position $\mathbf{2d_H}$ and ionic liquid $[BMIm]PF_6$ as a recyclable catalyst for the H_2O_2-based sulfoxidation.[15] The twitterionic form of the catalyst can be recycled up to seven times without loss of



Scheme 9 Structures of representative flavin catalysts.



Scheme 10 Sulfoxidation with H_2O_2 by the twitterion catalyst **2d$_H$** and the phase- transfer-catalyst **3a**.

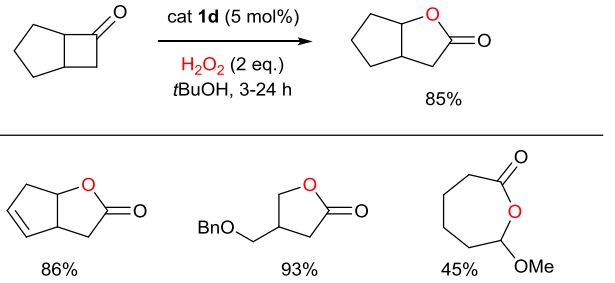
selectivity and yield. Cibulka et al. used phase-transfer catalysts such as amphiphilic 1,10-ethylene-bridged 3-alkylalloxazinium salt **3a** in chloroform/water for the sulfoxidation.[16] The efficiency of the catalytic oxidation depended substantially on the pH of the aqueous phase to reach maximum values at pH 7. Under such conditions, complete conversion of sulfides occurred within a maximum of 24 h.

Flavin-catalysed oxidation of carbonyl compounds with H_2O_2

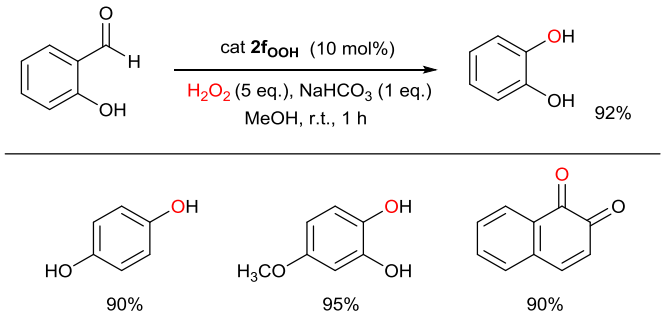
The Bayer-Villiger (BV) reaction is one of the important functions of flavoenzymes, and the catalytic oxidations with enzymes and modified enzymes have been studied extensively.[4f,17] Furstoss et al. reported the first flavin-catalysed BV oxidation of ketones with H_2O_2. Using flavin compound **1d** as a catalyst, ketones can be converted to the corresponding lactones in good yields (Scheme 11).[18] The catalytic reaction proceeds chemoselectively, and the mechanism is similar to that shown for the sulfoxidation with catalyst **1a**.

Foss and co-workers reported the first organocatalytic Dakin oxidation of electron-rich aryl aldehydes to phenols under mild, basic conditions. Catechols are readily prepared in the presence of flavin hydroperoxide catalyst **2f$_{OOH}$**, which is derived from **2f**, followed by treatment with air (Scheme 12).[19]

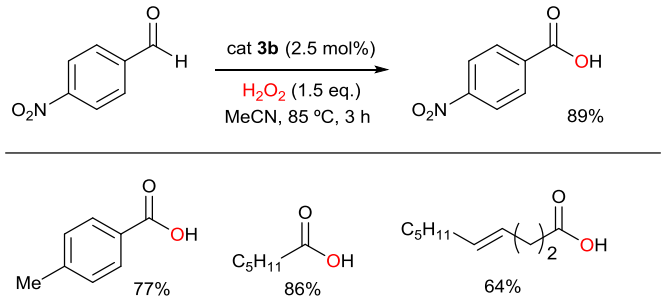
Carbery et al. reported the flavin-catalysed oxidation of aldehydes to carboxylic acids. The oxidation of alkyl and aryl aldehydes with H_2O_2 in the presence of the bridged flavin catalyst **3b** in acetonitrile at 85 °C gave the corresponding carboxylic acids. The proposed mechanism is shown in Scheme



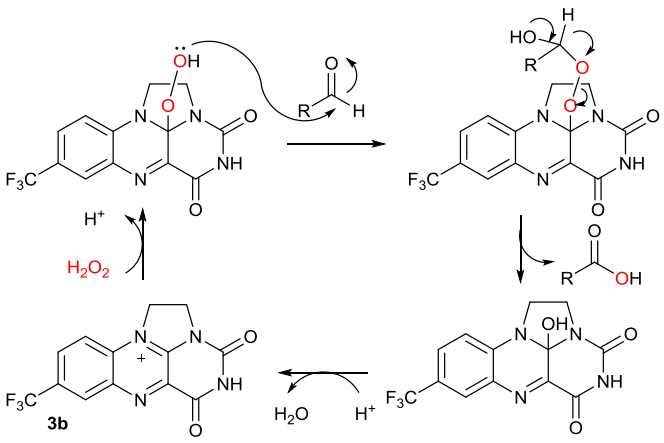
Scheme 11 Flavin-**1d**-catalysed BV oxidation with H_2O_2.



Scheme 12 Flavin-**2f$_{OOH}$**-catalyzed Dakin oxidation.



Scheme 13 Flavin-**3b**-catalysed oxidative transformation of aldehydes to carboxylic acids.

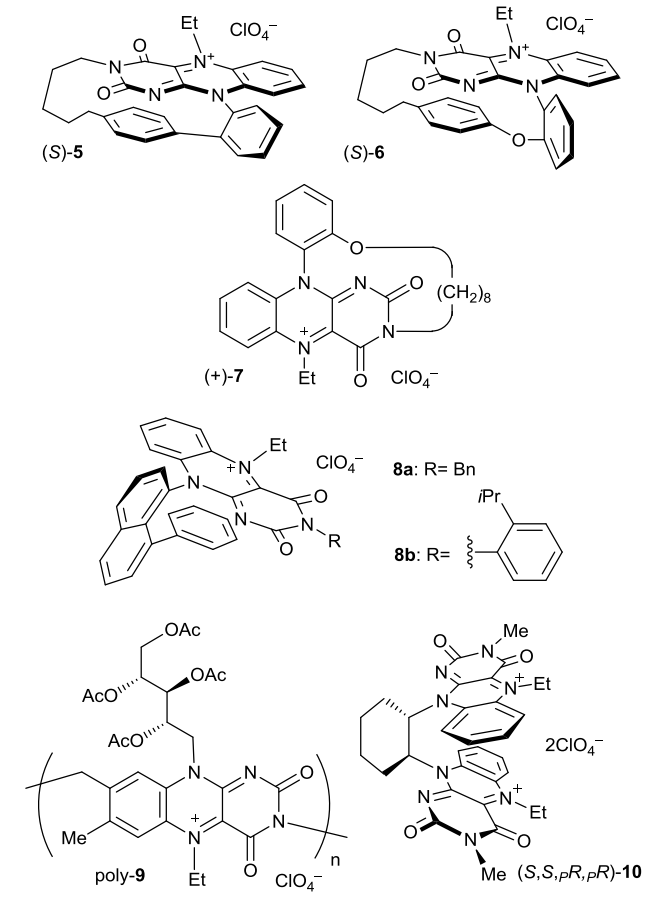


Scheme 14 Proposed mechanism of the oxidation of aldehydes.

14.[20] The hydroperoxyflavin derived from **3b** and H_2O_2 undergoes reaction with aldehyde to form a peroxohemiacetal. Thermal collapse via 1,2-hydride migration with resultant O–O bond cleavage forms a carboxylic acid and hydroxyflavin, which undergoes dehydration to regenerate the catalyst **3b**.

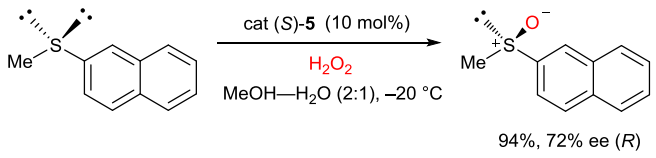
Flavin-catalysed asymmetric oxidation reaction with H_2O_2

It has been reported that the interaction of substrate with a particular flavoprotein involved interaction with the *si*- or *re*-face of the flavin. The reason is to fix the chiral reaction site by hydrogen bonding and π–π stacking interactions. Asymmetric catalytic oxidations of organic substrates can be performed using a suitable chiral flavin catalyst. Representative examples of chiral flavin catalysts are shown in Scheme 15.

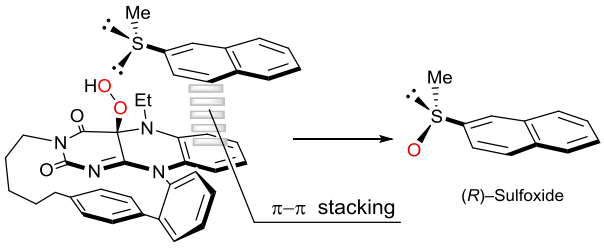


Scheme 15 Chiral flavin catalysts.

The oxidation reaction of methyl *p*-tolyl sulfide with a 30% aqueous H_2O_2 solution in dichloromethane in the presence of 10 mol% of tetraacetyl-5-ethyl-1,5-dihydroriboflavin, TAcFlEtH (**1f$_H$**) gave (*R*)-(+)-methyl *p*-tolyl sulfoxide in 25% *ee* in 94% yield.[21] This is a rather surprising result, because the chiral part is located far from the hydroperoxide. This asymmetric induction is not due to a simple steric effect. The optical induction depends on the concentration of the catalyst, indicating the formation of a dimer by the stacking of tetraacetylriboflavin. The substrate must approach from the outside of the flavin dimer to induce asymmetric induction. Based on this result, capped chiral planar flavin catalysts were designed. Homochiral hydroperoxyflavins can be obtained by nucleophilic addition of H_2O_2 from one side. Substrates also attack from the same side to give the chiral oxidized product. Chiral capped flavin catalysts (*S*)-**5** and (*S*)-**6** have been prepared, and their structures were proved by X-ray analyses.



Scheme 16 Capped-flavin-(*S*)-**5**-catalysed asymmetric oxidation.



solvent	isolated yield, %	%*ee* (HPLC)
CH_2Cl_2	77	5
MeCN	97	3
MeOH	86	23
MeOH—H_2O (4:1)	75	37
MeOH—H_2O (2:1)	82	40

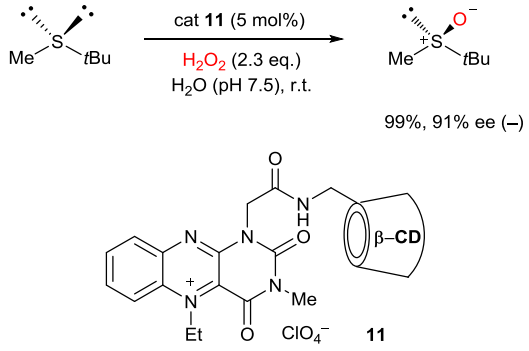
Scheme 17 Solvent effect for the capped-flavin-catalysed oxidation.

Using the capped-flavins (*S*)-**5** and (*S*)-**6** as catalysts, the oxidation of methyl naphthyl sulfide with H_2O_2 gave the corresponding sulfoxide in excellent isolated yields, and the enantiomeric excess obtained was 72% *ee* for catalyst (*S*)-**5** and 51% *ee* for catalyst (*S*)-**6**.[2a,21]

The reason for the enantioselectivity is the π–π stacking interaction of these two aromatic rings. The solvent effect for the enantioselectivity in the oxidation of methyl naphthyl sulfide is drastic (Scheme 17). Using a polar solvent that contains water, higher enantioselectivity was obtained, indicating that π–π stacking between two aromatic rings is effective for higher enantioselectivity.

Shinkai et al. reported asymmetric sulfoxidation of methyl phenyl sulfide using capped flavin catalyst (+)-**7** with 65% *ee* using a recycle system.[22] Although the enantiomeric excesses obtained are not so high, these asymmetric catalytic oxidations are highly useful examples of the catalytic oxidation reactions catalysed by non-acid and non-base organic compounds.

N^1,N^{10}-ethylene-bridged flavinium salt **3c** derived from L-valinol is active for the oxidation of sulfides with H_2O_2; however, the asymmetric induction is low.[23] Cibulka and co-workers prepared a planar chiral 3-benzyl-5-ethyl-10-(8-phenylnaphthalen-1-yl)isoalloxazinium perchlorate (**8a**), which bears a phenyl cap that covers one side of the isoalloxazium skeleton plane.[24] The enantiomerically pure **8a** was derived from the HPLC separation of the racemic precursors. The H_2O_2 oxidation of sulfides with **8a** or modified catalysts such as **8b** gave the corresponding sulfides with enantiomeric excesses of up to 61% *ee* for aromatic sulfides and of up to 65% *ee* for *tert*-butyl methyl sulfide. Recently, Cibulka and Kraus used cyclodextrin to improve the selectivity of a flavin catalyst.[25] The use of a cyclodextrin macrocycle as a chiral auxiliary covalently attached to the flavinium moiety would give preorganization of the substrates by complexation inside the cyclodextrin cavity to enhance both the rate and enantioselectivity of sulfoxidation. Using modified *N*5-ethylflavin catalyst **11** conjugated by an alloxazinium moiety attached to the primary rim of the β-cyclodextrins at the C-6



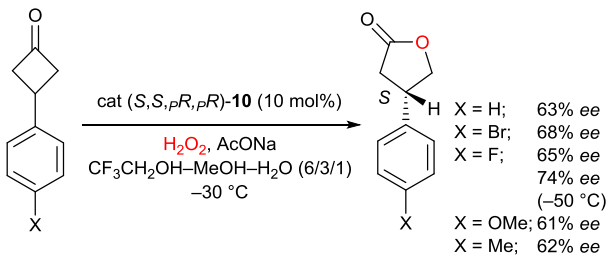
Scheme 18 Enantioselective sulfoxidation with H_2O_2 by modified *N*5-ethylflavin supported on β-cyclodextrin.

position via spacer with an appropriate length, the oxidation of sulfides with H_2O_2 in neat aqueous media gave excellent conversions and very high enantioselectivity (up to 91% *ee*).

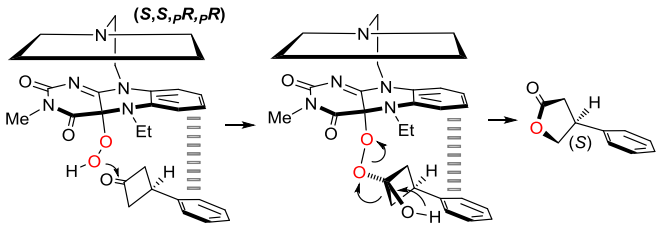
Iida and Yashima reported that an optically active polymer composed almost entirely of the 5-ethylriboflavinium cation as the main chain (poly-**9**) is an excellent catalyst for enantioselective oxidation of methyl *p*-tolyl sulfide with H_2O_2 in THF to give up to 60% *ee*.[26]

Another function of flavoenzyme is the asymmetric BV reaction. Based on the results of the asymmetric oxidation of sulfides with capped flavin catalysts **5** and **6**, a planar-chiral bisflavin catalyst was designed. The planar flavin catalysts were prepared using a tedious method and need optical resolution with preparative HPLC. In order to prepare a chiral flavin catalyst without optical resolution a new planar-chiral bisflavin catalyst (*S*,*S*,*pR*,*pR*)-**10** was prepared using diastereoselctive reaction of optically active *trans*-1,2-cyclohexanediamine with fluoronitrobenzene followed by condensation with alloxane. The asymmetric BV oxidation of the cyclobutanones in the presence of the flavin catalyst **10**[27] gave the corresponding γ-butyrolactones in up to 74% enantiomeric excess (Scheme 19). Sodium acetate was added to trap perchloric acid, which was formed under the reaction conditions and promoted the non-asymmetric oxidation.

The reaction mechanism can be rationalized as shown in Scheme 20. The bis-flavinium perchlorate was converted to its acetate salt, which is converted into hydroperoxyflavin upon reaction with hydrogen peroxide. Because of the π–π stacking, nucleophilic attack of the hydroperoxide on the carbonyl group occurs from the opposite side to the phenyl group. Then, intramolecular rearrangement occurs from anti-periplanar of



Scheme 19 Planar-chiral bisflavin-**10**-catalysed asymmetric BV oxidation with H_2O_2.



Scheme 20 Mechanism of the bisflavin-**10**-catalysed asymmetric BV oxidation with H_2O_2.

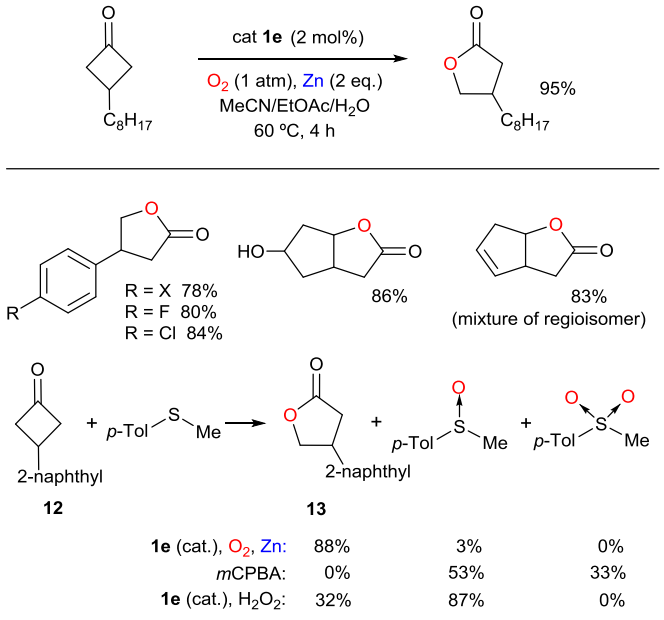
the leaving group to give (*S*)- γ-butyrolactone.[27]

Flavin-catalysed oxidation with molecular oxygen

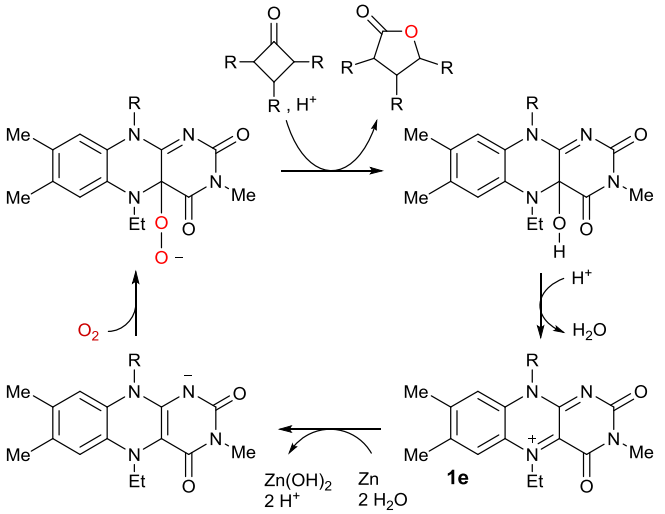
Oxidation with H_2O_2 corresponds to the shunt process in Scheme 3. The actual enzymatic cycle uses molecular oxygen directly. The next target is the construction of flavin-catalysed oxidation with molecular oxygen, because direct use of molecular oxygen is more environmentally benign and valuable in organic synthesis. The oxidation of the reduced flavin (FlEtH) with molecular oxygen occurs readily to give hydroperoxide (FlEtOOH); therefore, the crucial step of the catalytic cycle of the oxidation with molecular oxygen is the reduction of $FlEt^+$ to FlEtH with an appropriate reductant which may correspond to NAD(P)H (Scheme 3). Actually flavin-catalysed oxidations with molecular oxygen under mild conditions can be performed highly efficiently using reductants such as zinc, hydrazine hydrate, ascorbic acid, and formic acid.

Flavin-catalysed BV oxidation reaction with molecular oxygen

Imada et al. discovered that biomimetic flavin-catalysed BV oxidation with molecular oxygen was achieved by selecting zinc as the reductant.[28] Treatment of ketones in the presence of 2 mol % of flavin catalyst **1e** and zinc dust in a mixture of



Scheme 21 Flavin-**1e**-catalysed BV oxidation with molecular oxygen.

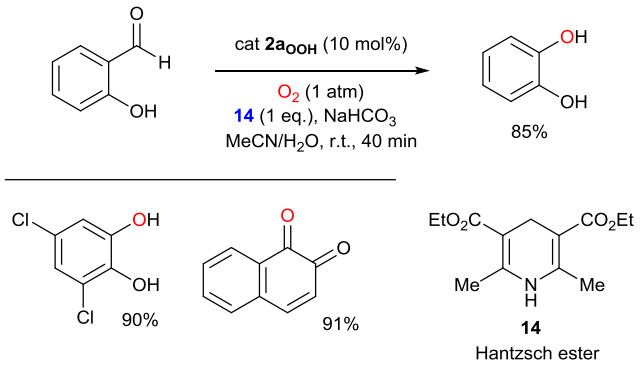


Scheme 22 Catalytic cycle of aerobic BV reaction.

CH_3CN—EtOAc—water under molecular oxygen (balloon) at 80 °C gave lactones in excellent yields (Scheme 21). The products can be isolated simply by filtration of insoluble $Zn(OH)_2$ followed by extraction.

This is a highly useful method. The conventional method for BV oxidations still uses a reagent such as *m*CPBA, although there is an inexpensive and safe method for aerobic oxidation in the presence of benzaldehyde and Fe_2O_3 catalyst.[29]

One of the unsolved problems of BV oxidations is the lack of chemoselectivity for nucleophilic oxidations over electrophilic oxidations. There is no report on a chemoselective catalytic method in the presence of heteroatomic moieties, because oxidants usually result in electrophilic oxidation of heteroatomic compounds. The chemoselective oxidation of ketones in the presence of highly reactive cyclopentanol and cyclopentene moieties can be performed under the conditions. Furthermore, the chemoselectivity between ketones and sulfides is clear. The flavin catalysed reaction of an equimolar mixture of 3-(2-naphthyl)cyclobutanone (**12**) and methyl *p*-tolyl sulfide afforded the corresponding lactone **13** with extraordinarily high selectivity. This is in contrast to the result of the oxidation with *m*CPBA, which produced a mixture of sulfoxide and over oxidation product of sulfone. Noteworthy is that catalytic oxidation with H_2O_2 gave **13** along with sulfoxide mainly. The reaction can be rationalized by assuming the mechanism shown in Scheme 22.[27] The flavinium cation $FlEt^+$ **1e** undergoes a two-electron reduction with zinc to afford the reduced flavin $FlEt^-$. In co-operation with molecular oxygen $FlEt^-$ gives the flavin 4a-peroxy anion $FlEtOO^-$, which undergoes nucleophilic reaction with ketones to give the corresponding lactones. Chemoselective BV oxidation in this process can be ascribed to the neutral character of the reaction medium and highly nucleophilic character of the anionic peroxy intermediate.[30]



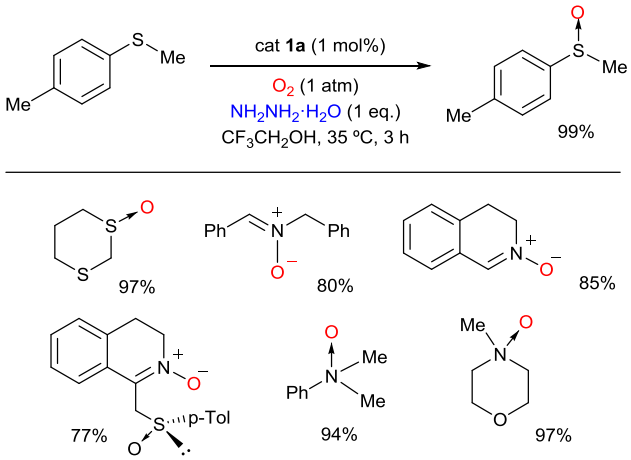
Scheme 23 Flavin-**2a**$_{OOH}$-catalysed Dakin oxidation with molecular oxygen.

Flavin-catalysed oxidation of benzaldehydes to phenols (Dakin oxidation) with molecular oxygen

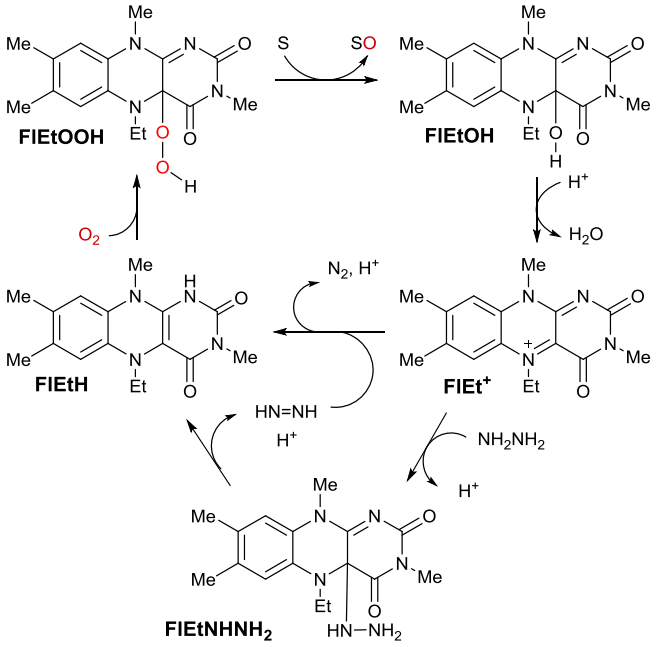
Foss et al. reported that catalytic oxidation of phenolic aldehydes with molecular oxygen in the presence of Hantzsch ester (**14**) gave catechols and electron-rich phenols highly efficiently. The flavin catalyst **2a**$_{OOH}$ derived from **2a** is the most efficient to perform transition-metal free Dakin oxidation (Scheme 23).[31] Dakin reaction can also be carried out similarly using zinc as the reducing reagent.[19]

Flavin-catalysed oxidation of sulfides, secondary amines, and tertiary amines with molecular oxygen in the presence of hydrazine hydrate

Based on the fact that hydrazine derivatives are inhibitors of flavoenzymes, Murahashi and Imada found that the hydrazine hydrate serves as an excellent reductant and discovered that the aerobic oxidation of sulfides, secondary amines, *N*-hydroxylamines, and tertiary amines occurs in the presence of FlEt$^+$ClO$_4^-$ catalyst (**1a**) and hydrazine hydrate in 2,2,2-trifluoroethanol (TFE) to give the corresponding oxidized products with excellent yields (Scheme 24).[32] Treatment of methyl *p*-tolyl sulfide with hydrazine hydrate (1 equiv.) in TFE in the presence of 1 mol % of **1a** at room temperature for 3 h gave the corresponding sulfoxide in 99% yield along with water and molecular nitrogen as the environmentally benign by-products.



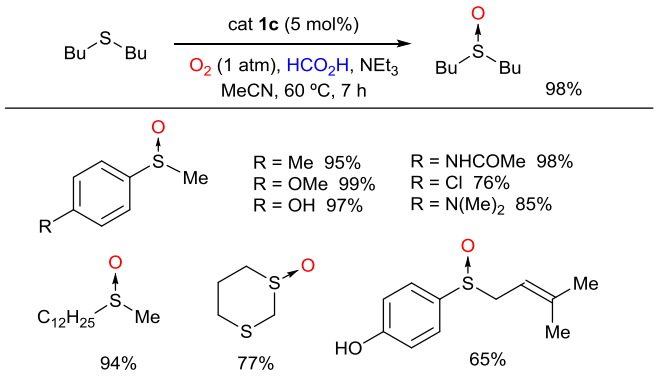
Scheme 24 Flavin-**1a**-catalysed oxidation with molecular oxygen.



Scheme 25 Proposed mechanism of the aerobic oxidation with NH_2NH_2.

This is the first demonstration of environmentally benign oxidation using molecular oxygen and organocatalysts. The solvent effect of the aerobic oxidation is dramatic. Fluorinated alcohols such as TFE are essential for the aerobic oxidation. Precise analysis showed that 0.5 equiv. of hydrazine and 1 equiv. of molecular oxygen are required for oxidation of sulfides, giving sulfoxide along with water and 0.5 equiv. of molecular nitrogen. The catalytic reaction is very clean, and the catalytic activity is very high. The turn-over-number reached 19,000. The oxidative transformation of secondary amines or *N*-hydroxylamines to nitrones and that of tertiary amines to *N*-oxides can be performed cleanly. The reaction can be rationalized by assuming the mechanism shown in Scheme 25. The intermediacy of FlEtOOH was confirmed by comparison of the relative rates of the oxidation of para-substituted phenyl methyl sulfides. Hammett treatment gave a free-energy relationship, giving a ρ-value of –1.69, which is similar to the ρ value (ρ = –1.90) obtained by the catalytic oxidation of sulfides with H_2O_2, indicating that oxidation of sulfides with FlEtOOH occurs electrophilically to give sulfoxides and FlEtOH. The FlEtOH undergoes elimination of water to give H_2O and FlEt$^+$, which is reduced with hydrazine hydrate to give FlEtH. Thus, hydrazine would attack at the 4a(C) position of the isoalloxazine ring of FlEt$^+$ to form the 4a-adduct (FlEtNHNH$_2$), which undergoes β-elimination of diimide NH=NH to afford FlEtH. Diimide thus formed again reacts with FlEt$^+$ to afford FlEtH and molecular nitrogen. The FlEtH thus formed would undergo reaction with molecular oxygen to form FlEtOOH to complete the catalytic cycle.[32,33]

The flavin-catalysed oxidation with molecular oxygen requires a reductant that may correspond to NAD(P)H. Imada et al. reported that excess ascorbic acid could be used as a reductant for the oxidation with molecular oxygen.[34]

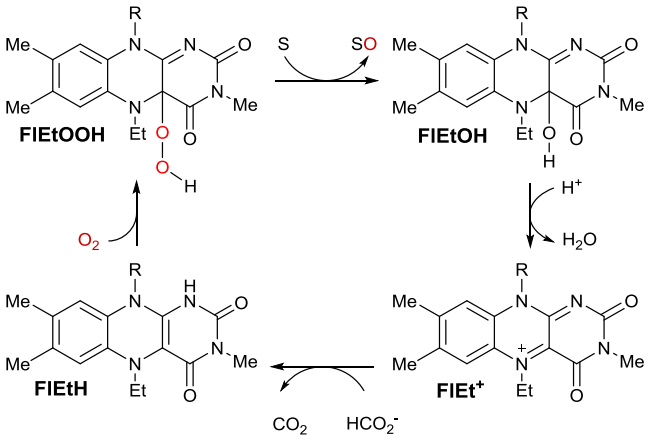


Scheme 26 Flavin-catalysed oxidation of sulfides with molecular oxygen in the presence of HCOOH/TEA.

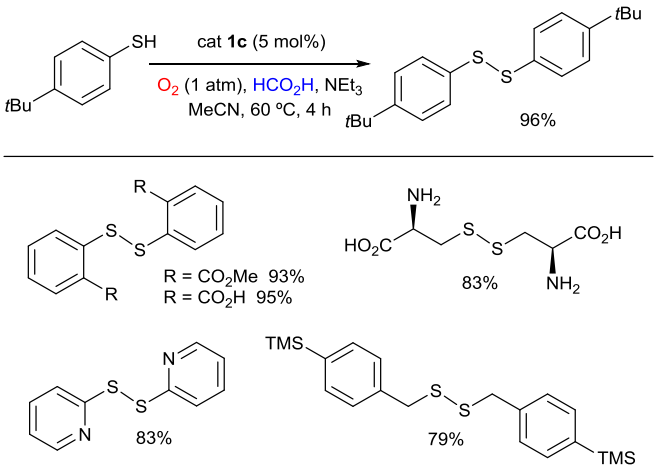
Murahashi and Meguro found that formic acid is an excellent reducing reagent for the oxidation with molecular oxygen.[35] Formic acid is a key compound in the construction of low-carbon society and is an excellent hydrogen source for catalytic transfer hydrogenation.[36] Flavin-catalysed oxidation of sulfides with molecular oxygen can be carried out in the presence of a mixture of formic acid and trimethylamine (TEA) (8:1) and catalyst **1c** in MeCN under molecular oxygen (1 atm, balloon) at 60 °C as shown in Scheme 26.[35] Electron-rich sulfides were oxidized faster than electron-deficient sulfides. The oxidation proceeds smoothly, when tertiary amine and olefin are present. Disulfides were selectively converted to the corresponding monosulfoxides. Overoxidation products could not be detected. The method is suitable for large-scale preparative oxidations.

The reaction mechanism can be rationalized by assuming the pathway depicted by Scheme 27. The reaction of sulfides with FlEtOOH occurs electrophilically to give sulfoxides and FlEtOH, which undergoes a pseudo-first-order reaction to give $FlEt^+$ and water. The reaction of $FlEt^+$ with $HCOO^-$ would give FlEtH together with carbon dioxide. FlEtH thus formed would undergo reaction with molecular oxygen to form FlEtOOH and complete the catalytic cycle.[35]

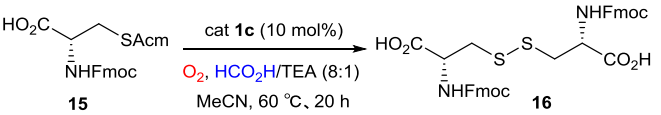
This practical method has been applied to the aerobic catalytic oxidative transformation of thiols to disulfides.[37] In



Scheme 27 Flavin-**1c**-catalysed oxidation with molecular oxygen in the presence of HCOOH/TEA.



Scheme 28 Flavin-**1c**-catalysed oxidation of thiols with molecular oxygen in the presence of HCOOH/TEA.



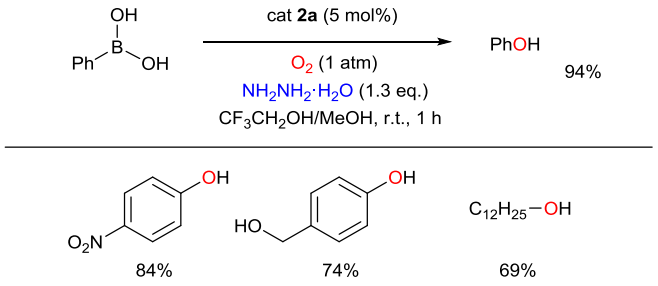
Scheme 29 Direct synthesis of disulfides for S-protected thiols.

general, aerobic oxidation of thiols is performed in the presence of a base or heavy metal ions; however, metal-free conditions are often required in the synthesis of biologically active compounds and medicines.

Flavin-promoted oxidation of thiols takes place under basic conditions via the nucleophilic attack of thiols at the C(4a) position to form a covalent adduct, followed by nucleophilic attack of the second thiol anion, affording the corresponding disulfide.[37] Flavin-catalysed aerobic oxidation of thiols under the present acidic conditions gave the corresponding disulfides with excellent yields (Scheme 28).[35] The aerobic oxidation tolerates various functional groups. The method is highly useful for the direct synthesis of disulfides from *S*-protected thiols, because some thiols are very sensitive and difficult to handle from a synthetic perspective. The aerobic oxidation of *S*-[(acetylamino)methyl]-*N*-[(9*H*-fluoren-9-ylmethoxy)carbonyl]-1-cystein (**15**) in the presence of the flavin catalyst **1c** gave *N*,*N*-bis[(9*H*-fluoren-9-ylmethoxy)carbonyl]-1-cysteine (**16**) selectively with an isolated yield of 84%. The present method is highly useful for the synthesis of some complex disulfides to be used as drugs.

Flavin-catalysed hydroxylation of aryl boronic acids to phenols with molecular oxygen

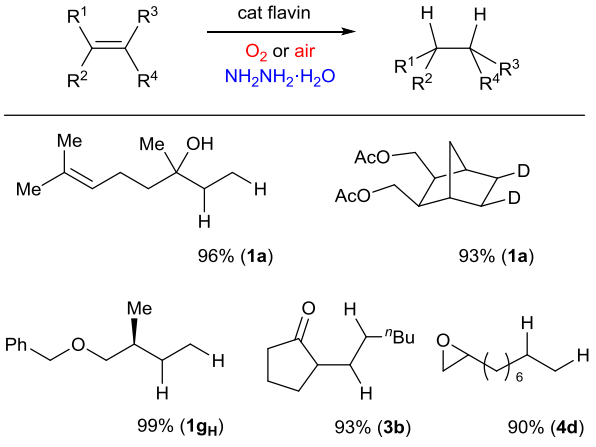
The flavin-catalysed oxidation with molecular oxygen in the presence of hydrazine can be applied to the oxidation of aryl boronic acids as shown in Scheme 30.[38]



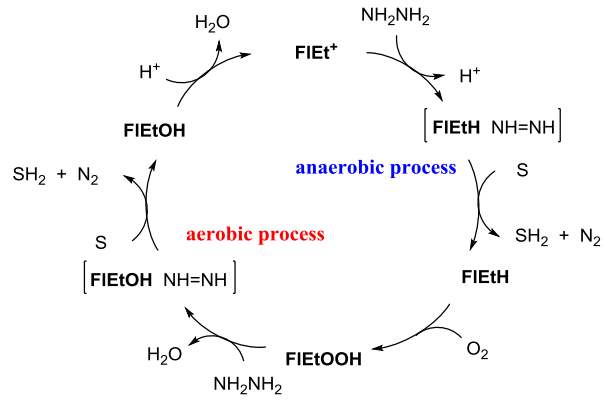
Scheme 30 Flavin-**2a**-catalysed oxidative hydroxylation of aryl boronic acids.

Flavin-catalysed aerobic hydrogenation of alkenes in the presence of hydrazine hydrate.

In the flavin-catalysed aerobic oxidation, diimide plays an important role in the redox cycle, as shown in Scheme 25. The principle of the flavin-catalysed oxidative formation of diimide from hydrazine leads to environmentally benign flavin-catalysed hydrogenation of alkenes. Imada, Iida and Naota discovered flavin-catalysed oxidative hydrogenation of alkenes.[39,40] Treatment of alkenes in the presence of 1–2 equiv. of hydrazine hydrate and 2 mol % of flavin catalyst at room temperature under a molecular oxygen atmosphere gave alkanes in excellent yields. The new catalytic oxidative hydrogenation of alkenes is extremely important in organic synthesis. Linear and cyclic olefins can be converted quantitatively to the corresponding alkanes. Reactive functional groups, such as tertiary amines, alcohols and amides are tolerated in the reductions. Chemoselective hydrogenation can be performed in complex molecules that are prone to racemization, olefin isomerization or hydrogenolysis in transition-metal-catalysed hydrogenations.[40] It is noteworthy that the selective *cis*-1,2-deuteration of olefins can be achieved with a little over 1 equiv. of ND_2ND_2. Flavinium cation catalyst **1a** shows the highest catalytic activity among those examined, and a series of robust 5-unsubstituted neutral flavin catalysts **4** showed comparably high activities. Using these catalysts a high reusability of the catalysts arising from their thermal and chemical stability can be expected. Various catalysts such as **1a**,[39a] **1g$_H$**[41], **3b**[42], and **4d**,[39b] have been



Scheme 31 Flavin-catalysed hydrogenation of alkenes.

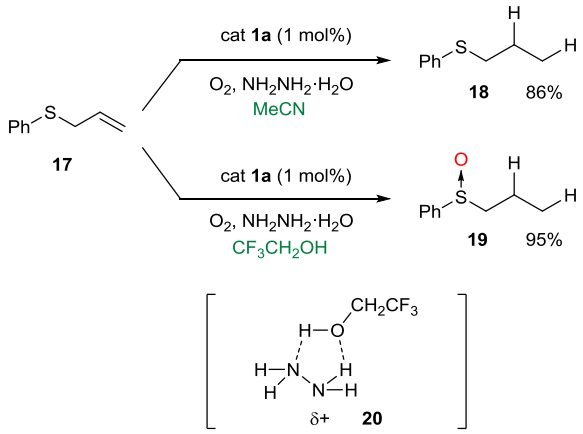


Scheme 32 Proposed catalytic cycle of the flavin **1a**-catalysed oxidative hydrogenation of alkenes.

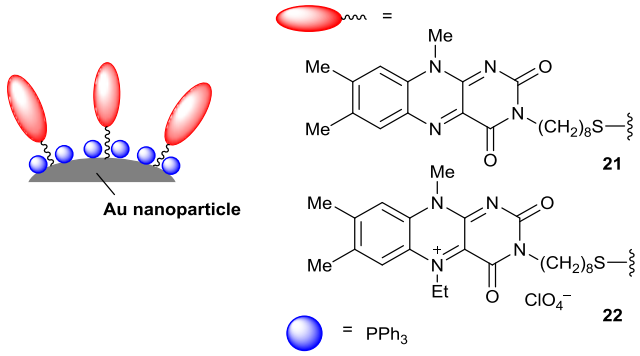
reported to be used for oxidative hydrogenation of alkenes (Scheme 31).

The Flavin-**1a**-catalysed reaction can be rationalized by assuming the mechanism shown in Scheme 32. The addition of hydrazine to the flavinium cation $FlEt^+$ is followed by elimination of the diimide to form the diimide/flavin complex [FlEtH NH=NH], which undergoes reaction with alkenes to form alkanes, FlEtH and molecular nitrogen. The FlEtH undergoes reaction with molecular oxygen to form FlEtOOH in the oxidation reaction. In this catalytic system, FlEtOOH undergoes reaction with hydrazine and elimination to give diimide/flavin complex [FlEtOH NH=NH], which again reduces alkene to give FlEtOH. The FlEtOH obtained undergoes ionization to give $FlEt^+$ to complete the catalytic cycle.[39]

The aerobic reaction of allyl phenyl sulfide **17** in the presence of flavin catalyst **1a** and hydrazine hydrate in acetonitrile under molecular oxygen gave **18** (86%), while the reaction in TFE gave **19** (95%). By changing the solvent, a drastic change in the reaction product was observed. The reason would be as follows. ElEtOOH could attack hydrazine generally rather than sulfide in acetonitrile, giving the diimide/flavin complex [FlEtOH NH=NH], resulting in the hydrogenation of olefins. In TFE bearing an acidic hydroxy group, hydrazine may form complex **20** by hydrogen bonding with the acidic hydroxy group, as shown in Scheme 33. The



Scheme 33 Solvent effect for the aerobic reaction of sulfide **17** with hydrazine.



Scheme 34 Flavin-functionalized gold nanoparticle.

electrophilic FlEtOOH attacks sulfides to afford sulfoxides rather than attacking hydrazine **20**.[33]

Naota and Imada reported that gold nanoparticles with 3-(8-thiooctyl)lumiflavin **21** or its 5-ethyllumiflavinium cation **22** are useful for oxidative hydrogenation of alkenes or oxidation of sulfides, respectively.[43] The nanoparticle catalysts have advantages over non-supported lumiflavin catalysts in terms of their activity and reusability. The equilibrated formation of the association complexes in specific cavities generated at particle surfaces with the long-carbon-chain-linked flavin is a key factor in enhancing catalytic activities (Scheme 34).

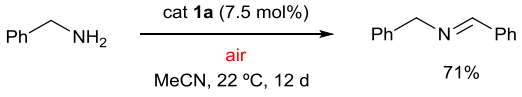
Simulation of the function of oxidase

One of the functions of flavoenzyme is an oxidase, as shown in Scheme 2. Oxidized flavins undergo dehydrogenation of a substrate SH_2, and reduced flavins are oxidized with molecular oxygen to recover the oxidized flavins along with generation of H_2O_2. The catalytic reaction using this principle is limited to a few examples. Aerobic oxidation of benzylamine with flavinium catalyst **1a**[44] or 3-methyllumiflavin catalyst **4a**[45] gave benzylidenebenzylamine with a slow reaction rate (Scheme 35).

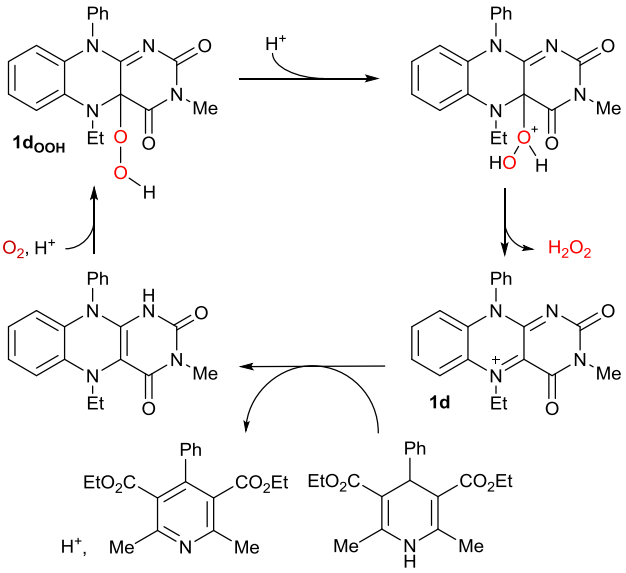
Flavin-promoted oxidations of thiols have been reported.[46] The reaction of 3-methyl-10-phenylisoalloxazine (**4b**) induced oxidation of $HS(CH_2)_4SH$ in ethanol under aerobic conditions to give tetramethylenebis(sulfide) and 1,5-dihydroflavin.[37]

Foss et al. reported that oxidation of dihydropyridines in the presence of flavin catalyst $\mathbf{1d_{OOH}}$ and $HClO_4$ in methanol under oxygen gave the corresponding pyridines by aerobic oxidative aromatization in over 95% yields. The catalytic cycle for the aerobic oxidative aromatization with acid promotion is shown in Scheme 36.[47]

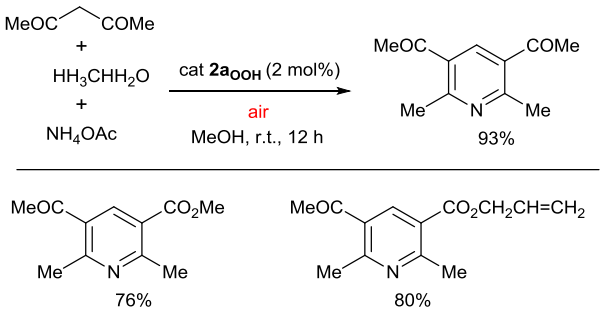
Flavin-catalysed oxidative aromatizations facilitated one-pot multicomponent synthesis of pyridines from various aldehydes, dicarbonyl compounds and ammonium acetate in 55–95% yields, and benzothiazoles from 2-aminothiophenol and various aldehydes in 78–95% yields (Scheme 37).[47]



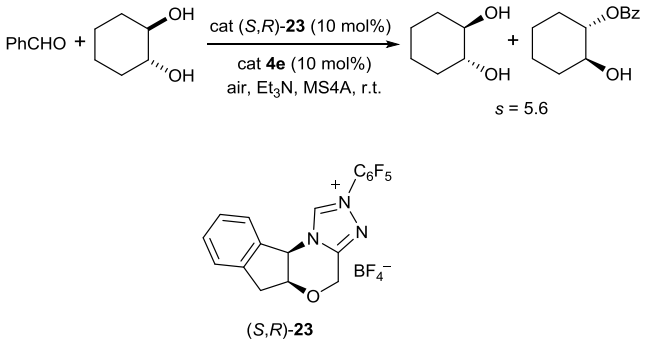
Scheme 35 Flavin-**1a**-catalysed reaction of benzylamine.



Scheme 36 Catalytic cycle for aerobic oxidative aromatization with acid promotion.

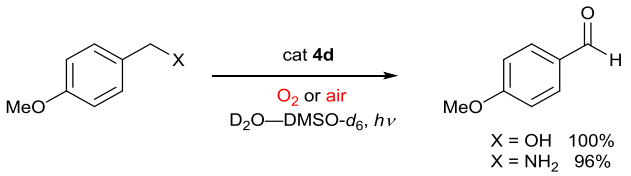


Scheme 37 Flavin-$\mathbf{2a_{OOH}}$-catalysed synthesis of Hantzsch pyridines.

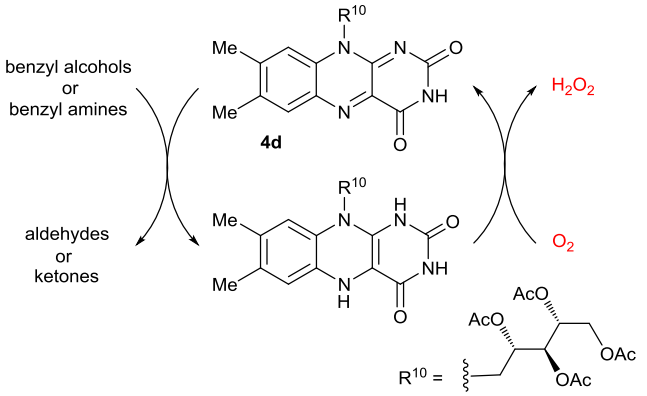


Scheme 38 Oxidative acylation catalysed by NHC/flavin catalyst **4e**.

A combination of flavin and achiral azolium-derived *N*-heterocyclic carbene was reported to catalyse oxidative esterification of aldehydes with alcohols under molecular oxygen.[48] Iida et al. reported that the oxidative esterification of benzaldehyde and racemic 1-phenylethanol with (*S,R*)-catalyst **23** and flavin catalyst **4e** gave the (*R*)-ester with a moderate enantiomeric excess (44% *ee*), where the flavin catalyst **4e** promoted the catalytic oxidation of the Breslow intermediate derived from **23** and the aldehyde. Kinetic resolution of *trans*-1,2-cyclohexanol provided a modest selectivity factor (*s*) of 5.6 (Scheme 38).[49]



Scheme 39 Flavin-**4d**-catalysed photo-oxidation with molecular oxygen.



Scheme 40 Catalytic cycle of flavin-**4d**-mediated photo-oxidation of benzyl alcohols and benzylamine with molecular oxygen.

Photoinduced oxidation of benzyl alcohols with molecular oxygen has been performed in the presence of simple flavin catalysts and additives such as **4b**–$Mg(ClO_4)_2$,[50a] **4d**–$HClO_4$,[50b] **4d**–$Lu(OTf)_3$,[50c] **4d**–$C_{12}H_{25}SO_3Na$[50d] and **4c**–thiourea.[50e] Recently, the photo-oxidation has been performed in water without an additive. Thus, the photo-oxidation of benzyl alcohol with molecular oxygen in the presence of tetraacetylriboflavin catalyst (**4d**) in D_2O-DMSO proceeds highly efficiently.[51] These photochemical oxidations have substrate limitations to benzyl derivatives; however, it is very important to solve the electron-transfer mechanism of flavin-catalysed photo-oxidations.[52] The method can be applied to the photochemical oxidative deamination of benzylamine to benzaldehyde.[53]

Flavin-mediated photo-oxidation of benzyl alcohols uses the increased oxidation power of the isoalloxazine chromophore in its oxidized form **4d** upon excitation by light. Subsequent two-electron reduction and protonation give dihydroflavin, which is oxidized back to **4d** by molecular oxygen as the terminal oxidant, yielding H_2O_2 (Scheme 40).

Recently, catalytic oxidations with riboflavin-related compounds have been explored in wider fields.[54]

Conclusions

In conclusion, simple, convenient, environmentally benign catalytic methods for oxidation of various substrates with H_2O_2 or molecular oxygen in the presence of flavin-related catalysts under mild conditions have been shown. This principle can be applied to various catalytic oxidative transformations for organic synthesis, including asymmetric synthesis.

Notes and references

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