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Synthetic applications of flavin photocatalysis: a review

Vishal Srivastava, [a] Pravin K. Singh,[a] Arjita Srivastava [a] and Praveen P. Singh *[b]

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Encouraging developments in the field of photocatalysis in last decades, biomolecules namely flavins have been observed to act as a catalyst in several photoredox-catalysed synthetic methodologies. Due to its excellent redox window and good chemical stability, this promising photoactive biological molecule has emerged as a powerful and attractive metal-free organophotocatalyst. This review highlights the design, properties, biosynthesis and application of flavin photoredox catalysts and is expected to contribute to a great extent towards the advancement and development of synthetic methodologies.

1. Introduction

In recent years, both academia and industry[1–10] have attracted extensive interest in the context of green and sustainable chemistry due to the development of clean, economical and efficient chemical processes. Over the last decade, visible light photocatalysis has evolved into a widely used method in organic syntheses as it is the most sustainable reaction inducer and has been increasingly used as a powerful strategy to promote numerous synthetic transformations in organic chemistry[11] as it is a safe, renewable, and inexpensive source of chemical energy. Solar energy (visible light) has great prospects in developing sustainable and eco-friendly protocols and can be used in organic synthesis[12] because it is clean, easy to handle and an unlimited energy source. The conversion of solar energy into chemical energy for chemical transformations,[13,14] has fascinated some researchers, who have incorporated an excellent tactic for the implementation of photoredox catalysts to commence single electron transfer (SET) processes.[15,16] In organic synthesis, the visible light photoredox catalysis has received considerable attention owing to the ready availability, non-toxicity and ease-of-handling.[17] In the last few decades, several metal-free organic dyes, such as eosin Y, rose bengal, Nile red, fluorescein, rhodamine B and perylene, have been applied as inexpensive and environmentally benign preferable alternatives to Ru(II) and Ir(II) complexes in visible-light promoted organic transformations involving SET.[18,19] These organic dyes can serve as a superior alternative to transition metal photoredox catalysts, and have great potential for application in visible-light mediated organic synthesis.[20] In spite of these facts, the general synthetic utility of organic dyes is still rather limited due to relatively few catalyst options.

[a]*Department of Chemistry, CMP Degree College, University of Allahabad, Prayagraj 211002, India*

[b]*Department of Chemistry, United College of Engineering & Research, Naini, Prayagraj 211010, India. E-mail: ppsingh23@gmail.com*

Vishal Srivastava is working as Assistant Professor, Department of Chemistry, C. M. P. College, (Constituent P. G. College of Central University of Allahabad) Prayagraj, India. He has completed Graduation (B.Sc.), Post-Graduation (M.Sc.) in Organic Chemistry and Doctoral Degree (D.Phil.) from Department of Chemistry, University of Allahabad, India. His current research work involves the designing of novel biologically active photoredox catalysed synthetic organic compounds.

Pravin K. Singh is working as Assistant Professor, Department of Chemistry, C. M. P. College, Allahabad, India (Constituent P. G. College of Central University of Allahabad). Dr Singh is actively engaged in advanced research work for the development of environmentally benign, new synthetic routes for various bioactive heterocyclic compounds. He has completed his B.Sc., M.Sc., Doctorate (D.Phil.) and Post-Doctorate (D.Sc.) from the University of Allahabad, India.

The application of inexpensive organic dyes has received increasing attention since some chromophores allow access to unique chemical reactivity.[21] Their use has been restrained[22] due to far more limited availability of their spectroscopic, kinetic, and electrochemical data in comparison to the transition-metal catalysts and for most organic dyes the reactive triplet state is not characterized by charge separation.[23] Furthermore, not all of these dyes can engage in both oxidative and reductive quenching, as well as due to its poor recyclability these organic dyes have limited widespread application.

Flavin catalysis is recognized as an attractive approach for designing green and sustainable transformations. Recently, one of the most widespread examples of dye-based photoredox catalysts is vitamin B_2, riboflavin (RF)[24] and its derivatives, which have received remarkable attention as unique redox organocatalysts that promote numerous catalytic oxidations.[25,26] Flavin derivatives (FLs), serving as the building blocks of redox-active coenzymes, are the reaction sites of numerous thermal and photoinduced processes and are tolerant to the variation of redox potentials.[27–29] Riboflavin and its derivatives exhibit some advantages: among others, they can have maximum absorption in the blue region of the visible light spectrum with high molar absorption coefficients. These photocatalysts are easily accessible, providing a versatile and green method for numerous organic chemical reactions.[30] (−)-Riboflavin (vitamin B_2) is a highly versatile organocatalyst for a variety of transformations[31] due to its inherent energy transfer (ET) and single electron transfer (SET) modes that can be activated upon irradiation.[32] Therefore, it is highly desirable to design new organic photocatalysts with broad redox capabilities. Thus, in modern organic synthesis, flavins exhibit a superior performance in comparison to other photocatalysts due to their better photostability, which will ultimately bring about the future development trend of organic photocatalysts.

Recently, flavin and its derivatives have been found to be ingenious photocatalysts for various reactions (Fig. 1) and emerged as outstanding organic photoredox catalysts for diverse synthetic organic transformations. As this is a robust emerging field, a summary of flavins for organic transformation is highly appreciable. In continuation of our study on photocatalysed organic syntheses,[33] in this study, the recent trends in using flavins as a visible light photocatalyst in organic synthesis are reviewed.

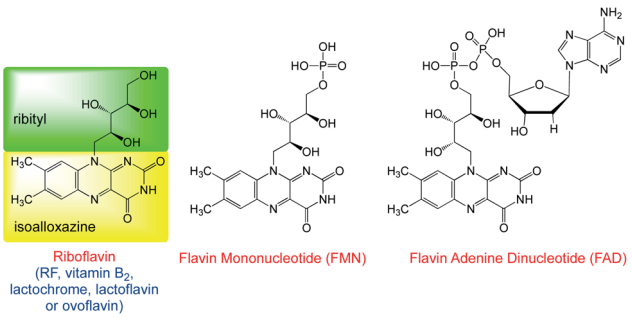


Fig. 1 Naturally occurring flavins.

2. Biosynthesis of riboflavin

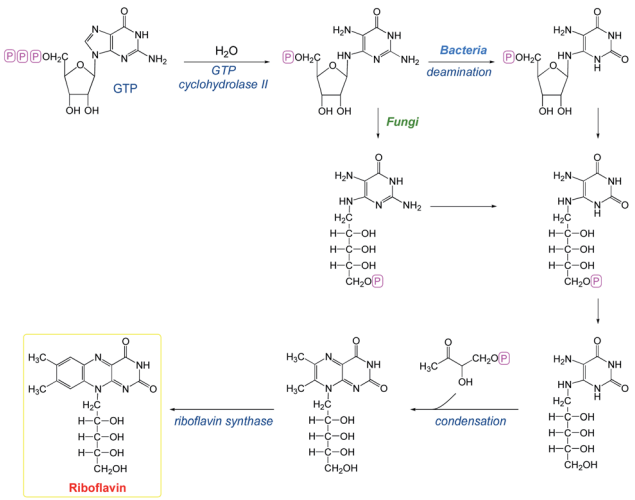
The biosynthesis of riboflavin was investigated by Bachner *et al.*[34] in 2000. One riboflavin molecule requires one molecule of GTP and two molecules of ribulose 5-phosphate as substrates (Scheme 1). Most commercial riboflavin is currently produced or was produced earlier *via* microbial synthesis using specially selected strains of bacteria and fungi.

3. Flavin-related compounds in photocatalysis

Besides flavin related compounds[48] that have also been applied in photoredox catalysis, some of them are naturally occurring, while few compounds are semi-synthetic (Fig. 2).

Arjita Srivastava is working as Assistant Professor in the Department of Chemistry, C. M. P. P. G College, Prayagraj. She has completed her B.Sc. from Ewing Christian College, University of Allahabad, and her M.Sc. in Organic Chemistry, D.Phil. from the Department of Chemistry, University of Allahabad, India. Her current research interest is mainly focused on utilizing visible light and efficient photocatalysts as green tools for the synthesis of bio-active compounds.

Praveen P. Singh is working as Assistant Professor in the Department of Chemistry at the United College of Engineering and Research, Prayagraj, India. He obtained his B.Sc., M.Sc. in Organic Chemistry from T. D. P. G. College (V. B. S. Purvanchal University) Jaunpur and D.Phil. from the Department of Chemistry, University of Allahabad, India. His current research interests include the development of synthetic receptors for the recognition of biological target structures and the application of visible light chemical photocatalysis towards organic synthesis.



Scheme 1 Biosynthesis of riboflavin.[34]

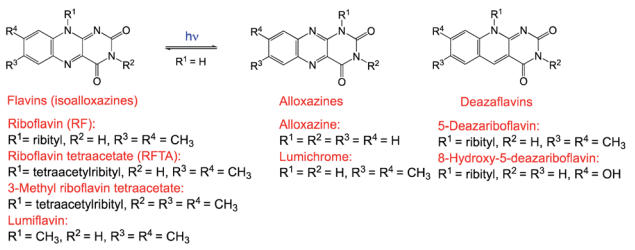


Fig. 2 Structure of flavin-related compounds.[48]

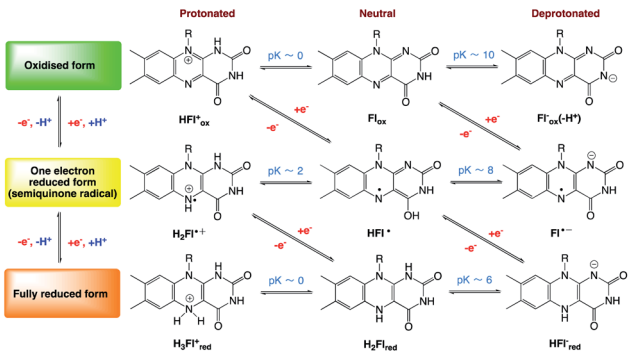
4. Photochemistry of flavin

Three redox states: oxidized, one-electron reduced (as semiquinone) or reduced by two electrons, exhibited by flavins, and each of these redox states has three different protonation states (Scheme 2). Substitution, noncovalent interactions such as hydrogen bonds, and nature of the surrounding protein affect the redox properties, absorption and reactivity of flavins. From electrochemical studies, in water and in protic organic solvents, flavins are reduced reversibly by a two-electron process; the reduction potential of RF is about −0.507 V (*vs.* ferrocene/ferrocenium (Fc/Fc^{+})) in water. Two consecutive one-electron reductions are observed in aprotic media. The reduction potentials of riboflavin tetraacetate (RFTA), −1.18 V and −1.87 V (*vs.* Fc/Fc^{+}), measured in acetonitrile.[35–48]

In flavin photocatalysis, its photocatalytic cycle starts with the irradiation of the oxidized form of flavin (Fl_{ox}) with blue light exciting it into the singlet state ($^{1}Fl^{*}$), followed by an intersystem crossing (ISC) to the triplet state ($^{3}Fl^{*}$) rapidly. In catalysis, the triplet state is the active species and key intermediate, which can then be reduced by an appropriate substrate to the radical anion ($Fl^{\bullet -}$), which is subsequently protonated and further reduced to the flavohydro-quinone anion (HFl_{red}^{-}).

The different redox and protonation states of flavin and their derivative compounds affect the photo absorption properties in context of fluorescence intensity and excited-state lifetimes, which have been found lower for alloxazines than those for flavins (Table 1 for comparison).[49]

The general mechanistic pathway for flavin photocatalysis has been depicted in Scheme 3.[50]



Scheme 2 Different redox and protonation states of flavins (10-substituted isoalloxazines).[35–48]

5. Synthetic applications of flavin

Flavin photocatalysis is an ingenious and green protocol for numerous organic transformations. Since riboflavin has emerged as a stable photocatalyst, as a result of which in recent years several new reactions have been reported indicating the scope and applicability of flavin, including cyclization, decarboxylative cyanation, aerobic oxidation, nitration, $E \rightarrow Z$ isomerization, chemoselective synthesis and oxyamination.

5.1. Cyclization of thiobenzanilides

Schmidt *et al.*[51] reported an efficient photochemical approach for the cyclisation of thiobenzanilides. They performed visible light irradiated synthesis of benzothiazoles from thiobenzanilides using riboflavin as a photocatalyst and potassium peroxydisulfate as a sacrificial oxidizing agent up to 97% yield (Scheme 4).

A plausible mechanism is shown in Scheme 5. Upon the photogeneration of singlet and/or triplet excited states of RFTA, thiobenzanilides can act as a quencher by an electron-transfer reaction, giving rise to the corresponding thiobenzanilide radical cation ($\mathbf{1}^{\bullet +}$) along with the radical anion $RFTA^{\bullet -}$. Notably, the riboflavin moiety can also act as a base (pKa of $[RFTA\text{-}H]^{\bullet} = 8.3$), assisting the deprotonation of $\mathbf{1}^{\bullet +}$. The deprotonation of the thiobenzanilide radical cation $\mathbf{1}^{\bullet +}$ gives the sulfur radical, which undergoes cyclization and further rearomatization by any oxidant species affording 2-substituted benzothiazoles **2**. Peroxydisulfate is necessary to close the catalytic cycle and return RFTA to its ground state.

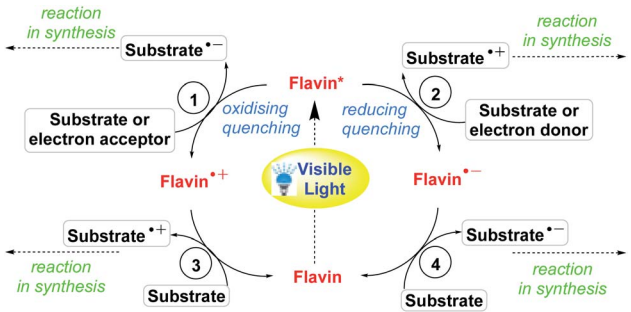
5.2. Direct cyclization

The photocatalytic synthesis of benzo-3,4-coumarins **4** directly from biaryl carboxylic acids **3** without the need for substrate prefunctionalization was investigated by Gilmour *et al.*[52] (Scheme 6). This disconnection relies on the oxidation

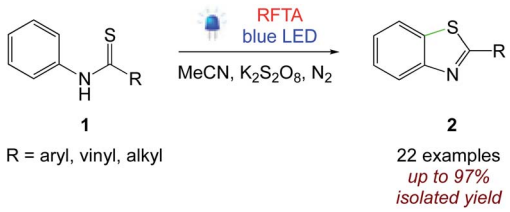
Table 1 Spectral and electrochemical characteristics of the selected flavin derivatives in acetonitrile[49]

Compound	λ_1[a] (nm)	λ_2[a] (nm)	λ_F[b] (nm)	Φ_F[c]	τ_F[d]	E^{0e} (V)
Riboflavin tetraacetate	440	343	505	0.37	6.8 ns	−1.18 (−1.87)
Lumiflavin	443	342	533	0.16	7.7 ns	−0.761
5-Deazariboflavin	399	329	457	0.11	4.03 ns	—
Lumichrome	380	334	437	0.028	0.64 ns	−1.3
$5EtFl^+ClO_4^-$	557	414	661	—	590 ps	0.306 (−0.389)[f]
5EtFlOH	348	—	496	0.0003	500 fs	—

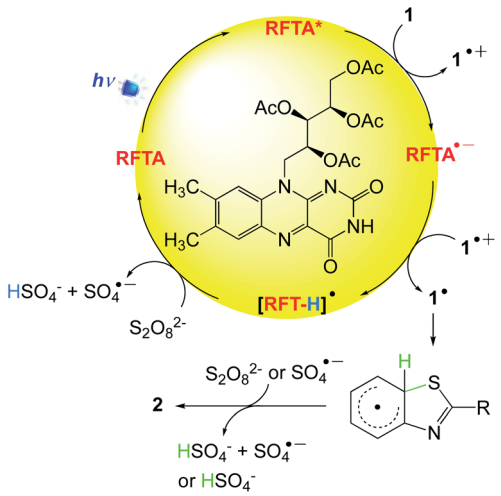
[a] λ_1 and λ_2 are the positions of the two lowest energy bands in the absorption spectra. [b] Maximum of the fluorescence emission spectrum. [c] Fluorescence quantum yield. [d] Fluorescence lifetime. [e] Reversible redox potentials (Fl → Fl^- and Fl^- → Fl^- in the brackets) measured by CV using SCE as standard electrode. [f] Value for 3,10-dimethyl-5-ethyl flavinium (R = Me).



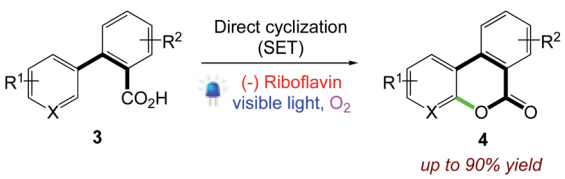
Scheme 3 General mechanisms of flavin catalysis.[50]



Scheme 4 Visible light-mediated cyclisation of thiobenzanilides.[51]



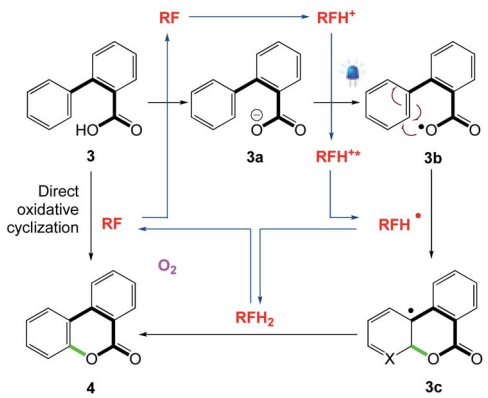
Scheme 5 A plausible mechanism for the cyclisation of thiobenzanilides *via* visible light photocatalysis.[51]



Scheme 6 Direct, photocatalytic synthesis of benzocoumarins *via* (−)-riboflavin-mediated electron transfer.[52]

competence of photoactivated (−)-riboflavin to generate the heterocyclic core *via* photoinduced single electron transfer.

They proposed that singlet state electron transfer from benzoic acid to excited state (−)-riboflavin [$E(^3RF^*/RF^{\bullet-})$ = 1.46 V *vs.* SCE] is operational (Scheme 7).[53] The catalytic cycle is likely initiated by the protonation of (−)-riboflavin (RF) with the strong absorption of the protonated flavin (Scheme 7, RFH^+) occurring at λ_{max} = 402 nm. Subsequent single electron transfer from the carboxylate anion (**3a**) to RFH+ yields the protonated flavin radical ($RFH^\bullet$) and the carboxy radical (**3b**), which can undergo rapid cyclization to intermediate **3c**. Final oxidation and rearomatization of **3c** with $RFH^\bullet$ in a hydrogen atom transfer or SET/deprotonation reaction releases the desired product. The reduced (−)-riboflavin (RFH_2) can, in turn, be reoxidized by molecular oxygen as well as the oxidation of



Scheme 7 A plausible mechanism for the direct, photocatalytic synthesis of benzocoumarins.[53]

intermediate **3c** and RFH$^{\bullet}$ by molecular oxygen cannot be ignored.

5.3. Decarboxylative cyanation of aliphatic carboxylic acids

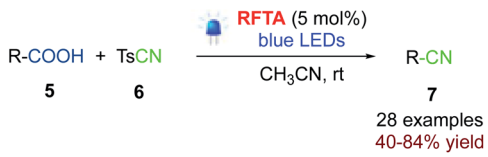
Gomez *et al.*[54] reported the decarboxylative cyanation of aliphatic carboxylic acids at room temperature. Riboflavin tetraacetate promotes the visible light-irradiated oxidation of carboxylic acids. After decarboxylation, the generated radicals are trapped by TsCN, yielding the desired nitriles without any further additive, in a redox-neutral process (Scheme 8). This protocol can be adapted to flow conditions.

Mechanistically, they anticipated that, upon irradiation with visible light ($\lambda_{max} \approx 450$ nm) and after rapid intersystem crossing, the long-lived triplet-excited state of flavin would be oxidant enough ($E_{red} = +1.50$ V *vs.* SCE) to undergo the single-electron oxidation of aliphatic carboxylates [E_{red} from +1.0 V to +1.50 V *vs.* SCE]. Importantly, the flavin moiety can also act as a base, favoring the deprotonation of carboxylic acid prior to its single electron oxidation, or in a proton-coupled electron transfer (PCET). After the rapid decarboxylation of the aliphatic acyloxyl radical, the generated radical is intercepted by Ts-CN, affording the desired nitrile and *p*-toluenesulfonyl radical (Ts$^{\bullet}$). The latter radical could be reduced by the hydroflavin radical, regenerating the photocatalyst and producing TsH after protonation, in a redox-neutral process. Alternatively, the *p*-toluenesulfonyl radical could abstract a hydrogen atom (HAT) from FH$^{\bullet}$ to turn over the photocatalyst (Scheme 9).

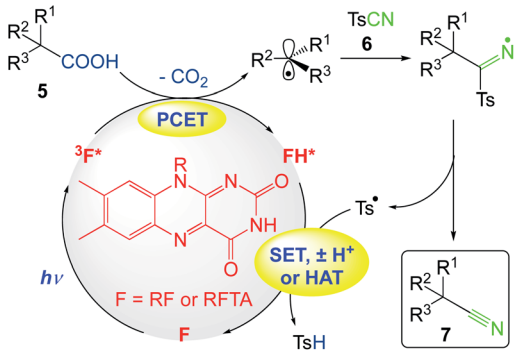
5.4. Aerobic oxidation of benzylic C–H bonds

Pasau and co-workers[55] reported a continuous mesofluidic process for benzylic C–H oxidation with moderate to good yields using a flavin photocatalyst upon visible-light irradiation and an iron additive [$Fe(ClO_4)_2$] *via* the incorporation of singlet oxygen ($^1O_2$) for the direct formation of oxidized C=O or CH–OH compounds (Scheme 10).

A plausible mechanism is shown in Scheme 11. Upon irradiation, photocatalyst (RFT), is excited to its triplet state (RFT*) and can undergo consecutive electron reduction and protonation, leading concomitantly to the formation of $RFTH_2$ and the radical (R$^{\bullet}$, **8a**). At this stage, the $^1O_2$ singlet will react with the radical species to generate the peroxo-radical (ROO$^{\bullet}$, **8b**) intermediate, affording the ketone or alcohol precursor of the desired products. $^1O_2$ will then oxidize the intermediate $RFTH_2$ in order to regenerate the catalyst and form the H_2O_2 side product. Finally, hydrogen peroxide is reduced to O_2 and H_2O in the presence of an iron additive.



Scheme 8 Decarboxylative cyanation of aliphatic carboxylic acids.[54]



Scheme 9 Plausible mechanism of the decarboxylative cyanation of aliphatic carboxylic acids.[54]

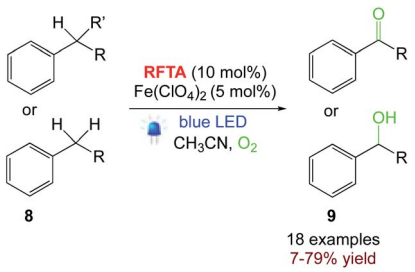
5.5. Nitration of protected anilines

König *et al.*[56] investigated the nitration of protected anilines with riboflavin tetraacetate (RFTA) upon visible light irradiation. In this protocol, sodium nitrite serves as the NO_2 source in the visible-light driven room temperature reaction. Numerous nitro anilines are obtained in moderate to good yields without the addition of acid or stoichiometric oxidation agents. The catalytic cycle is closed by aerial oxygen as the terminal oxidant (Scheme 12).

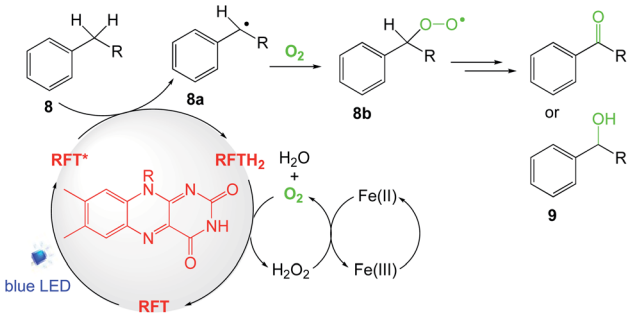
After excitation, photocatalyst (RFTA) oxidizes the aniline derivative **10**.[57,58] The acidity of radical cations increases compared to the neutral compound, so the consecutive formation of the stabilized radical **10a** *via* the loss of a proton can occur.[59,60] The radical species nitrogen dioxide is formed *via* different pathways and is able to react with **10a**.[61,62] After rearomatization, the desired *para*- and *ortho*-regioisomeric substitution products **11** are obtained (Scheme 13).

5.6. $E \rightarrow Z$ isomerization of polarized alkenes (olefins)

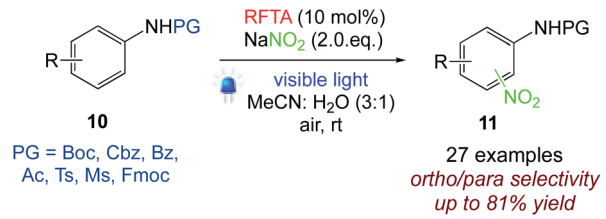
Metternich *et al.*[63,64] reported the first highly *Z*-selective isomerization **13** of polarized alkenes **12**, catalysed by riboflavin under visible light irradiation. This study was inspired by the susceptibility of crystalline (−)-riboflavin in the eyes of vertebrates to invert the intrinsic directionality of retinal isomerization. They demonstrated broad substrate scope (up to 99 : 1 *Z* : *E*) along with the evidence of mechanistic dichotomy *via* both singlet and triplet energy transfer mechanisms (Scheme 14). The simple $E \rightarrow Z$ isomerization of activated dienes, based



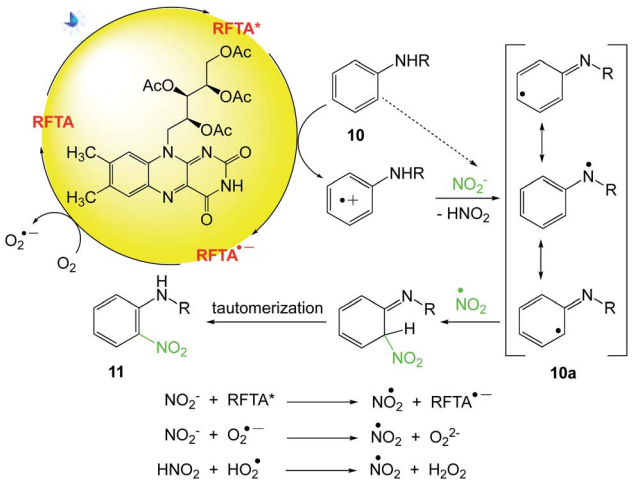
Scheme 10 Aerobic oxidation of benzylic C–H bonds.[55]



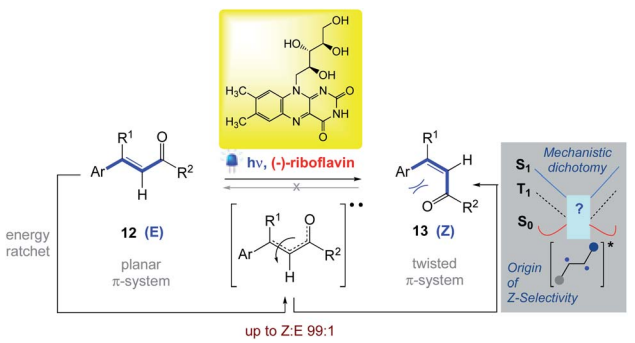
Scheme 11 Plausible mechanism of the aerobic oxidation of benzylic C–H bonds.[55]



Scheme 12 Nitration of protected anilines.[56]



Scheme 13 Plausible mechanism of nitration of protected anilines.[56]



Scheme 14 Photocatalytic isomerization of polarized alkenes.[63,64]

on the β-ionyl motif intrinsic to retinal, is also reported by Gilmour *et al.*[65] by using inexpensive (−)-riboflavin (vitamin B_2) under irradiation at 402 nm.

5.7. Chemoselective synthesis of unsymmetrical disulfides

Iida *et al.*[66] have developed the chemoselective synthesis of unsymmetrical disulfides using the oxidative heterocoupling reaction of two different thiols. The riboflavin-based catalyst successfully promoted the formation of the phototropin-like flavin–thiol adduct under visible light irradiation, the mild reactivity of adduct, played a crucial role in the chemoselective cross-coupling. This green oxidative transformation is driven by visible light due to the photo and redox-organocatalysis of flavin, and molecular oxygen under mild metal-free conditions (Scheme 15).

6. Cooperative catalysis

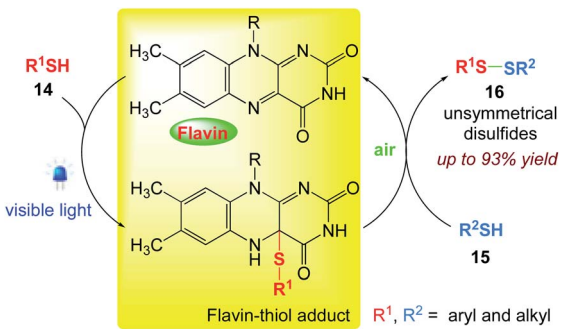
Cooperative catalysis is applicable when two catalysts and two catalytic cycles work in concert to generate a single new bond in organic transformations. Being a stable photocatalyst, flavin is also applied as a cooperative catalyst in combination with other organocatalyst and flavin–amine hybrid to carry out aerobic oxidations as well as oxyamination reactions.

6.1. Aerobic oxidation of unactivated benzylic substrates

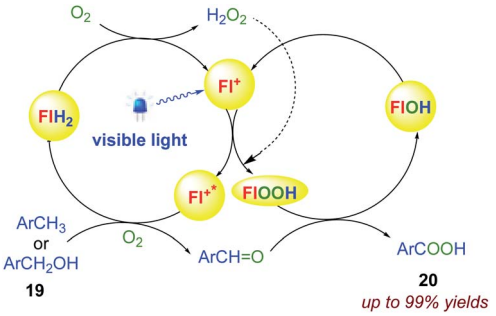
Cibulka *et al.*[67] reported a system with ethylene-bridged flavinium salt (combining flavin photocatalysis and organocatalysis **18b**), which catalyzes the aerobic oxidation of toluenes and benzyl alcohols **19** with high oxidation potential (E_{ox} > +2.5 V *vs.* SCE) to give the corresponding benzoic acids **20** under visible light irradiation (Scheme 17). This is caused by the high oxidizing power of excited **17b** ($E(2b^*)$ = +2.67 V *vs.* SCE) involved in photooxidation and by the accompanying dark organocatalytic oxygenation provided by the *in situ* formed flavin hydroperoxide **18b–OOH** (Scheme 16).[68–76]

6.2. Peptide bridged flavin–amine hybrid

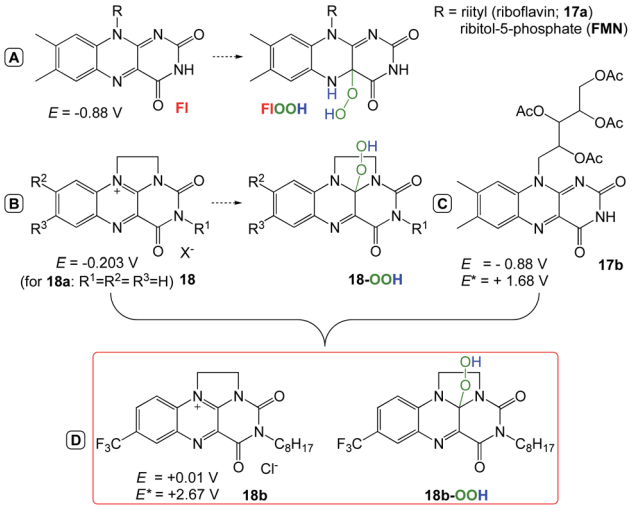
Imada *et al.*[77] reported a peptide-bridged flavin–amine hybrid that can catalyze the α-oxyamination of aldehydes **21** with



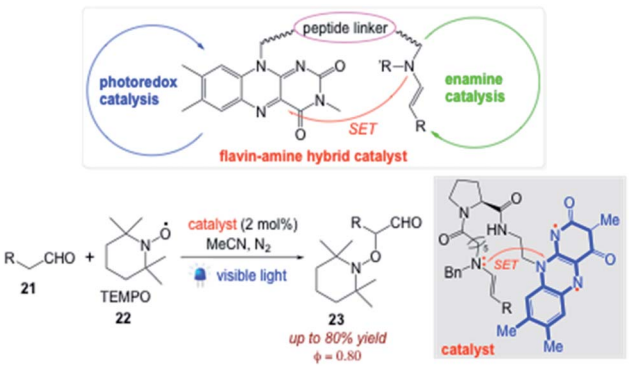
Scheme 15 Flavin–thiol adduct-mediated heterocoupling reaction.[66]



Scheme 16 Aerobic oxidation of unactivated benzylic substrates.[67]



Scheme 17 Activation modes of flavin "co-factors" for oxidations in natural and artificial systems.[68–76]



Scheme 18 Efficient use of photons in photoredox/enamine dual catalysis with a peptide-bridged flavin–amine hybrid.[77]

TEMPO **22** under weak blue light irradiation to achieve an extremely high quantum yield of reaction ($\Phi = 0.80$). The flavin ring system and a secondary amine have been integrated through a short peptide linker with the aim of using photons as efficiently as possible in the photoredox/enamine dual catalysis (Scheme 18).

7. Conclusions

Flavins and their derivatives can serve as a green and versatile catalyst to carry out several organic transformations. In the last few years, few flavin catalysed chemical reactions were reported that clearly indicate that properties and possible synthetic applications of flavins and their derivatives are still in their preliminary stage, which needs to be further explored to realize its full potential. The photostability of the flavin catalyst must be enhanced. For the application of the oxidised form of the flavin catalyst with higher substrate concentration and substrate binding sites, the ISC rate to triplet state after excitation must be enhanced and further exploration is needed to use the reduced form of flavin in organic transformations. In summary, flavins and their derivatives have been used as simple, economical and metal-free photocatalysts for organic transformation recently, with a view of exploring new routes for the development of a novel visible light-induced organic synthesis and it will explore a new era for the biomaterial-based photoredox synthesis.

Conflicts of interest

There are no conflicts to declare.

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