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Methyl Ester Modified Flavins and their Ring-Contracted Analogs for Photocatalytic Applications

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“And I knew exactly what to do.

But in a much more real sense, I had no idea what to do.”

Michael Scott

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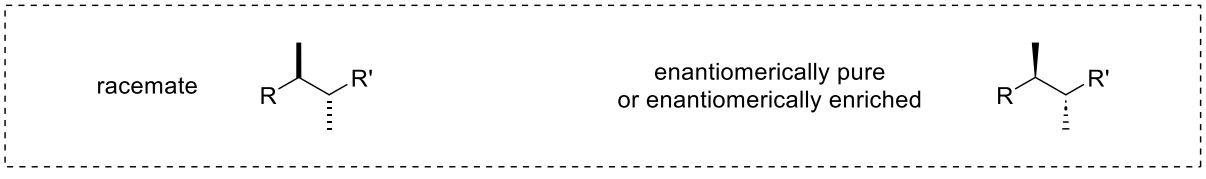
In this thesis, the relative configuration of racemates is represented by straight lines (bold or hashed). The absolute configuration of enantiomerically pure or enriched compounds is represented by wedge-shaped lines (bold or hashed).



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Abstract

The isoalloxazine scaffold is the catalytically active site of flavin-dependent enzymes in biological systems. Due to the protein environment and the associated stabilization of reactive intermediates, various transformations can be catalyzed by flavins in nature. However, if flavins are to be used in catalytic systems on a preparative scale in the laboratory, several problems arise as, for example, the absence of an enzymatic environment, which reduce catalytic activity. Here, we show that introducing a methyl ester functionality in the *C*6 position of the isoalloxazine backbone can stabilize photochemically generated, reactive intermediates even in the absence of an enzymatic environment. Organocatalysts modified in this way allow the functionalization of dehydroamino acids under the influence of visible light. We also show that this concept of "molecular editing" can be extended to ring-contracted flavins, which consist of an imidazolonequinoxaline core. We use these photocatalysts to convert α-tropolone diastereoselectively into *trans*-3,4-disubstituted cyclopentanones in a multistep synthesis with differently substituted benzaldehydes. Analogous catalysts without methyl ester substitution and other established photocatalysts, including unmodified flavins, are inactive in this reaction. Our results show that using functionalized isoalloxazine and imidazolonequinoxaline compounds allows for new catalytic transformations that were previously unfeasible or only possible in an enzymatic environment.

Kurzzusammenfassung

Das Isoalloxazin-Grundgerüst ist das katalytisch aktive Zentrum von Flavin-abhängigen Enzymen in biologischen Systemen. Aufgrund der Protein-Umgebung und der damit einhergehenden Stabilisierung reaktiver Intermediate können in der Natur eine Vielzahl verschiedener Transformationen durch Flavine katalysiert werden. Möchte man Flavine aber in katalytischen Systemen im präparativen Labormaßstab nutzen, ergeben sich eine Reihe von Problemen wie zum Beispiel die Abwesenheit einer enzymatischen Umgebung, die die katalytische Aktivität reduzieren. In dieser Arbeit zeigen wir, dass das Einbringen einer Methylester-Funktionalität in der *C*6-Position des Isoalloxazin-Grundgerüsts photochemisch generierte, reaktive Intermediate auch ohne das Vorhandensein einer enzymatischen Umgebung stabilisieren kann. Derart modifizierte Organokatalysatoren erlauben die Funktionalisierung von Dehydroaminosäuren unter Einfluss von sichtbarem Licht. Wir zeigen zudem, dass dieses Konzept des „Molekularen Editierens“ auch auf Ring-verengte Flavine, namentlich Imidazolonquinoxaline, ausgeweitet werden kann. Diese Photokatalysatoren nutzen wir, um α-Tropolon in einer Mehrschritt-Synthese mit verschieden substituierten Benzaldehyden diastereoselektiv zu *trans*-3,4-disubstituierten Cyclopentanonen umzusetzen. Analoge Katalysatoren ohne Methylester-Substitution und andere etablierte Photokatalysatoren, darunter auch unmodifizierte Flavine, sind in dieser Umsetzung inaktiv. Unsere Ergebnisse zeigen, dass der Einsatz funktionalisierter Isoalloxazin- und Imidazolonquinoxalinkörper neue katalytische Umwandlungen ermöglicht, die zuvor nur in enzymatischer Umgebung realisierbar oder komplett unzugänglich waren.

Abbreviations

3D	three-dimensional
Ac	acetyl
ADP	adenosine diphosphate
ADPS	*alkyl-dihydroxyacetone phosphate synthase*
Arg	arginine
*As*LOV2	phototropin 1 LOV 2 domain of *Avena sativa*
a. u.	arbitrary units
BDE	bond-dissociation energy
Bn	benzyl
Boc	*tert*-butyloxycarbonyl
Bu	butyl
BVMO	*Baeyer-Villiger* monooxygenases
Bz	benzoyl
Cbz	benzyloxycarbonyl
cf.	*conferatur* (confer)
CHD	cycloheptadiene
CPS	counts per second
Cys	cysteine
Δ	heat supply
DHA	dehydroamino acid
DHAP	dihydroxyacetone phosphates
DMSO	dimethyl sulfoxide
DNA	deoxyribonucleic acid
dtbpy	di-*tert*-butyl-2,2'-bipyridine
ED	electron diffraction
e.g.	*exempli gratia* (for example)
equiv.	equivalents
ESI†	electronic supplementary information
Et	ethyl
et al.	*et alia* (and others)
FAD	flavin adenine dinucleotide

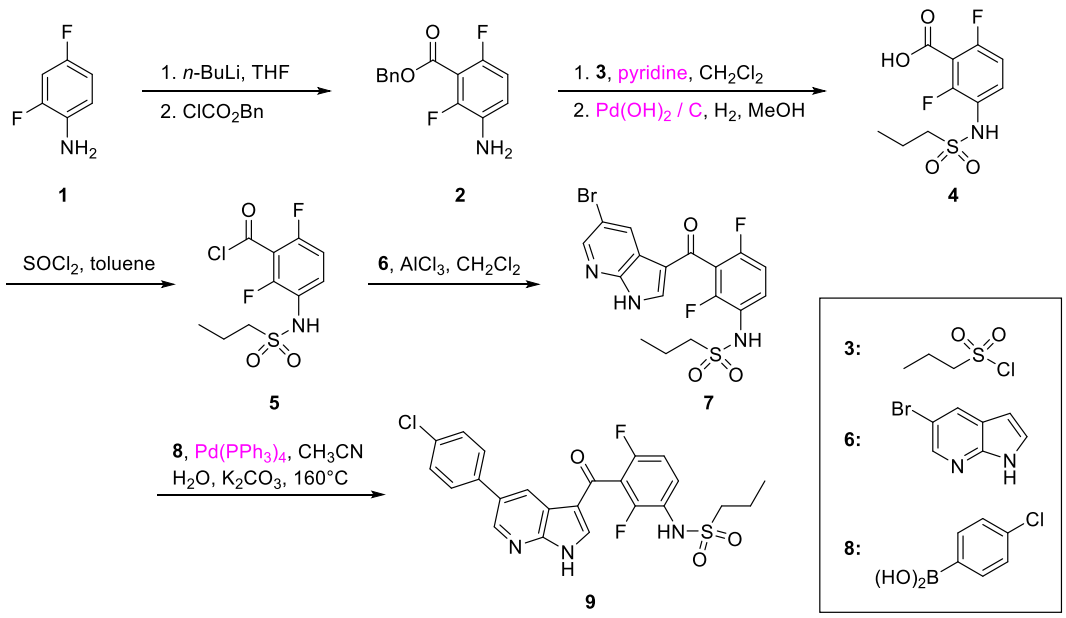
Fl	flavin
FMN	flavin mononucleotide
Gln	glutamine
HAT	hydrogen atom transfer
HFIP	1,1,1,3,3,3-hexafluoroisopropanol
His	histidine
HPLC	high-performance liquid chromatography
HR-ESI	high-resolution electrospray ionization
hv	indicates light, *h* is Planck's constant, *v* is photon frequency
ISC	intersystem crossing
λ	wavelength
LED	light emitting diode
LOV	light, oxygen, and voltage
MAO	*monoamine oxidase*
mCPBA	*meta*-chloroperoxybenzoic acid
Me	methyl
NAD(P)H	nicotinamide adenine dinucleotide (phosphate)
Bu	butyl
n. d.	no product formation was detected
NMR	nuclear magnetic resonance
NOE	nuclear *Overhauser* effect
Pr	propyl
PCET	proton coupled electron transfer
Ph	phenyl
PHBH	*4-hydroxy benzoate 3-hydroxylase*
Phth	phtalimidyl
PMHS	poly(methylhydrosiloxane)
ppm	parts per million
ppy	2-phenylpyridine
RF	riboflavin, vitamin B2
RFTA	riboflavin tetraacetate
r. t.	room temperature
SCE	saturated calomel electrode

SET	single-electron transfer
S_NAr	nucleophilic aromatic substitution
Φ_T	triplet quantum yield
τ	lifetime
TEMPO	(2,2,6,6-tetramethylpiperidin-1-yl)oxyl
TBADT	tetra-*n*-butylammonium decatungstate
TBA	tetra-*n*-butylammonium
TFE	trifluoroethanol
THF	tetrahydrofuran
TMP	2,2,6,6-tetramethylpiperidinyl
Tyr	tyrosine
UDP	*uridine diphosphate*
UGM	*uridine diphosphate galactopyranose mutase*
UV	ultraviolet
Val	valine
Vis	visible
vs.	*versus*

Contents

1. Introduction

Catalysis is a powerful tool in synthesizing various compounds, for example, sulfuric acid, pharmaceuticals and agrochemicals, since a catalyst changes the rate of a reaction without being consumed.[1] The activation energy of the process is reduced, which enables lower reaction pressures and lower reaction temperatures and, thus, allows for saving energy. The importance of the field of catalysis becomes even more apparent when the current active drugs in the pharmaceutical industry are considered, where roughly 60 % are small molecules (*vs* biologics).[2] Small molecules are typically synthesized in preparative manners, with most steps mediated by catalysts.[3] To illustrate this, the synthesis of Vemurafenib, a protein kinase inhibitor, is depicted in **scheme 1**.[3] If a catalyst is used for a transformation, it is marked in pink. The synthesis of Vemurafenib shows that catalysts are indispensable for the preparation of pharmaceuticals.



Scheme 1: Synthesis of Vemurafenib starting with 2,4-difluoroaniline;[3] Catalysts are marked in pink.

The significance of catalysts is the reason behind the awarding of the 2021 Nobel Prize in chemistry to Benjamin List and MacMillan. Both are engaged in organocatalysis, and the following passage represents an excerpt from *ARDalpha*'s coverage of the research conducted by Benjamin List and David MacMillan: „For a long time, scientists were convinced that, in principle, there were only two types of catalysts: metals and enzymes. However, Benjamin List and David MacMillan independently developed a third type of catalysis in 2000: it is known as asymmetric organocatalysis and is based on small organic molecules."[4] Indeed, their

investigations of using organic compounds as catalysts opened an entirely new field of chemistry and many organocatalysts have been developed since then.[5] The work of List and MacMillan is of importance because they not only add a third toolbox, which increases the spectrum of catalytic applications, but organic catalysts also have some significant advantages compared to metal-based catalysts: Organocatalysts are often less expensive, less toxic, more abundant, and environmentally more sustainable.[6] Moreover, they are often less prone to decomposition by air or moisture, and are frequently applicable under ambient conditions.[6]

The advances of organacatalysts compared to metal catalysts have boosted research in the field of organocatalysis in recent decades.[5] However, metal-catalyzed reactions are still the most dominant part of catalysis at industrial scales (*cf.* **scheme 1**).[3] This is due to the fact that reactions catalyzed by organocatalysts often require high catalyst loadings and do not exhibit the diversity of metal catalysts.[7] For sustainable catalysis to be carried out on a large scale in the future, further research in the field of organocatalysts is required in order to be able to use them extensively for a wide variety of industrial processes.

A promising class of organocatalysts are flavins. They can be isolated from various organisms or synthesized in a few steps in the laboratory with abundant starting materials and can be modified in this way. Several intriguing examples of flavin catalysis in synthetic chemistry have already been reported and will be highlighted here. However, many of these examples apply simple, unmodified flavins. It was the aim of this work to prepare tailor-made flavins and to investigate their application in catalysis.

2. Theoretical Background

2.1. Flavoenzymes: Flavin-Dependent Enzymes in Nature

2.1.1. General Information

The first discovered flavoprotein is the "old yellow enzyme".[8] It was isolated by *Warburg* and *Christian* in 1933 from Brewer's Bottom Yeast.[8] The fluorescent yellow appearance gave the protein its temporary name. Shortly before this discovery was made, the structure of the flavin chromophore (isoalloxazine) was elucidated.[9] Two years later, in 1935, *Theorell* identified the cofactor of the flavoprotein as riboflavin 5'-phosphate.[10] Since then, the interest in flavin-dependent enzymes and their effect on living organisms has grown substantially. To further understand their role in biological systems, hundreds of flavoenzymes have been isolated and characterized.[11] Due to their wide distribution in diverse organisms, flavoenzymes were extracted from various biological sources, ranging from microbes to mammals.[11] Flavoenzymes are able to catalyze both one- and two-electron oxidation or reduction reactions. This feature allows them to be a key component in the four electron transfer energy metabolism systems: photosynthesis, aerobic respiration, denitrification, and sulfur respiration.[12] In these systems, flavoenzymes and nicotinamide adenine dinucleotide (phosphate) (NAD(P)H) synergistically collaborate: NAD(P)H functions as a cofactor and displays an electron donor or acceptor, and the flavoenzyme transfers electrons from/to NAD(P)H.[12] In their role as electron carriers, flavoenzymes occur as flavin adenine dinucleotide (FAD, **10**) and flavin mononucleotide (FMN, **11**). Their structure can be further divided into riboflavin (RF; vitamin B2, **12**) and the active isoalloxazine core (**13**) (**figure 1**). *In vivo*, FAD and FMN are synthesized from riboflavin by the *FAD synthetase* and *riboflavin kinase*, respectively.[13]

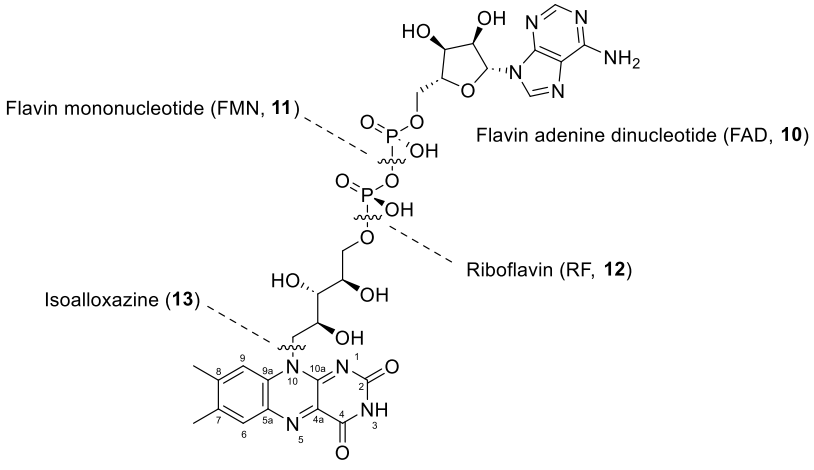
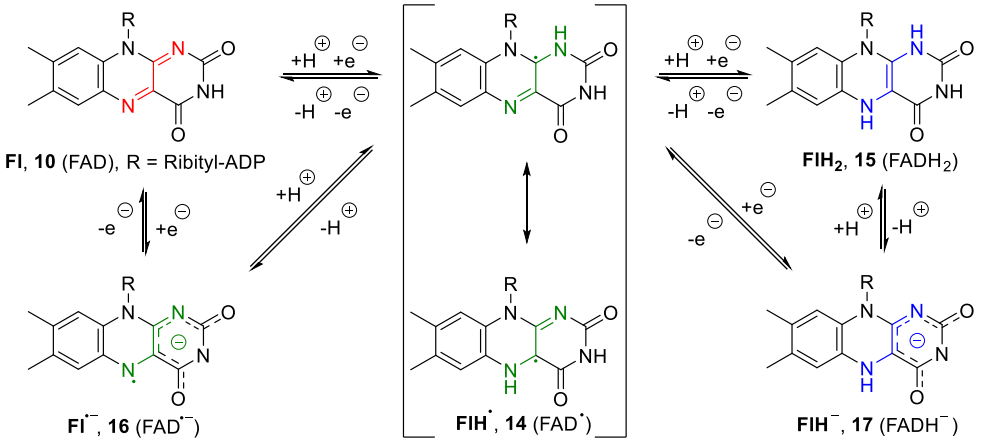
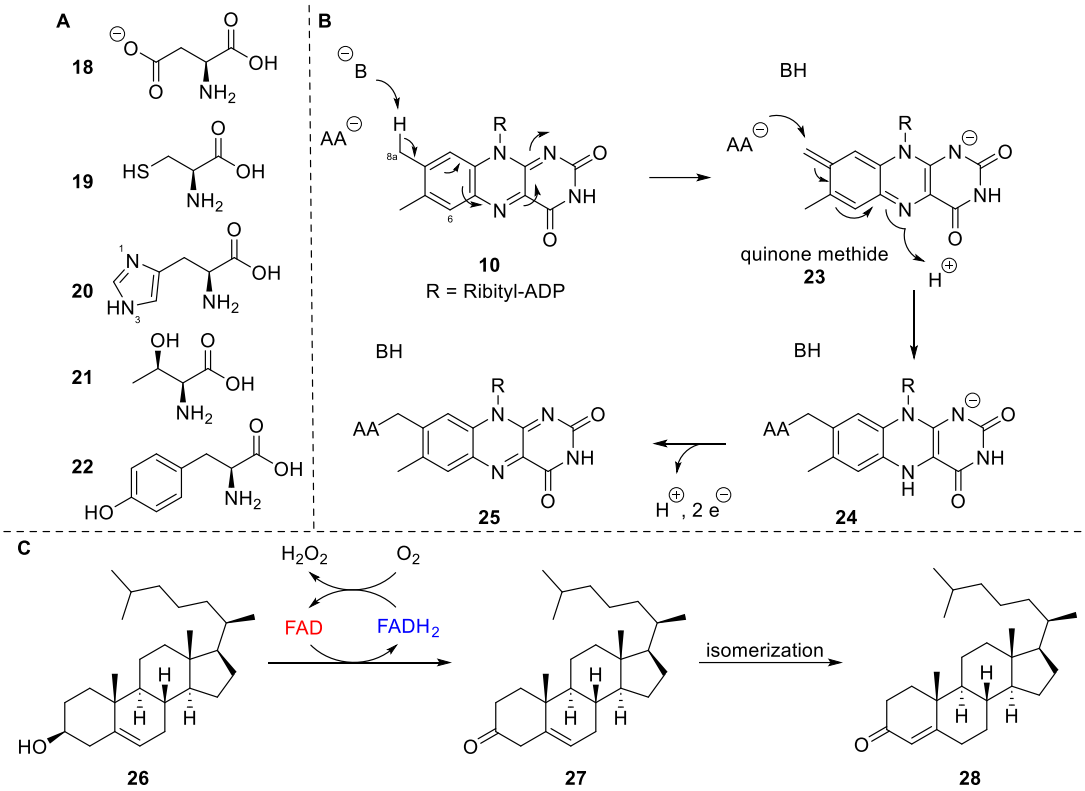


Figure 1: Structure of FAD, FMN, RF, and isoalloxazine (with numbering system).

The ability to perform one- and two-electron oxidation/reduction reactions stems from the unique electronic properties of flavins: The active isoalloxazine core can exist in mainly three distinctive electronic configurations. Predominantly, it exists in the oxidized (quinone, **Fl**, **10**) and reduced state (hydroquinone, **FlH_2**, **15**), less often in the one-electron reduced state (semiquinone, **$FlH^{\bullet}$**, **14**) (**scheme 2**).[11] Structurally, most flavin cofactors are bound tightly but non-covalently *via* a high-affinity binding pocket to the apoprotein active site.[14] In 1955, however, it was discovered that flavin cofactors can also be bound covalently to the enzyme.[15] This subtype makes up about 10 % of the flavoenzymes, with an amino acid attached at the *C*6 or *C*8a position of the isoalloxazine. Aspartate (**18**), cysteine (**19**), histidine (**20**), threonine (**21**), and tyrosine (**22**) are possible binding partners, whereby the *C*8a flavin *N*3 histidyl linkage is the most abundant (**schema 3 A**).[14] The linkage is not understood completely yet, but it is assumed to happen *via* the *quinone methide* mechanism. This is schematically shown for an attachment of an amino acid at the *C*8a position (**scheme 3 B**). Here, the *C*8a position is deprotonated by a nearby base (B), likely an amino acid side chain, to form a resonance-stabilized anion **23**. Due to acidic activation of the *N*5 position, the pseudo-anion is nucleophilically attacked at the *C*8a position by an amino acid to form a covalent linkage between the flavin cofactor and the enzyme (**24**). Lastly, the cofactor is oxidized to give the quinoid isoalloxazine heterocycle **25**.[16] This linkage modulates the redox cofactor in a way that these covalently bound flavins are able to perform thermodynamically more challenging reactions than their non-covalently bound analogs.[17] They are part of, for example, *cholesterol oxidase*[17a] (**scheme 3 C**)[18] and *sarcosine oxidase*.[17b]



Scheme 2: Oxidation states of isoalloxazine: quinoid Fl **10**, semiquinoid $FlH^{\bullet}$ **14**, and hydroquinoid FlH_2 **15**.



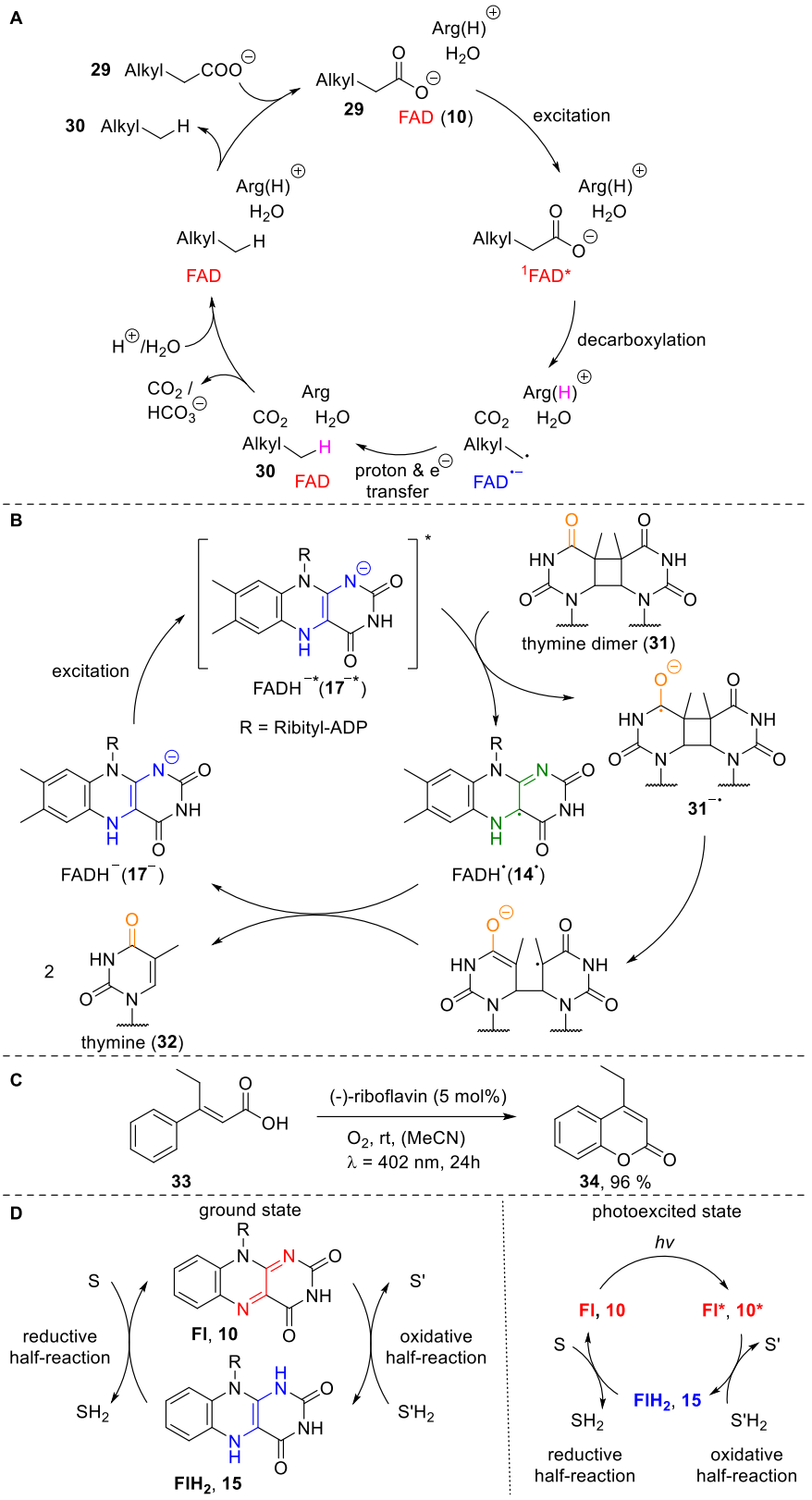
Scheme 3: **A**: Amino acids that form covalent bonds with flavins. **B**: *Quinone methide* mechanism for the covalent linkage of flavin *C*8a to an enzyme; 'B' represents a base; 'AA' indicates one of the five amino acids depicted in **A**. **C**: Illustration of *cholesterol oxidase* which oxidizes cholesterol (**26**) to 5-cholesten-3-one (**27**); the latter isomerizes to 4-cholesten-3-one (**28**).

Flavin-dependent enzymes catalyze a wide range of reactions.[11] Most flavoenzymes are oxidoreductases[19] which include monooxygenases as well as hydroxylases, oxidases, and dehydrogenases as well as reductases.[20] They catalyze electron transfers from a suitable electron donor to dioxygen as an electron acceptor.[21] Their categorization depends on the rate of the reaction with O_2 and the range of products. While typically flavins act as catalysts for non-photochemical transformations, they can also be excited by light. Flavins absorb light in the high energy visible range (λ = 450 nm),[22] which results in their bright yellow color. Both in nature and synthetic chemistry, there are examples of flavins applied in catalysis under photochemical conditions.[23] Among the photoactive flavoenzymes, the *fatty acid photodecarboxylase* is an intriguing example.[23a] This enzyme employs excited quinoid flavin in the decarboxylation of fatty acids (**scheme 4 A**). Upon light excitation, an electron transfer from the fatty acid anion (**29**) to photoexcited ^{1}FAD* occurs, followed by a quasi-instantaneous decarboxylation. Electron and proton transfer to the alkyl radical are presumably coupled and infra-red studies suggest arginine as the final proton donor. Quinoid flavin is regenerated and CO_2 is released – mostly as bicarbonate. Alkane **30** leaves the active site and new substrate (**29**) is bound to complete the catalytic cycle.[23a]

Among the photoactive flavoenzymes, the *deoxyribonucleic acid* (*DNA) photolyase* is also of particular interest. Unlike other photoactive flavoenzymes, which employ the excited oxidized isoalloxazine core, *DNA photolyase* utilizes the excited reduced isoalloxazine core and cleaves thymine dimers to form two equivalents of monomeric thymine (**scheme 4 B**).[24] Thymine dimers are a result of ultraviolet (UV)-light-mediated [2+2]-cycloaddition of two thymine monomers, and hinder the replication of DNA.[23c] Therefore, *DNA photolyase* is a form of repair mechanism that can operate by activating the isoalloxazine core with visible light. Reduced, deprotonated $FADH^-$ (**17**$^-$) is activated into its excited state **17**$^{-}$* by irradiation with light. Excited $FADH^{-}$* is a strong reductant and donates an electron to the thymine dimer (**31**). The ketyl radical **31**$^{-\bullet}$ undergoes cyclobutane ring-opening and back electron transfer to semiquinoid flavin **14**$^{\bullet}$. This closes the catalytic cycle and releases two equivalents of thymine (**32**).[24]

A synthetic example is the catalytic $E \rightarrow Z$ isomerization of activated olefins, reported in 2015 by the *Gilmour* group.[23d] This energetically unfavorable transformation is achieved by triplet energy transfer, which is mediated by excited quinoid (–)-riboflavin. The subsequent cyclization proceeds *via* a radical pathway also catalyzed by the flavin.[23d] By subjecting (*E*)-cinnamic acid **33** to these reaction conditions, the formation of the corresponding 4-substituted coumarin **34** was observed (**scheme 4 C**). This example shows that flavins cannot only be incorporated greatly into preparative methods but also that different aspects of flavin catalysis can be combined to achieve multi-step reactions with one catalyst.

The catalytic cycle of flavins consists of two separate half-reactions. Typically, the flavin alternates between its oxidized (**Fl**, **10**) and its reduced (**FlH_2**, **15**) state. In its oxidized form, the flavin oxidizes a certain substrate and is, in turn, reduced (oxidative half-reaction). The reduced form of the flavin reduces an electron acceptor (*e. g.* molecular oxygen) and is, in turn, oxidized (reductive half-reaction).[25] This is true both for ground-state catalysis and for photochemical catalysis of flavins (**scheme 4 D**). However, there are cases in which the half-reactions do not undergo two-electron processes, but only one-electron process, and therefore either the oxidized form or the reduced form of the isoalloxazine core is not involved.[23b] This is, for example, true for the shown reaction of the *DNA photolyase*, which does not include the oxidized form of isoalloxazine (**Fl**, **10**) (**scheme 4 B**). In this case, the reductive half-reaction is the reduction of thymine dimer and the formation of the semiquinoid flavin $FADH^{\bullet}$ (**14**$^{\bullet}$). The oxidative half-reaction consists of the dimer cleavage and the one-electron transfer to $FADH^{\bullet}$ (**14**$^{\bullet}$) to reform the active catalyst $FADH^-$ (**17**$^-$). Here, the oxidized and reduced substrate is the same molecule.

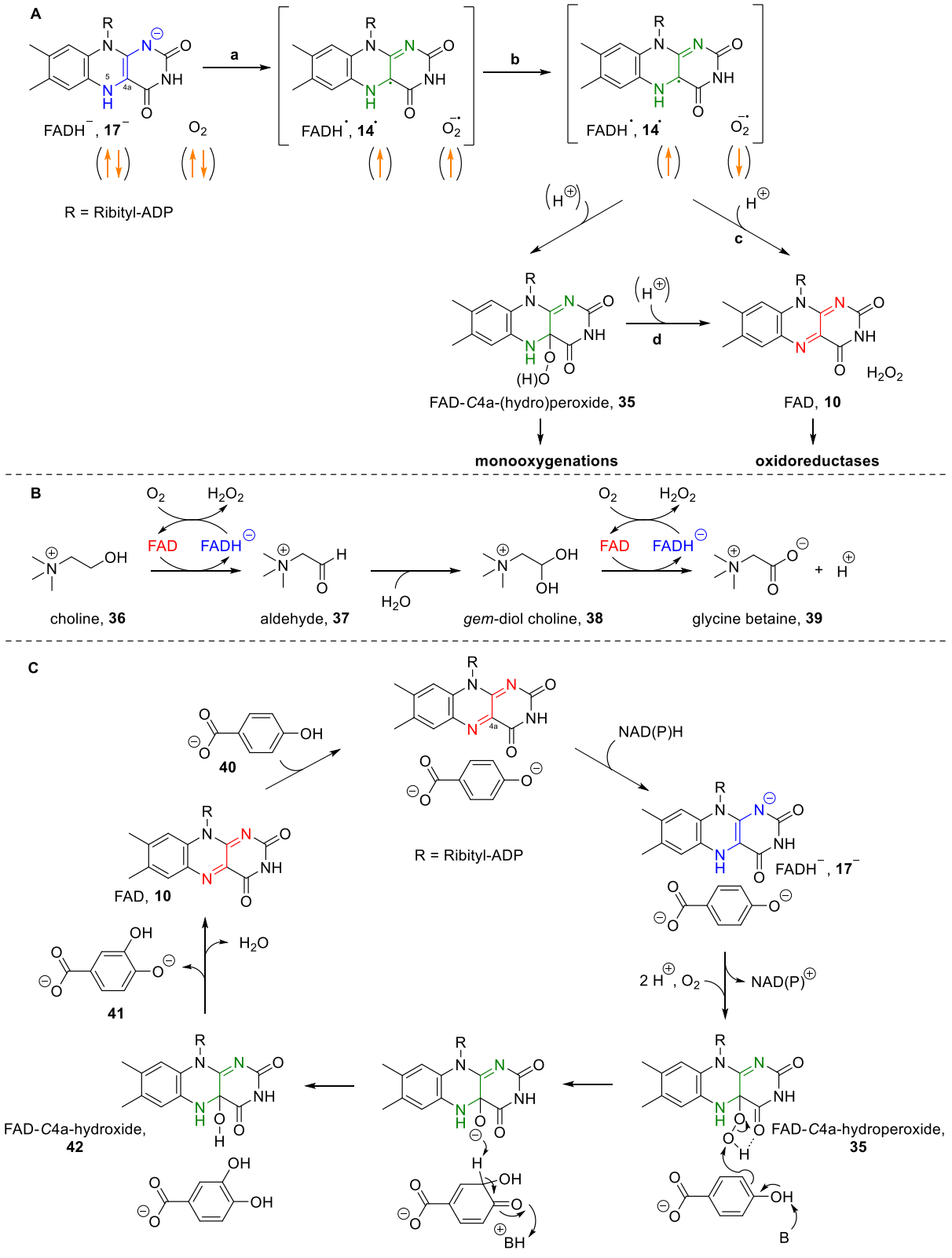


Scheme 4: **A** and **B**: Flavins as photocatalysts in nature: mechanism of the *fatty acid photodecarboxylase* (**A**) and mechanism of the *DNA photolyase* (**B**). **C**: Flavins as photocatalysts in synthesis: preparation of coumarins from (*E*)-cinnamic acid. **D**: General mechanism for the reduction and oxidation of flavins. Flavins in photocatalytic transformations can also operate as one-electron catalysts (*cf.* **scheme 4B** & **15**); 'S' and 'S'' represent suitable substrates.

2.1.2. Covalent Adducts of Flavins in Flavoenzymes

2.1.2.1. Covalent Adducts of Reduced Flavins

Typically, flavoenzymes are understood almost exclusively as oxidoreductases.[26] This applies for a plethora of flavin-bound proteins that use the flavin cofactor as an oxidant for a diverse range of substrates. An external oxidant, in many cases molecular oxygen from air, serves as a re-oxidant for the reduced flavin cofactor. However, as many applications of this diverse cofactor have been uncovered over the years since its discovery, the historical definition of flavoproteins as ”oxidoreductases” has been found to be an oversimplification.[27] Flavins catalyze many different reactions, and many do not exhibit a net redox change,[28] among which is the thymine dimer cleavage (*cf.* **scheme 4 B**). Another example of a non-classical function of flavoproteins is their ability to form covalent flavin-substrate adducts at either the cofactor *N*5 or *C*4a position. The most prominent example of adducts in flavin chemistry is the formation of a flavin-*C*4a-hydroperoxide adduct **35** in monooxygenases and hydroxylases. Here, the hydroquinoid isoalloxazine core reduces dioxygen to form the corresponding *C*4a-adduct (**scheme 5 A**).[29] However, this adduct can be an intermediate in oxidoreductases as well. The first step of the flavin-hydroperoxide formation is a single-electron transfer (SET) from the hydroquinoid flavin to dioxygen. The transfer is thermodynamically unfavorable, which leads to a slow reduction of O_2 in solution (second-order rate constants of ~250 M^{-1} s^{-1}). However, in the enzyme environment, the rate is strongly increased and is almost a hundred to a thousand times faster.[30] The protein environment both channels O_2 directly to the reaction site and improves the solubility and the geometry of the reaction site.[30] On top of that, protein positive charges, for example, are beneficial since they electrostatically stabilize the transition state of the SET that forms the $O_2^{-\bullet}$/flavin semiquinone radical pair.[30] However, in the case of *choline oxidase*, the same effect is achieved by the trimethylammonium group of the reaction product despite the presence of three histidine side chains in the active site (**scheme 5 B**). For *choline oxidase*, another beneficial contribution has been identified. A non-polar site, namely Val464, in proximity to the flavin-*C*4a position, increases the desolvation and geometry of dioxygen. Experiments with mutated enzymes show that substituting Val464 with alanine decreases the rate of the oxidative half-reaction by fifty times.[31] *Choline oxidase* is a “classic” oxidoreductase since it proceeds *via* the schematic mechanism depicted in **scheme 4 D**. However, with O_2 as an oxidant, the flavin adducts also play a role in this class of enzymes.

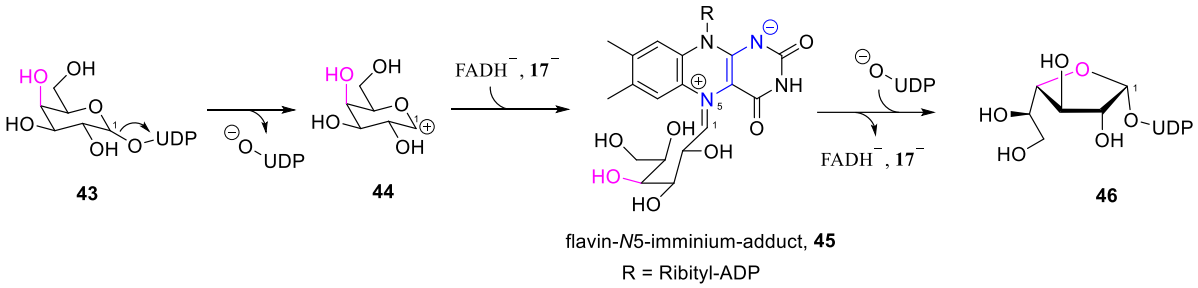


Scheme 5: **A**: Oxidative half-reaction with dioxygen. Displayed are the electronic states (orange) and **a)** the SET from $FADH^-$ (**17**$^-$) to O_2 to form the $O_2^{-\bullet}$/flavin semiquinone radical pair, **b)** the spin inversion of the radical pair, **c)** the direct oxidation to quinoid flavin **10** and H_2O_2 and **d)** the elimination of H_2O_2 to give FAD (**10**). **B**: Oxidation of choline (**36**) to glycine betaine (**39**) by *choline oxidase*. **C**: Catalytic cycle of hydroxylases, *e. g.* for the oxidation of 4-hydroxy benzoate (**40**) to 3,4-dihydroxy benzoate (**41**). 'B' represents a hydrogen bonding network.

4-Hydroxy benzoate 3-hydroxylase (PHBH) is a hydroxylase and part of the family of monooxygenases. The mechanism of the oxidation of 4-hydroxy benzoate to 3,4-dihydroxy benzoate is in stark contrast to the mechanism of classic oxidoreductases (**scheme 5 C**): Hydroxylases transfer an oxygen atom instead of using dioxygen as a terminal oxidant.[29] PHBH is the most-studied hydroxylase and is contained in *Pseudomonas fluorescens*.[32] Hydroxylases use NADPH or NADH as reducing agents. The catalytic cycle starts with the formation of a ternary complex that consists of enzyme-bound, oxidized FAD, NADPH, and the phenolic substrate **40**. Deprotonation of the substrate is facilitated by the hydrogen bond network.[33] The nucleophilic character of the substrate is enhanced, and it undergoes a conformational change. This is important to allow the approach of FAD to the NADPH cofactor. The spatial proximity of the two cofactors ensures rapid reduction of the oxidized flavin cofactor. $NADP^+$ is released and dioxygen is incorporated into the system. The flavin-*C*4a-hydroperoxide adduct **35** is formed as shown in the mechanism depicted in **scheme 5 A**. Following a protonation/deprotonation sequence, the phenolate nucleophilically attacks the hydroperoxide adduct **35** to yield 3,4-dihydroxy benzoate (**41**) and flavin-*C*4a-hydroxide **42**. The latter eliminates water to close the catalytic cycle.[29]

Two other prominent examples of monooxygenases use the flavin-*C*4a-hydroperoxide in a non-classical fashion. *Baeyer-Villiger* monooxygenases (BVMO) catalyze *Baeyer-Villiger* reactions, oxidations of both aldehydes and heteroatoms, as well as epoxidations.[34] This enzyme class uses the flavin-*C*4a-hydroperoxide as an oxygen atom transfer reagent.[29] Halogenases, on the other hand, introduce chloride or bromide atoms into activated substrates. Here, the flavin-*C*4a-hydroperoxide serves as an oxidant for halide salts. A halide salt nucleophilically attacks the hydroperoxide adduct and yields the corresponding hypohalous acid and flavin-*C*4a-hydroxide. Through further activation by the protein environment, the hypohalous acid ultimately ensures the halogenation of the substrate.[29]

The reduced flavin cofactor can form covalent adducts not only at the *C*4a, but also at the *N*5 position. In *uridine diphosphate* (UDP) *galactopyranose mutase* (UGM), for example, *N*5 nucleophilically attacks the electrophilic galactose oxocarbenium cation **44** and forms the iminium adduct **45** (**scheme 6**).[35] The existence of the latter was demonstrated by chemical trapping[36] and by crystallization of the substrate-derived covalent flavin-*N*5-adduct **45**.[37] Upon an intramolecular attack of the hydroxyl group (pink) and UDP at *C*1, $FADH^-$ (**17**$^-$) is eliminated, and UDP-galactofuranose (**46**) is formed.[27]



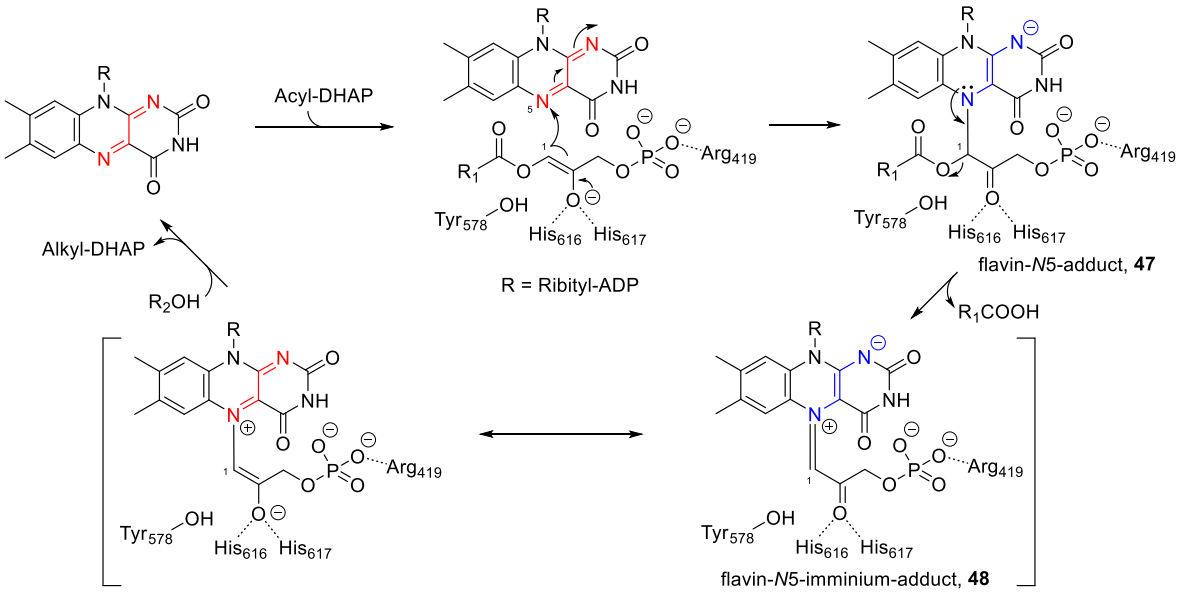
Scheme 6: Isomerization of UDP-galactopyranose (**43**) to UDP-galactofuranose (**46**) catalyzed by FADH⁻ (**17**⁻) *via* the flavin-*N*5-imminium-adduct **45**.

Furthermore, flavin-*N*5-adducts that originate from reduced FADH⁻ (**17**⁻), are intermediates in enzymes that *inter alia* perform methylene transfer reactions,[38] decarboxylations,[39] and oxygenation/dehydrogenation sequences.[40]

2.1.2.2. Covalent Adducts of Oxidized Flavins

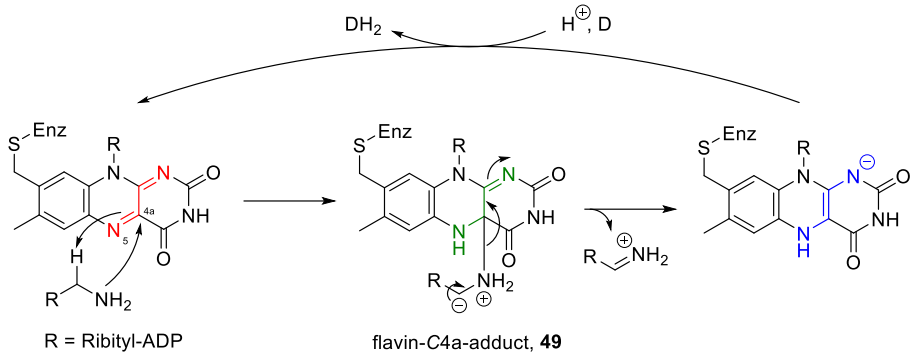
Besides the plethora of examples of *C*4a- and *N*5-adducts with the hydroquinoid state of the flavin cofactor, there is also literature on adducts formed with the oxidized form of the isoalloxazine core. *Alkyl-dihydroxyacetone phosphate synthase* (ADPS), for example, forms a flavin-*N*5-substrate adduct by applying the quinoid form of the isoalloxazine core in catalysis.[27] ADPS generates basic building blocks for the biosynthesis of ether phospholipids.[27] Since these lipids are essential components of eukaryotic cell membranes, their imbalance is associated with various disease conditions.[41] The enzyme transforms acyl dihydroxyacetone phosphates (acyl-DHAP) to alkyl dihydroxyacetone phosphates (alkyl-DHAP), by exchanging the fatty acid moiety with a fatty alcohol (**scheme 7**).[42] In ADPS, the enzymatic environment is ideally suited to host the acyl-DHAP substrate, which exhibits a fatty acid chain hydrophobic tail, the central three-carbon unit, and the negatively charged phosphate group. The enzyme holds a V-shaped tunnel, whose longest arm accommodates the aliphatic moiety of the fatty acid chain. The length of the tunnel is perfectly designed for 16- and 18-carbon chains.[42] This coincides with the fact that ADPS is active with hexadecanoyl- and octadecanoyl-DHAP as substrates but is inactive with shorter-chain substrates.[43] The shorter arm of the enzyme is decorated with several hydrophilic amino acid chains, including Arg419 and two threonine residues. Their ability to perform hydrogen bond interactions is suited to host the negatively charged phosphate group. The two arms are bridged by a short unit of the peptide that exhibits two histidine residues, His616 and His617, and a tyrosine residue, Tyr578. These amino acids are arranged exactly in front of the active part of the cofactor, the flavin-*N*5 atom, and guarantee the perfect embedment of the substrate and, thus, the prerequisite for a successful catalytic conversion.[42] The first step in the catalytic cycle of ADPS is the nucleophilic attack

of *C*1 of acyl-DHAP on the flavin-*N*5 atom. The resulting flavin-*N5*-adduct **47** is unstable and eliminates the fatty acid chain to form a zwitterionic flavin-*N*5-imminium-adduct **48**, which can be depicted by different resonance structures. A fatty alcohol attacks at the *C*1 position *via* an addition-elimination sequence and yields alkyl-DHAP and oxidized FAD, which closes the catalytic cycle.[42]



Scheme 7: Proposed mechanism of ADPS *via* the flavin-*N*5(-imminium)-adduct **47** and **48**, respectively. DHAP: dihydroxyacetone phosphate.

Few examples are known for enzymes that form covalent flavin-*C*4a-adducts from oxidized flavin.[44] One is *monoamine oxidase* (MAO), which oxidizes primary, secondary, and tertiary amines to the corresponding imine. The latter hydrolyzes non-enzymatically to the ketone or aldehyde. Although the mechanism is not understood entirely and the discussion of whether this process is of radical or nucleophilic nature is still ongoing, several pieces of evidence hint towards a nucleophilic mechanism.[44] This mechanism includes a flavin-*C*4a-nitrogen adduct. The free amine nucleophilically attacks the electrophilic flavin-*C*4a of isoalloxazine. The proton in α-position is abstracted by flavin's *N*5-atom, and the covalent flavin-*C*4a-adduct **49** is formed. Elimination of the imine yields the reduced flavin cofactor, which can be re-oxidized by a suitable oxidant *D* to close the catalytic cycle (**scheme 8**).[44]



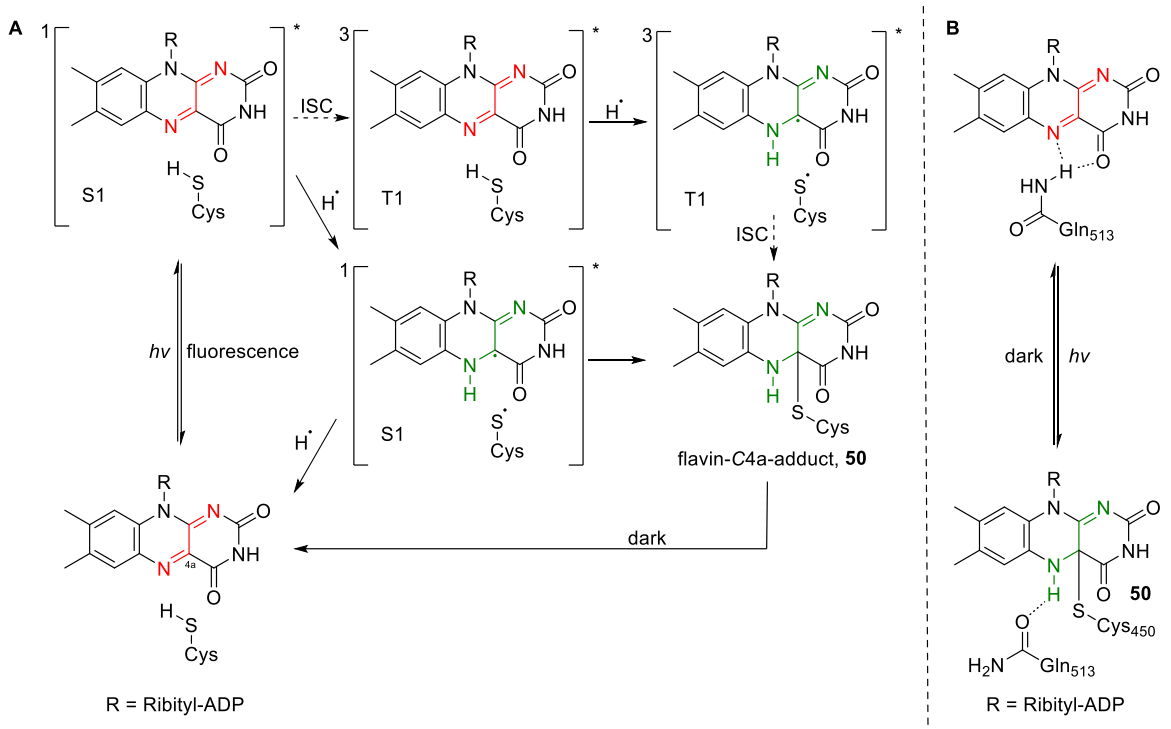
Scheme 8: Mechanism of *monoamine oxidase*, which transforms amines into the corresponding imines *via* the flavin-*C*4a-adduct **49**. 'D' represent an external oxidant.

A more prominent and well-studied example of *C*4a-adducts of oxidized flavins is the flavin-*C*4a-cysteine adduct in light, oxygen, and voltage (LOV) domains.[45] LOV domains were first identified in the enzyme group of phototropins,[46] which were discovered in algae and plants, where they display a group of serine and threonine kinases. The kinases are activated by blue light, which allows them to play the primary sensory role in the process of phototropism. Later, LOV domains were also discovered in fungal and bacterial systems.[47] In these organisms, the LOV domains are part of histidine kinases, transcription factors, and discrete "short" LOV proteins that contain only the photosensor domain itself.[45c] By 2018, over 7000 LOV domains had been discovered,[47] with the effector *C*-terminally attached to the LOV sensor in most of these proteins.[45c]

LOV domains specifically bind to flavins, giving them their photosensory activity. In the dark, the quinoid isoalloxazine core is bound non-covalently within the LOV domain. Upon photochemical activation, a conserved cysteine residue reacts with the flavin-*C*4a carbon to yield a covalent bond and, thereby, the flavin-*C*4a-cysteine adduct. Although there are no conclusive studies on whether the adduct formation is an ionic or radical reaction, many studies support a radical mechanism.[45b, 45d, 48] In addition, a reaction *via* the singlet or the triplet excited state comes into question when considering the radical mechanism. Here, it may even be the case that a reaction to the adduct takes place *via* both states, depending on the conformers in the flavin-based photoreceptor LOV domains (**scheme 9 A**).[48g] Since protonation of flavin-*N*5 happens concomitant to adduct formation, structural changes occur within the enzyme scaffold. In the widely studied phototropin 1 LOV 2 domain of *Avena sativa* (*As*LOV2), for example, the photochemical formation of the flavin-*C*4a-cysteine adduct triggers several structural transitions.[45c] The most important of these is the reversal of the hydrogen bonding activity of Gln_{513} in the LOV β sheet. Gln_{513} switches from a hydrogen bond donating character to a

hydrogen bond accepting one (**schema 9 B**).[45c] In *As*LOV2, this change, along with others, ultimately ensures that the *C*-terminal α helix will unfold reversibly.[49]

The flavin-*C*4a-adduct decays spontaneously (*e.g.*, thermally) over a period of seconds to hours, depending on the protein sequence and the structure surrounding the flavin chromophore. The cleavage of the flavin-*C*4a-cysteine bond restores the status of the dark-adapted, non-covalently bound chromophore in the protein.[45c]



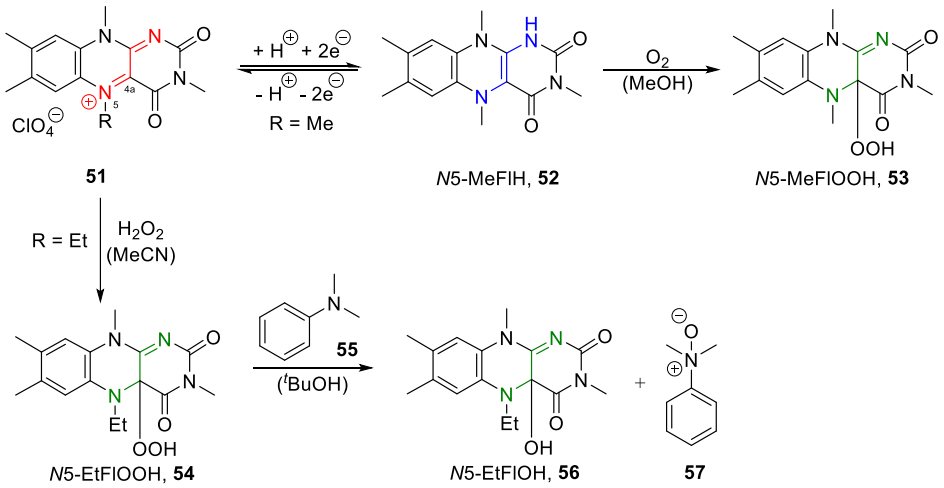
Scheme 9: **A**: Photoactivation of flavin and its singlet or triplet reaction with cysteine to form the flavin-*C*4a-cysteine adduct **50**. **B**: Reversal of the hydrogen bonding activity of Gln_{513} (in *As*LOV2) upon formation of the flavin-*C*4a-cysteine adduct **50**.

Combining all the facts of adduct-forming flavoenzymes (*cf.* **2.1.2.**) demonstrates that these proteins are tremendously complex, and the interactions and processes need to be better understood to reproduce and apply the versatility of flavins in the laboratory.

2.2. Molecular Flavins in Synthetic Organic Chemistry

2.2.1. Covalent Adducts of Molecular Flavins in Thermal Reactions

The aim to avoid harsh conditions and reagents has motivated the utilization of flavins in molecular systems that can activate O_2 or H_2O_2. In analogy to nature, adduct-forming flavins can be used in a catalytic fashion to achieve a variety of transformations, which will be displayed in the following chapter. Without the enzymatic environment, the artificial, neutral flavin-*C*4a-hydroperoxide adduct has a very short half-life of $t_{1/2} \approx 2.5$ ms, which renders it unsuitable for organic catalysis.[50] The reason for this is the fast elimination of hydrogen peroxide. Nevertheless, diverse methods have devised solutions to bypass this issue. The flavin-*C*4a-hydroperoxide adduct was first isolated by *Bruice et al.* in 1976 and 1977.[51] They introduced an alkyl moiety at the flavin-*N*5 position and, thus, were able to prevent elimination of hydrogen peroxide. They achieved the formation of the flavin-*C*4a-hydroperoxide with reduced *N*5-methyl-flavin (*N*5-MeFlH) **52** and O_2 as well as with the *N*5-ethyl-flavinium salt (*N*5-EtFl$^+$•ClO_4^-) **51** and hydrogen peroxide (**scheme 10**). Additionally, in 1979, the research group established the first stoichiometric oxygen transfer to a substrate, which attacks the flavin-*C*4a-hydroperoxide adduct in a nucleophilic manner.[52] This achievement was attained through the stoichiometric consumption of the flavin-*C*4a-hydroperoxide adduct itself (**scheme 10**).

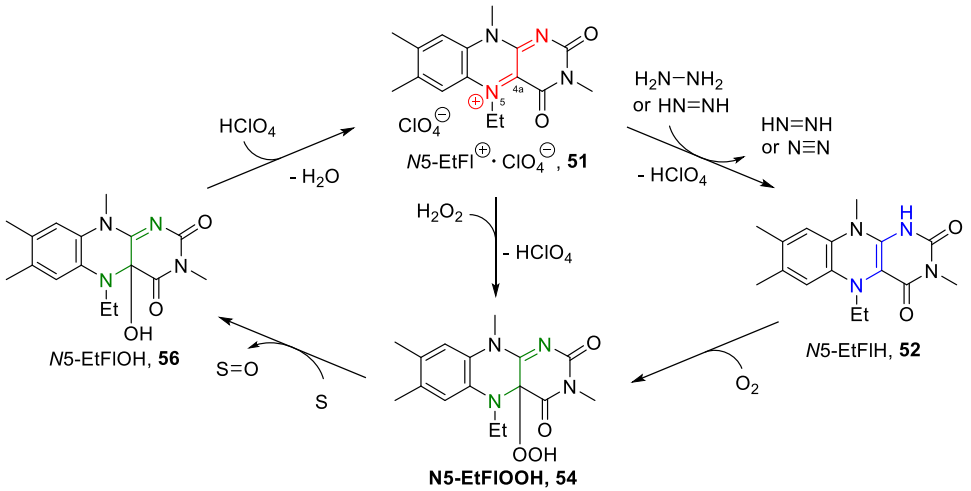


Scheme 10: Stoichiometric formation of stable flavin-*C*4a-hydroperoxide adducts and their application in the oxidation of *N*,*N*-dimethylaniline to *N*,*N*-dimethylaniline oxide.

Studies have unveiled that the *N*5-ethyl flavin-*C*4a-hydroperoxide (*N*5-EtFlOOH) **54** exhibits greater oxidizing capabilities compared to hydrogen peroxide, albeit with lower reactivity than *meta*-chloroperoxybenzoic acid (mCPBA).[53] This finely tuned reactivity accounts for the remarkable chemoselectivity observed in sulfide oxidation using *N*5-EtFlOOH **54**. Importantly,

this tuned reactivity profile prevents the formation of sulfones *via* overoxidation, yielding only sulfoxides instead.[50] Due to these features and the ability of *N*5-ethyl flavinium salts to form stable flavin-*C*4a-hydroperoxide adducts, researchers were eager to find ways to apply these flavins in a catalytic fashion.

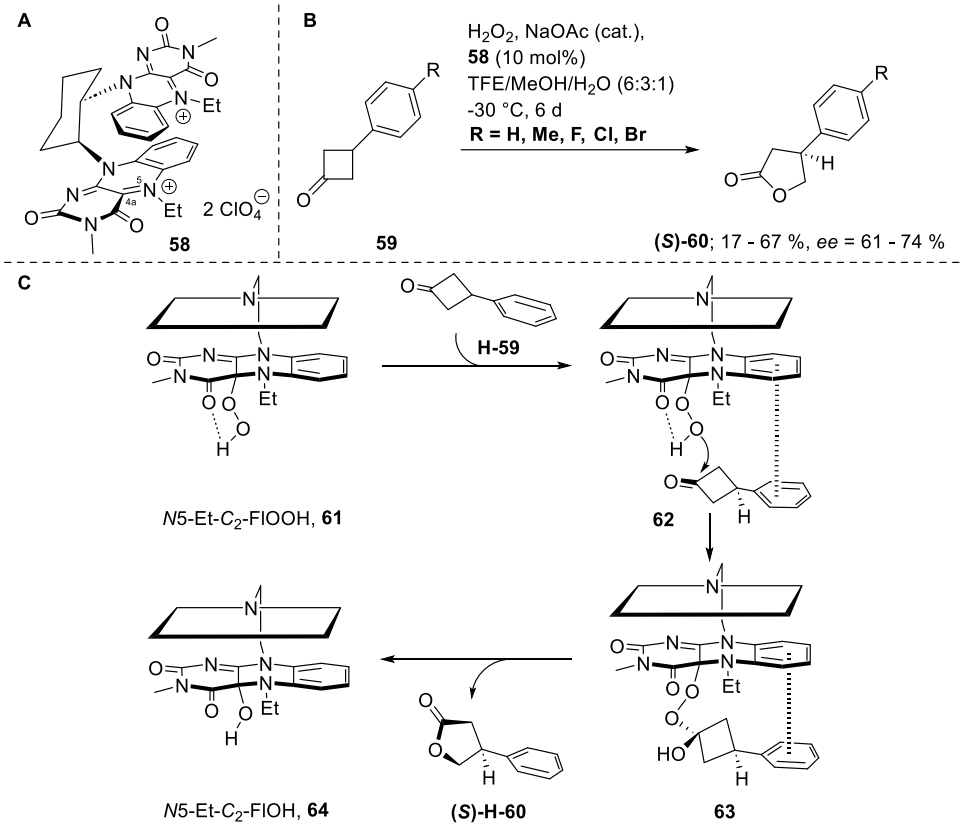
In 1989, *Murahashi et al.* accomplished the first catalytic oxidation of substrates utilizing an *N*5-ethyl-flavinium salt catalyst (*N*5-EtFl$^+$•ClO_4^-) **51** in conjunction with hydrogen peroxide as the oxidant.[54] In this system, catalyst **51** serves as a robust and effective organocatalyst for *N*-oxidations and sulfoxidations. The active species, *N*5-EtFlOOH, is generated reversibly *in situ* by the addition of hydrogen peroxide to *N*5-EtFl$^+$•ClO_4^-. Following substrate oxidation, the resulting catalyst product, *N*5-EtFlOH **56**, reacts with perchloric acid to regenerate the corresponding flavinium salt. This final step, crucial for the rate of the process, occurs exclusively in the presence of an acid (**scheme 11**). Later, the same research group conducted *N*-oxidations and sulfoxidations using catalyst **51** and O_2 as the oxidant.[55] Employing hydrazine monohydrate as a reductant exclusively yields water and nitrogen as side-products, rendering it an environmentally sustainable synthesis pathway. The catalyst undergoes a similar cycle as it does when H_2O_2 serves as the oxidant (**scheme 11**). The choice of solvent plays a pivotal role in this reaction. Fluorinated alcohols like 1,1,1,3,3,3-hexafluoroisopropanol (HFIP) or trifluoroethanol (TFE) are indispensable for the aerobic oxidation.



Scheme 11: Catalytic cycle of the oxidation of a suitable substrate 'S' by either O_2 in the presence of a stoichiometric amount of hydrazine as reductant or by H_2O_2.

Further examples of aerobic organocatalytic oxidation were carried out with diethyl 1,4-dihydro-2,6-dimethyl-3,5-pyridinecarboxylate (*Hantzsch* ester),[56] formic acid/triethylamine,[57] zinc dust,[58] or ascorbic acid as reductants.[59]

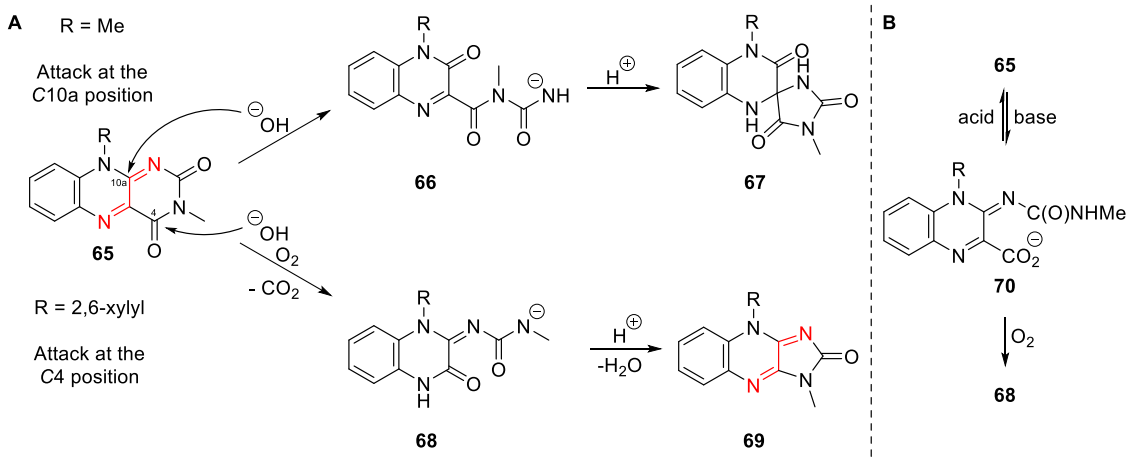
More complex flavin systems were established to perform catalytic oxidations stereoselectively. In 2002, *Murahashi et al.* introduced C_2-symmetrical bisflavin **58** that enabled stereoselective *Baeyer-Villiger* oxidations of prochiral 3-arylcyclobutanones (**scheme 12 A** & **B**).[60] The synthesis of this complex catalyst is accomplished in five steps, starting with (1*S*,2*S*)-cyclohexane-1,2-diamine. Owing to rotational constraints between the two flavin planes, solely one stereoisomer is generated.[60] Enantioselectivity and yield are significantly influenced by the choice of solvent and additives. The induction of chirality occurs primarily through π-π interactions, which are facilitated by protic solvents. However, methanol or a methanol/water (2:1) mixture resulted in low enantioselectivities and yields due to the formation of the corresponding diketal of **59**. The use of fluorinated solvents such as TFE or HFIP also leads to low enantioselectivities, as the acid-catalyzed background reaction occurs rapidly in the absence of the C_2-symmetrical catalyst. The product was only observed in reasonable yields and enantioselectivities when employing a mixture of TFE/MeOH/H_2O (6:3:1) as a solvent and sodium acetate as an additive.[60] This certain solvent mixture inhibits diketal formation and prevents the acid-catalyzed oxidation by intercepting perchloric acid. The C_2-symmetry of the catalyst shields one face, allowing only the other side to bind H_2O_2 at the flavin-*C*4a position. Chirality appears to be induced through face selectivity in the formation of the *Criegee* adduct and *via* π-π stacking between the aromatic moiety of the catalyst and the phenyl residue of the substrate. The latter fixes the orientation of the bound substrate, enabling the nucleophilic attack of flavin-*C*4a-hydroperoxide exclusively at the opposite side of the phenyl group. As intramolecular rearrangement occurs antiperiplanar to the leaving group, predominantly (*S*)-γ-butyrolactone is produced. The mechanism can be elucidated by considering the proposed procedure outlined in **scheme 12 C**.



Scheme 12: **A**: C_2-symmetrical flavin catalyst **58**. **B**: Stereoselective *Baeyer-Villiger* oxidation of 3-arylcyclobutanones **59**. **C**: Supposed reaction mechanism of the stereoselective *Baeyer-Villiger* oxidation employing chiral flavin catalyst **58**.

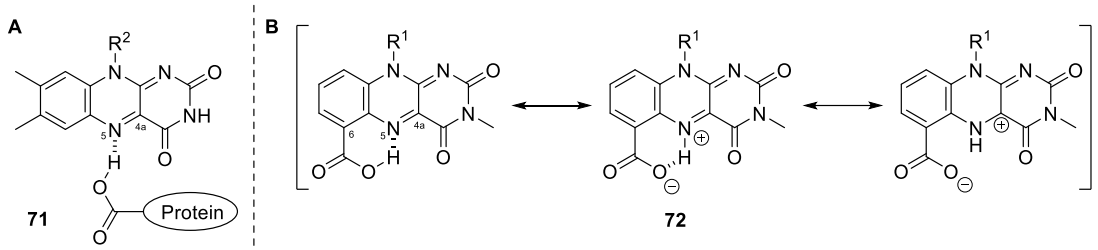
The significance of covalent adducts involving the isoalloxazine core has spurred a series of synthetic investigations, aiming to unravel the reactivity of various heterocycle positions towards incoming nucleophiles in the organic laboratory. *Guttman et al.*, *Bruice* and *Smith*, as well as *Yoneda et al.* investigated the reaction of hydroxide anions with the flavin core. The former have demonstrated that *N*3-unsubstituted flavins are attacked by hydroxide ions at the flavin-*C*10a position, leading to the cleavage of the *N*1-*C*10a bond.[61] Deprotonation of the *N*3-proton deactivates the *C*4 position regarding a nucleophilic attack. However, when *N*3-alkylated flavins are employed in alkaline hydrolysis, *Bruice* and *Smith* as well as *Yoneda et al.* identified both the flavin-*C*10a and the -*C*4 position as sites for initial bond formation.[62] In both cases, the nucleophilic attack of hydroxide anions results in a ring-opening and the formation of quinoxalinone **66** and **68**, respectively. The steric demand of the flavin-*N*10 residue influences the site of attack in this process. Groups with low steric demand such as methyl allow for the addition of hydroxide anions at the flavin-*C*10a position, while sterically demanding moieties preferentially direct the attack to the *C*4 position. The respective quinoxalinones undergo a C-N bond formation to yield either spirohydantoin **67** or imidazolonequinoxaline **69**, with the latter heterocycle still exhibiting the classic quinoid

system (**scheme 13 A**). Interestingly, the formation of quinoxalinone **68** only occurs in the presence of dioxygen. Under anaerobic conditions the hydrolysis of flavin **65** is completely reversible by adjusting to a pH of 4.0 or less (**scheme 13 B**).[62a]



Scheme 13: **A**: Depending on the site of the attack, the addition of hydroxide ions to the flavin framework results in the formation of two different heterocycles: spirohydantoins **67** or imidazolonequinoxalines **69**. **B**: Reversibility of the addition of hydroxide anions to the flavin-*C*4 position under anaerobic conditions.

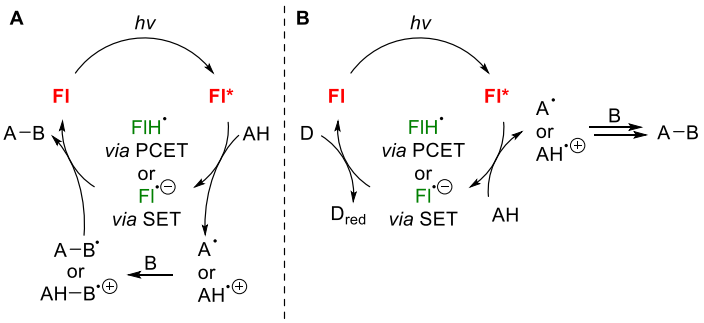
With this knowledge, research aimed at activating specific positions of the flavin heterocycle. Attempts have been made to find ways of stabilizing flavin-*C*4a-hydroperoxide adducts other than the introduction of a residue in the *N*5 position. A promising strategy for prolonging the lifetime of the adduct involves activation through hydrogen bonding. While flavin-dependent enzymes are capable of forming these bonds intermolecularly within their highly intricate active site, achieving intermolecular hydrogen bond interaction with the flavin-*N*5 position is challenging in artificial systems (**scheme 14 A**).[63] An alternative approach involves utilizing an intramolecular hydrogen bond between the flavin-*N*5 atom and a hydrogen bond donating group attached to the flavin-*C*6 position. Through this configuration, the *N*5 atom acquires a partial positive charge, thereby imparting an increased electrophilic character to the *C*4a position. An illustration of such a system is the flavin-*C*6 carboxylic acid, which establishes a robust intramolecular hydrogen bond (**scheme 14 B**). By activating the flavin in this manner, it becomes feasible to stabilize the transient *C*4a-hydroperoxid adduct and facilitate the oxidation of various sulfides to their corresponding sulfoxides.[63]



Scheme 14: Activation of the flavin-*C*4a position *via* an intramolecular hydrogen bond interaction with an acid side chain to the *N*5 atom in enzymatic systems (**A**) and *via* intermolecular coordination of an acid to the *N*5 atom in artificial systems (**B**).

2.2.2. Photochemistry of Molecular Flavins

Quinoid flavins absorb light within the visible spectrum, peaking in the blue range at a wavelength of 450 nm.[22] Upon excitation, flavins transition to their singlet excited state (^{1}Fl*, τ_S = 5.0 ns (for riboflavin in water, pH = 7)[64]), followed by rapid intersystem crossing (ISC) to the longer-lived triplet excited state (^{3}Fl*, τ_T = 3.7 µs (for riboflavin in methanol)[65]) (Φ_T = 0.375 ± 0.05 for riboflavin in aqueous solution at pH = 7.0,[66] Φ_T = 0.54 for *N*3-methyl-riboflavin tetraacetate (RFTA) in methanolic solutions[67]).[68] Photoexcitation of flavins results in significantly elevated redox potentials (E^0(RFTA/RFTA$^{\bullet-}$) = −0.81 V vs SCE, E^0(^{3}RFTA*/RFTA$^{\bullet-}$) = +1.37 V vs SCE, E^0(^{1}RFTA*/RFTA$^{\bullet-}$) = +1.67 V vs SCE), thereby enabling reactions that are otherwise inaccessible in the ground state (*cf.* **scheme 18** for structure of RFTA).[69] Due to the prolonged lifetime, the triplet state of riboflavin displays the active species and the key intermediate in many photochemical transformations.[70] Photochemically excited flavins can interact with and oxidize suitable substrates. A single electron transfer (SET) takes place and the isoalloxazine core is in turn reduced to the flavin radical anion (Fl$^{\bullet-}$). Due to the basicity of the latter, the reduction often occurs concomitant to a proton transfer, which is known as a proton coupled electron transfer (PCET). The quinoid flavin can be regenerated by transferring an electron to an intermediate (redox neutral process. **scheme 15 A**) or by interaction with a sacrificial oxidant 'D' (**scheme 15 B**). Less often, two electrons are transferred in flavin-catalyzed photoreactions, which would lead to FlH_2 in the catalytic cycle (*cf.* **scheme 4**).

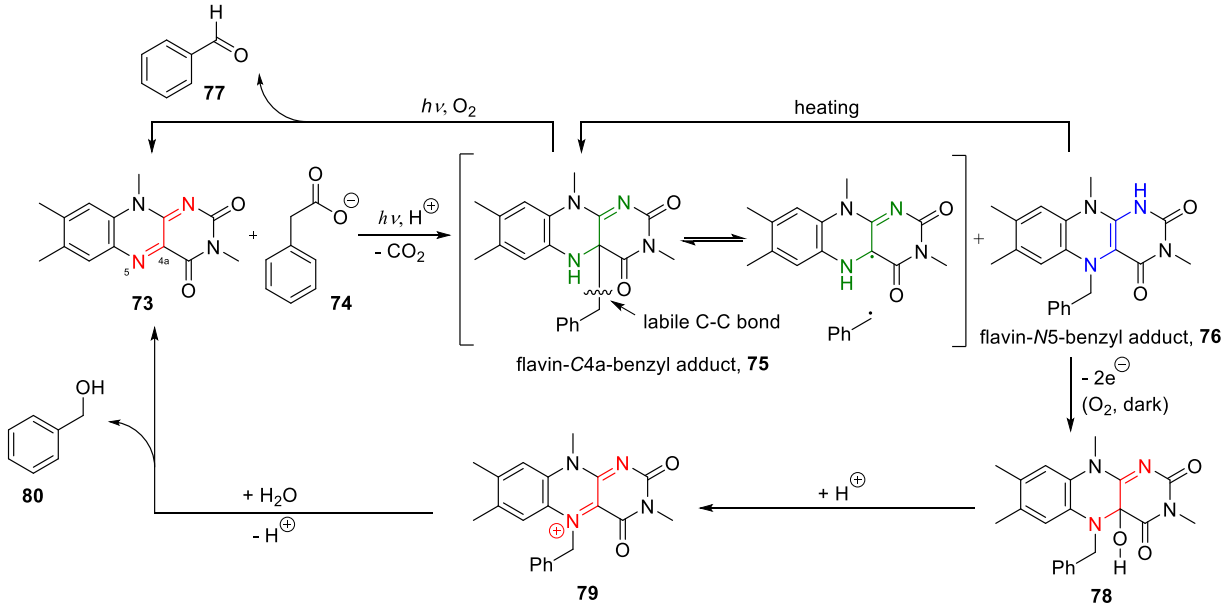


Scheme 15: Catalytic cycle of flavin-based photochemistry for **A**) a redox neutral process and **B**) with a sacrificial oxidant 'D'; 'A' and 'B' represent suitable substrates.

2.2.2.1. Covalent Adducts of Molecular Flavins in Photochemical Reactions

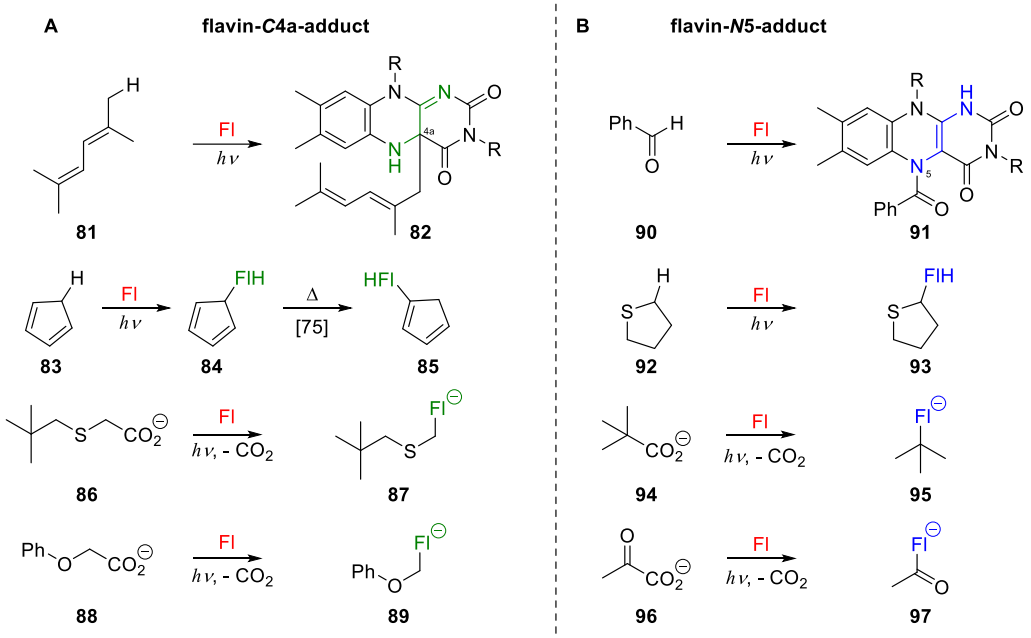
In 1967, *Hemmerich et al.* made use of the excited flavin's property as a strong one-electron oxidant. Prior studies suggested that flavoenzymes were restricted to form flavin-*C*4a-adducts solely with heteroatoms. However, *Hemmerich* and his colleagues demonstrated that artificial flavins can also form *C*4a-adducts involving a newly formed carbon-carbon bond. They based

this finding on the first isolation of a flavin-substrate adduct.[71] By irradiating lumiflavin **73** under anaerobic conditions in a phenylacetate buffer overnight, the formation of the flavin-*N*5- and flavin-*C*4a-benzyl adduct (**76** & **75**) was observed. They propose that the first step of this reaction is the decarboxylation of phenylacetate, which results in the formation of the covalent flavin-*C*4a-benzyl adduct **75**. The adduct can be homolytically cleaved to appear as its diradical form, which is instable under the reaction conditions. The alkylated flavin can exist in two distinct forms: either as the *C*4a-alkylated **75** or *N*5-alkylated species **76**, influenced by factors such as temperature, pH value, and substitution pattern. The flavin-*N*5-alkylated variant can be converted to the flavin-*C*4a-alkylated form *via* heating (50 °C). Two pathways exist for the regeneration of oxidized flavin to complete the catalytic cycle, depending on the site of alkylation. In the absence of light but with access to dioxygen, the *N*5-alkylated form generates benzyl alcohol (**80**) *via* the oxidized *N*5-benzylflavinium cation. On the other hand, the *C*4a substituted adduct reacts with dioxygen only under irradiation, yielding benzaldehyde (**77**) and the catalytically active quinoid flavin **73** (**scheme 16**).[72] While *Hemmerich et al.* proposed that the decarboxylative adduct formation is a nucleophilic process, *Bruice et al.* later showed that it is in fact a radical mechanism.[73]



Scheme 16: Decarboxylative photoreaction of lumiflavin (**73**) with phenylacetate (**74**) to flavin-*C*4a-benzyl adduct **75** and flavin-*N*5-benzyl adduct **76**, respectively. The catalytic cycle closes depending on the substitution pattern as well as the reaction conditions and yields benzaldehyde (**77**) and benzyl alcohol (**80**), respectively.

Hemmerich and *Knappe* later identified numerous additional substrates capable of forming adducts with flavins under light stimulation.[74] They categorize the flavin adducts based on the site of adduct formation and suggest that *C*4a- and *N*5-adducts are interconvertible under certain conditions. Furthermore, they isolated a plethora of flavin-substrate adducts and describe their stability towards dioxygen, light and acids. A selection of substrates and the position of their adduct formation is shown in **scheme 17**. Despite the broad substrate scope, no subsequent applications of these adducts in catalytic conversions are reported.

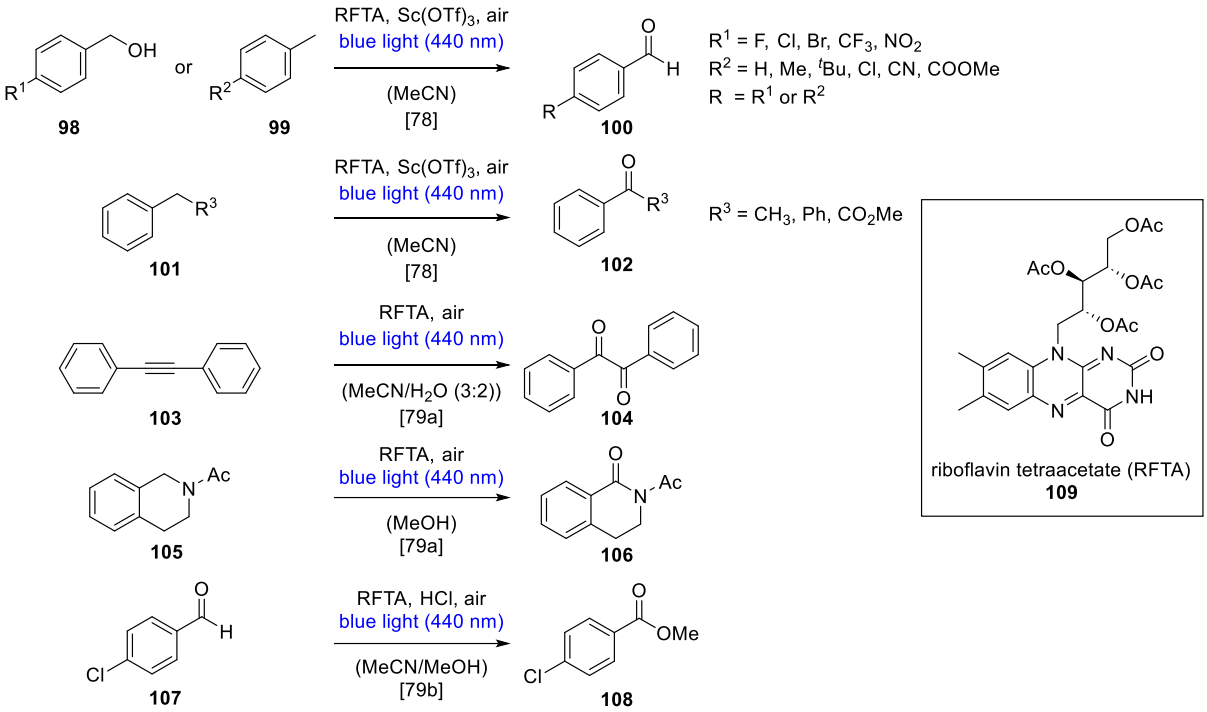


Scheme 17: Flavin-substrate adducts in the *C*4a position (**A**) and in the *N*5 position (**B**). [1,5]-Sigmatropic rearrangement of cyclopentadiens was described by *Elizarova et al.*.[75]

2.2.2.2. Photocatalytic Applications of Molecular Flavins

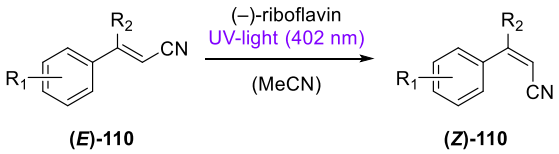
Photoexcited flavins have been shown to be effective redox catalysts for a plethora of substrates that are challenging to oxidize. In 1989, *Fukuzumi et al.* reported an effective and substrate-selective oxidation method for various benzyl alcohols using a positively charged flavin derivative as a photocatalyst and O_2 as the oxidant.[76] This approach was further enhanced by the addition of a *Lewis* acid, which coordinates to the catalyst's carbonyl groups. This coordination positively shifts the reduction potential of the singlet excited state by several hundred millivolts, thereby increasing the chemical quantum yield. Additionally, the interaction within the metal-flavin complex enhances the oxidation capability of flavin's excited state (Fl*).[77] By means of these contributions, the oxidation of alkylbenzenes and electron-deficient benzyl alcohols becomes feasible (**scheme 18**).[78] The mechanism in these transformations is considered similar to the one proposed by *Fukuzumi et al.*.[77] The singlet excited state of the complex acts as an oxidant, and the alkylbenzene performs an SET. *Mühldorf* and *Wolf*, as well

as *König et al.*, introduced photochemical applications of flavins, which contributed to the broadening of the substrate scope (**scheme 18**).[78-79]



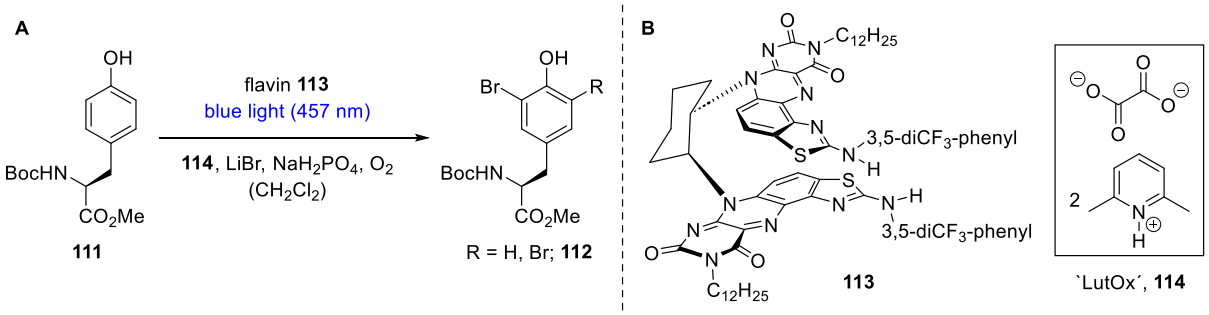
Scheme 18: Application of RFTA in photocatalytic oxidations of aromatic substrates.[78-79]

Next to their enhanced oxidation power, another characteristic of excited flavins is their ability to act as a photosensitizer and perform energy transfers to substrates. Exploiting this feature, in 2017 *Gilmour et al.* introduced the first highly *Z*-selective isomerization protocol for polarized alkenes, leveraging commercially available (–)-riboflavin and UV light (**scheme 19**).[80] Inspired by the enzymatic activity of retinal isomerization in the mammalian visual cycle, a novel organocatalytic method emerged, employing (–)-riboflavin and cinnamonitrile chromophores as a surrogate for retinal. This photoinduced reaction demonstrates remarkable selectivity (*Z*:*E* up to 99:1), attributed to an *in situ* formed selective excitation manifold facilitating exclusive and efficient energy transfer between the activated flavin catalyst and the *E*-isomeric substrate. Therefore, reversibility of the reaction, like under thermal/non-irradiative conditions, is avoided.



Scheme 19: Application of (–)-riboflavin in the photocatalytic *E* → *Z* isomerization of polarized alkenes provides high stereoselectivity *via* energy transfer.

These findings, along with extensive investigations into flavin reactivity, have led to a substantial advancement in the comprehension of this unique heterocycle. Consequently, chemists have not only been able to employ established flavin catalysts in novel transformations but have also pursued an alternative approach: the design and synthesis of tailor-made flavins for applications previously out of reach. In 2020, our group provided a compelling demonstration of the efficacy of these customized flavins in photocatalysis through the bromination of electron-rich arenes.[81] Employing C_2-symmetric 2-aminobenzothiazol flavin **113** in this transformation ensures good yields and a low rate of decomposition. Latter is attributed to the slow release of oxidants upon the flavin's activation of O_2, while productivity of the reaction is ascribed to the coordination of hypobromite species to the catalyst's active site by the aminobenzothiazol functionality (**scheme 20**).



Scheme 20:Aerobic bromination of arenes (**A**) by employing C_2-symmetric 2-aminobenzothiazol flavin **113** as highly potent photocatalyst and `LutOx´(**114**) as a stoichiometric reductant (**B**).

3. Aim and Motivation

In the previous sections, an overview of flavin-substrate adducts in flavoenzymes as well as in molecular flavins is given. Here, the focus was placed on the instability of the adducts and it was demonstrated that carbon-carbon adducts can only be generated under light exposure. Furthermore, it was shown that, unlike carbon-heteroatom adducts, carbon-based flavin-*C*4a-adducts have so far only been characterized, but have not been integrated into catalytic cycles. This is unfortunate, as the substrate classes capable of forming such adducts represent intriguing building blocks for functionalizations. Hence, under photochemical conditions, it is imperative to discover methods for their stabilization and to apply them in catalytic transformations rather than dismissing them as dead-end side products.

Moreover, ring-contracted flavins, imidazolonequinoxalines, are an unexplored class of heterocycles. This is intriguing as they exhibit the same semiquinoid system as flavins and may be applied in novel (photo)catalytic transformations.

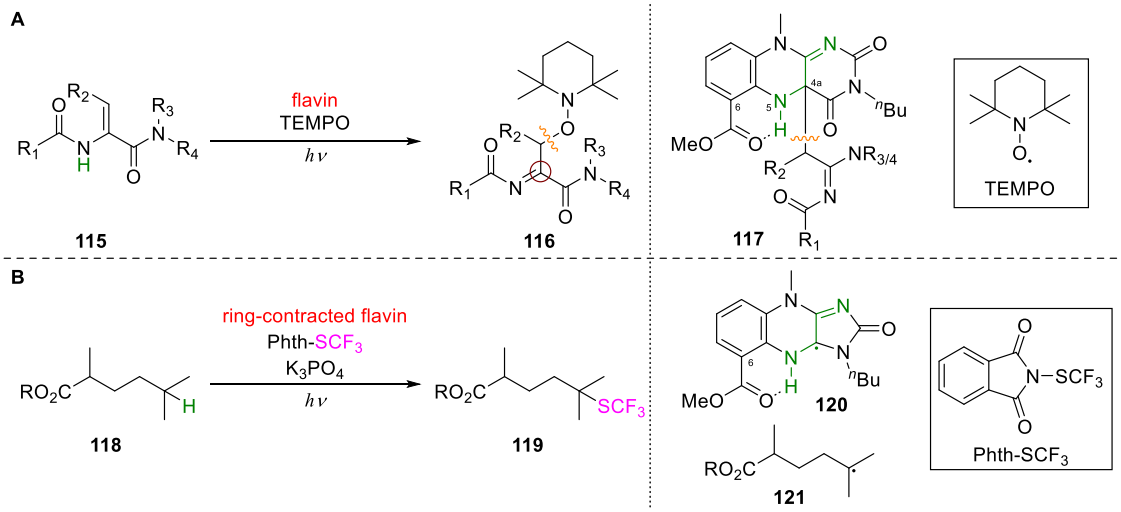
The goal of this work is the design and synthesis of novel, *C*6-modified isoalloxazine and imidazolonequinoxaline cores that allow the employment of *C*4a-substrate adducts with a newly formed carbon-carbon bond or the respective diradical in catalytic transformations. For the substitution in *C*6 position we choose amide and ester groups. They are able to increase the electrophilicity of the *C*4a position through their electron-withdrawing effect. Additionally, we envision that they can potentially capture the *N*5 proton of the semiquinoid (ring-contracted) flavin through an intramolecular hydrogen bond. The latter leads to the stabilization of either the *C*4a-adduct state or its corresponding diradical existence (*cf.* **scheme 16** & **21**). As target transformations, firstly the oxidative functionalization of dehydroamino acids (DHAs) with (2,2,6,6-tetramethylpiperidin-1-yl)oxyl (TEMPO) and secondly the SCF_3-functionalization of methine positions were chosen. Both transformations benefit from a *C*6 methyl ester modification of the (ring-contracted) flavin core (**scheme 21 A** & **B**).

Dehydroamino acids constitute a compound class that holds significant representation within pharmaceuticals. Their functionalization is eagerly sought after, either to unravel their mode of action or to access novel bioactive compounds suitable for drug application. There are several examples to functionalize this structural motive. However, only one of those approaches features the oxidation of amino acids and the subsequent intermolecular reaction to yield acylimines. The reported example utilizes harsh conditions, employing a temperature of 80 °C, a metal catalyst, and is only applicable for one dipeptide.[82] The scope of dehydroamino acid

functionalization would thus greatly benefit from employing a photocatalytic method that provides acylimines under mild conditions. The challenges herein involve:

a) establishing conditions that allow the formation of a flavin-substrate adduct, which is labile enough to provide the cleavage of the *C*4a-carbon-carbon bond by a reagent and yet stable enough to persist until an interaction with the reagent takes place.
b) finding suitable reagents that can intercept the flavin-*C*4a-adduct and, thus, complete the catalytic cycle.

Furthermore, we are interested in the synthesis and the characterization of ring-contracted flavins, imidazolonequinoxalines. Based on the acquired information, we aim to apply them in photochemical transformations. Photocatalytic C-H activation of unactivated hydrocarbons and their transformation into trifluormethylthiolated compounds is reported by utilizing a catalytic system containing phtalimidyl-SCF_3 as SCF_3-source, a metal photocatalyst and an additional HAT-catalyst. Due to its pronounced hydrophobicity and electron-withdrawing characteristics, the incorporation of SCF_3-groups into organic compounds holds significant appeal in pharmaceutical chemistry. We propose that methyl ester modified ring-contracted flavins can be active as a photoexcited HAT-catalyst in the trifluoromethylthiolation of methine positions. Thus, the employment of a coupled catalytic system can be substituted by utilization of one organocatalyst. The challenge herein lies in the necessity for our catalyst to demonstrate dual modes of reactivity, namely photocatalytic and HAT-reactivity.



Scheme 21: **A**: Flavin catalyzed oxidative functionalization of dehydroamino acids **115** to highly reactive acylimines **116** *via* flavin-*C*4a-substrate adduct **117**; Orange wavy line displays a weak, easily cleavable bond; Brown circle displays the reactive acylimine function that can act as a handle for further transformations. **B**: Ring-contracted flavin catalyzed SCF_3-functionalization of methine positions *via* HAT-generated radical pair **120**/**121**.

4. Molecular Flavin Catalysts for C-H Functionalization and Derivatization of Dehydroamino Acids

Title: "Molecular flavin catalysts for C-H functionalisation and derivatisation of dehydroamino acids"

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Authors: Andreas Rehpenn, Alexandra Walter, Golo Storch

Content: In this publication, the design, synthesis and characterization of novel *C*6 methyl ester, *C*7 methyl ester and *C*6 methyl amide modified flavin catalysts is presented. The adduct formation of *C*6 methyl ester substituted flavin was investigated with 1,3-cycloheptadiene (CHD) as substrate. We characterized the flavin-*C*4a-cycloheptadiene adduct by ^{1}H (1D), ^{1}H (2D) and ^{13}C{^{1}H} NMR spectroscopy as well as by high-resolution mass spectrometry. Furthermore, we achieved adduct formation with dehydroamino acid substrates. We provided evidence, that dehydroamino acid adducts are not formed at the allylic position but rather at the β-position *via* oxidation and subsequent radical migration. Both allylic adducts and dehydroamino acid adducts could be intercepted by the addition of three equivalents of TEMPO. Here, one equivalent was required to regenerate the catalyst. In this transformation, the methyl ester substituted flavin provided superior results compared to established flavin photocatalysts. We applied this protocol to 16 different dehydroamino acids and showcased a diverse array of follow-up reactions for the resulting acylimines.

Author Contributions: All synthetic and catalytic experiments were performed and characterized by A. Rehpenn. Catalyst design was provided by A. Rehpenn and G. Storch. The catalytic experiments were planned, performed and analyzed by A. Rehpenn. A. Walter performed and analyzed the cyclic voltammetry measurements. J. Großkopf performed spectroscopic measurements. The manuscript was written by A. Rehpenn, A. Walter and G. Storch. A. Rehpenn wrote the supplementary information file which contains all experimental data.

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Molecular flavin catalysts for C–H functionalisation and derivatisation of dehydroamino acids†

Andreas Rehpenn, Alexandra Walter and Golo Storch *

In nature, the isoalloxazine heterocycle of flavin cofactors undergoes reversible covalent bond formation with a variety of different reaction partners. These intermediates play a crucial role *inter alia* as the signalling states and in selective catalysis reactions. In the organic laboratory, covalent adducts with a new carbon–carbon bond have been observed with photochemically excited flavins but have, so far, only been regarded as dead-end side products. We have identified a series of molecular flavins that form adducts resulting in a new C–C bond at the C4a-position through allylic C–H activation and dehydroamino acid oxidation. Typically, these reactions are of radical nature and a stepwise pathway is assumed. We could demonstrate that these adducts are no dead-end and that the labile C–C bond can be cleaved by adding the persistent radical TEMPO leading to flavin regeneration and alkoxyamine-functionalised substrates. Our method allows for the catalytic oxidation of dehydroamino acids (16 examples) and we show that the acylimine products serve as versatile starting points for diversification. The present results are envisioned to stimulate the design of further catalytic reactions involving intermediates at the flavin C4a-position and their reactivity towards metal complexes or other persistent organic radicals. Our method for dehydrobutyrine derivatisation is orthogonal to the currently used methods (*i.e.*, nucleophilic attack or radical addition) and offers new perspectives for peptide natural product diversification.

Introduction

The isoalloxazine core of flavins has a strong tendency to form covalent adducts with several reagents.[1] In nature (Fig. 1A), flavin adenine dinucleotide (FAD, **1**) and flavin adenine mononucleotide (FMN) reversibly form covalent C–S bonds in the C4a-position with cysteine in light, oxygen, and voltage (LOV) photoreceptors to yield covalent intermediate **2**.[2] In a second example from flavoenzymes, the reduced cofactor $FADH_2$ (**3**) reacts with oxygen to yield C4a-hydroperoxide **4** which is involved in oxygenation reactions.[3] Besides these well-studied types of intermediates, the reversible formation of a carbon–carbon single bond at the flavin's C4a-position is less common. In the organic laboratory, Hemmerich *et al.* (Fig. 1B) have reported the photochemical decarboxylation of phenylacetic acid by quinoid lumiflavin derivative **5**, which results in the clean formation of a C4a-benzyl flavin **6**.[4,5] The authors expanded on these findings and could observe that a number of organic substances undergo photochemical reactions yielding covalent C–C bonds in the C4a-position. One example is compound **7** which resulted from the reaction with 2,5-dimethyl-2,4-hexadiene.[6] Related C4a-benzyl adducts have also been observed by photochemical oxidation of benzylamines.[7] Such flavin species with a new covalent C–C bond at the C4a-position were often found to be unstable when exposed to air.

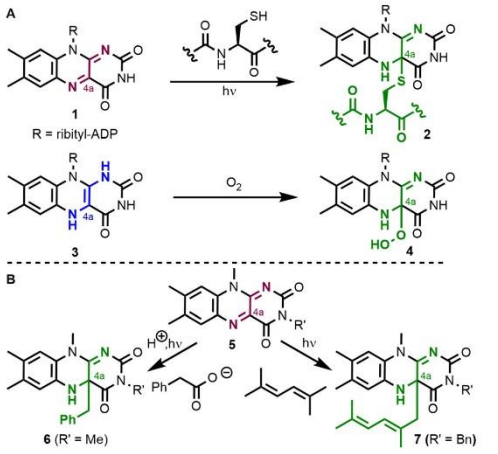

Fig. 1 Covalent adducts of molecular flavins in the C4a-position. Oxygen and sulfur heteroatom–carbon bonds are formed in LOV domains and oxygenating flavoenzymes (A) while C–C bonds are known from photochemical oxidations (B).

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Both the formation of covalent C–C adducts at the C4a-position and presumably also their reaction with O_2 are typically radical pathways. We wondered whether the formal homolysis step would allow using flavin C–C adducts as a reservoir for carbon-centred substrate radicals. Following this rationale, the adducts should also react with other radical species besides O_2 and we were particularly interested in the reaction with the persistent radical TEMPO. On the substrate side, we focused on the activation of allylic C–H positions in olefins and the oxidation of dehydroamino acids. Radical addition reactions of the latter substrates are a perfect tool for the diversification of peptide natural products,[8] which are of high pharmaceutical relevance.[9] The typical protocol relies on radical generation and addition to a dehydroamino acid's β-position.[10] An iridium-mediated generation of heteroatom-stabilized radicals from dimethylanilines and their subsequent addition to a short peptide **8** yielding conjugate **9** serves as a representative example here (Fig. 2A).[11] The orthogonal approach, which relies on the oxidation of a dehydroamino acid and its subsequent intermolecular reaction is, however, much less explored. This reactivity was found in PCET-type[12] oxidation of dehydrophenylalanine **10** (BDFE = 456 kJ mol^{-1}) with Ag_2O to an intermediate radical **11**, which reacts with TEMPO at the β-position yielding alkoxyamine product **12** (Fig. 2B).[13] Related TEMPO-functionalisation of peptides has also been accomplished by dechalcogenation.[14]

We wondered whether such functionalisation of dehydroamino acids could be performed catalytically with molecular flavins.[15] While their use as photo-oxidants is well-established,[16] we were in particular interested in using covalent intermediates at the flavin's C4a-position as stabilised substrate radicals (Fig. 2C).

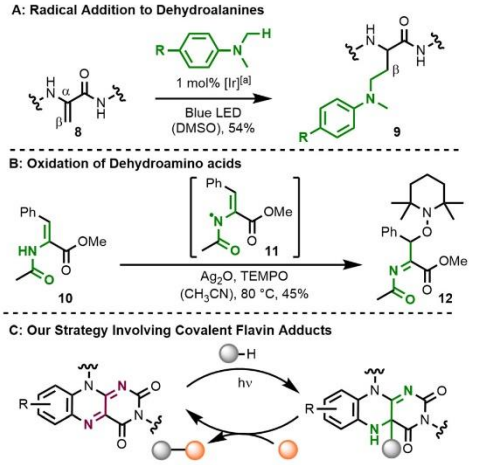

Fig. 2 Radical functionalisation of dehydroamino acids. (A) The addition of C-centred radicals to dehydroalanine-containing peptides allows access to conjugates, which contain diverse substituents (in the R-position) such as drug compounds. (B) Silver(I)oxide was found to be a capable base and oxidant for PCET-activation of dehydroamino acids. (C) Our concept for the use of flavin catalysts as substrate oxidants. [a] Iridium catalyst: $[Ir(dF(CF_3)ppy)_2(dtbbpy)](PF_6)$.

Results and discussion

We first prepared a series of molecular flavins which contain electron-withdrawing substituents.[17] Flavin synthesis starts with a sequence of S_NAr-reaction and nitro group reduction to *ortho*-diaminoaryls **13** (Fig. 3). The isoalloxazine core is then formed by a two-step reaction involving oxidation of monobutyl barbituric acid followed by its condensation with diamines **13**. We prepared flavins with a methyl carboxylate (**14**) and methyl carboxamide (**15**) in the C6-position. For comparison reasons we also prepared the C7-methyl carboxylate **16** and the parent alkyl-substituted isoalloxazine **17**. This choice of substitution pattern was based on the possibility of forming a stabilising intramolecular hydrogen bond in semiquinone **18**, which has been observed in similar cases.[18]

Following our design principle, we directly started with ester-modified flavin **14** and interrogated the photochemical allylic activation of cycloheptadiene (BDE for allylic C–H bond is 347.3 kJ mol^{-1})[19] as a model substrate. Indeed, when irradiating a solution of flavin and diene in CD_2Cl_2 under inert conditions in a J Young NMR tube, we observed the clean formation of covalent adduct **19** (as a set of two diastereomers), which has a newly established C–C bond at the C4a-position (Fig. 4A). This compound was characterized by 2D-NMR and HR-ESI (see ESI† for details). Upon contact with air, quinoid flavin **14** was regenerated. We then studied whether the new C–C bond is weak enough to be cleaved upon the addition of a persistent radical and treated adduct **19** with TEMPO under inert conditions (Fig. 4B). Again, we observed the formation of quinoid flavin **14** but we could also detect the stoichiometric release of alkoxyamine-functionalised diene **20** in the NMR tube (Fig. 4C).

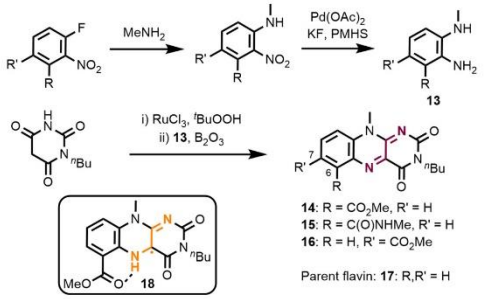

Fig. 3 Flavin catalyst synthesis. For reaction conditions and yields of diamines **13**, see the ESI.† Flavin synthesis: 2.5 equiv. *N*-butyl barbituric acid, 3 mol% $RuCl_3 \cdot (H_2O)_3$, 5.0 equiv. ^{t}BuOOH (CH_2Cl_2/H_2O), r.t., 22 h; then 1.0 equiv. B_2O_3 (AcOH), r.t., o/n. Yields for this two-step procedure: 59% (**14**), 42% (**15**), and 33% (**16**). PMHS: poly(methylhydrosiloxane).

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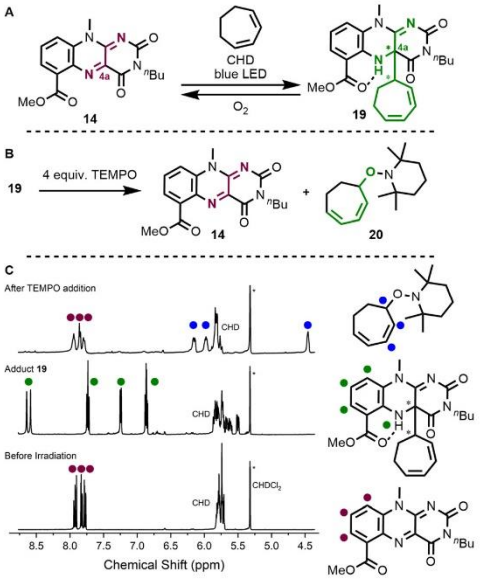


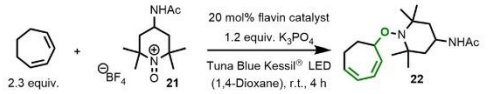
Fig. 4 Studies of covalent adduct formation. The reaction of flavin **14** with cycloheptadiene (CHD) was found to liberate quinoid flavin when the adduct is exposed to air (A). When conducted under inert conditions, the weak C–C bond at the C4a-position can also be cleaved by addition of TEMPO (B and C).

From a synthetic standpoint, the formation of alkoxyamine **20** reminded us of the known reactivity of alkenes towards nitroxyl radicals[20] and oxoammonium cations,[21] which is typically very low with disubstituted olefins. We wondered, whether our flavin activation method might offer a way to catalyse these reactions and found that a flavin-mediated method with TEMPO as a reactant and oxidant indeed leads to product formation (Table 1, entry #1). When using Bobbitt's salt (**21**) instead of TEMPO, only one equivalent of the reagent is required since the oxoammonium salt not only acts as an oxidant (E_{mp} [nitroxo$^+$/nitroxyl$^\bullet$] = +0.65 V *vs.* Ag/AgCl (+0.61 V *vs.* SCE)),[22] but also liberates the persistent radical reaction partner. Potassium phosphate is added as a base to trap the released fluoroboric acid (entry #2). The parent flavin RFTA(Me) performed worse (entry #3) and all control experiments verified that a photochemically excited flavin is required (entries #4 and #5).

With these encouraging results in hand, we investigated whether flavin catalysis would also allow the oxidative TEMPO-functionalisation of more complex substrates such as dehydroamino acids (*c.f.* Fig. 2). We chose dehydrobutyrine **23** as a model substrate and indeed, the formation of acylimine **24** was achieved.

Here, the use of TEMPO (3.0 equiv.) was found to result in better yields when compared to Bobbitt's salt **21** (Table 2, entries #1 and #2). The carboxamide flavin **15**, C7-substituted

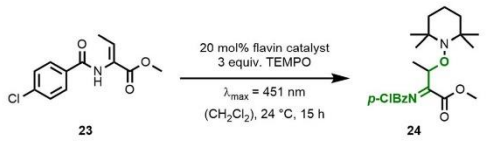
Table 1 Catalytic C–H activation and alkoxyamine formation with a molecular flavin and Bobbitt's salt **21** as limiting reagent



Entry	Catalyst	Change of conditions	Yield[a,b]
#1	**14**	TEMPO instead of **21**	27%[c]
#2	**14**	—	42% (37%)[d]
#3	RFTA(Me)[e]	—	17%
#4	**14**	No irradiation	n.d./n.d.[c]
#5	None	—	n.d./n.d.[c]

[a] Determined by NMR *vs.* internal standard. [b] n.d. = no product formation was detected. [c] TEMPO (without a base) was used instead of Bobbitt's salt **21** leading to product **20**. [d] Isolated yield. [e] (−)-*N*-3-Methyl riboflavin tetraacetate.

Table 2 Flavin catalysts for oxidative β-functionalisation of dehydrobutyrine substrate **23**



Entry	Catalyst	Change of conditions	Yield[a,b]
#1	**14**	—	60%[c]
#2	**14**	**21** instead of TEMPO	6%[d]
#3	**15**	—	15%
#4	**16**	—	35%
#5	**17**	—	43%
#6	**14**	With 10 equiv. H_2O	<5%
#7	**14**	No irradiation	n.d./n.d.[d]
#8	None	—	n.d./n.d.[d]

[a] Determined by NMR *vs.* internal standard. [b] n.d. = no product formation was detected. [c] Acylimine **24** slowly hydrolyses during purification by column chromatography and a significantly reduced isolated yield (14%) was obtained. [d] Reagent **21** (1.0 equiv. together with K_3PO_4 as a base) was used instead of TEMPO leading to product $\mathbf{24}^{\mathbf{NHAc}}$ with an acetamide substituent in the piperidine's 4-position.

ester **16**, and parent flavin **17** all resulted in lower yields (entries #3–#5). Since catalysis product **24** is sensitive towards hydrolysis, the addition of water (10 equiv.) to the reaction mixture resulted in only a trace amount of product (entry #6). The control reactions (entries #7 and #8) confirmed that the reaction is driven by a photochemically excited flavin catalyst.

We were intrigued by the improved activity of ester-modified flavin **14** and went on to study similarities and differences when compared to RFTA(Me). Both quinoid flavins show relatively similar spectroscopic properties (Fig. 5A, see ESI† for details): λ_{max}^{abs} = 442 nm, $E(S_0 \leftarrow S_1)$ = 246 kJ mol^{-1} (EtOH, r.t.), and $E(S_0 \leftarrow T_1)$ = 205 kJ mol^{-1} (EtOH, 77 K) (**14**) *vs.* λ_{max}^{abs} = 448 nm,

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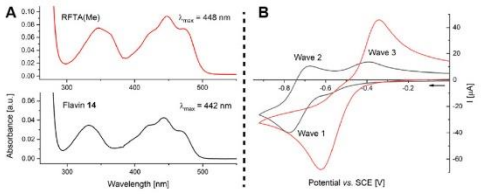
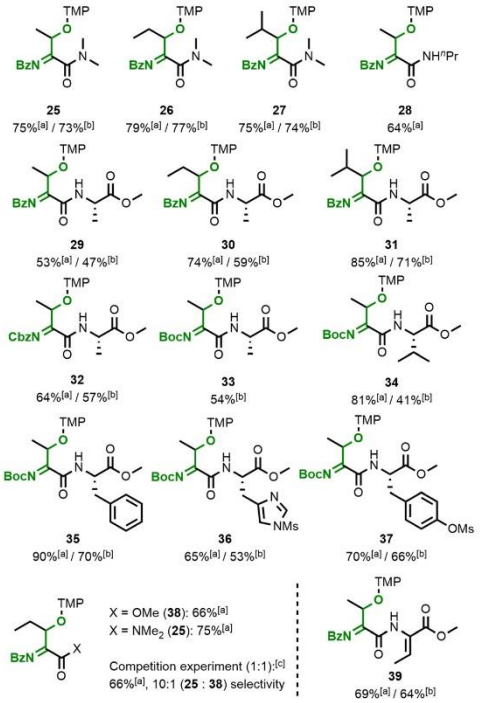


Fig. 5 Studies of flavin **14** by UV/Vis spectroscopy and cyclic voltammetry. (A) Absorption spectra of RFTA(Me) (top, red) and flavin **14** (bottom, black) in CH_2Cl_2 (0.1 mM). (B) Cyclic voltammetry of flavin **14** in 0.1 M $TBAPF_6/CH_3CN$ with a scan rate of 0.5 V s^{-1} (in black) and in the presence of 0.4 equiv. AcOH (in red).

$E(S_0 \leftarrow S_1) = 244$ kJ mol^{-1} (EtOH, r.t.), and $E(S_0 \leftarrow T_1) = 205$ kJ mol^{-1} (EtOH, 77 K) (RFTA(Me)). Cyclic voltammetry, however, revealed characteristic differences: The *N*3-alkylated flavin RFTA(Me) shows a simple cyclic voltammogram with a reversible reduction process ($E_{1/2} = -0.86$ V *vs.* SCE, see ESI† for details).[23] Under analogous conditions, flavin **14** shows two separate oxidation waves (waves 2 and 3) and a half-wave potential of $E_{1/2} = -0.72$ V *vs.* SCE for the reversible reduction. We rationalise this observation by a significantly faster protonation of the immediately formed anion $\mathbf{14}^{\bullet-}$ to the neutral radical **18**, which is reasonable based on the favoured intramolecular hydrogen bonding. This neutral semiquinone **18** is easier to reduce than quinoid flavin **14** and, therefore, it is converted to hydroquinoid $\mathbf{18}^-$ in wave 1. Reoxidation of $\mathbf{14}^{\bullet-}$ (wave 2) and $\mathbf{18}^-$ (wave 3) then occur separately. In order to prove this hypothesis, we accelerated the protonation step by measuring cyclic voltammograms in the presence of acetic acid.[24] Indeed, this resulted in the detection of only one oxidation wave, which corresponds to the oxidation of $\mathbf{18}^-$ (Fig. 5B, see ESI† for details).

The flavin-catalysed method was successfully applied to the oxidative modification of a variety of dehydroamino acid substrates (Fig. 6), which also do not show any uncatalysed reactivity under our conditions with either TEMPO or Bobbitt's salt (see ESI† for attempted conversion of a dehydrobutyrine substrate to acylimine **25**). Owing to the decreased electrophilicity of the acylimine amides compared to ester-derived product **24**, the former are significantly less reactive towards water hydrolysis and their isolation is straightforward. Similar results were observed when increasing the size of the alkyl chain on the substrate's C–C double bond or the amide (products **25**–**28**). The acylamides **29**–**31** from amides consisting of two amino acid residues were also successfully formed. We found that our method is not limited to benzamide substrates and the readily available Boc- and Cbz-protected products **32**–**34** were obtained in reasonable yields as well. Aromatic amino acid side chains such as phenylalanine (**35**) or protected histidine (**36**) and tyrosine (**37**) are also tolerated. Dehydroamino acid amides are significantly more reactive compared to the analogous esters, which allowed the selective formation of acylimine **25** with only negligible amounts of ester **38** in a competition experiment. The same preference was observed in an intramolecular setting,



25 75%[a] / 73%[b]
26 79%[a] / 77%[b]
27 75%[a] / 74%[b]
28 64%[a]
29 53%[a] / 47%[b]
30 74%[a] / 59%[b]
31 85%[a] / 71%[b]
32 64%[a] / 57%[b]
33 54%[b]
34 81%[a] / 41%[b]
35 90%[a] / 70%[b]
36 65%[a] / 53%[b]
37 70%[a] / 66%[b]
39 69%[a] / 64%[b]

Fig. 6 Scope of the flavin-catalysed oxidative functionalisation of dehydroamino acids. Conditions: 20 mol% flavin **14**, 3.0 equiv. TEMPO, $\lambda_{max} = 451$ nm (CH_2Cl_2), 15 °C, 15 h. Compound **28** evaded isolation due to hydrolysis and the NMR yield of **33** could not be obtained due to overlapping signals. [a]: Determined by NMR *vs.* internal standard. [b]: Isolated yield. [c]: 2.0 equiv. TEMPO used. TMP = tetramethylpiperidine.

where mono-functionalised acylimine **39** was the only species we observed when using a substrate with two dehydrobutyrine residues.

We subsequently interrogated the mechanism of dehydroamino acid activation. Consistent with initial radical formation at the amide nitrogen position yielding an *N*-centered radical, we did not observe any conversion of *N*-methylated substrate (*E*)-**41** under standard catalysis conditions (see ESI†). When irradiating this amino acid substrate together with flavin **14** in a J Young NMR tube under the exclusion of air, we confirmed that neither *E*/*Z*-isomerisation[25] nor substrate conversion takes place (Fig. 7). This also holds true for the isomeric (*Z*)-**41**, which was also not converted under these conditions. In contrast, oxidation of both (*E*)- and (*Z*)-**40** results in radical formation at the dehydroamino acid's β-position. When we conducted such experiments in J Young NMR tubes with the exclusion of air and without TEMPO, we observed the formation of covalent flavin adducts within minutes and confirmed this by HR-ESI measurements. Careful inspection of

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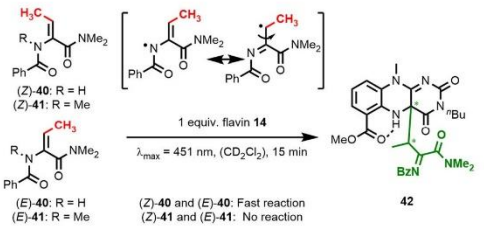

Fig. 7 Irradiation experiments with dehydrobutyrine substrates **40** and **41** in J Young NMR tubes under the exclusion of air.

2D-NMR spectra and NOE-contacts corroborated our assignment of a covalent C–C adduct at the C4a-position (see ESI† for details). Flavin adduct **42** is formed as an almost equal mixture of two diastereomers. When adduct **42** is irradiated in the presence of TEMPO, quinoid flavin **14** is regenerated and acylimine **25** is released.

Acylimines are easily reduced to the corresponding amides by sodium borohydride, which leaves the TEMPO-functionalisation unaltered (Fig. 8A). Also, the relatively weak C–O bond in TEMPO-containing organic products allows subsequent transformations,[26,27] and we demonstrated the oxidation of alkoxyamine **43** to ketone **44** by *m*CPBA. All of the obtained acylimine products resemble reactive electrophiles and, therefore, offer the possibility for one-pot reactions leading to diversified amino acid products. Acylimine **28** was found to be unstable during chromatography with silica gel, but when subjected to a one-pot malonate addition sequence,[28] the formation of stable pyrrolidine-2,5-dione **45** was observed (Fig. 8B). We confirmed the relative stereochemistry in the five-membered ring by NOE-contacts. There are also literature protocols for the reduction of acylimines to the corresponding amides.[29] As a representative example for transforming the weak C–O bond in the alkoxyamine products, we performed a one-pot three-step sequence starting from dehydrobutyrine **23** with subsequent malonate addition and *m*CPBA oxidation to ketone **46** (Fig. 8C). These examples shall demonstrate that flavin catalysis is a powerful tool for the functionalisation of dehydroamino acid derivatives.

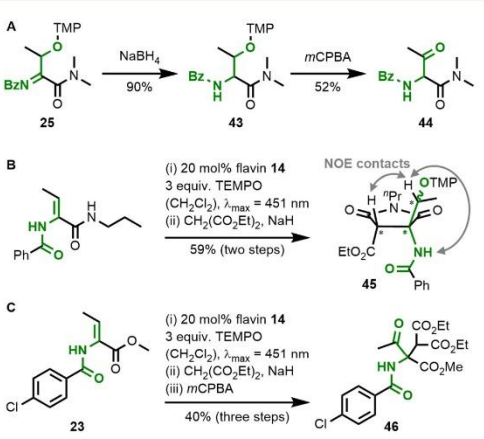

Fig. 8 Examples of synthetic one-pot modifications of dehydrobutyrine substrates in the β-position mediated by flavin catalysts: (A) reduction of acylimine **25** and subsequent TEMPO cleavage. (B) Two-step TEMPO-functionalisation and subsequent malonate addition. (C) Three-step reaction with oxidation of the alkoxyamine product to ketone **46**.

Conclusions

This proof-of-concept study of the reversible formation of covalent C–C bonds at the flavin's C4a-position demonstrates that such compounds can indeed be intermediates in catalytic cycles rather than only dead-end structures. In the presented transformations, flavin catalysis allows the functionalisation of dehydroamino acid substrates in the β-position. Such acylimine products offer a variety of different follow-up reactions and, therefore, our method is envisioned to be a valuable tool for amino acid diversification. Building on the general reactivity of flavin adducts at the C4a-position, we also expect other transformations to make use of such intermediates in the future. The dehydroamino acid derivatisation strategies may add to the toolbox of useful strategies in peptide natural product diversification.

Data availability

Original NMR datasets (FIDs) are available at Open Science-Framework at **https://osf.io/jyf9p/**.

Author contributions

A. R. performed and analysed the experiments. A. R. and G. S. designed the experiments and wrote the manuscript. G. S. supervised the project. A. W. performed and analysed the cyclic voltammetry measurements. All authors contributed to the analysis of data and reviewed the manuscript.

Conflicts of interest

There are no conflicts to declare.

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5. Enhancing Flavins Photochemical Activity in Hydrogen Atom Abstraction and Triplet Sensitization through Ring-Contraction

Title: "Enhancing Flavins Photochemical Activity in Hydrogen Atom Abstraction and Triplet Sensitization through Ring-Contraction"

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Journal: *Angew. Chem. Int. Ed.* **2024**, e202318590.

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Authors: A. Rehpenn, S. Hindelang, K.-N. Truong, A. Pöthig, G. Storch

Content: This publication addresses the design and synthesis of a variety of ring-contracted flavins, also known as imidazolonequinoxalines. We systematically investigated their properties: singlet and triplet energies, absorption spectra as well as oxidation potentials of unmodified and methyl ester modified imidazolonequinoxalines were provided. It was demonstrated that upon irradiation, excited ring-contracted flavins act as potent hydrogen atom transfer catalysts, enabling the SCF_3 functionalization of methine positions and aldehydes. Only modified imidazolonequinoxalines were active in these transformations. Unmodified analogs and flavins did not react with the substrate. Moreover, it was discovered that ring-contracted flavins exhibit exceptional photosensitizing properties, owing to their high triplet energy. This characteristic, coupled with their remarkable capacity for hydrogen atom abstraction, facilitated the sequential conversion of α-tropolone to *trans*-3,4-disubstituted cyclopentanones with benzaldehydes. This transformation was viable with various benzaldehydes and yields one single diastereomer.

Author Contributions: All synthetic and catalytic experiments were planned and analyzed by A. Rehpenn. S. Hindelang contributed conceptually and synthetically to the *Lewis* acid activation. Crystallographic data were gathered and analyzed by K.-N. Truong, A. Pöthig and J. Zuber. Electrochemical measurements were performed and analyzed by A. Walter. Spectroscopic measurements were performed by J. Großkopf and K. Hintzer. The manuscript was written by A. Rehpenn, S. Hindelang, K.-N. Truong, A. Pöthig and G. Storch. A. Rehpenn wrote the supplementary information file which contains all experimental data.

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Photochemistry

Enhancing Flavins Photochemical Activity in Hydrogen Atom Abstraction and Triplet Sensitization through Ring-Contraction

*Andreas Rehpenn, Stephan Hindelang, Khai-Nghi Truong, Alexander Pöthig, and Golo Storch**

Abstract: The isoalloxazine heterocycle of flavin cofactors reacts with various nucleophiles to form covalent adducts with important functions in enzymes. Molecular flavin models allow for the characterization of such adducts and the study of their properties. A fascinating set of reactions occurs when flavins react with hydroxide base, which leads to imidazolonequinoxalines, ring-contracted flavins, with so far unexplored activity. We report a systematic study of the photophysical properties of this new chromophore by absorption and emission spectroscopy as well as cyclic voltammetry. Excited, ring-contracted flavins are significantly stronger hydrogen atom abstractors when compared to the parent flavins, which allowed the direct trifluoromethylthiolation of aliphatic methine positions (bond dissociation energy (BDE) of 400.8 kJ mol^{-1}). In an orthogonal activity, their increased triplet energy ($E(S_0 \leftarrow T_1)$= 244 kJ mol^{-1}) made sensitized reactions possible which exceeded the power of standard flavins. Combining both properties, ring-contracted flavin catalysts enabled the one-pot, five-step transformation of α-tropolone into *trans*-3,4-disubstituted cyclopentanones. We envision this new class of flavin-derived chromophores to open up new modes of reactivity that are currently impossible with unmodified flavins.

Introduction

The reaction of flavin mononucleotide (FMN) and flavin adenine dinucleotide (FAD) cofactors with nucleophiles leads to covalent adducts. The exact reaction position depends on the hard or soft nature of the nucleophile, and also the steric properties of surrounding substituents. Covalent adducts play a vital role in flavoenzyme-mediated catalytic reactions (Figure 1A).[1,2] The C4a-hydroperoxides **1** are formed by reductive activation of O_2 from air and are the central cornerstone of oxygenating activity under aerobic conditions.[3] In recent years, these adducts have been structurally expanded by the observation of similar N5-hydroperoxides by the groups of *Teufel* and *Moore*.[4] Covalent carbon-sulfur bonds, reversibly formed between the C4a-position and a cysteine thiol group (2), are key intermediates in light, oxygen, and voltage (LOV) photoreceptors.[5] With sulfites, covalent adducts are formed

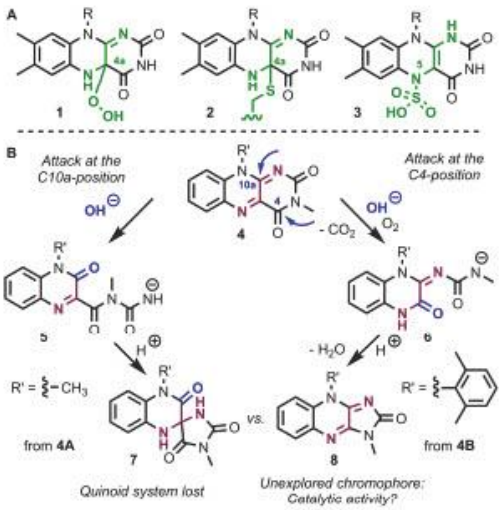

Figure 1. Covalent adducts of flavins with nucleophiles. A) Reversible formation of covalent adducts is an essential step in flavoenzymatic mechanisms. B) The reaction of molecular flavins with hydroxide nucleophiles proceeds via divergent pathways depending on the initial position of attack. R = Ribityl-ADP (FAD). ADP = Adenosine diphosphate.

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at the N5-position (**3**) and are central as intermediates for forming mixed anhydrides.[6] Carbanions also preferentially attack the N5-position, which is the pivotal first step in nitroalkane oxidation by *amino acid oxidases*.[7]

The importance of covalent adducts with the isoalloxazine core has prompted a series of synthetic studies, which aimed to elucidate the reactivity of different heterocycle positions towards incoming nucleophiles in the organic laboratory. *Brutce* and *Yoneda* investigated the reaction of simple isoalloxazines (**4**) with strong bases.[8] When exposed to hydroxide nucleophiles,[9] the authors identified two sites of initial bond formation, namely C4 and C10a (Figure 1B). Both pathways lead to a heterocycle ring-opening and either the formation of quinoxalinone **5** or **6**, respectively. The relative tendency of hydroxide attack to either position was found to be dependent on the steric effect of the R'-substituent. With a sterically demanding 2,6-xylyl substituent (from flavin **4B**), the C10a-position was found to be blocked, and the addition at the C4-position dominated. Both intermediates underwent irreversible C–N bond formation. In the case of quinoxalinone **5**, this led to spirohydantoin **7**, which does not possess a quinoid system and, therefore, does not resemble a flavin analogue anymore. On the other hand, quinoxalinone **6** cyclized to imidazolonequinoxaline **8**, which still contains the flavin-type quinoid system. No studies regarding the properties and catalytic activity of this compound class have been reported so far.

We aimed to systematically study the ring-contraction reaction with modified flavin catalysts and to investigate their photophysical properties. With these results in hand, we were interested in their ability to participate in catalytic transformations.[10,11] Novel redox-active organic compounds are also interesting regarding their application for energy storage in batteries.[12]

Results and Discussion

Synthesis and Spectroscopic Characterization

Building on the initial reports by *Brutce* and *Yoneda*, isoalloxazine **9** was first treated with lithium hydroxide, and imidazolonequinoxaline **10** was obtained (Figure 2). As expected, this reaction was found to be very unselective, and several reaction products were observed. The ring-contracted flavin **10** could be isolated albeit in a low yield of only 18 %. Interestingly, the analogous reaction was much cleaner with the C6-CO_2Me (**11**) and C6-C(O)NHMe (**12**) derivatives,[13] resulting in ring-contracted flavins **13** (42 %) and **14** (37 %). We rationalized this improvement with increased reactivity of the C4-position towards hydroxide nucleophiles in flavins with electron-withdrawing substituents. The ring-contraction of flavin **11** occurred concomitant to saponification, and carboxylic acid **13** was isolated. The solid-state structure of **13** was elucidated directly from the powder sample by continuous rotation 3D electron diffraction (3D ED, Figure 2 top right).[14] The bulk product of **13** consisted of two isostructural polymorphs confirmed via both complementary techniques, *vtz*. 3D ED and X-ray

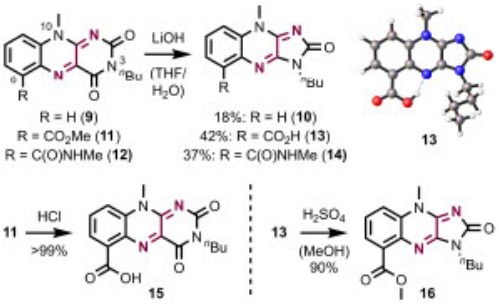

Figure 2. Ring-contraction of flavins under basic reaction conditions. Top right: ED structure of ring-contracted flavin **13** in the solid state (see the Supporting Information for details).

powder diffraction (see the Supporting Information for details).[15] In order to have a complete set of flavins and their ring-contracted analogs available, ester cleavage of flavin **11** was performed under acidic conditions yielding flavin **15**,[16] and the esterification of ring-contracted flavin **13** with methanol gave ester **16**. This set of synthetic procedures led to flavins and ring-contracted flavins with the following substituents in the C6-position: H, C(O)NHMe, CO_2Me, and CO_2H.

The redox potentials of ring-contracted flavins were then determined by cyclic voltammetry. In the ground state, N3,N10-dialkyl flavins (isoalloxazines) are weak oxidants with $E_{1/2} = -0.83$ V vs. SCE (CH_3CN).[17] The analogous ring-contracted flavin **10** has a significantly more negative redox potential of $E_{1/2} = -1.68$ V vs. SCE (CH_3CN). In other words, the imidazolonequinoxalines are less oxidizing in the ground state, which can be explained by the missing carbonyl group (Figure 3A). The carboxylic ester substituent in ring-contracted flavin **16** (Figure 3B) slightly moves the

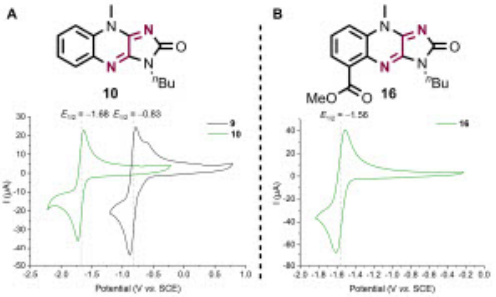

Figure 3. Comparison study of flavins and ring-contracted analogs by cyclic voltammetry. The unsubstituted core structures **9** and **10** are shown (A), and also ester-substituted ring-contracted flavin **16** (B). All data were recorded in acetonitrile solution with tetra-*n*-butylammonium hexafluorophosphate ($TBAPF_6$) as the electrolyte (see the Supporting Information for details).

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redox potential back toward the positive direction with a value of $E_{1/2} = -1.56$ V vs. SCE (CH_3CN).

All ring-contracted flavins are colorless solids, which sets them apart from the intensively yellow-colored parent flavins.[18] The naturally occurring (–)-riboflavin has an absorption maximum at $\lambda = 443$ nm (EtOH solution). In contrast, both ring-contracted flavins **10** (Figure 4A) and **16** (Figure 4B) have similarly shaped absorption spectra with maxima at $\lambda = 352$ nm (**10**) and $\lambda = 347$ nm (**16**), which explains their appearance. Both compounds show fluorescence emission at $\lambda_{max} = 395$ nm. When determined from the intersection of absorption and emission spectra, both compounds have a similar singlet excited state energy of $E(S_0 \leftarrow S_1) = 319\ kJ\,mol^{-1}$, which is significantly higher compared to (–)-riboflavin ($E(S_0 \leftarrow S_1) = 244\ kJ\,mol^{-1}$).[18] Both compounds are relatively strong oxidants in the photochemically excited singlet state ($E^* = 1.63$ V (**10**) and 1.75 V (**16**) vs. SCE). The phosphorescence signals of ring-contracted flavins **10** and **16** were resolved by measuring the two compounds in a saturated solution of potassium iodide in ethanol,[19] which led to $E(S_0 \leftarrow T_1) = 244\ kJ\,mol^{-1}$ when measured at 77 K in both cases (see the Supporting Information for details). Again, this value is significantly higher compared to (–)-riboflavin ($E(S_0 \leftarrow T_1) = 205\ kJ\,mol^{-1}$).[18,20]

In addition to these photophysical characteristics, we probed for the activity of ring-contracted flavins as hydrogen atom abstractors in the excited state.[21] Model substrate **17** was chosen, which has a methine position (marked in red) with a relatively high bond dissociation energy (BDE) of 400.8 $kJ\,mol^{-1}$ (for CH_3-CH_2-C*H*(CH_3)$_2$).[22] Indeed, deuteration of this methine position occurred and **17**-d was detected when irradiating a solution of substrate **17** and a catalytic amount of ring-contracted flavin **16** in a mixture of D_2O and CD_3CN (Figure 5). This result was observed by ^2H NMR (see the Supporting Information for details).[23] No deuteration occurred under analogous conditions when flavin **11** was used as the catalyst. Evidence for a reaction between excited flavin **16** and substrate **17** was also obtained by a *Stern–Volmer* quenching study (see the Supporting Information for details).

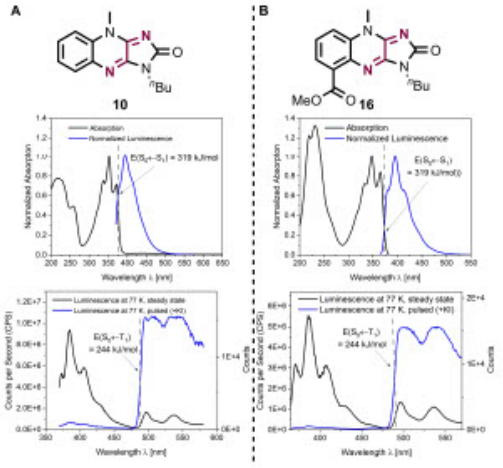

Figure 4. Spectroscopic characterization of ring-contracted flavins **10** (A) and **16** (B). Absorption and luminescence spectra (excitation at $\lambda = 365$ nm) were recorded in ethanol (80 μM solution). The phosphorescence spectra (50 μs delay) were recorded in a solution of saturated potassium iodide in ethanol at 77 K.

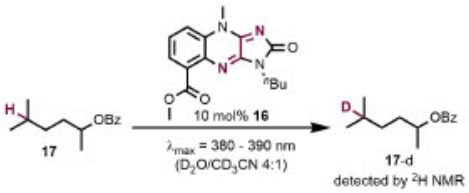

Figure 5. Deuteration experiment with ring-contracted flavin **16** as hydrogen atom abstractor in the excited state. The irradiation (50 mM with respect to **17**) was performed at room temperature for 16 h.

Catalytic Applications

The activity of ring-contracted flavin **16** in hydrogen atom abstraction led us to commence the catalytic studies with a reaction that initially requires this elementary step. The trifluoromethylthiolation[24,25] of organic molecules is of particular interest in pharmaceutical chemistry due to the high hydrophobicity (*Hansch* parameter of $\pi = 1.44$ vs. CF_3: $\pi = 0.88$) and electron withdrawing properties (*Hammett* parameter $\sigma_p = 0.50$ vs. CF_3: $\sigma_p = 0.54$) of the SCF_3-group.[26] The trifluoromethylthiolation of substrate **17** with *N*-(trifluoromethylthio)phthalimide[27] **18** was studied by *Glortus* and requires an oxidizing iridium photocatalyst [Ir(dF(CF_3)ppy)$_2$(dtbbpy)]PF_6 together with a hydrogen atom abstraction catalyst such as benzoate.[28] We wondered whether ring-contracted flavins would combine both catalytic activities (Table 1). An initial series of experiments revealed that the usual isoalloxazine-based flavins are incapable of mediating the reaction independent of irradiation wavelength and additional base (entries 1–3). Formation of thioether product **19** was observed when tetra-*n*-butylammonium benzoate ($BzONBu_4$) was added, albeit in a low yield of 18% (entries 4 and 5). It was concluded that excited flavins serve as oxidants for benzoate which in turn abstracts a hydrogen atom from substrate **17**. However, excited flavins themselves are incapable of mediating the reaction.

Indeed, switching to ring-contracted flavins led to product formation without any additive, consistent with a stronger hydrogen atom abstraction strength (entries 6–9). Only low levels of thioether **19** were formed with the carboxylic acid-containing catalyst **13**, while the unmodified ring-contracted flavin **10** was completely inactive. Catalyst

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Table 1: The catalytic trifluoromethylthiolation mediated by flavins.

Entry	Catalyst with Substitution	Wavelength	Additive[a]	Yield[b]
1	Flavin **15** CO_2H	451 nm	–	n.d.
2	Flavin **11** CO_2Me	451 nm	–	n.d.
3	Flavin **11** CO_2Me	451 nm[c]	K_3PO_4	n.d.
4	Flavin **15** CO_2H	451 nm	$BzONBu_4$	18%
5	Flavin **15** CO_2H	451 nm	K_3PO_4	n.d.
6	Contracted **13** CO_2H	380–390 nm	–	10%
7	Contracted **10** H	380–390 nm	–	n.d.
8	Contracted **14** C(O)NHMe	380–390 nm	–	35%
9	Contracted **16** CO_2Me	380–390 nm	–	43%[d]
10	Contracted **13** CO_2H	380–390 nm	K_3PO_4	45%
11	Contracted **16** CO_2Me	380–390 nm	K_3PO_4	88%
12	TBADT	380–390 nm	K_3PO_4	19%
13	Benzophenone	365 nm	K_3PO_4	3%

All reactions were run for 16 h at room temperature. [a] Applied in a quantity of 5 mol %. [b] Yields were determined by NMR spectroscopy versus the internal standard trimethyl 1,3,5-benzenetricarboxylate. [c] Irradiation at 380–390 nm led to unchanged results. [d] The analogous experiment without catalyst resulted in no product formation. n.d. = No product was detected.

variants with amide (**14**) and ester (**16**) substituents led to improved results of 35% and 43% yield, respectively. The addition of potassium phosphate base improved the results significantly and an optimal yield of 88% was obtained with ring-contracted flavin **16** (entries 10 and 11). The acetonitrile solvent and an LED light source of 380–390 nm resulted from an extended screening for reaction conditions (see the Supporting Information for details). The established hydrogen atom abstraction photocatalysts tetra-*n*-butylammonium decatungstate (TBADT) and benzophenone only led to poor levels of product formation (entries 12 and 13).

The catalytic trifluoromethylthiolation with ring-contracted flavins is not limited to model substrate **17**, and ester substituents with cyclopropyl (**20**), thiophenyl (**21**), and pyridyl (**22**) groups are well-tolerated (Figure 6A). Based on the deuteration experiment (*cf.* Figure 5), selective hydrogen atom abstraction from the methine position by excited ring-contracted flavin **16*** is the plausible first step. Subsequent reaction of carbon-centred radical **23** with SCF_3-reagent **18** leads to the formation of thioether product **19**. The latter step releases a phthalimidyl radical, which likely regenerates the ring-contracted flavin **16**.[28,29] This photochemically excited catalyst **16*** was also successful in abstracting a hydrogen atom from aromatic aldehydes (see the Supporting Information for a *Stern–Volmer* quenching study), and allowed converting benzaldehyde derivative **24** into thioester **25** (Figure 6B).[30] Trapping adduct **26** was detected when the photochemical reaction was conducted in the presence of the persistent radical TEMPO, which corroborates the

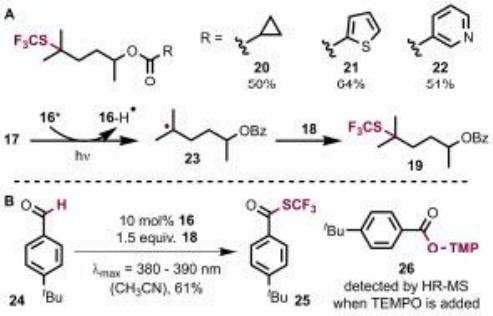

Figure 6. Application of ring-contracted flavin **16** in catalytic reactions. A) Trifluoromethylthiolation of the methine position in different substrates (conditions analogous to Table 1, entry 11). B) Catalytic conversion of aromatic aldehyde **24** into thioester **25**. All yields refer to isolated material. TMP: 2,2,6,6-Tetramethylpiperidinyl.

intermediate formation of acyl radicals by hydrogen atom abstraction.

The sensitization activity of ring-contracted flavins was then studied based on their significantly increased triplet energy E_T (*cf.* Figure 4).[31] Cycloheptadiene (**27**) seemed a suitable model substrate for probing reactivity differences between flavins and their ring-contracted analogues since its triplet energy $E_T(27) = 228\ kJmol^{-1}$ lies between that of the two catalysts.[32] It was already shown that ester-modified flavin **11** is cleanly converted into the covalent adduct **28** by photochemical excitation (Figure 7A).[13] When an excess of cycloheptadiene was used, the remaining material stayed untouched during irradiation. In stark contrast, ring-con-

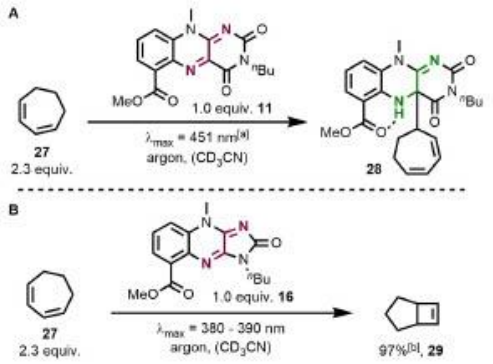

Figure 7. Comparison of flavin reactivity and their ring-contracted analogs towards cycloheptadiene (**27**). The substrate is not converted by irradiation without a catalyst at either $\lambda_{max} = 380–390$ nm or $\lambda_{max} = 451$ nm. [a] No conversion was observed when an LED of $\lambda_{max} = 380–390$ nm was used. [b] This is a volatile product and the yield was determined by NMR spectroscopy versus the internal standard trimethyl 1,3,5-benzenetricarboxylate.

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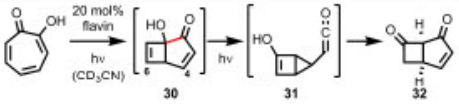
tracted flavin **16** acted as a triplet sensitizer under analogous conditions, and the clean formation of bicycloheptene **29** was observed (Figure 7B). This reaction was rationalized by a triplet-sensitized *E*/*Z*-isomerization of cycloheptadiene followed by a rapid, thermal cyclization to bicycloheptene **29**, and highlights the divergent reactivity between flavins and their ring-contracted analogues.[33]

Driven by the aim to apply ring-contracted flavins in a sequential multi-step reaction that combines both activities, namely energy transfer and hydrogen atom abstraction, α-tropolones were chosen as substrates (Table 2).[34] The electrocyclisation of α-tropolone methyl ethers[35] has attracted widespread attention and found several applications in total synthesis.[36] On the other hand, free α-tropolone was studied much less, although an early report by *Day* describes the formation of photoproducts **30** and **32** by direct excitation.[37] With careful control of the reaction conditions, intermediate **30** can be obtained by direct excitation at 300 nm,[38] but preparative synthesis and further applications of final product **32** (formed via its enol tautomer) are elusive. When α-tropolone was irradiated at λ_{max} = 380–390 nm, product **32** was not accumulated in significant quantities and decomposition dominated (entry 1). The reaction proceeded much cleaner in the presence of flavin **11**. However, the predominant formation of intermediate **30** occurred at λ_{max} = 380–390 nm, while λ_{max} = 451 nm was ineffective (entries 2 and 3). In contrast, ring-contracted flavin **16** provided cyclopentenone **32** in good efficiency with 86 % yield (entry 4). In the presence of piperylene as a triplet quencher,[39] the formation of cyclopentenone **32** was significantly suppressed. A diminished yield of only 44 % was observed, while the overall mass balance was still good (entry 5).

Based on seminal work by *Day* and *Chapman* on tropolone photochemistry,[40] the following mechanistic rationale is plausible for explaining the results. A 4π-electrocyclization of α-tropolone to cyclobutene **30** is triggered by direct irradiation at λ_{max} = 380–390 nm (α-tropolone absorption at λ_{max} = 354 nm).[41] However, this primary photoproduct is unstable under the reaction conditions, and the second photochemical step seems inefficient under direct irradiation at this wavelength. The subsequent reaction of intermediate **30** to cyclopropyl ketene **31** resembles an initial α-cleavage (C–C bond marked in red) of the photochemically excited enone and a subsequent C–C bond formation between positions C4 and C6.[42] The α-cleavage of cyclopentenones and the formation of cyclopropyl ketenes are well-studied, and it has been shown that these reactions can proceed on the triplet hypersurface, which opens up the possibility of using a triplet sensitizer.[43] Therefore, the improved reactivity with flavin **16** is likely explained by triplet sensitization of this second photochemical step, which rapidly converts intermediate **30** into **32**. Sensitization is more efficient with a ring-contracted flavin due to its higher triplet energy, and this second photochemical reaction is suppressed by the triplet quencher piperylene. Consistent with this analysis, the first photochemical step of the reaction sequence is not affected by the added piperylene (see entries 6 to 8 after only 15 min irradiation time). The final conversion of cyclopropyl ketene **31** to cyclopentenone **32** is a thermal reaction that resembles the well-studied isomerization of this substrate class.[44] Careful monitoring of the photochemical reaction in intervals of 15 min corroborated the improved activity of ring-contracted flavin **16** (see the Supporting Information for details).

The three-step α-tropolone photoreaction was then embedded into a one-pot reaction sequence mediated by ring-contracted flavin **16**. Based on the successful hydrogen atom abstraction with aromatic aldehyde substrates (*cf.* Figure 6B), we aimed to add acyl radicals, analogously generated by flavin-mediated hydrogen atom abstraction, to the cyclopentenone part of bicyclic photoproduct **32**.[45] Indeed, when a mixture of aromatic aldehyde **24** and α-tropolone was irradiated in the presence of ring-contracted flavin **16**, the formation of triketone **33** was identified in the crude mixture (Figure 8). However, its high

Table 2: Three-step cyclization of unsubstituted α-tropolone.



Entry	Catalyst	Wavelength[a]	Tropolone[b]	30[b]	32[b]
1	none	380–390 nm	–	–	9%
2	**11**	380–390 nm	8%	65%	18%
3	**11**	451 nm	>99%	–	–
4	**16**	380–390 nm	–	–	86%
5[c]	**16**	380–390 nm	2%	41%	44%
6[d]	none	380–390 nm	35%	28%	4%
7[d]	**16**	380–390 nm	67%	23%	5%
8[c,d]	**16**	380–390 nm	70%	27%	3%

All samples were irradiated for 105 min (unless noted otherwise) at room temperature under an atmosphere of argon. [a] Wavelength of the LED used for irradiation (λ_{max}). [b] Yields were determined by NMR spectroscopy versus the internal standard trimethyl 1,3,5-benzenetricarboxylate. [c] With 10 equiv. of piperylene. [d] Only 15 min of irradiation.

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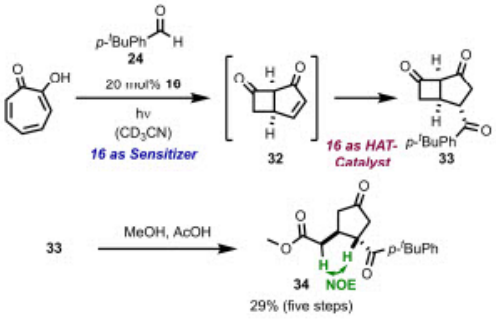


Figure 8. Sequential multi-step reaction leading to cyclopentanone **34**. The yield was determined with isolated material. It refers to the entire five-step sequence and is given with respect to α-tropolone.

reactivity made purification attempts unsuccessful. We therefore performed a subsequent methanolysis under acidic conditions, which led to a clean cyclobutane ring opening and *trans*-3,4-disubstituted cyclopentanone **34**. The latter was formed as a single diastereomer in 29 % yield, and the relative configuration was determined by NOE (nuclear *Overhauser* effect) contacts (see the Supporting Information for details).

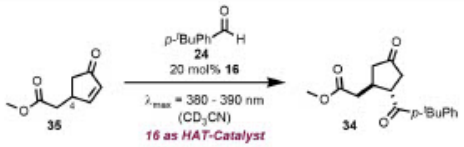
The α-tropolone was fully consumed during the reaction and no other side products were detected in the crude NMR spectrum. This observation was rationalized by the instability of the reactive photoproducts **30** and **32** under prolonged irradiation, leading to a diminished yield. Therefore, the order of reaction steps was switched. Methanolysis of photoproduct **32** to the more stable cyclopentenone **35** was performed first, followed by acyl radical addition. This reaction was initially probed with cyclopentenone material that was generated separately by the photochemical method (Table 3).[46]

However, cyclopentenone **35** was significantly less reactive towards radical addition when compared to bicycle **32**, and no product was formed initially (entry 1). Fortunately, the addition of *Lewis* acids could restore catalytic activity. While boron trifluoride and lithium chloride gave low to moderate yields (entries 2 and 3), the addition of one equivalent of zinc chloride resulted in 54 % yield of the corresponding *trans*-3,4-disubstituted cyclopentanone **34** (entry 4). The same stereoisomer was formed under these reaction conditions compared to the previous addition to bicycle **32** since the same enone face is blocked by the substituent in the 4-position.

With these conditions in hand, the entire one-pot reaction sequence was investigated (Figure 9). Photoproduct **32** was initially obtained within 105 min irradiation time (*cf.* Table 2) and methanolic acetic acid was then added to the reaction mixture. Methanolysis to cyclopentenone **35** was completed after three hours as indicated by TLC analysis. The crude solution was then combined with aldehyde **24** and zinc chloride, and again irradiated for 16 h. Under these conditions, the *trans*-3,4-disubstituted cyclopentanone **34** was isolated in a significantly improved yield of 52 %. No product formation was detected with benzophenone, xanthone, or $[Ir(dF(CF_3)ppy)_2(bpy)]PF_6$ catalysts in the analogous sequence,[47] while dominant substrate and catalyst decomposition was observed instead. This result highlights the stability and effectiveness of ring-contracted flavin **16**.

Different aldehyde reaction partners were then studied and we were pleased to see that the one-pot, five-step procedure worked for various substituted aromatic aldehydes (Figure 10). Both fluoro (**36**) and bromo (**37**) substituents gave similar or even higher yields compared to *tert*-butyl derivative **34**. Chloro substituents in *para* (**38**) and *meta* (**39**) position were also tolerated. This new method offers direct access to *trans*-3,4-disubstituted cyclopentanones from α-tropolone with several handles for further modifications.

Table 3: Acyl radical addition to cyclopentenone **35**.



Entry	Lewis Acid[a]	34[b]
1	none	–
2	$BF_3 \cdot OEt_2$	11 %
3	LiCl	40 %
4	$ZnCl_2$	54 %

Reactions were run for 16 h at room temperature. [a] One equivalent of the *Lewis* acid was used. [b] Yields were determined by NMR spectroscopy versus the internal standard trimethyl 1,3,5-benzenetricarboxylate.

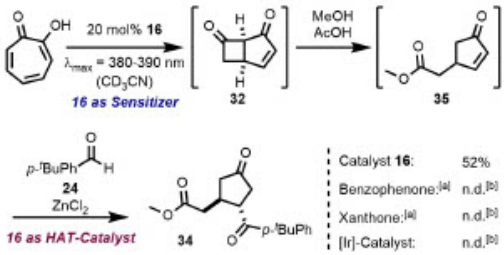


Figure 9. Sequential multi-step reaction leading to cyclopentanone **34**. The yield refers to isolated material and is given with respect to the α-tropolone starting material. [a] Either by irradiation at $\lambda_{max} = 365$ nm or $\lambda_{max} = 380–390$ nm. [b] No product formation was detected with these catalysts. [Ir]: $[Ir(dF(CF_3)ppy)_2(bpy)]PF_6$.

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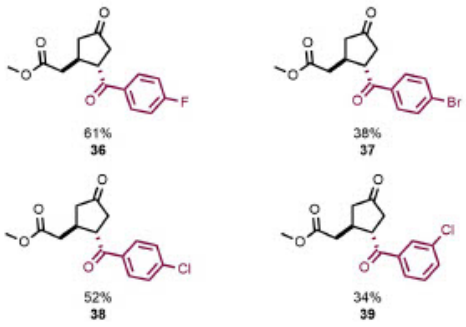

Figure 10. Reaction products of the five-step sequence. All yields refer to isolated material and are given with respect to the α-tropolone starting material.

Conclusion

Imidazolonequinoxalines were obtained from modified molecular flavins by a selective ring-contraction reaction under hydroxide basic conditions. The redox-active species maintain the crucial quinoid system and are characterized by a weaker oxidation strength in the ground state. In the photochemically excited state, they are significantly stronger hydrogen atom abstractors and display a higher triplet energy compared to their parent flavins. Catalytic applications for all increased activities are shown, and it is clear that ring-contracted flavins unlock reactivity which is otherwise inaccessible with flavins. By combining triplet sensitization and hydrogen atom abstraction, we developed a one-pot, five-step reaction sequence with ring-contracted flavins. From unsubstituted α-tropolone, this method allows direct access to *trans*-3,4-disubstituted cyclopentanones. We envision these new redox-active organic molecules to find various applications ranging from homogeneous catalysis to other fields such as energy storage.

Supporting Information

The data that support the findings of this study are available in the supplementary material of this article.

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Conflict of Interest

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available in the supplementary material of this article.

Keywords: Photochemistry - Homogeneous Catalysis - Flavin Catalysis - Triplet Sensitization - Hydrogen Atom Abstraction

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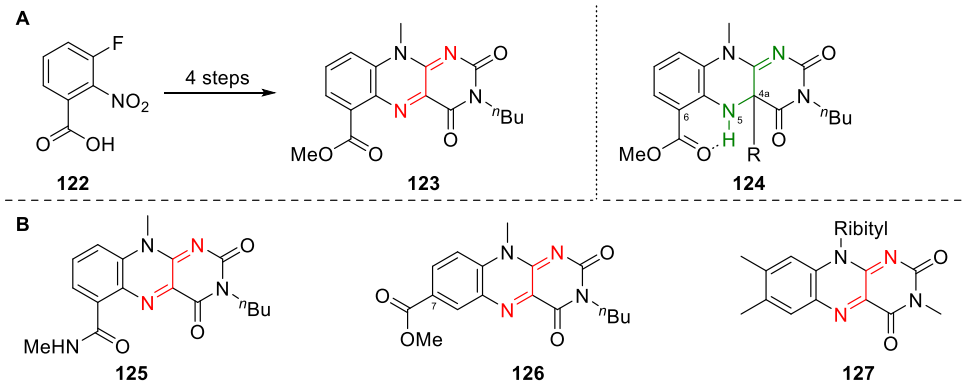
6. Summary

For the synthesis and characterization of flavin-*C*4a-substrate adducts, a reliable route for the synthesis of *C*6 methyl ester decorated flavin **123** was developed. The synthesis was achieved from commercially available 3-fluoro-2-nitrobenzoic acid (**122**) in four steps (**scheme 22 A**). The methyl ester group served as a hydrogen bond accepting moiety for *N*5-H in semiquinoid flavin **124** (**scheme 22 A**). To demonstrate the importance of trapping the semiquinoid *N*5-H in a hydrogen bond, we also prepared flavin catalysts **125-127** (**scheme 22 B**). Catalyst **125** exhibits a methyl amide moiety in the *C*6 position and like the methyl ester moiety, the methyl amide group participates in a hydrogen-bonding event. Catalyst **126** exhibits a methyl ester moiety in the *C*7 position, and similarly to catalysts **123** and **125**, catalyst **126** features an electron-withdrawing group on its aromatic scaffold. However, *C*7 methyl ester flavin is unable to form a hydrogen bond with *N*5-H due to the spatial distance. Lastly, we synthesized literature-known *N*3-methyl-RFTA (**127**) to compare our catalysts to established catalysts.



Scheme 22: **A**: Synthesis of *C*6 methyl ester decorated flavin **123** and our concept of trapping the *N*5-H of flavin adducts in a hydrogen bond interaction (**124**). **B**: Further flavin catalyst **125-127**, which we investigated regarding their performance in comparison to flavin catalyst **123**.

We identified *C*6 methyl ester decorated flavin **123** as a potent compound in the formation of *C*4a-adducts with CHD under the irradiation with LED light (λ_{max} = 451 nm) and an atmosphere of argon. We were able to characterize the flavin-*C*4a-cycloheptadiene adduct *via* ^{1}H (1D), ^{1}H (2D) and ^{13}C{^{1}H} NMR spectroscopy as well as with HR-ESI spectrometry. It was possible to intercept the adduct under argon with TEMPO to form the corresponding alkoxyamine, namely 1-(cyclohepta-2,4-dien-1-yloxy)-2,2,6,6-tetramethylpiperidine (**figure 2**).

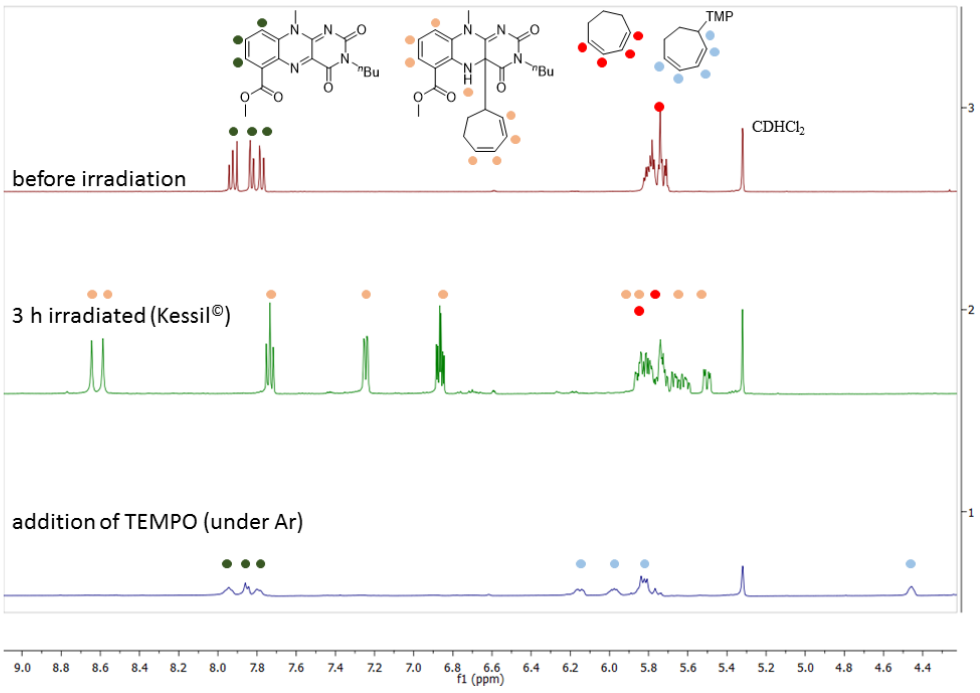
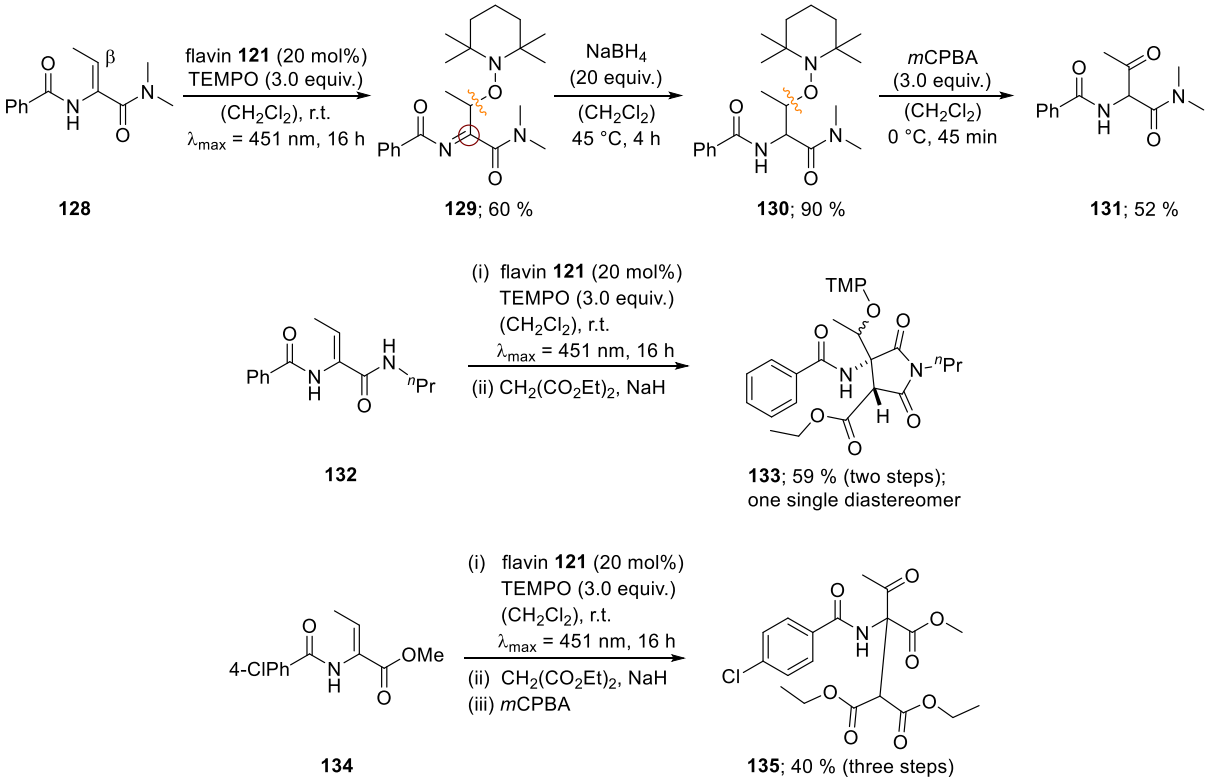


Figure 2: *Top*: ^{1}H NMR spectrum of catalyst **123** (green) and CHD (2.3 equiv.; red) before irradiation (LED (λ_{max} = 451 nm, 1W)). *Middle*: The ^{1}H NMR spectrum shows the clean conversion of catalyst **123** to the flavin-*C*4a-CHD adduct (two diastereomers; orange). *Bottom*: Adding TEMPO under argon and letting it react for one hour yields 1-(cyclohepta-2,4-dien-1-yloxy)-2,2,6,6-tetramethylpiperidine (blue).

Not only was it possible to form flavin-*C*4a-adducts with CHD but also with dehydroamino acids. Dehydroamino acids did not react at the allylic position such as CHD but at the β-position instead. DHAs were initially oxidized at the nitrogen atom by the flavin catalyst, followed by radical migration to the β-position to form a C-C-bond with the flavin. It was possible to apply the adduct formation in a catalytic fashion and use 20 mol% of methyl ester decorated flavin catalyst **123** for the TEMPO-functionalization of dehydroamino acids. This transformation allowed for the isolation of acylimines (**scheme 23**; **128** → **129**). In a dehydroamino acid model reaction, we compared catalyst **123** with catalysts **125-127** and identified methyl ester-decorated catalyst **123** as the most potent catalyst. With flavin **123** as the catalyst of choice it was possible to expand the substrate scope to 16 dehydroamino acids. Yields of the corresponding TEMPO-functionalized acylimines of up to 90 % were obtained. For the compound class of acylimines we developed several follow-up reactions (**scheme 23**). Acylimines can be reduced to the corresponding amides by sodium borohydride, which leaves the TEMPO-moiety unaltered. We showed this for the transformation of **129** to **130**. The weak C-O bond of the latter was oxidatively cleaved by *m*CPBA to form ketone **131**. Furthermore, it was possible to transform the acylimine moiety in a one-pot reaction with a malonate

carbon-nucleophile. In the case of acylimine **132**, this led to the formation of cyclic pyrrolidine-2,5-dione **133** (*via* nucleophilic malonate addition and subsequent intramolecular imide formation). In the case of acylimine **134**, addition of a malonate carbon-nucleophile and subsequent oxidation resulted in the formation of ketone **135**.

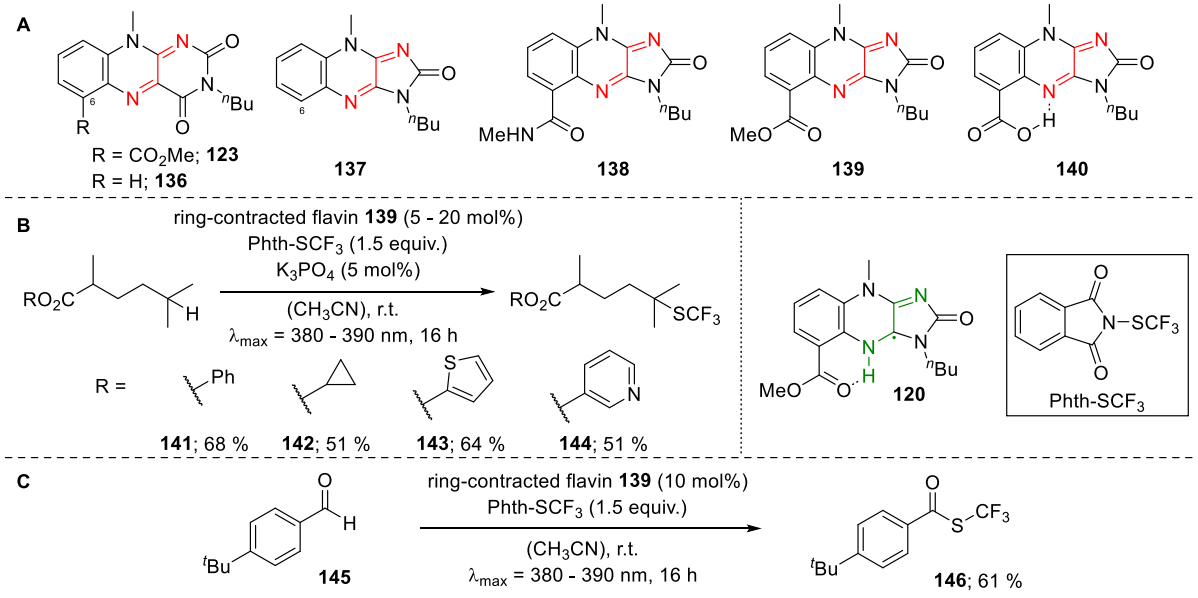


Scheme 23: Follow-up reactions for acylimine photoproducts to demonstrate the power of flavin catalysis regarding the functionalization of dehydroamino acid derivatives; Orange wavy line displays a weak, easily cleavable bond; Brown circle displays the reactive acylimine function that can act as a handle for further transformations.

This proof-of-concept study shows that carbon-based flavin-*C*4a-adducts are no dead-end side product but can be incorporated into catalytic transformations. This was demonstrated with methyl ester decorated flavin **123** for the catalytic transformation of dehydroamino acids to TEMPO-functionalized acylimines. Acylimines are a handle for further modification and, thus, our method of dehydroamino acid functionalization may add to the toolbox of useful strategies in peptide natural product diversification.[83]

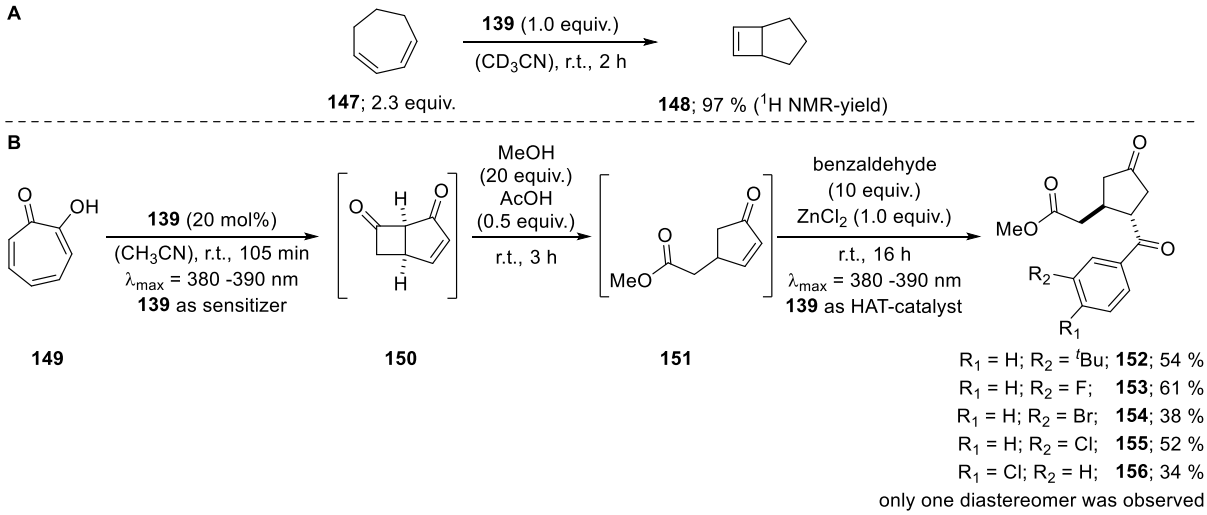
In a second project, ring-contracted flavins, imidazolonequinoxalines, were systematically investigated. Therefore, a set of ring-contracted flavins with the following substituents in the *C*6 position was prepared: H (**137**), C(O)NHMe (**138**), CO_2Me (**139**), CO_2H (**140**) (**scheme 24 A**). Ring-contracted flavins were synthesized from flavins through the addition of lithium hydroxide. Using cyclic voltammetry, it was demonstrated that ring-contracted flavins

exhibit a weaker oxidation potential compared to flavins: $E_{1/2}$ = -0.83 V *vs.* SCE for unmodified flavin **136**; $E_{1/2}$ = -0.72 V *vs.* SCE for methyl ester decorated flavin **123**; $E_{1/2}$ = -1.68 V *vs.* SCE for unmodified ring-contracted flavin **137**; $E_{1/2}$ = -1.56 V *vs.* SCE for methyl ester decorated ring-flavin **139**. This result can be explained by the missing carbonyl group of ring-contracted flavins compared to flavins. Ring-contracted flavins were obtained as colorless solids, exhibiting light absorption in the UV region (λ_{max} = 350 nm) and fluorescence emission at λ_{max} = 395 nm. The singlet excited state energy of unmodified **137** and methyl ester modified ring-contracted flavin **139** are identical ($E(S_0 \leftarrow S_1)$ = 319 kJ•mol^{-1}) and higher in comparison to (–)-riboflavin ($E(S_0 \leftarrow S_1)$ = 244 kJ•mol^{-1}). Both ring contracted flavins represent relatively strong oxidants in the photochemically excited singlet state (E^* = 1.63 V (**137**) and 1.75 V (**139**) *vs.* SCE). Phosphorescence measurements provided a triplet excited state energy of $E(S_0 \leftarrow T_1)$ = 244 kJ•mol^{-1} for both ring-contracted flavins (**137** and **139**), which is again higher compared to (–)-riboflavin ($E(S_0 \leftarrow T_1)$ = 205 kJ•mol^{-1}). Additionally, we demonstrated that ring-contracted flavins are exceptional hydrogen atom abstractors in the excited state. This characteristic was leveraged in employing methyl ester decorated ring-contracted flavin **139** as a catalyst in the C-H activation of substrates containing a methine position. Intercepting the radical compounds with phtalimidyl-SCF_3 enabled the isolation of trifluoromethylthiolated products **141-144** (**scheme 24 B**). This protocol was also suitable for the transformation of benzaldehyde **145** to the corresponding thioester **146** (**scheme 24 C**).



Scheme 24: **A**: Set of ring-contracted flavins **137-140** (and flavins **123** & **136**). **B**: Synthesis of trifluormethylthiolated products **141-144** (*left*) and the hypothesis of why the catalyst is a potent HAT-catalyst (*right*). **C**: Transformation of benzaldehyde **145** to the corresponding thioester **146**.

Methyl ester decorated ring-contracted flavin **139** is the most potent catalyst for the transformations depicted in **scheme 24 B & C**. Interestingly, flavin **123** and unmodified ring-contracted flavin **137** did not show any product formation at all. When irradiated with 1,3-cycloheptadiene, methyl ester modified catalyst **139** showed another divergent reactivity compared to flavins. Instead of forming the adduct with CHD (*cf.* **figure 2**), ring-contracted flavin **139** converted CHD to bicyclo[3.2.0]hept-6-ene (**148**) *via* sensitization (**scheme 25 A**). We further investigated the sensitization ability of ring-contracted flavins and found that they transform α-tropolone (**149**) to bicycloheptenedione **150** under irradiation. In a one-pot, multi-step reaction sequence, we combined the ring-contracted flavin's ability to be a good sensitizer and a strong hydrogen atom abstractor: in the presence of catalyst **139**, α-tropolone (**149**) was converted photochemically to bicycloheptenedione **150**, which was ring-opened in a thermal reaction with methanol and acetic acid to intermediate **151**; **151** was then irradiated in the presence of the ring-contracted flavin **139**, $ZnCl_2$ and a variety of benzaldehydes to form *trans*-3,4-disubstituted cylopentanones **152-156** (**scheme 25 B**). This transformation occurred diastereoselectively. Other established photocatalysts, such as iridium-based photocatalysts, benzophenone and xanthone did not yield any product in this reaction sequence.



Scheme 25: **A**: Irradiation of CHD (**147**) in the presence of methyl ester decorated ring-contracted flavin **139** results in the formation of bicyclo[3.2.0]hept-6-ene (**148**) *via* sensitization. **B**: One-pot, multi-step reaction catalyzed by ring-contracted flavin **139** (as sensitizer and HAT-catalyst) provides diastereomerically pure *trans*-3,4-disubstituted cyclopentanones **152-156**.

This study shows the potential of ring-contracted flavins as photocatalysts. In the photochemically excited state, they represent strong hydrogen atom abstractors and exhibit a high triplet energy. We combined these characteristics to transform α-tropolone to *trans*-3,4-disubstituted cyclopentanones. Other photocatalysts are ineffective in this transformation.[84]

7. Licenses

Both publications “Molecular flavin catalysts for C-H functionalisation and derivatisation of dehydroamino acids” and “Enhancing Flavins Photochemical Activity in Hydrogen Atom Abstraction and Triplet Sensitization through Ring-Contraction” are “open access” publications. Therefore, no licenses are needed and the publications as well as the respective supplementary information can be accessed free of charge *via* the following links:

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https://onlinelibrary.wiley.com/doi/10.1002/anie.202318590

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