Organocatalytic Strategies to Stereoselectively Trap Photochemically Generated Hydroxy-*o*-quinodimethanes

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Abstract: Light excitation of *ortho*-alkyl aromatic ketones and aldehydes enables access to hydroxy-*o*-quinodimethanes. These reactive electron-rich intermediates are sufficiently long-lived to productively engage in chemical processes, mainly acting as dienes in [4+2]-cycloadditions with electron-poor alkenes. Since the early discovery of this photoenolization mechanism, which dates back to 1961, a variety of transformations has been developed, providing a photochemical alternative to classical Diels-Alder chemistry. However, enantioselective catalytic versions of the photoenoliza-

tion/Diels-Alder sequence have remained elusive until recently. This review describes how the field of enantioselective organocatalysis has provided suitable tools to stereoselectively trap photochemically generated hydroxy-*o*-quinodimethanes. Recent studies also demonstrated that the chemistry is not limited to cycloaddition-type manifolds, but it can be expanded to develop intermolecular enantioselective addition processes.

1. Introduction

In recent decades, synthetic photochemistry has become highly sophisticated.^[1] Many light-driven reactions have been used to build structurally complex organic molecules,^[2] considerably enriching the synthetic repertoire of modern chemists. One such reaction is the photoenolization of *ortho*-alkyl aromatic ketones and aldehydes **1** to afford transient hydroxy-*o*-quino-

dimethanes **A** (Figure 1a),^[3] a venerable photochemical process established in 1961.^[4] The unique reactivity of the generated photoenols **A**, which can act as dienes in [4+2]-cycloadditions with electron-poor alkenes **2**, provides a photochemical alternative to classical Diels-Alder chemistry.^[5] The resulting chiral benzannulated carbocyclic products **3** are privileged cores found in marketed drugs^[6] and naturally occurring substances.^[7] Because of the versatility and the synthetic potential of the photoenolization/Diels-Alder (PEDA) sequence, this light-driven process has attracted great interest within the chemistry community over the years.

Figure 1. a) The photochemical enolization process of *ortho*-alkyl aromatic ketones and aldehydes **1** generating the reactive hydroxy-*ortho*-quinodimethane **A**. The unique reactivity of photoenols **A**, which can act as dienes in [4+2]-cycloadditions with electron-poor alkenes **2**, provides access to chiral cyclic adducts. (b) The pioneering work by Yang and Rivas [Ref. 4].

1.1. Historical Background and Mechanistic Insights

In 1961, Yang and Rivas^[4] were the first to recognize the ability of *ortho*-alkyl aromatic ketones and aldehydes **1** to form the corresponding hydroxy-*ortho*-quinodimethane **A** upon excitation by ultraviolet light (Figure 1a). This photochemically generated transient intermediate is long-lived enough ($\tau = 1 \cdot 10^{-6} \text{ s}$)^[8] to allow chemical trapping with dienophiles **2** in a Diels-Alder fashion, leading to valuable chiral products **3**. In the original study (Figure 1b), the formation of cycloadduct **6** was secured by irradiation of an equimolar solution of 2-methylbenzophenone **4** and acetylene-dicarboxylate **5** with a high-intensity mercury lamp.^[4] This process served as the inspiration for developing other photoenolization/Diels-Alder (PEDA) sequences using a variety of dienophiles.^[3]

The mechanism of formation of the photoenol intermediate **A** (Figure 2) has been the subject of intense research.^[9] Laser flash photolysis^[10] has allowed the characterization of the transient species involved in the formation of **A**. Light absorption by the carbonyl group in **1** generates a singlet excited state **S₁-B**, which decays to the triplet state **T₁-B** by intersystem crossing

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(ISC).^[11] Upon 1,5-hydrogen transfer, which occurs in **T₁-B**, the 1,4-diradical intermediate (**Z-C**) is formed. The 1,4-diradical (**Z-C**) exists in fast equilibrium with its conformer (**E-C**).^[9] Both conformers can undergo an additional ISC process to yield the corresponding (**E-A**) and (**Z-A**) dienols in the ground state. The short-lived ground state dienol (**Z-A**) rapidly reverts to the starting 2-alkylphenylketone **1** via a 1,5-sigmatropic hydrogen transfer. In contrast, the reketonization of the photoenol (**E-A**) requires an intermolecular proton transfer that may occur either by protonation of the methylene group by an acid, or by proton transfer from the enol to the solvent or to a base, followed by carbon protonation of the dienol anion.^[3c] Overall, the difficult reketonization mechanism confers a longer lifetime to the photoenol (**E-A**). Its chemical trapping with a suitable dienophile feasible. The lifetimes of all the transient species involved in the photoenol formation are strongly solvent dependent and vary considerably for different *ortho*-alkylbenzophenones.^[3a,c]

Figure 2. a) The photoenolization mechanism and the main transient species involved in the formation of the reactive (**E**)-photoenol **A**. S₁: singlet excited state; T₁: triplet excited state; ISC: Intersystem crossing.

1.2. Synthetic Applications and Aims of the Microreview

The utility of the PEDAs sequence in synthetic endeavours has been demonstrated in the total synthesis of naturally-occurring and biologically active substances (Figure 3).^[6,7,12] For example, Kraus and co-workers used this light-driven process to synthesize biologically active *podophyllotoxin*^[13a] and *pleutorin* derivatives.^[13b] K. C. Nicolau successfully prepared a variety of

compounds belonging to the *hamigerans* family. The key step here was the Diels-Alder reaction of photoenols, photogenerated from substituted benzaldehydes.^[7a-d]

Figure 3. Examples of naturally occurring substances synthesized through PEDAs sequences.

Despite the many applications based on PEDAs processes reported over more than 50 years,^[3,7,14] enantioselective catalytic variants have remained elusive until recently. In the context of a Diels-Alder-type trapping of the photoenol **A**, control of the relative stereochemistry is secured by the innate stereospecificity of the cycloaddition process. Owing to the well-defined geometry of the reactive (**E**)-**A** (Figure 2) and upon judicious choice of the dienophile geometry, the *endo* or *exo* Diels-Alder products of type **3** (Figure 1a) can be predictably and selectively formed. However, controlling the absolute configuration of the products using catalytic methods has proven challenging.

Here we discuss how the field of enantioselective organocatalysis^[15] has provided suitable tools to stereoselectively intercept photochemically generated hydroxy-o-quinodimethanes. In addition, although the inherent reactivity of **A** is permeated by its propensity to act as diene in [4+2]-cycloaddition pathways, recent studies demonstrated that the photogenerated enols can also engage in direct intermolecular enantioselective addition processes, including Michael,^[16] Mannich,^[17] and aldol-type^[18] reactions (Figure 4). We will discuss the strategies and the chiral organocatalytic

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intermediates, which have been used to stereoselectively trap the fleeting photoenol **A**.

Figure 4. Outline: this microreview discusses the stereoselective organocatalytic trap of the photoenol **A** through different reactivity pathways: (i) Diels-Alder-type; (ii) Michael-type; (iii) Mannich-type, and (iv) aldol-type reaction.

2. Enantioselective Variant: Initial Attempts

Two fundamental issues have historically hampered the development of a highly enantioselective Diels-Alder trapping of the reactive photoenols **A**: (i) their fleeting nature ($\tau \approx 1 - 10^{-6}$ s), which complicates the stereoselective trapping event, and (ii) the difficulty of avoiding racemic background reactions, which occur by direct interception of the photoenol **A** from the dienophile without the assistance of the chiral agent/catalyst.

One example of effective asymmetric method was reported by Bach in 2003 (Figure 5).^[19] In this strategy, a stoichiometric amount of a complexing chiral agent **10** was used to bind a purposely designed 2-alkyl carbonyl compound **7**, adorned with a lactam ring serving as a hydrogen-bond (H-bond) binding site. Such H-bond interaction^[20] secured an effective differentiation of the two enantiotopic faces of the photochemically generated photoenol **7'**, thus channelling the PEDAs sequence toward an enantioselective pattern. The optimal conditions required a stoichiometric amount (at least 1.2 equivalents) of the

Figure 5. The first highly enantioselective PEDAs sequence required stoichiometric amounts of the chiral complexing agent **10** [Ref. 19].

chiral agent **10** and a reaction temperature as low as -60 °C to afford the cycloaddition products **9** with fairly good yields, excellent enantioselectivities and good diastereoselectivities.

Attempts were also conducted to use a chiral catalyst to render the PEDAs sequence stereoselective. However, these attempts were largely unsuccessful. K. C. Nicolau used (*R*)-BINOL- TiCl_2 **14** as the metal-based catalyst to intercept the photoenol, generated upon excitation of aldehyde **11**, with methyl vinyl ketone **12** (Figure 6).^[7c] The benzannulated product **13** was achieved with a measurable enantioselectivity (25% ee) only when using a catalyst loading as high as 75 mol%.

Figure 6. A low-enantioselective PEDAs sequence using metal-based catalysis [Ref. 7c].

These few precedents testified to the difficulty of developing enantioselective catalytic variants of the photoenolization/Diels-Alder sequence.

3. Organocatalysis for the Enantioselective Diels-Alder Trapping of Photoenols

Recently, our research laboratories reported a strategy to fill this gap in catalytic enantioselective methodology, demonstrating that organocatalysis offers effective tools to stereoselectively intercept the fleeting photoenols. Our studies were motivated by our interest in using chiral organic catalysts to control the stereoselective outcome of photochemical reactions, in addition to their established potential in promoting asymmetric thermal reactions.^[21] In developing a stereoselective catalytic PEDAs reaction, the main idea was to use a chiral organocatalyst that could rely on multiple, non-covalent weak attractive interactions to activate the dienophile. An extensive screening of different H-bond donor organocatalysts identified the cinchona-thiourea **17**^[22] as a suitable catalyst for efficiently mediating the stereoselective Diels-Alder trapping of photoenols, derived from *o*-alkylbenzophenones **15**, with maleimides **16** (Figure 7).^[23] An array of functionalized tetrahydronaphthalenols **18** was accessed in good-to-excellent yields and with high levels of stereoselectivity. As a limitation of the method, the *N*-unprotected maleimide afforded the corresponding product **18f** with poor enantiocontrol (50% ee).

Further investigations revealed a more intricate, and perhaps more interesting, mechanism than expected. During optimization studies, we observed that the uncatalyzed racemic background process between 2-methyl benzophenone **15a** and maleimide **16a** was significantly faster than the stereoselective reaction catalyzed by the cinchona-thiourea **17** (Figure 8). Since reducing the rate of the uncatalyzed pathway is generally crucial to

Figure 7. The first example of a highly enantioselective (organo)catalytic PEDA sequence [Ref. 23].

successfully developing any photochemical catalytic asymmetric reaction,^[24] we tried to rationalize this puzzling observation. Optical absorption spectroscopic studies excluded the formation of any photoabsorbing substrate/catalyst **17** aggregation, confirming that α -alkylbenzophenone **15** was responsible for the absorption at 365 nm (the operative λ of the system). We then performed kinetic measurements to investigate how the kinetic of the PDA process was affected by the individual fragments of the organocatalyst **17**: the quinuclidine and the thiourea moieties. We found that a catalytic amount of the achiral thiourea **19** accelerated the reaction, in consonance with a selective activation of the maleimide **16a** facilitating the trapping of the photoenol (Figure 8). In contrast, quinuclidine **20** greatly inhibited the process. The last observation can be explained with the established ability of tertiary amines,^[25] including quinuclidine,^[26] to quench the triplet state of benzophenones, the key precursor intermediate in the formation of photoenols (**T1-B** in Figure 2). Laser flash photolysis studies confirmed that the quinuclidine core within catalyst **17** could reduce the formation of the photoenol.^[27]

Overall, these studies suggested that the cinchona-thiourea **17** played two opposite yet cooperative roles when promoting the PEDA reaction (Figure 8). The quinuclidine moiety interfered with the photoenolization mechanism, acting as an inhibitor of the PEDA sequence. This light-wasting process, by lowering the amount of reactive photoenol available, decreased the possibility that the background racemic reaction could take place. Concurrently, the thiourea moiety in **17** acted as a chiral catalyst, increasing the dienophilic character of the maleimide **16** upon H-bonding activation, while channeling the Diels-Alder process toward an enantioselective pattern.

Figure 8. Reactivity of the PEDA reaction of **15a** and **16a** in the absence of any catalyst (racemic background process), or in the presence of 20 mol% of chiral cinchona-thiourea **17**, *N,N*-dicyclohexylthiourea **19**, and quinuclidine **20**.

Aside from the mechanistic implications, this study^[23] demonstrated that a readily available chiral organic catalyst could address a longstanding and elusive problem in the realm of photo-mediated enantioselective catalysis.

4. Organocatalysis for the Enantioselective Intermolecular Trapping of Photoenols

The demonstration that a chiral organic catalyst could be used to develop an enantioselective PEDA sequence motivated our research group to seek other chiral organocatalytic intermediates that could stereoselectively intercept the fleeting photoenols. These investigations came about with an unanticipated reactivity, since the resulting light-triggered processes did not lead to the expected Diels-Alder cyclic adducts. Instead, the linear addition products were exclusively formed (Figure 4, paths *ii-iv*). Overall, these studies demonstrated that the chemistry of hydroxy- α -quinodimethanes is not limited to cycloaddition-type manifolds. Rather, it can be expanded to develop intermolecular addition processes that stereoselectively form one carbon-carbon bond.

4.1. Michael-Type Trapping of Photoenols

Iminium ion activation is an established mode of organocatalytic reactivity that has found many applications in enantioselective conjugate additions of soft nucleophiles to unsaturated carbonyl compounds.^[28] It relies on the electrophilic character of the iminium ion intermediate of type **21** (Figure 9), generated upon condensation of the unsaturated carbonyl substrate with a chiral amine catalyst. We wondered if intermediate **21** was electrophilic enough for successfully intercept the photoenol. The feasibility of this idea was tested by reacting *ortho*-methylbenzophenone derivatives **22** and α,β -unsaturated aldehydes **23** in the presence of commercially available diphenylprolinol trimethylsilylether **25**^[29] as the chiral amine catalyst.^[16] The experiments were conducted under irradiation by an ordinary 15 W black light bulb (BLB, $\lambda_{\text{max}} = 365$ nm).

Figure 9. The photoenolization/ β -benzylation sequence following an unconventional Michael-type addition manifold [Ref. 16]; TBS = *tert*-butyldimethylsilyl, BLB = black light bulb, DPP = diphenylphosphoric acid, *o*-Cl₂C₆H₄ = 1,2-dichlorobenzene.

The light-triggered process led to the exclusive formation of the conjugate addition product **24**. No traces were detected of the cycloaddition adduct, arising from the expected PEDAs sequence. From a synthetic perspective, the chemistry provided a straightforward method for the direct β -benzylation of enals **23**, a transformation for which there are few effective catalytic enantioselective precedents.^[30] This Michael-type addition manifold led to a variety of chiral β -benzylated aldehydes **24** in good to moderate yields and with high enantioselectivities. Complete diastereoselectivity was obtained when using *o*-benzylbenzophenone as the photoenolizable substrate (product **24e**).

Aside from its synthetic interest, this transformation^[16] was mechanistically intriguing because of the uncommon ability of the photoenol to exclusively undergo a conjugate addition. Generally, the formation of conjugate addition-type adducts is rationalized on the basis of a [4+2] cycloaddition of the photoenol followed by the opening of the resulting cyclic intermediate.^[14a,31] However, we did not find any experimental evidence supporting this pathway. For example, when an authentic sample of the cyclic adduct, synthesized according to a reported procedure,^[32] was subjected to the optimized photochemical organocatalytic condition, we did not detect the open product of type **24** to any extent, which excluded a possible ring-opening step. We then investigated the mechanism using a density functional theory (DFT) computational study (M06-2X level in a toluene solvent), which suggested the crucial role of water in dictating the product distribution. Experimentally, we had noticed how the use of rigorously dry solvents caused an appreciable decrease in reactivity. The computational studies revealed that the intrinsic preference for the cycloaddition product was offset by a network of proton transfer mechanisms, facilitated by the presence of water (Figure 10).

Figure 10. Free-energy profile of the Michael-type trapping of the photoenol with iminium ions assisted by water acting as a proton shuttle. The optimized structure of intermediate **27** (at -29.7 kcal·mol⁻¹) is highlighted. Free energies in kcal·mol⁻¹; TBS = *tert*-butyldimethylsilyl.

Specifically, in the computed preferred pathway for the reaction between the transiently generated photoenol and the chiral iminium ion **21** (structure in Figure 9), a water molecule engaged in a hydrogen-bonding network with the photoenol to form adduct **26** (Figure 10). The approach of **26** to the iminium ion **21** led to transition state (TS-H₂O), which is 2.2 kcal·mol⁻¹ lower than the free energy for the Diels-Alder type manifold (not shown in Figure 10). This explained why the Michael addition dominated over the classical cycloaddition mechanism. TS-H₂O then exclusively relaxed to intermediate **27**, with the proton being transferred from the photoenol to the iminium ion nitrogen atom via a water-assisted proton shuttle mechanism. From the enammonium ion intermediate **27**, an intramolecular proton transfer readily

Figure 11. Organocatalytic enantioselective photoenolization/Michael addition sequence using α,β -unsaturated ketones as Michael acceptors [Ref. 33].

formed the intermediate **28**, which released the Michael addition product **24** and the catalyst **21** after hydrolysis.

Shortly thereafter, Ye's research group reported a similar Michael-type addition manifold^[33]. The group described how the chiral iminium ions, generated upon condensation of cyclic enones **29** with the chiral amino ester catalyst **31**, could stereoselectively capture the photoenols derived from *ortho*-alkylbenzophenones **30** (Figure 11).

A variety of cyclic enones of different size were tolerated, providing the corresponding β -benzylated ketones **31** in moderate-to-good yields and with excellent enantioselectivities. The method could be extended to include acyclic α,β -unsaturated ketones, providing products of type **31c** with high stereocontrol. In addition, quaternary carbon stereocenters could be formed with high fidelity when using 3-alkyl-2-cyclohexenones (products **31e** and **31f**), albeit with moderate yields.

4.2. Mannich-Type Trapping of Photoenols

Given the ability of the photoenol to participate in stereoselective Michael reactions,^[16] we wondered whether these transient species could also serve as nucleophiles in other classical addition processes, such as the Mannich reaction. In addition, in the previously developed stereoselective PEDAs sequence (Figure 7)^[23] we demonstrated that the photoenols could be stereoselectively trapped by activating the dienophiles, by means of H-bonding interactions with a suitable chiral organocatalyst. Since imines are primed to noncovalent mechanisms of organocatalytic activations,^[34] we considered it feasible to develop a stereoselective organocatalytic photoenolization/Mannich-type process (Figure 12). While linear imines proved unreactive, the highly electrophilic cyclic benzoxathiazine-2,2-diones **34**^[35] intercepted the photoenols generated upon irradiation of **33** by a single black-light-

Figure 12. Organocatalytic enantioselective photoenolization/Mannich addition sequence using cyclic benzoxathiazine-2,2-diones as electrophiles [Ref. 17].

emitting diode (black LED, $\lambda_{\max}$ = 365 nm). An extensive screening of H-bond chiral organic catalysts identified the dimeric cinchona alkaloid derivative (DHQ)₂PHAL **36**, commonly employed as a ligand for Sharpless asymmetric dihydroxylation,^[36] as the best candidate to promote the transformation.^[17] This process, which has no precedents in the racemic regime too, led to the exclusive formation of chiral amines **35** (with moderate stereoselectivity) *via* a formal Mannich-type reaction manifold. Here too, we detected no formation of the [4+2]-cycloaddition adduct.

Regarding the mechanism, flash photolysis studies revealed that the generation of the transient photoenol was not affected in the presence of catalyst **36**, thus suggesting that **36** controlled the stereochemical outcome of the reaction by solely interacting with the imine substrate **34**.

4.3. Aldol-Type Trapping of Photoenols

Our previous studies demonstrated that photoenols could participate in stereoselective intermolecular addition processes promoted by chiral organic catalysts. To demonstrate the generality of this reactivity framework, the next goal was to exploit the nucleophilicity of hydroxy-*o*-quinodimethanes to develop aldol-type addition reactions. Specifically, we recently developed an organocatalytic strategy for the desymmetrization of achiral 2-substituted-2-fluorocyclopentane-1,3-diketones **37**, where a prochiral fluorine-containing carbon was preinstalled (Figure 13).^[18] The chemistry capitalized upon the high reactivity of photoenols and the ability of the readily available chiral amidothiourea catalyst **40** to choose between enantiotopic carbonyl groups within **37** while facilitating a desymmetric intermolecular aldol process.^[37] The resulting symmetry-breaking process generated two stereocenters simultaneously, and forged a C-F stereogenic unit within products **39**. Since fluorine-containing functional groups can greatly alter the intrinsic properties of organic compounds,^[38] the catalytic production of fluorine-containing stereogenicity is a centrally important methodological goal.

Figure 13. Photochemical organocatalytic intermolecular aldol-based desymmetrization process [Ref. 18]; *o*-Cl₂C₆H₄ = 1,2-dichlorobenzene.

The photochemical approach provided straightforward access to valuable chiral 2-fluoro-3-hydroxycyclopentanones **39** in moderate to high yields and high stereoselectivities. Interestingly, similar fluorinated products were previously prepared in racemic fashion, and used for the synthesis of pyrrolopyridazine JAK3 inhibitors for the treatment of inflammatory and autoimmune diseases.^[39]

5. Conclusions

The formation of hydroxy-*o*-quinodinomethanes upon light excitation of *ortho*-alkyl aromatic carbonyl substrates is a venerable photochemical process established as far as 1961. When coupled with Diels-Alder chemistry, this photoenolization mechanism has historically offered the synthetic community with a straightforward access to synthetically valuable cyclic compounds. However, developing a catalytic enantioselective variant of this transformation has remained elusive over the years. Recently, using the tools of enantioselective organocatalysis, this longstanding and elusive problem was addressed. By means of covalent and noncovalent mechanisms of substrate activation, readily available chiral organic catalysts could activate electrophilic substrates toward the stereoselective interception of the fleeting hydroxy-*o*-quinodimethanes. Importantly, it was demonstrated that the chemistry is not limited to cycloaddition-type manifolds. Rather, it can be expanded to develop intermolecular enantioselective carbon-carbon bond forming addition processes. We believe that this catalytic blueprint will find applications in other enantioselective photoenol-trapping processes. Overall, these examples further demonstrate how the field of enantioselective organocatalysis can provide suitable tools for overcoming the challenges of modern asymmetric synthesis, expanding the way chemists think about making chiral molecules sustainably.

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Keywords: Asymmetric catalysis • Organocatalysis • Photochemistry • Photoenols • Synthetic methods

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Organocatalysis

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Organocatalytic Strategies to Stereoselectively Trap Photochemically Generated Hydroxy-o-quinodimethanes

Light excitation of 2-alkylbenzophenones **1** affords transient hydroxy-o-quinodimethanes **A**. For a long time, because of its high reactivity and fleeting nature, **A** could not be trapped in a stereoselective

catalytic fashion. This minireview describes how the field of enantioselective organocatalysis has provided suitable tools to effectively address this long-standing problem.