Enantioselective Photochemical Organocascade Catalysis

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Abstract: Reported herein is a photochemical cascade process that combines the excited-state and ground-state reactivity of chiral organocatalytic intermediates. This strategy directly converts racemic cyclopropanols and α,β-unsaturated aldehydes into stereochemically dense cyclopentanols with exquisite stereoselectivity. Mechanistic investigations have enabled elucidating the origin of the stereoconvergence, which is governed by a kinetic resolution process.

Cascade reactions are valuable tools for streamlining the synthesis of structurally complex chiral molecules in a single operation and from readily available substrates.[1] Their combination with asymmetric aminocatalysis[2] has recently led to innovative techniques for the one-step enantioselective preparation of stereochemically dense molecules.[3] The iminium ion–enamine activation sequence depicted in Figure 1a was crucial to fully harnessing the synthetic potential of organocascade catalysis.[4] The domino process is initiated by the conjugated addition of a nucleophile to the electrophilic iminium ion intermediate I, generated from enals I and the chiral amine catalyst, followed by α-functionalization of the resulting electron-rich enamines II with an electrophile. In this well-defined sequence, the chiral catalyst has an active role in both bond-forming steps. This strategy, which relies on the established ground-state polar reactivity of intermediates I and II, has reached high levels of efficiency, as seen in applications for the total synthesis of natural products.[5]

Recently, our laboratories found that the synthetic potential of aminocatalytic intermediates is not limited to the ground-state domain, but can be expanded by exploiting their photochemical activity.[6] For example, the photoexcitation of iminium ions can switch on novel catalytic functions that are unavailable to ground-state reactivity.[7] Specifically, selective excitation with a violet light emitting diode (LED) brings an iminium ion I into an electronically excited state (I* in Figure 1b). This turns an electrophilic species into a strong oxidant, which could trigger the formation of benzylic radicals IV through single electron transfer (SET) oxidative cleavage of the silicon–carbon bond within benzyl trimethylsilane derivatives III. Importantly, compounds III are non-nucleophilic substrates that are recalcitrant to classical ground-state conjugate addition manifolds. The subsequent stereoselective coupling between IV and the chiral β-enaminyl radical V, emerging from the SET, leads to the enamine derivative VI, which affords the final β-benzylazide product after hydrolysis. We reasoned that if the ground-state nucleophilic reactivity of intermediate VI could be exploited to trigger a subsequent process, this might form a basis with which to implement a photochemical enantioselective cascade process. A crucial
step would be to identify a suitable radical precursor 2 that, upon SET oxidation from the excited iminium ion 1*, could generate an intermediate VII with ambivalent reactivity (Figure 1c). Initially, VII should behave as a radical to then unveil, after stereocentered radical coupling governed by V, an electrophilic reactive center amenable to an enamine-mediated cyclization. Herein, we detail the successful realization of this idea, which allowed us to expand the potential of organocascade catalysis by including photochemical reactivity as a new design principle for enantioselective domino reactions.

Mariano and co-workers, who exploited the photoactivity of preformed cyclic non-conjugated iminium ions to oxidize cyclopropanols of type 2 in the 1980s,[10] We selected cinnamaldehyde (1a) as the model substrate while using the gem-difluorinated diarylprolinol silyl ether catalyst A[7] to promote the formation of the chiral iminium ion 1a (Table 1). The experiments were conducted in CH2CN under irradiation with a single high power (HP) LED (λmax = 415 nm) with an irradiance of 25 mW cm−2.[8] A summary of the relevant data is listed in Table 1. The excited iminium ion has a reduction potential (Eox = +1.66 V) versus Ag/Ag+ in CH2CN, and the excited iminium ion has a reduction potential (Eoa = +2.4 V) versus Ag/Ag+ in CH2CN, as estimated from electrochemical and spectroscopic measurements.[7] The SET oxidation of 2a is therefore thermodynamically feasible. This reasoning was confirmed experimentally, as the cyclopropanol product 3a was generated with high stereoselectivity (81:1 d.r., 95% ee for the major diastereoisomer), albeit in moderate chemical yield (53% yield, entry 1), when performing the reaction at ambient temperature. During control experiments, no product formation was detected in the absence of amine catalyst A or light (entry 2), demonstrating that the photoexcitation of the chiral iminium ion 1a, which absorbs up to 440 nm, is essential to promote the cascade reaction. Lowering the temperature to 0°C slightly increases the reaction yield (65%; entry 3). We next found that the addition of 1,1′-biphenyl (BP), commonly used as a redox mediator,[11] positively influenced the reactivity,[12] without affecting the stereoselectivity (entry 4). As a catalytic amount of biphenyl slightly decreased the overall efficiency, we used the conditions described in Table 1, entry 4 to demonstrate the generality of the photochemical organocascade process.

Figure 2. Mechanistic proposal for the excited iminium ion/enamine cascade sequence. Central to this study is the ability of the excited iminium ion 1*, acting as an oxidant, to drive the generation of intermediate IX, which displays radical and electrophilic behavior.

![Figure 2](image_url)

| Entry | Additive | Yield [%] | d.r. [%] | ee [%] |
|-------|----------|-----------|----------|--------|
| 1[a]  | –        | 53        | 8:1      | 95     |
| 2[b]  | –        | 0         | –        | –      |
| 3      | BP (1 equiv) | 65       | 8:1      | 97     |
| 4      | BP (1 equiv) | 88       | 8:1      | 97     |
| 5      | BP (0.2 equiv) | 75       | 8:1      | 97     |

[a] Reactions performed at 0°C on a 0.1 mmol scale using 2 equiv of 1a under illumination with a single high power (HP) LED (λmax = 415 nm) with an irradiance of 25 mW cm−2. [b] Yield of 3a isolated as a mixture of diastereomers. [c] Diastereomeric ratio inferred by 1H NMR analysis of the crude mixture. [d] Enantiomeric excess of 3a determined by UPC2 analysis on a chiral stationary phase. [e] Performed at ambient temperature. [f] In the dark. BP = 1,1′-biphenyl, TDS = triethyl(dimethyl)silyl, TFA = trifluoroacetic acid.
substrates, enabling access to a variety of complex cyclopentanols with three stereocenters. Cyclopropanols bearing linear and branched alkyl (adducts 3a–3f), benzyl (3g), and heterocyclic (3h, 3i) substituents all reacted to give the products with good yields and exquisite selectivity. The method also tolerates the presence of a cyclopropyl ring (adduct 3d), a valuable fragment that frequently appears in complex small molecules with drug-like properties [13]. Spiro-cyclic compounds could also be effectively synthesized (products 3e and 3f). In terms of the scope with respect to α,β-unsaturated aldehydes, different substitution patterns at the β-aromatic moiety were tolerated well, regardless of their electronic and steric properties and position on the aryl ring (products 3j–3p). As a limitation of the method, the presence of a β-alkyl fragment in 1 completely inhibited the reaction. In addition, the dialkyl substitution pattern on the cyclopropanol was necessary to facilitate the cyclization, owing to the Thorpe–Ingold effect, and the formation of the cascade adduct (see Section D3 in the Supporting Information for details). Crystals from compound 3q were suitable for X-ray crystallographic analysis, which established the relative and absolute configurations of the three stereogenic centers.

The results in Figure 3 indicate that the cascade reactions provide the cyclopentanol adducts essentially with perfect selectivity, since a single stereoisomer out of the eight possible isomers is generally formed. It is well-established that the combination of multiple asymmetric catalytic transformations in a cascade sequence imparts increased enantiomeric excess to the final product compared to the corresponding discrete transformations [15]. However, the asymmetric amplification observed during successive cycles of a cascade comes at the expense of the diastereoselectivity. In general, the products are generated with high optical purity but a moderate d.r. As the very high diastereoselectivity of the photochemical cascade process was incongruent with this general behavior, we performed control experiments to elucidate the origin of the stereoselectivity.

We studied the reaction of 1a with the racemic substrate 2c because the enamine-mediated cyclization step was relatively slow to allow for isolation of the non-cyclized open adduct 4c (Table 2). Thus we could monitor the yield and the enantiomeric excess of both cyclopentanol 3c and its predecessor 4c during the progression of the photochemical cascade reaction.

After 3 hours, the cyclic adduct 3c, arising from the photocatalytic iminium ion/enamine cascade sequence, was formed in 16% yield and 99% ee. The open product 4c, emerging from the light-triggered radical coupling event, was generated in 40% yield and 92% ee. The increased enantiopurity of 3c with respect to 4c demonstrates that the chiral secondary amine catalyst A controls both steps of the cascade process. We also observed that the optical purity of the open product 4c decreased with the progression of 3c formation (entries 2–4). This behavior is consonant with a kinetic resolution regime governing the enamine-mediated cyclization, where the chiral catalyst A selects the major enantiomer.
of 4c for selective cyclization to afford 3c as a single stereoisomer, while the minor enantiomer of 4c remains essentially unreacted. This scenario was confirmed by reacting independently prepared racemic open adduct 4c with the enantipure catalyst A in the absence of light irradiation (Scheme 1). After 2 hours, a single diastereomer of the cascade adduct 3c was formed in 31% yield and 88% ee, while the unreacted 4c was enantioenriched (47% ee). In consonance with the proposed path, unreacted 4c had the opposite absolute configuration than in the experiment depicted in Table 2.

Overall, these studies suggest that the two stereocontrolled steps of the cascade reaction operate sequentially to drive the formation of the cyclopentanol product 3c essentially as a single stereoisomer. The enamine-mediated aldol reaction magnifies the original stereoselectivity of the photochemical step (about 92% ee, as inferred from entry 1 in Table 2), selecting exclusively the major enantiomer of the intermediari open adduct 4 for cyclization.

In summary, we have developed an enantioselective cascade process that combines the excited-state and ground-state reactivity of chiral organocatalytic intermediates. This transformation demonstrates the possibility of effectively merging a stereocontrolled radical pattern with a classical ionic process in a cascade sequence. Further studies are ongoing to develop photochemical radical cascade processes\(^\text{[2]}\) to rapidly generate structural and stereochemical complexity from simple starting materials.

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**Conflict of interest**

The authors declare no conflict of interest.

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Redox mediators are generally used to facilitate exergonic redox processes that are kinetically slow, or to mitigate the occurrence of a back-electron transfer. In this system, a possible alternative role of 1,1′-biphenyl (BP) is to prevent the SET oxidation of the secondary amine catalyst A, which leads to decomposition ($E_{\text{ox}}(\text{BP}^+/\text{BP}) = +1.90 \text{ V}$, $E_{\text{ox}}(\text{A}^+/\text{A}) = +2.20 \text{ V}$ vs. Ag/Ag⁺) in CH₃CN. In consonance with this scenario, preliminary kinetic measurements indicate that the presence of BP does not influence the initial rate of the cascade process. In contrast, a large amount of catalyst A remains at the end of the reaction when adding BP while catalyst degradation is much more significant in the absence of the redox mediator.

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