Photo-Organocatalytic Enantioselective Radical Cascade Reactions of Unactivated Olefins

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Abstract: Radical cascade processes are invaluable for their ability to rapidly construct complex chiral molecules from simple substrates. However, implementing catalytic asymmetric variants is difficult. Reported herein is a visible-light-mediated organocatalytic strategy that exploits the excited-state reactivity of chiral iminium ions to trigger radical cascade reactions with high enantioselectivity. By combining two sequential radical-based bond-forming events, the method converts unactivated olefins and α,β-unsaturated aldehydes into chiral adducts in a single step. The implementation of an asymmetric three-component radical cascade further demonstrates the complexity-generating power of this photochemical strategy.

Cascade processes are powerful strategies for rapidly increasing structural and stereochemical complexity while delivering complex chiral molecules in one step.[1] The high reactivity and selectivity of open-shell intermediates makes radical chemistry perfectly suited for implementing cascades.[2] However, the intrinsic challenge of carrying out reactions with radicals in a stereocontrolled fashion has greatly limited the development of enantioselective variants. The majority of the reported strategies rely on either chiral substrates or stoichiometric ligands.[3a,4,5] Recently, photo-redox catalysis[6] has provided effective tools to enable single-electron transfer (SET) mediated radical cascade processes under mild reaction conditions.[3a] The combination with chiral Lewis acid catalysts has allowed the ensuing radical cascade process to be channeled towards a stereocонтrolled pattern.[7] Although effective, these catalytic asymmetric methods are generally limited to either formal [2+2][7a] or [3+2][7b,c] photocycloaddition reactions or cation radical Diels–Alder processes.[7d,8]

Recently, our laboratories identified a new photochemical catalytic mode of substrate activation that exploits the excited-state reactivity of chiral iminium ions (I) to generate radicals upon SET oxidation of suitable substrates (II; Figure 1a).[9] The resulting chiral intermediate III can also govern the ensuing radical coupling step with high stereoselectivity. We wondered if this new photochemical activation mode could be used to expand the synthetic potential of enantioselective radical cascades beyond the reactivity constraints of formal cycloaddition chemistry.[9] In an initial attempt, we combined the excited-state iminium ion chemistry with the ground-state reactivity of enamines to access cyclopentanols, from cyclopropanols, with high stereochemistry (Figure 1b).[10] However, while the first carbon–carbon bond-forming step in this cascade sequence is a radical process, the subsequent carbon–carbon bond formation follows a two-electron pathway. Herein, we detail how the photochemistry of iminium ions has served to successfully implement an enantioselective catalytic radical cascade.

Figure 1. a) Our previous study demonstrated that light excitation turns iminium ions (I) into chiral oxidants, and the resulting SET-based mechanism for generating radicals from precursors II bearing a redox auxiliary (RA). b) A cascade reaction proceeding by an excited iminium ion/ground-state enamine sequence, where a stereocontrolled radical path is combined with polar reactivity. c) Proposed enantioselective catalytic radical cascade proceeding by two sequential radical steps: upon SET oxidation of an unactivated olefin, an anti-Markovnikov addition to the radical cation IV is followed by a stereocontrolled radical coupling. SET—single-electron transfer.
reaction that combines two sequential radical-based bond-forming processes without mechanistically relying on a cycloaddition manifold (Figure 1c). This organocatalytic photochemical process converts readily available enals and unactivated olefins, bearing an oxygen-centered nucleophilic handle, into complex chiral molecules containing butyro lactone[14a] or tetrahydrofuran moieties.[11b] These two structural elements are present in numerous biologically active and naturally occurring molecules.

Figure 2 details our proposed strategy to develop an enantioselective SET-triggered radical cascade. We envisioned a catalytic cycle wherein a chiral amine catalyst would form the colored iminium intermediate I upon condensation with the enal I. Selective excitation with a violet-light-emitting diode (LED) turns I into a strong oxidant (I*), as implied by its reduction potential, which was estimated at about +2.4 V (E_red (I*/I) vs. Ag/AgCl in CH_3CN) using electrochemical and spectroscopic methods.[9a] Therefore, the photoexcited iminium ion can oxidize an alkene substrate (2)[12] adorned with a suitable oxygen-centred nucleophilic handle (alkenes 2 used in this study have oxidation potentials ranging from +2.03 V to +2.19 V vs. Ag/AgCl in MeCN, see section D in the Supporting Information for details). The SET activation of 2 would concomitantly form the chiral 5n-intermediate III and the alkene radical cation IV. The nucleophilic moiety within IV would then trigger a polar-radical-crossover cycladdition,[13,14] capitalizing on the simultaneous polar and radical nature of such radical cation species. This process would proceed with an anti-Markovnikov selectivity to afford the more stable tertiary radical intermediate V.[15] At this juncture, a stereocontrolled radical coupling with III would afford the cascade product 3 with high enantioselectivity. This mechanistic plan finds support in the high reactivity of the distonic intermediate IV, which has been extensively investigated by Nicewicz to develop anti-Markovnikov hydrofunctionalizations of olefins,[14–16] and its tendency to initiate cycloaddition sequences leading to heterocyclic products.[14,16]

To test the feasibility of our photochemical plan, we selected cinnamaldehyde (1a) and the gem-difluorinated diarylprolinol silyl ether catalyst A[9a] for the formation of the chiral iminium ion (Table 1). The experiments were conducted in CH_3CN using a single high-power (HP) LED (λ_max = 420 nm) with an irradiance of 30 mW cm\(^{-2}\), as controlled by an external power supply (full details of the illumination setup are reported in Figure S1 of the Supporting Information). The alkenoic acid 2a was selected as the model substrate based on its oxidation potential (E_red = 2.4 V vs. Ag/AgCl in MeCN/Hex, 1:1) determined by \(^1\)H NMR analysis of the crude reaction mixture using trichloroethylene as the internal standard. Yields of the isolated 3a are reported within parentheses. [c] Enantiomeric excess determined by HPLC analysis on a chiral stationary phase. Hex = tetradecafluorohexane, TDS = tert-hexyldimethylsilyl, TFA = trifluoroacetic acid.

Table 1: Optimization studies.

| Entry | Catalyst | Reaction conditions | Yield [%][a] | ee [%][b] |
|-------|----------|---------------------|-------------|----------|
| 1     | A        | 40% TFA             | 55          | 88       |
| 2     | A        | 60% TFA             | 62          | 88       |
| 3     | B        | 60% TFA             | 63          | 91       |
| 4     | C        | 60% TFA             | 60          | 33       |
| 5     | B        | CH_3CN/Hex (1:1)    | 72          | 91       |
| 7     | A        | no light            | 0           |          |
| 8     | –        | no catalyst          | 0           |          |

[a] Reactions performed on a 0.1 mmol scale at 30 °C for 16 h using 0.2 mL of solvent under illumination by a single high-power (HP) LED (λ_max = 420 nm) with an irradiance of 30 mW cm\(^{-2}\). [b] Yield of 3a determined by \(^1\)H NMR analysis of the crude reaction mixture using trichloroethylene as the internal standard. Yields of the isolated 3a are reported within parentheses. [c] Enantiomeric excess determined by HPLC analysis on a chiral stationary phase. Hex = tetradecafluorohexane, TDS = tert-hexyldimethylsilyl, TFA = trifluoroacetic acid.
fluorohexane in a 1:1 ratio to CH$_3$CN, further increased the yield of the reaction (72% yield, entry 5). Control experiments indicated that both the light and the amine catalyst are required for reactivity (entries 7 and 8), while the addition of a radical trapping agent (TEMPO, 1 equiv) completely inhibited the process.

Using the optimized reaction conditions described in entry 5 of Table 1, we then turned our attention to the scope of the photocatalytic asymmetric radical cascade process (Figure 3). We first evaluated the possibility of using differently substituted olefins. The presence of geminal methyl groups at the α-position of 2 significantly improved the yield and enantioselectivity (adduct 3b, 75% yield and 94% ee). An ethyl fragment could also be installed (3c), while the inclusion of an acyclohexyl group afforded the spirocyclic adduct 3d in moderate yield and high enantioselectivity. The absence of an α-substituent in 2 did not significantly affect the overall efficiency (product 3e). This observation indicates that the Thorpe–Ingold effect is not critical to the cascade process. Concerning the substitution of the double bond, introducing a cyclohexyl in place of the dimethyl moiety slightly increased the diastereoselectivity to 1:3:1 (3f) while maintaining a high chemical yield and enantioselectivity. Importantly, tetrahydrofuran derivatives 4a and 4b could also be synthesized when decorating the alkene substrate with an alcohol acting as the nucleophilic moiety.

Crystals from the compound 3a were suitable for X-ray crystallographic analysis which established the stereochemical course of the radical cascade process.

Regarding the scope of the α,β-unsaturated aldehydes 1, moderately electron-withdrawing and electron-donating groups on the aromatic ring are tolerated without diminishing either the yield or enantioselectivity (Figure 4). The substituent can also be moved around the ring without impeding reactivity (3g–l). Notably, synthetically useful groups, which can undergo further functionalization, were tolerated. These included halogens (3g–j), trimethylsilyl (3m), and pinacolborane (3n). One limitation of this reaction is that aliphatic enals, including tert-butylacroleine and (E)-2-octenal, remained unreacted under the reaction conditions.

We then focused on the design of a three-component radical cascade process to assemble complex chiral molecules from simple substrates in a single step. Specifically, we surmised that the excited iminium ion $I^*$ could oxidize amylene (5), an unfunctionalized alkene hydrocarbon ($E_r$ = 2.03 V vs. Ag/AgCl in MeCN; Figure 5). The anti-Markovnikov intermolecular addition of a carboxylic acid to the less substituted position of the resulting VI would then provide the key radical intermediate VII, which would eventually engage in a stereoselective radical coupling governed by the chiral 5α-intermediate VIII (structure shown in Figure 2). This catalytic asymmetric cascade process, which

![Figure 3](image1.png)

**Figure 3.** Survey of the alkenoic acids and alkenols (2) that can participate in the radical cascade process with 1a. Reactions performed on a 0.1 mmol scale using a 1:1 mixture of acetonitrile and tetradecafluorohexane. Yields and enantiomeric excesses of the isolated products 3 are indicated below each entry (average of two runs per substrate). Enantiomeric excesses measured on the enoate derivatives of 3, obtained upon olefination of the aldehyde with $\text{PPh}_3\text{CHCO}_2\text{Et}$. The d.r. values were inferred by $^1$H NMR analysis of the crude reaction mixture. [a] Reaction performed using the catalyst A in acetonitrile.

![Figure 4](image2.png)

**Figure 4.** Survey of the enals 1 which can participate in the radical cascade process with 2b. Reactions performed on a 0.1 mmol scale using a 1:1 mixture of acetonitrile and tetradecafluorohexane. Yields of the isolated products are indicated below each entry (average of two runs per substrate). Enantiomeric excesses measured on the enoate derivatives of adducts 3, obtained upon olefination of the aldehyde with $\text{PPh}_3\text{CHCO}_2\text{Et}$. The d.r. values were inferred by $^1$H NMR analysis of the crude reaction mixture.
combines two intermolecular radical steps, would provide a one-step access to complex aldehydes (7).

The use of α,α-difluorinated acids (6) enabled the successful realization of this enantioselective three-component cascade. The aldehydes 7 were converted into enoates 8a–c, which could be isolated in moderate yields and enantioslectivities (Figure 5). The acids play a dual role in this transformation, since they assist the iminium ion formation while acting as nucleophilic substrates in the three-component cascade.

In summary, the photochemical activity of a chiral iminium ion has been exploited to activate unfunctionalized olefins and trigger an enantioselective radical cascade process. We expect that this photochemical organocatalytic activation mode could be useful for designing other radical cascade processes and for stereoselectively synthesizing more complex chiral scaffolds.

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**Conflict of interest**

The authors declare no conflict of interest.

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improved reactivity in the two-phase solvent system can be rationalized by the preferential solvation of B in the fluorinated phase, which permits its slow release into the acetonitrile phase. This mechanism minimizes the oxidative degradation of the catalyst (\( E_{\text{ox}}^{\text{A/C+}} = +2.20 \text{ V} \), \( E_{\text{ox}}^{\text{B/C+}} = +2.40 \text{ V} \)) by the photoexcited iminium ion \( I^* \) (estimated \( E_{\text{red}}^{*} = +2.40 \text{ V} \) vs. Ag/AgCl in CH\(_3\)CN), see Ref. [9a] for details.

CCDC 1854258 (3a) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.

Attempts to perform a three-component radical cascade using 2,3-dimethylbut-2-ene, which would afford products having a single stereogenic center, met with failure. Given the reduction potential of this olefin (\( E_{\text{red}}^{\text{reduction}} = +1.74 \text{ V} \) vs. Ag/AgNO\(_3\) in CH\(_3\)CN), the lack of reactivity is ascribable to steric hindrance hampering the acid addition into the cation radical resulting from SET oxidation. For information on the redox properties of the olefin, see: T. Shono, Y. Matsumura, Bull. Chem. Soc. Jpn. 1975, 48, 2861–2864.

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