



A General Organocatalytic System for Enantioselective Radical Conjugate Additions to Enals

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Abstract: Herein, we report a general iminium ion-based catalytic method for the enantioselective conjugate addition of carbon-centered radicals to aliphatic and aromatic enals. The process uses an organic photoredox catalyst, which absorbs blue light to generate radicals from stable precursors, in combination with a chiral amine catalyst, which secures a consistently high level of stereoselectivity. The generality of this catalytic platform is demonstrated by the stereoselective interception of a wide variety of radicals, including non-stabilized primary ones which are generally difficult to engage in asymmetric processes. The system also served to develop organocatalytic cascade reactions that combine an iminium-ion-based radical trap with an enamine-mediated step, affording stereochemically dense chiral products in one-step.

Introduction

The conjugate addition of carbon-centered radicals to electron-deficient olefins is a powerful strategy for C–C bond formation.^[1] Because of the high reactivity of radicals,^[2] developing catalytic stereocontrolled processes is greatly complicated by the presence of a significant racemic background reaction. The seminal work by Porter and Sibi^[3] showcased the potential of chiral Lewis acid-mediated catalysis to dictate the enantioselectivity of radical conjugate additions to a variety of α,β -unsaturated carbonyl substrates (Figure 1a, path i).^[4] Further developments^[5] have been spurred by the combination of chiral Lewis acids with

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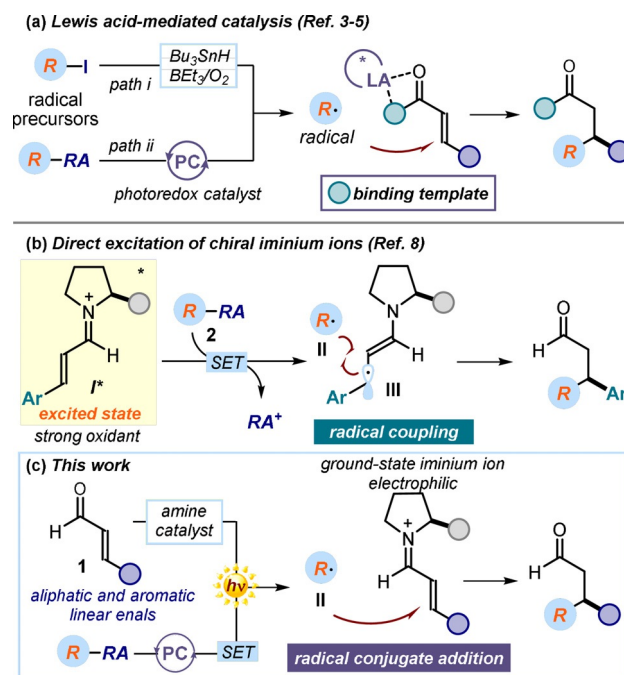


Figure 1. (a) Lewis-acid-catalyzed asymmetric radical conjugate additions generally require a purposely designed substrate bearing a binding template. (b) Our previous study on the radical β functionalization of aromatic enals based on the excitation of iminium ions **I***; the stereo-defining step was a radical coupling between **II** and **III**. (c) Design plan for the radical conjugate addition to aromatic and aliphatic enals: the photoredox catalyst (PC) generates radicals **II** that are stereoselectively intercepted by the ground-state chiral iminium ion **I**. SET: single-electron transfer; RA: redox-auxiliary group.

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a visible-light-activated photoredox catalyst,^[6] which generates radicals from stable precursors while avoiding the use of undesirable tin and BEt_3 reagents (Figure 1a, path ii). While effective, these enantioselective catalytic Lewis acid-based approaches require the systematic use of substrates bearing a preinstalled anchoring point. The two-point binding activation of the substrate is essential for stereocontrol since it facilitates the coordination of the chiral Lewis acid catalyst while ensuring optimal geometry control over the activated intermediate. A few methods can bypass the structural requirement of a binding template, but they are limited to cyclic enones.^[7]

Recently, our laboratories reported a method that could overcome some of these substrate limitations. Specifically, we found that iminium ions **I**, formed by condensation of a chiral amine catalyst with aromatic enals **1**, could be excited upon

absorption of visible light to become strong oxidants (Figure 1b).^[8] Single-electron transfer (SET) oxidation of substrates **2**, adorned with a redox-auxiliary (RA) group, afforded radicals **II**. A stereoselective radical coupling of **II**, governed by the chiral β -enaminy radical intermediate **III** arising from **I**, finally set the β stereocenter. The net reaction was an enantioselective radical β functionalization of enals. The main limitation of this approach was the need for an aromatic substituent at the β position of enals, since an aliphatic group shut down the excited-state reactivity of the iminium ion.

We surmised that a useful strategy to overcome this limitation could rely on an external photoredox catalyst to independently generate radicals **II**, which would then add onto a ground-state iminium ion **I** (Figure 1c). Since the iminium ion would not need to reach an excited state, the presence of aliphatic substituents on enals **1** should be tolerated. Herein, we report the realization of this idea, which led to a general iminium-ion-based system for radical conjugate additions to *aliphatic and aromatic* enals. The chemistry uses an organic photoredox catalyst, which selectively absorbs blue light to generate radicals from stable radical precursors, in combination with a chiral amine catalyst, which provides a consistently high level of stereoselectivity. This catalytic system offered a wide generality since a variety of radicals could be effectively intercepted with high stereocontrol, including non-stabilized primary radicals, which, due to their high reactivity, are generally recalcitrant to asymmetric bond-forming processes. Overall, the method expands the potential of enantioselective iminium-ion-mediated catalysis from established polar conjugate additions^[9] to include the realm of radical chemistry.

Results and Discussion

For initial explorations (Table 1), we selected 3,6-di-*tert*-butyl-9-mesityl-10-phenylacridinium tetrafluoroborate **4a** as the organic photocatalyst ($E^*(\mathbf{4a}^*/\mathbf{4a}^-) = +2.08$ V vs. SCE in CH_3CN)^[10] and α -silylamine **2a**, adorned with oxidizable trimethylsilyl group ($E_p(\mathbf{2a}^+/\mathbf{2a}) = +1.78$ V vs. Ag/AgCl in CH_3CN), as the substrate. The choice of **2a** was informed by the tendency of the ensuing α -amino radical to undergo addition to electron-deficient alkenes.^[11] Crotonaldehyde **1a** was selected as the model acceptor because it was unsuitable for the β -functionalization strategy based on the excitation of chiral iminium ions.^[8] In addition, the small size of the methyl fragment poses an additional challenge for the chiral catalyst to infer high stereoselectivity in the radical conjugate addition. The experiments were conducted at -10°C in CH_3CN using a blue LED ($\lambda_{\text{max}} = 460$ nm) with an irradiance at 60 mW cm^{-2} , as controlled by an external power supply. This irradiation secured selective excitation of the photocatalyst **4a** against the transient iminium ion (aromatic iminium ions absorb light below 430 nm, while the aliphatic counterpart absorbs in the near UV region).

We first used amine catalysts with an established profile in promoting asymmetric iminium-ion-mediated processes. The diarylprolinol silylether **A**^[12] afforded product **3a** with poor

Table 1: Optimization studies and control experiments.^[a]

Entry	Amine	4	[%] Yield ^[b]	[%] <i>ee</i> ^[c]
1	A	4a	30	33]
2	B	4a	99 (85)	64
3	C	4a	99 (87)	91
4 ^[d]	C	4b	34	–
5	C	4c	12	–
6 ^[e]	C	4a	0	–
7	C	<i>none</i>	0	–
8	<i>none</i>	4a	35	0

[a] Reactions performed on a 0.1 mmol scale for 16 h using 0.4 mL of CH_3CN under illumination by a single high-power (HP) LED ($\lambda_{\text{max}} = 460$ nm, 60 mW cm^{-2}) and 2 equiv of **1a**. [b] Yield of **3a** determined by ^1H NMR analysis of the crude mixture using trichloroethylene as the internal standard; yields of isolated **3a** are reported in brackets. [c] Enantiomeric excess of **3a**. [d] $\lambda_{\text{max}} = 420$ nm. [e] Reaction in the dark. TFA: trifluoroacetic acid; TDS: thexylidimethylsilyl.

yield and stereocontrol (entry 1), while better results were obtained using the imidazolidinone catalyst **B**^[9b] (entry 2, 85% yield and 64% *ee*). Both catalysts were largely outperformed by the *gem*-difluorinated diarylprolinol silylether catalyst **C** (entry 3, 87% yield and 91% *ee*),^[13] which we previously designed for the photoactivation of iminium ions.^[8] The high catalytic activity of **C** is ascribable to the enhanced electrophilicity imparted to the iminium ion by the electron-withdrawing fluorine atoms, which facilitates a stereoselective radical trap (see Section F4 in the Supporting Information for further discussion). Other photoredox catalysts (**4b–c**) were not suitable to efficiently promote the model reaction (entries 4–5).^[14] Control experiments indicated that the photocatalyst and light were both essential for the reaction (entries 6–7). The reactivity observed in the absence of amine **C** (entry 8) implied that the rate acceleration offered by iminium ion activation is large enough to overcome the racemic background process.^[15]

We then evaluated the synthetic potential of this strategy adopting the optimized conditions described in Table 1, entry 3. We first examined the enals that could intercept the α -amino radical generated from substrate **2a**. A wide range of aliphatic substituents at the β position of enals were tolerated well (Figure 2a), with the corresponding adducts being formed with consistently high stereoselectivity (products

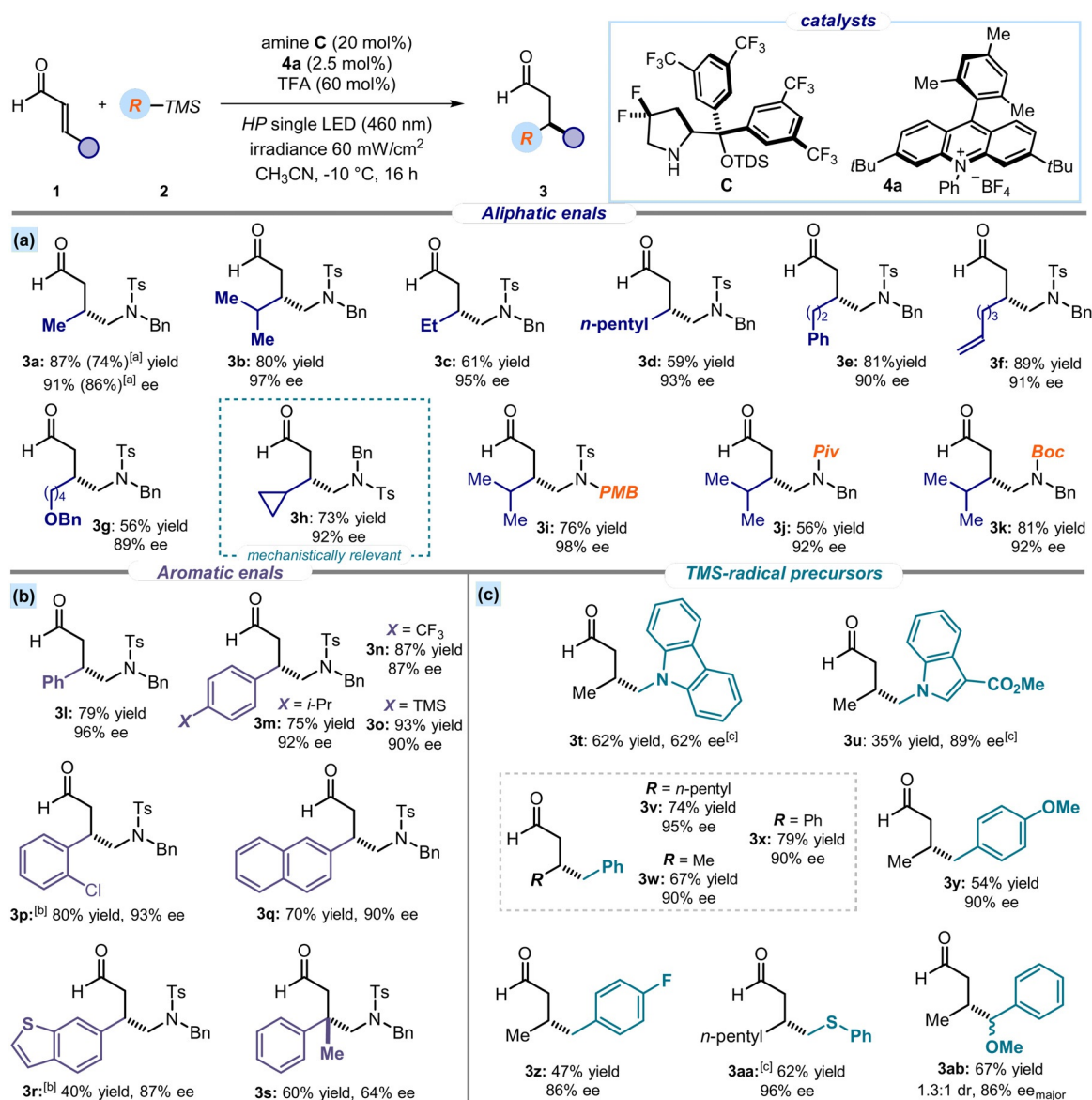


Figure 2. Substrate scope for the radical conjugate additions to enals. Survey of the (a) aliphatic and (b) aromatic enals, and of (c) the silyl radical precursors that can participate in the reaction. Reactions performed on a 0.1 mmol scale using 2 equiv of enal **1** in 0.4 mL of CH₃CN under illumination at 460 nm. Yields and enantiomeric excesses of the isolated products **3** are reported below each entry (average of two runs per substrate).^[a] Results between brackets refer to a 1 mmol scale reaction.^[b] Reaction time: 48 h.^[c] Performed in a CH₃CN/H₂O mixture (3:1) as solvent. Ts: toluenesulfonyl; Bn: benzyl; PMB: p-methoxybenzyl; Piv: pivaloyl; Boc: *tert*-butyloxycarbonyl.

3a–e, ees higher than 90%). The presence of a terminal olefin did not lead to undesired side reactions, smoothly affording product **3f**. An ether functionality was also tolerated (product **3g**). The reaction of (*E*)-3-cyclopropylacrylaldehyde led to the exclusive formation of the β -alkylated product **3h**, with the cyclopropyl fragment left untouched. This result is mechanistically relevant, since it excludes the formation of the β -enaminy radical of type **III** (Figure 1b) during the process. The α -silyl amine radical precursors **2** could be modified without affecting the efficiency of the radical conjugate addition (products **3i–3k**). Performing the model reaction on a 1 mmol scale only slightly affected the efficiency of the process (**3a** formed in 74% yield and 86% ee), showing that the method is amenable to synthetically useful purposes.

Aromatic enals^[16] were equally suitable substrates for the protocol (Figure 2b, products **3l–s**). Different substitution patterns at the aromatic moiety of enals **1** were well-tolerated, regardless of their electronic and steric properties and position on the phenyl ring. The reaction of a heteroaromatic enal was more sluggish but still delivered the β -alkylated product **3r** in high enantioselectivity. We also tested the ability of our protocol to stereoselectively forge quaternary carbon stereocenters. The reaction of β,β' -disubstituted (*E*)-3-phenylbut-2-enal led to the formation of the product **3s** with moderate yield and enantioselectivity.

We then evaluated other silyl radical precursors suitable for this method (Figure 2c). The protocol enabled the stereoselective installation of *N*-heterocyclic fragments of

pharmaceutical interest within products **3**, such as a carbazole and an indole moiety (adducts **3t** and **3u**, respectively). Benzyl silanes, bearing both electron-releasing and electron-withdrawing substituents on the aryl ring, were successfully used (Figure 2c, products **3v–3z**). We found that also α -silyl thioethers and ethers could be used in the radical conjugate addition (products **3aa** and **3ab**). As a limitation of the system, the use of allyl silane led to the β -allylation product with low efficiency, while α -silyl cyclic amines remained unreacted (see Figure S1 in the Supporting Information, which includes a list of moderately successful and unsuccessful substrates).

We then tested the possibility of activating radical precursors with a redox auxiliary group other than trimethylsilane (Figure 3). The use of a trifluoroborate salt **5a** enabled the incorporation of a cyclopentyl fragment at the β position of octenal (product **6a**, Figure 3a). Dihydropyridines proved useful to stereoselectively functionalize cinnamaldehyde with an isopropyl moiety, a derivative of the insecticide *carbaryl*, and a 3,4-dihydroquinolone, leading to products **6b–d**, respectively (Figure 3b). One limitation is that dihydropyridine derivatives provided poor yields in the radical conjugate addition to aliphatic enals (e.g. the cyclopentyl group could be installed within octenal with 92% *ee* but with 20% yield, see Figure S1 for further details). The alkylsilylate^[17] **5e** accounted for the stereoselective incorporation of a cyclohexyl

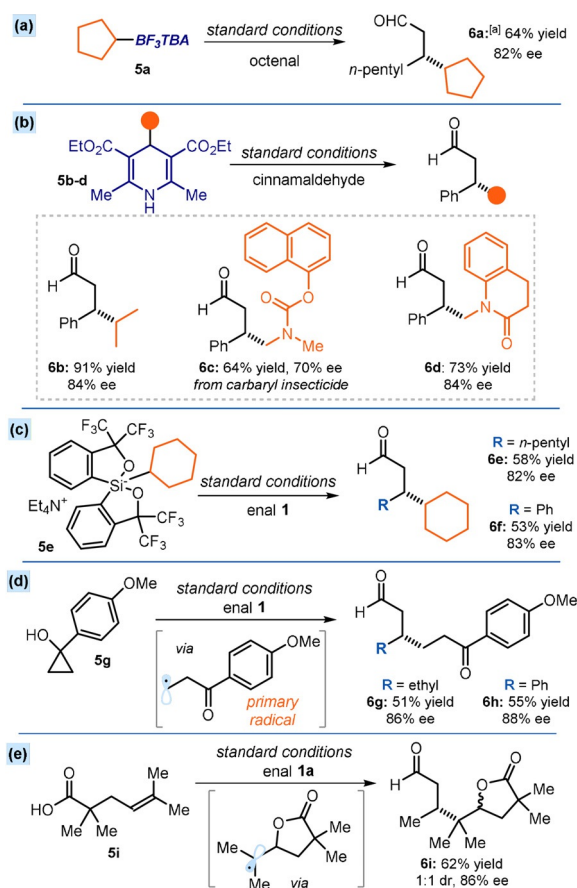
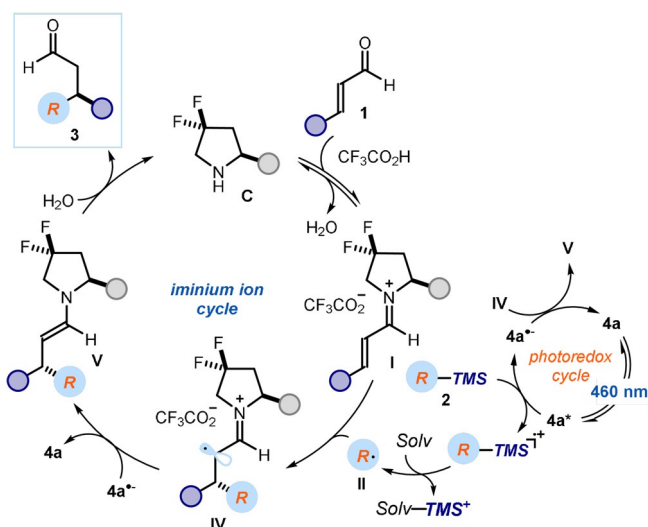


Figure 3. Further applications and use of different radical precursors.^[a]Using 1.1 equiv of octenal.

moiety in both aromatic and aliphatic enals (Figure 3c, products **6e** and **6f**). Importantly, we could also use the cyclopropanol **5g** as a suitable radical precursor (Figure 3d).^[18] Upon SET oxidation-mediated ring-opening, the resulting non-stabilized *primary radical* could be effectively intercepted with high stereocontrol to afford products **6g** and **6h**. This result is particularly relevant since the stereocontrolled interception of highly reactive primary alkyl radicals is a difficult goal, for which few asymmetric catalytic strategies are available.^[19] Finally, the alkenoic acid **5i**, which generates a tertiary radical upon SET oxidation-mediated anti-Markovnikov lactonization,^[20] afforded product **6i** (Figure 3e). This example shows the potential of the system to promote an asymmetric radical cascade reaction which combines two sequential radical-based bond-forming events. The overall cascade converts an unactivated olefin and α,β -unsaturated aldehyde into chiral adducts in a single step.

A plausible mechanism for the enantioselective radical conjugate addition is depicted in Figure 4. Blue light irradiation brings the organic photocatalyst **4a** into the excited state **4a***, from where it can activate substrate **2** via SET oxidation. The TMS redox-auxiliary group in **2**, by facilitating oxidation and undergoing solvent-assisted fragmentation,^[21] leads to radical **II**, which is stereoselectively intercepted by the ground-state electrophilic iminium ion **I**, generated upon condensation of catalyst **C** with the enal **1**. The radical conjugate addition delivers the unstable α -iminyl radical cation **IV**, which is reduced via SET by the reduced form of the photoredox catalyst ($E_{1/2}(\mathbf{4a}/\mathbf{4a}^{\bullet-}) = -0.59$ V vs. SCE in CH_3CN).^[10] The last step delivers the enamine **V**, which, upon hydrolysis, forms the β -functionalized product **3**, while turning over both the aminocatalyst **C** and the photocatalyst **4a**.

In consonance with this proposal, a series of Stern–Volmer studies, detailed in section F of the Supporting Information, revealed that silane **2a** effectively quenched the excited state of photocatalyst **4a**, thus supporting an initial reductive quenching of **4a**. We also measured the quantum yield of the model reaction between **1a** and substrate **2a**, which was found to be as low as $\Phi = 0.02$.^[22] This fractional



value is congruent with the closed photoredox cycle depicted in Figure 4.^[23] Finally, the exclusive formation of product **3h** (Figure 2a) and the absence of any cyclopropyl ring-opening adduct excludes a path (analogous to the mechanism in Figure 1b) proceeding through SET reduction of the iminium ion and formation of radical **III**.

The mechanism of this strategy requires the formation of the enamine intermediate **V** to close the aminocatalytic cycle. We therefore sought to capitalize on the nucleophilic nature of this chiral intermediate **V** to design cascade processes initiated by an iminium-ion-triggered radical conjugate addition. In a first approach, we used radical precursor **7** adorned with an electrophilic keto-functionality, which provided a suitable handle for an *intramolecular* aldol step catalyzed by the chiral enamine (Figure 5a). This cascade, which performed better in the presence of biphenyl as an electron mediator, led to the one-step preparation of biologically relevant and stereochemically dense piperidines (**8a–8c**).^[24] The stereochemistry of the major diastereoisomer of product **8c** was established by single crystal X-ray crystallographic analysis.^[25]

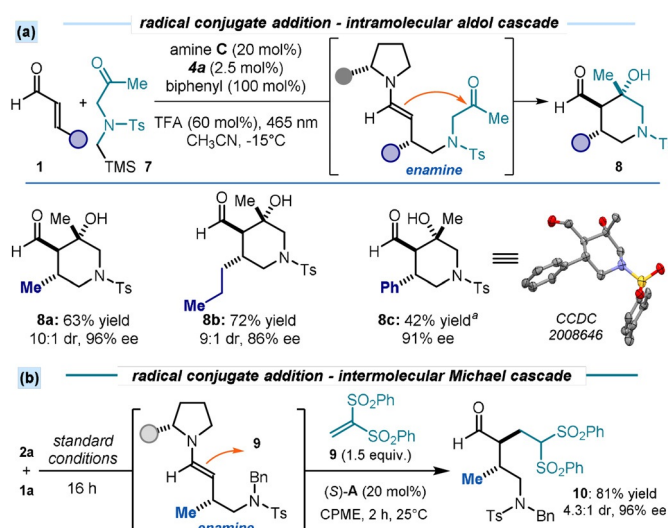


Figure 5. Iminium ion-enamine cascade processes: (a) Radical conjugate addition/*intramolecular* aldol sequence and (b) one-pot radical conjugate addition/*intermolecular* Michael addition. ^aThe process afforded a 2:1 dr, but the pure major diastereoisomer **8c** could be isolated. CPME: cyclopentyl methyl ether.

We also implemented a different cascade (Figure 5b), where the Michael acceptor **9** was intercepted *intermolecularly* by the transient enamine. After completion of the conjugate radical addition, we added **9** along with aminocatalyst (S)-**A** (20 mol%), which assisted the enamine step of the cascade. This one-pot procedure granted access to the 2,3-disubstituted product **10** with high enantioselectivity and good *anti* diastereoselectivity.

Conclusion

In summary, we have developed a general catalytic strategy to stereoselectively intercept photochemically generated carbon-centered radicals with chiral iminium ions. The chemistry requires a readily available organic photocatalyst and a chiral amine catalyst and uses blue light irradiation to stereoselectively functionalize simple aliphatic and aromatic enals with a variety of stable radical precursors. Importantly, the system is flexible and effective enough to allow for the interception of highly reactive primary radicals and for designing asymmetric radical cascade processes. Overall, this study expands the established potential of iminium-ion-mediated catalysis to promote highly stereoselective asymmetric conjugate additions of nucleophiles to include radicals.

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Conflict of interest

The authors declare no conflict of interest.

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