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Photo-organocatalytic Enantioselective Perfluoroalkylation of β-Ketoesters

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Supporting Information

ABSTRACT: The visible-light-driven, phase-transfer-catalyzed, enantioselective perfluoroalkylation and trifluoromethylation of cyclic β-ketoesters is described. The photo-organocatalytic process, which occurs at ambient temperature and under visible light illumination, is triggered by the photochemical activity of *in situ*-generated electron donor–acceptor complexes, arising from the association of chiral enolates and perfluoroalkyl iodides. Preliminary mechanistic studies are reported.

Visible-light-driven enantioselective catalytic processes hold great potential for the sustainable preparation of chiral molecules.[1] Their development, however, is challenging.[2] A central theme of modern stereoselective chemistry is the identification of strategies for exploring the untapped potential of enantioselective photocatalysis.[3,4] In this context, our laboratory recently introduced a unique approach[5] based on the ability of chiral enamines, key intermediates in thermal organocatalytic asymmetric processes,[6] to actively participate in the photoexcitation of substrates while inducing the stereocontrolled formation of chiral products. The photo-organocatalytic strategy, which did not require external photosensitizers, relied upon the formation of photoactive electron donor–acceptor (EDA) complexes,[7] arising from the ground-state association of the electron-rich enamine **I** with electron-deficient alkyl bromides **II** (Figure 1a). Visible light irradiation of the colored EDA complex **III** induced a single electron transfer (SET), allowing access to radical species under mild conditions. This reactivity enabled the development of a light-driven stereoselective α-alkylation of carbonyl compounds,[5] a process which could not be realized under thermal activation.

In this Communication, we further advance the EDA complex activation concept to develop a photochemical enantioselective perfluoroalkylation of β-ketoesters **1** (Figure 1b). Conceptually, this study demonstrates that chiral enolates **IV**, generated upon deprotonation of **1**, can serve as suitable donors for EDA complex formation. The chemistry occurs at ambient temperature and requires visible light irradiation to proceed. It provides straightforward access to highly valuable products **3** bearing an R_F-containing quaternary stereocenter[8] (R_F indicates the perfluoroalkyl fragment). Since fluorine-containing functional groups can greatly alter the intrinsic properties of organic compounds,[9] the catalytic production of perfluoralkyl-containing stereogenicity is a centrally important methodological goal.[10]

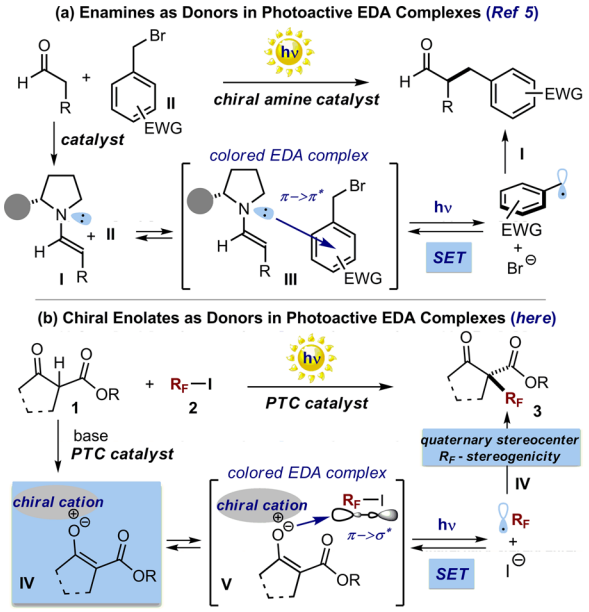

Figure 1. EDA complex activation strategy for designing light-driven enantioselective catalytic reactions: (a) chiral enamines as the donor; (b) chiral enolates as the donor. The gray circles represent the chiral organocatalyst scaffold; PTC = phase transfer catalysis.

Our initial investigations were motivated by the desire to conceive novel and synthetically useful photo-organocatalytic asymmetric transformations. Specifically, we wondered if the EDA complex activation strategy could be expanded to include electron-rich chiral organocatalytic intermediates other than enamines **I**. Given the electronic similarities with **I**, *in situ*-generated enolates of type **IV** were considered as suitable donors.[11] Perfluoroalkyl iodides (R_FI, **2**) were selected as electron-accepting substrates, since a few literature precedents[12] qualify them as potential acceptors for facilitating EDA associations in the ground state. In addition, the electrophilic character of perfluoroalkyl radicals ($R_F^{\bullet}$),[9c] emerging from the photoinduced SET, should facilitate trapping by the chiral enolate ion-pair **IV**.[13] The chemistry of chiral enolates has a rich history in enantioselective catalysis, with many different approaches available. One effective strategy relies on phase transfer catalysis (PTC),[14,15] where chiral quaternary ammonium salts can be used to generate a chiral ion-pair **IV** after

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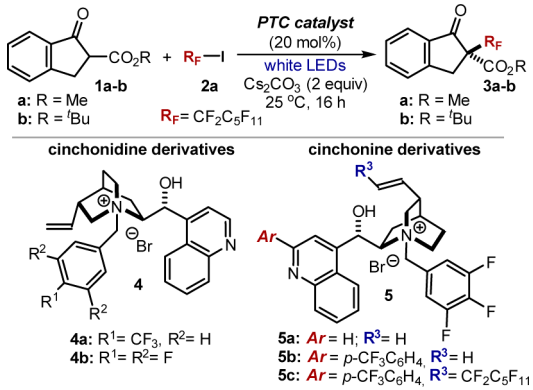
deprotonation of β-ketoesters **1** by an inorganic base (Figure 1b). We anticipated **IV** to be electron-rich enough to form an EDA complex with R_FI and then trap the resulting radical, forging a quaternary carbon stereocenter within product **3**.

The feasibility of our plan was tested by reacting the methyl ester of the indanone-derivative **1a** with perfluorohexyl iodide **2a** in dichloromethane (DCM) under visible light irradiation by white light-emitting diodes (LEDs)[16] (Table 1). Performing the reaction in the presence of the commercially available cinchona-derived PTC catalyst **4a** and Cs_2CO_3 (2 equiv), so as to form the corresponding chiral enolate of type **IV**, provided the product **3a** in good chemical yield, albeit with low stereocontrol (entry 1). Irradiation by a compact fluorescent light (CFL) bulb resulted in reduced reactivity (entry 2). We noticed that, after mixing with the iodide **2a**, the achromatic solution of the enolate **IVa** derived from **1a** developed a yellow color (Figure 2a), while its optical absorption spectrum showed a bathochromic shift to the visible spectral region, diagnostic of an EDA complex (Figure 2b, blue line).

Control experiments revealed how the exclusion of any of the reaction components, i.e., light (entry 3), PTC catalyst, and Cs_2CO_3, completely suppressed the process. Inhibition of the reactivity also occurred under an aerobic atmosphere or in the presence of TEMPO (1 equiv), the latter experiment being indicative of a radical mechanism. Additionally, an experiment using a 300 W xenon lamp, equipped with a band-pass filter at 400 nm so to exclude high-energy photons, did not significantly alter the reaction efficiency (entry 4). This result is mechanistically relevant since it excluded both possible homolytic cleavage of the C–I bond in **2a** and direct photoexcitation of the enolate **IVa** (which is unable to absorb at 400 nm, red line in Figure 2) as pathways for $R_F^{\bullet}$ generation. All of these observations are consonant with the EDA complex-driven photochemical mechanism proposed in Figure 1b.

We next focused on identifying a chiral PTC organocatalyst that could infer high stereocontrol in the photochemical perfluoroalkylation of **1a**. Representative results of our extensive investigations are listed in Table 1, with more details reported in the Supporting Information. We found that the substitution pattern of the benzyl moiety within the PTC catalyst had a direct influence on the stereoselectivity (catalyst **4b**, entry 5). Gratifyingly, the pseudo-enantiomeric cinchonine derivative **5a** inferred a higher level of stereocontrol (entry 6). Using chlorobenzene as solvent provided the product **3a** with 86% ee, albeit with a greatly attenuated reactivity (entry 7). A final cycle of catalyst optimization revealed that the stereocontrol was sensitive to structural modifications at the 2′ position of the quinoline ring. Of the investigated catalysts, **5b** provided the best results. Conducting the reaction with an excess of **2a** (3 equiv) for a 64-h time period afforded the adduct **3a** with 92% ee and a moderate yield (entry 8). Further evaluation of the reaction medium indicated that a chlorobenzene/perfluorooctane combination (in a 2:1 ratio) positively influenced the reactivity, without affecting the stereoselectivity of the process (**3a** formed

Table 1. Optimization of the Model Reaction[a]



entry	4	1	solvent	light	% yield[b]	% ee[c]
1	**4a**	**1a**	DCM	white LED	79	13
2	**4a**	**1a**	DCM	23 W CFL	34	15
3	**4a**	**1a**	DCM	no	0	–
4[d]	**4a**	**1a**	DCM	band-pass at 400 nm	53	13
5	**4b**	**1a**	DCM	white LED	61	35
6	**5a**	**1a**	DCM	white LED	65	65
7	**5a**	**1a**	C_6H_5Cl	white LED	12	86
8[e]	**5b**	**1a**	C_6H_5Cl	white LED	41	92
9[e]	**5b**	**1a**	C_6H_5Cl/C_8F_{18}	white LED	59	93
10[e]	**5b**	**1b**	C_6H_5Cl/C_8F_{18}	white LED	71	93
11[e]	**5c**	**1b**	C_6H_5Cl/C_8F_{18}	white LED	60	86

[a]C_8F_{18} = perfluorooctane. Reactions performed over 16 h on a 0.1 mmol scale using 1,2 equiv of **1a** and a white LED strip to illuminate the reaction vessel. [b]Yield of **3a** determined after isolation by chromatography. [c]Enantiomeric excess determined by HPLC analysis on a chiral stationary phase. [d]Using a 300 W xenon lamp. [e]Reaction time, 64 h; 3 equiv of **2a**.

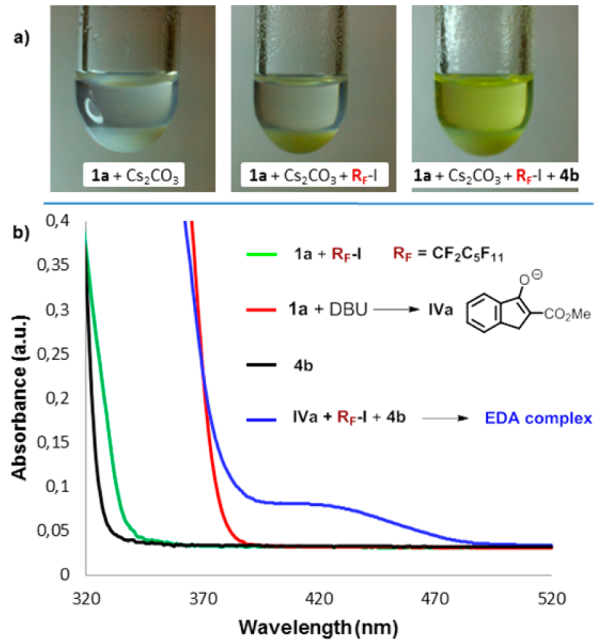


Figure 2. (a) Images showing the formation of the EDA complex (yellow) on the surface of Cs_2CO_3 (white solid) and its subsequent dispersion into the organic phase (chlorobenzene) upon addition of the PTC catalyst **4b**. (b) Optical absorption spectra recorded in chlorobenzene in a 1 cm path quartz cuvettes using a Shimadzu 2401PC UV–visible spectrophotometer; [R_F-I] = 15 μM, [**1a**] = 15 μM; [DBU] = 30 μM, [**4b**] = 15 μM. While the substrates **1a** and **2a** are achromatic, the resulting enolate **IVa** (formed upon mixing **1a** with 2 equiv of DBU) showed a weak absorption at about 380 nm (red line); its combination with perfluorohexyl iodide **2a** determines a strong bathochromic shift (blue line). The optical absorption spectrum of the reaction mixture under PTC conditions (recorded upon filtration of Cs_2CO_3) perfectly overlaid the blue line. DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene.

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in 59% yield and 93% ee, entry 9). Under the same conditions, the *tert*-butyl ketoester **1b** was converted into the chiral adduct **3b** with an improved chemical yield while retaining the stereoselectivity (71% yield, 93% ee, entry 10).

During the optimization studies, we noticed that the catalyst **5b** was partially converted into the perfluorohexyl derivative **5c**, due to an atom transfer radical addition[17] of **2a** to the olefinic catalyst moiety followed by a net HI elimination. We found that **5c**, isolated in 51% yield at the end of the reaction detailed in entry 10, was also a competent catalyst of the model reaction, providing only slightly inferior results than the progenitor **5b** (compare entries 10 and 11).

We then evaluated the synthetic potential of the photo-organocatalytic asymmetric perfluoroalkylation strategy, reacting differently substituted indanone-derived β-ketoesters with perfluorohexyl iodide **2a** under the catalysis of **5b**.

As detailed in Figure 3b, a variety of electron-withdrawing substituents were well tolerated, independently of their position

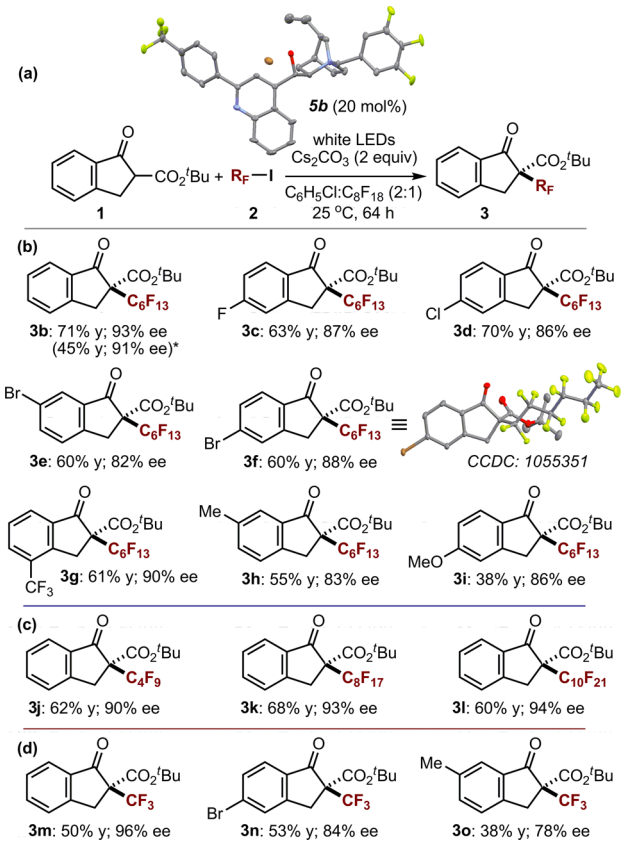

Figure 3. Photochemical enantioselective perfluoroalkylation of indanone-derived β-ketoesters under PTC conditions. (a) Reactions performed using the optimized conditions from entry 10 in Table 1. Yields are of isolated products **3**. The X-ray structure of catalyst **5b** is shown. (b) Scope of the β-ketoesters **1** using perfluorohexyl iodide **2b**. (c) Scope of perfluoroalkylating agents. (d) Enantioselective trifluoromethylation. *1 mmol scale reaction.

on the aromatic ring. The desired products **3b–g** were obtained in good yields and high enantioselectivities. The presence of electron-donating substituents somewhat lowered the reactivity (products **3h** and **3i**). The process is amenable to scale up (1 mmol, product **3a**), but with a slightly reduced yield, likely a consequence of a lower photon/mole ratio. Our efforts to react six-membered cyclic and linear substrates require further optimization, as only traces of the corresponding perfluoralkylated adducts could be obtained. Crystals of adduct **3f** were suitable for X-ray crystallographic analysis, which established the stereochemical outcome of the photo-organocatalytic process.[18] We next found that the system is amenable to using other perfluoralkyl iodides (Figure 3c). Both shorter and longer perfluorinated chains could be installed in **1a** in a good yield and with a high stereocontrol (ee ranging from 90% to 94%, product **3j–l**). Notably, trifluoromethyl-containing quaternary stereocenters could be forged with high fidelity when reacting β-ketoesters with CF_3I (Figure 3d, products **3m–o**).

As for the mechanism of this asymmetric photochemical perfluoroalkylation, we propose a radical chain propagation pathway, as depicted in Figure 4.[19] The chain reaction is initiated

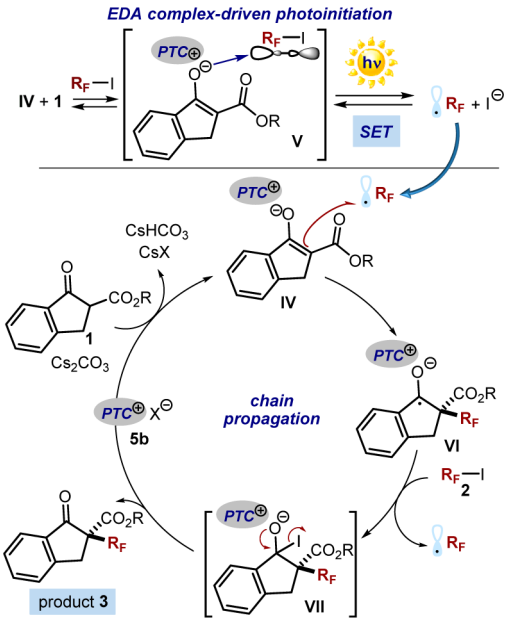

Figure 4. Proposed mechanism: initiation, triggered by the photoactivity of the EDA complex, and radical chain propagation; X = I, Br.

by the photochemical activity of the EDA complex of type **V**, formed upon the aggregation of the chiral enolate **IV** with R_FI **2**.[20] A visible-light-promoted electron transfer leads to the formation of the electron-deficient perfluoralkyl radical through the reductive cleavage of the C–I bond within **2**. Consistent with a SET pathway, the model reaction was completely inhibited when performed in the presence of a redox trap such as 1,4-dinitrobenzene (0.2 equiv). The electrophilic perfluoroalkyl radical is next trapped by the chiral enolate **IV** in a stereocontrolled fashion. The resulting ketyl intermediate **VI** would then abstract an iodine atom from **2**, thereby regenerating $R_F^{\bullet}$.[21] The adduct **VII** is not stable and collapses to release the product **3** and the PTC catalyst **5b**. At the present level of investigation, an alternative electron transfer process, where the ketyl intermediate **VI** reduces R_FI to directly afford the final product **3**, cannot be excluded.

In conclusion, we have developed a photochemical enantioselective perfluoroalkylation of cyclic β-ketoesters. The chemistry utilizes readily available substrates and proceeds at ambient temperature under visible light illumination. This study establishes the ability of chiral enolates, generated under PTC conditions, to be suitable donors in photoactive EDA complex while providing effective asymmetric induction in the trapping of

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the resulting radical species. Other applications of EDA complex as an activation strategy for the design of novel light-driven transformations are underway in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and spectral data. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(18) Crystallographic data for catalyst **5b** and **3f** are available free of charge from the Cambridge Crystallographic Data Centre, accession numbers CCDC 1056560 and CCDC 1055351, respectively.

(19) A quantum yield (Φ) of 1.2 (λ = 400 nm) was determined for the model reaction (ketoester **1b**) promoted by DBU (2 equiv), corroborating a radical chain mechanism as the main pathway. DBU is a competent promoter of the photochemical perfluoroalkylation, providing the corresponding product **3b** in 73% yield under the conditions set out in Table 1, entry 10. Our attempts to determine the quantum yield under PTC conditions were frustrated by the heterogeneity of the reaction mixture, which precluded a homogeneous illumination, a crucial requirement for a reliable quantum yield determination.

(20) Within the EDA-complex-mediated photochemical initiation, the chiral enolate serves as a sacrificial initiator of the chain mechanism, with the ketyl radical resulting from the SET event (structure not shown) lying outside of the productive manifold (a combination with the perfluoralkyl radical is unlikely).

(21) A similar mechanism, based on the formation of the fleeting intermediate **VII**, was proposed in ref 13b.

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