Accepted Article

This manuscript has been accepted after peer review and appears as an Accepted Article online prior to editing, proofing, and formal publication of the final Version of Record (VoR). This work is currently citable by using the Digital Object Identifier (DOI) given below. The VoR will be published online in Early View as soon as possible and may be different to this Accepted Article as a result of editing. Readers should obtain the VoR from the journal website shown below when it is published to ensure accuracy of information. The authors are responsible for the content of this Accepted Article.

Angewandte
Communications

Photo-Organocatalytic Enantioselective Radical Cascade Reactions of Unactivated Olefins**

Pablo Bonilla,[†] Yannick P. Rey,[†] Catherine M. Holden, and Paolo Melchiorre

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. Herein we report 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[2] makes radical chemistry perfectly suited for implementing cascades.[3] However, the intrinsic challenge of carrying out reactions with radicals in a stereocontrolled fashion[4] has greatly limited the development of enantioselective variants. The majority of the reported strategies rely on chiral substrates or stoichiometric ligands.[3c,4-5] Recently, photoredox catalysis[6] has provided effective tools to enable single-electron transfer (SET)-mediated radical cascade processes under mild conditions.[3a] The combination with chiral Lewis acid catalysts has allowed the ensuing radical cascade process to be channeled towards a stereocontrolled pattern.[7] Although effective, these catalytic asymmetric methods are generally limited to 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.[8] 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 stereoselectivity (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 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 butyrolactone[11a] or tetrahydrofuran moieties.[11b] These two structural elements are present in numerous biologically active and naturally occurring molecules.
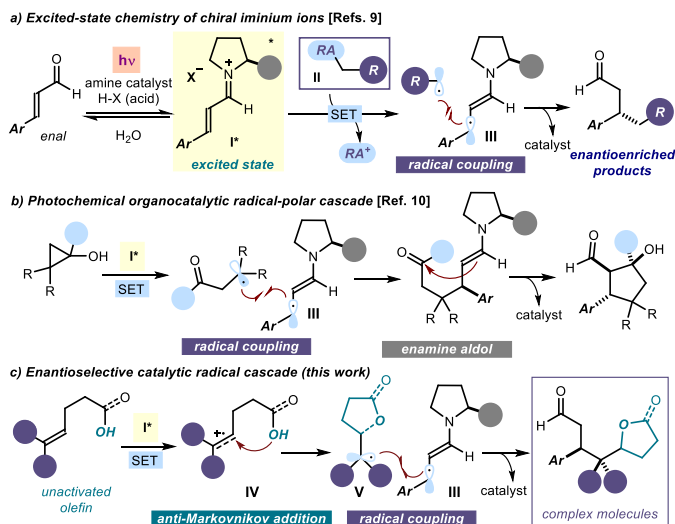

Figure 1. a) Our previous study demonstrating that light excitation turns iminium ions **I** into chiral oxidants, and the resulting SET-based mechanism for generating radicals from precursors **II** bearing a redox auxiliary (RA). b) A cascade reaction proceeding via an excited-iminium ion/ground-state enamine sequence, where a stereocontrolled radical path is combined with polar reactivity. c) Proposed enantioselective catalytic radical cascade proceeding via 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.

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 ion intermediate **I** upon condensation with enal **1**. Selective

[*] Prof. Dr. P. Melchiorre
ICREA - Catalan Institution for Research and Advanced Studies,
Passeig Lluís Companys 23 – 08010, Barcelona, Spain

P. Bonilla, Dr. Y. P. Rey, Dr. C. M. Holden, and Prof. Dr. P. Melchiorre
ICIQ - Institute of Chemical Research of Catalonia
the Barcelona Institute of Science and Technology,
Avenida Països Catalans 16 – 43007, Tarragona, Spain
E-mail: pmelchiorre@iciq.es
Homepage: http://www.iciq.org/research/research_group/prof-paolo-melchiorre/

[†] These authors contributed equally to this work.

WILEY
ONLINE LIBRARY

excitation with a violet-light-emitting diode (LED) turns **I** into a strong oxidant (**I***), as implied by its reduction potential, which was estimated as ≈+2.4 V ($E*_{red}$ (**I***/**I⁻**) *vs* Ag/Ag⁺ in CH₃CN) using electrochemical and spectroscopic methods.[9a] Therefore, the photo-excited 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 to +2.19 V *vs* Ag/AgCl in MeCN, see section D in the Supplementary Information for details). The SET activation of olefin **2** would concomitantly form the chiral 5π-intermediate **III** and the alkene radical cation **IV**. The nucleophilic moiety within **IV** would then trigger a polar-radical-crossover cycloaddition,[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 stereo-controlled 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]
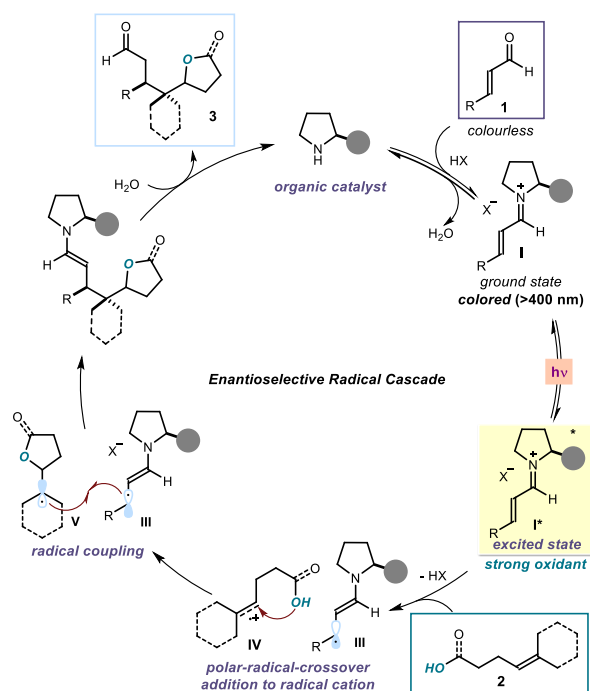

Figure 2. Mechanistic proposal for a SET-triggered asymmetric photocatalytic radical cascade process.

To test the feasibility of our photochemical plan, we selected cinnamaldehyde **1a** and the *gem*-difluorinated diarylprolinol silylether catalyst **A**[9a] for the formation of the chiral iminium ion (Table 1). The experiments were conducted in CH₃CN using a single high-power (HP) LED (λ$_{max}$ = 420 nm) with an irradiance at 30 mW/cm², as controlled by an external power supply (full details of the illumination set-up are reported in the Supporting Information, Figure S1). The alkenoic acid **2a** was selected as the model substrate based on the oxidation potential (E_p^{ox} (**2a**•⁺/**2a**) = +2.09 V *vs* Ag/AgCl in MeCN) and its tendency to undergo SET oxidation-mediated anti-Markovnikov lactonization.[16a] Using 40% of trifluoroacetic acid (TFA) to assist the formation of the iminium ion **I**, the desired product **3a** was obtained at ambient temperature in 55% yield, 88% ee, and

1:1 dr (entry 1). Increasing the amount of TFA to 60 mol% improved the yield to 62% (entry 2). The chiral amine catalyst **B**, possessing bulkier perfluoro-isopropyl groups on the arene scaffold, improved the enantioselectivity (91% ee, entry 3), whereas the chiral imidazolidinone catalyst **C** afforded the product with low stereocontrol (entry 4). Implementation of a two-phase solvent system, using tetradecafluorohexane in a 1:1 ratio to CH₃CN, further increased the yield of the reaction (72% yield, entry 5).[17] 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.

Table 1. Optimization studies.[a]

entry	catalyst	conditions	[%] yield[b]	[%] ee[c]
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	CH₃CN/Hex$_F$ (1:1)	72 (58)	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/cm². [b] Yield of **3a** determined by ¹H NMR analysis of the crude mixture using trichloroethylene as the internal standard; yields of the isolated **3a** are reported in brackets. [c] Enantiomeric excess determined by HPLC analysis on a chiral stationary phase. TFA: trifluoroacetic acid; TDS: thexyl-dimethylsilyl; Hex$_F$: tetradecafluorohexane.

Using the optimized conditions described in Table 1, entry 5, 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 alpha position of the alkenoic acid substrate **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 a cyclohexyl group afforded the spirocyclic adduct **3d** in moderate yield and high enantioselectivity. The absence of α-substituents in substrate **2** did not significantly affect the overall efficiency (product **3e**). This 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 compound **3a** were suitable for X-ray crystallographic analysis,[18] which established the stereochemical course of the radical cascade process.
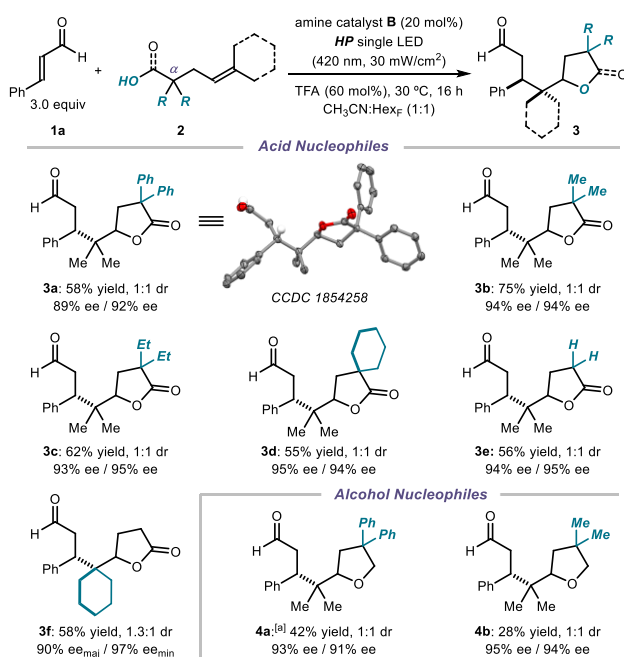
Angewandte Communications

Figure 3. Survey of the alkenoic acids and alkenols **2** that can participate in the radical cascade process with cinnamaldehyde **1a**. Reactions performed on 0.1 mmol scale using 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 adducts **3** obtained upon olefination of the aldehyde with PPh₃CHCO₂Et. Dr was inferred by ¹H NMR analysis of the crude mixture. [a]Reaction performed using catalyst **A** in acetonitrile.
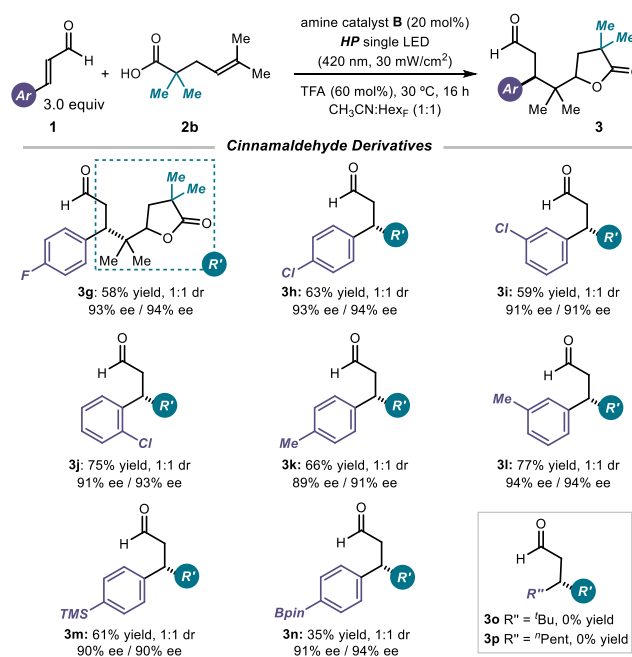

Figure 4. Survey of the enals **1** that can participate in the radical cascade process with alkenoic acid **2b**. Reactions performed on 0.1 mmol scale using 1:1 mixture of acetonitrile and tetradecafluorohexane. Yields of the isolated products are indicated below each entry (average of two runs per substrate). Enantiomeric excesses measured on the enoate derivatives of adducts **3** obtained upon olefination of the aldehyde with PPh₃CHCO₂Et. Dr was inferred by ¹H NMR analysis of the crude mixture.

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 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_p^{ox} (**5·⁺/5**) = + 2.03 V *vs* Ag/AgCl in MeCN).[19] The anti-Markovnikov intermolecular addition of a carboxylic acid[20] to the less substituted position of the resulting cation radical **VI** would then provide the key radical intermediate **VII** (Figure 5). **VII** would eventually engage in a stereoselective radical coupling governed by the chiral 5π-intermediate **III** (structure shown in Figure 2). This catalytic asymmetric cascade process, which 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 enantioselectivities. 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.
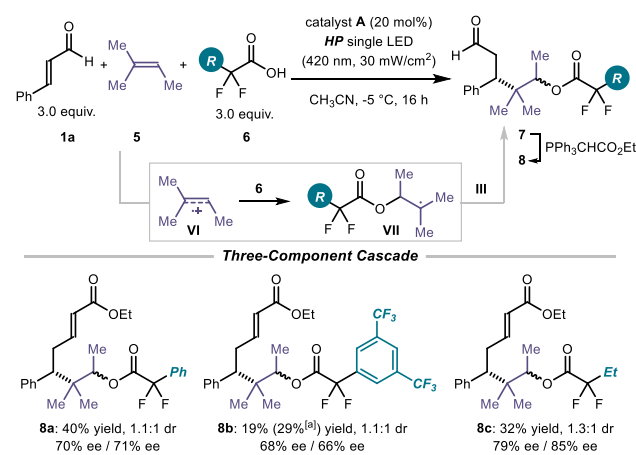

Figure 5. Catalytic enantioselective three-component radical cascade process that combines two intermolecular radical steps. Reactions performed on 0.1 mmol scale in CH₃CN. Yields and enantiomeric excess given on the isolated enoate derivatives **8** obtained upon olefination of the aldehyde precursor (average of two experiments). Dr was inferred by ¹H NMR analysis of the crude mixture. [a]Yield of the isolated intermediate aldehyde **7b**.

Angewandte Communications

In summary, the photochemical activity of chiral iminium ions 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.

[1] a) K. C. Nicolaou, D. J. Edmonds, P. G. Bulger, *Angew. Chem. Int. Ed.* **2006**, *45*, 7134–7186; *Angew. Chem.* **2006**, *118*, 7292–7344; b) L. F. Tietze, G. Brasche, K. M. Gericke, in *Domino Reactions in Organic Synthesis*, Wiley-VCH, Weinheim, 2006; c) P.-F. Xu, W. Wang, in *Catalytic Cascade Reactions*, Wiley-VCH, Weinheim, 2013.

[2] a) P. Renaud, M. P. Sibi, (Eds.), *Radicals in Organic Synthesis,* Wiley-VCH: Weinheim, 2001; b) M. Yan, J. C. Lo, J. T. Edwards, P. S. Baran, *J. Am. Chem. Soc.* **2016**, *138*, 12692−12714; c) C. Chatgilialoglu, A. Studer (Eds.), *Encyclopedia of Radicals in Chemistry, Biology and Materials*, John Wiley & Sons, 2012.

[3] a) M. P. Plesniak, H.-M. Huang, D. J. Procter *Nat. Rev. Chem.* **2017**, *1*, 0077; b) L. J. Sebren, J. J. Devery, C. R. J. Stephenson, *ACS Catal.* **2014**, *4*, 703–716; c) H. Miyabe, A. Kawashima, E. Yoshioka, S. Kohtani, *Chem. Eur. J.* **2017**, *23*, 6225–6236.

[4] a) D. P. Curran, N. A. Porter, B. Giese, (Eds.) *Stereochemistry of Radical Reactions: Concepts, Guidelines, and Synthetic Applications*, VCH Verlag, Weinheim, 2008; b) M. P. Sibi, S. Manyem, J. Zimmerman, *Chem. Rev.* **2003**, *103*, 3263–3296.

[5] For an excellent recent example: N. Kern, M. P. Plesniak, J. J. W. McDouall, D. J. Procter, *Nat. Chem.* **2017**, *9*, 1198–1204.

[6] M. H. Shaw, J. Twilton, D. W. C. MacMillan, *J. Org. Chem.* **2016** *81*, 6898–6926.

[7] a) J. Du, K. L. Skubi, D. M. Schultz, T. P. Yoon, *Science* **2014**, *344*, 392–396; b) A. G. Amador, E. M. Sherbrook, T. P. Yoon, *J. Am. Chem. Soc.* **2016**, *138*, 4722–4725; c) X. Huang, J. Lin, T. Shen, K. Harms, M. Marchini, P. Ceroni, E. Meggers, *Angew. Chem. Int. Ed.* **2018**, *57*, 5454–5458; *Angew. Chem.* **2018**, *130*, 5552–5556; d) P. D. Morse, T. M. Nguyen, C. L. Cruz, D. A. Nicewicz, *Tetrahedron* **2018**, *74*, 3266–3272. For an example of catalytic asymmetric multicomponent radical reaction that does not proceed via an annulation manifold, see: e) J. Ma, X. Xie, E. Meggers, *Chem. Eur. J.* **2018**, *24*, 259–265

[8] For reviews on enantioselective photochemical reactions, see: a) R. Brimioulle, D. Lenhart, M. M. Maturi, T. Bach, *Angew. Chem. Int. Ed.* **2015**, *54*, 3872–3890; *Angew. Chem.* **2015**, *127*, 3944–3963; b) C. Brenninger, J. D. Jolliffe, T. Bach, *Angew. Chem. Int. Ed.* **2018**, in press, DOI: 10.1002/anie.201804006.

[9] a) M. Silvi, C. Verrier, Y. P. Rey, L. Buzzetti, P. Melchiorre, *Nat. Chem.* **2017** *9*, 868–873; b) C. Verrier, N. Alandini, C. Pezzetta, M. Moliterno, L. Buzzetti, H. B. Hepburn, A. Vega-Peñaloza, M. Silvi, P. Melchiorre, *ACS Catal.* **2018**, *8*, 1062–1066; c) D. Mazzarella, G. E. M. Crisenza, P. Melchiorre, *J. Am. Chem. Soc.* **2018**, *140*, 8439–8443. For a review, see: d) M. Silvi, P. Melchiorre, *Nature* **2018**, *554*, 41–49.

[10] Ł. Woźniak, G. Magagnano, P. Melchiorre, *Angew. Chem. Int. Ed.* **2018**, *57*, 1068–1072; *Angew. Chem.* **2018**, *130*, 1080–1084.

[11] a) R. R. A. Kitson, A. Millemaggi, R. J. K. Taylor, *Angew. Chem. Int. Ed.* **2009**, 48, 9426–9451; *Angew. Chem.* **2009**, *121*, 9590–9615; b) J. P. Wolfe, M. B. Hay, *Tetrahedron* **2007**, *63*, 261–290.

[12] For seminal works on the SET oxidation of alkenes, see: a) P. S. Mariano, *Tetrahedron* **1983**, *39*, 3845–3879; b) J.-L. Stavinoha, P. S. Mariano, *J. Am. Chem. Soc.* **1978**, *100*, 7114–7116.

[13] a) B. Giese, X. Beyrich-Graf, J. Burger, C. Kesselheim, M. Senn, T. Shäfer, *Angew. Chem. Int. Ed. Engl.* **1993**, *32*, 1742–1743; *Angew. Chem.* **1993**, *105*, 1850–1852; b) D. Crich, X. Huang, M. Newcomb, *J. Org. Chem.* **2000**, *65*, 523–529; c) D. Crich, K. Ranganathan, S. Neelamkavil, X. Huang, *J. Am. Chem. Soc.* **2003**, *125*, 7942–7947.

[14] a) J.-M. M. Grandjean, D. A. Nicewicz, *Angew. Chem. Int. Ed.* **2013**, *52*, 3967–3971; *Angew. Chem.* **2013**, *125*, 4059–4063; b) M. A. Zeller, M. Riener, D. A. Nicewicz, *Org. Lett.* **2014**, *16*, 4810–4813; c) N. J. Gesmundo, J.-M. M. Grandjean, D. A. Nicewicz, *Org. Lett.* **2015**, *17*, 1316–1319; d) C. L. Cavanaugh, D. A. Nicewicz, *Org. Lett.* **2015**, *17*, 6082–6085.

[15] K. A. Margrey, D. A. Nicewicz, *Acc. Chem. Res.* **2016** *49*, 1997–2006; b) N. A. Romero, D. A. Nicewicz, *J. Am. Chem. Soc.* **2014**, *136*, 17024–17035; c) D. A. Nicewicz, D. S. Hamilton, *Synlett* **2014**, 1191–1196.

[16] a) D. S. Hamilton, D. A. Nicewicz, *J. Am. Chem. Soc.* **2012**, *134*, 18577–18580; b) T. M. Nguyen, D. A. Nicewicz, *J. Am. Chem. Soc.* **2013**, *135*, 9588–9591.

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

[18] Crystallographic data for compound **3a** has been deposited with the Cambridge Crystallographic Data Centre, accession number CCDC 1854258.

[19] 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 ($E_{p/2}$ = +1.74V (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. Japan* **1975**, *48*, 2861−2864.

[20] a) Y. Shigemitsu, D. R. Arnold, *J. Chem. Soc. Chem. Comm.* **1975**, 407–408; b) P. G. Gassman, K. J. Bottorhoff, *Tetrahedron Lett.* **1987**, *28*, 5449–5452; c) A. J. Perkowski, D. A. Nicewicz, *J. Am. Chem. Soc.* **2013**, *135*, 10334−10337.

Angewandte
Communications

Enantioselective Photochemistry

Pablo Bonilla, Yannick P. Rey, Catherine M. Holden, and Paolo Melchiorre* _____ **Page – Page**

Photo-Organocatalytic Enantioselective Radical Cascade Reactions of Unactivated Olefins
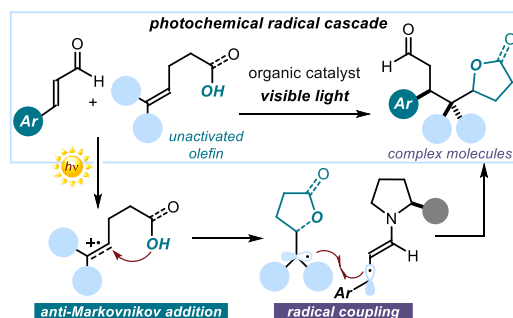
A radical approach. A photochemical asymmetric radical cascade process that converts unactivated olefins and α,β-unsaturated aldehydes into chiral adducts in a single step is reported. This enantioselective strategy, which is triggered by the excited-state reactivity of chiral iminium ion intermediates, combines two sequential radical-based bond-forming events.