

## Melchiorre Research Group



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### Abstract

The group's research interests are broadly based on the use of *enantioselective organocatalysis* (which involves only organic elements in the active principle) for the preparation of chiral molecules. Our strategy relies on the combination metal-free enantioselective organocatalysis and visible light photocatalysis, two powerful strategies of

modern chemical research with extraordinary potential for the sustainable preparation of organic molecules. The main focus is on the discovery and mechanistic elucidation of new enantioselective organocatalytic and photochemical processes that address unsolved problems in synthetic methodology. The final aim is to develop environmentally friendly and innovative catalytic methods that can find widespread use in modern organic synthesis.

### Enantioselective Photo-organocatalysis

Recently, we have started a programme directed toward the use of solar energy to drive synthetically useful organic processes. Our motivation is that using light excitation to bring a molecule from its ground state to an electronically excited state could open new dimensions for chemistry, since the chemical reactivity of electronically excited molecules differs fundamentally from that in the ground state. The 'excited state reactivity' could provide unexplored possibilities for developing processes which cannot be realised using thermal activation. Photochemistry itself is by no means a novel approach, since light-driven reactions have been observed for as long as chemistry has been studied. Still, we believe that reconsidering photochemical reactivity using the knowledge, perspective, and tools of a modern organic chemist will offer new opportunities for asymmetric catalytic synthesis, particularly when faced with the universal need for more environmentally responsible chemical processes.

A central theme of modern stereoselective chemistry is the identification of strategies for exploring the untapped potential of enantioselective photocatalysis. In this context, our laboratory recently introduced a unique approach based on the ability of chiral enamines, key intermediates in thermal organocatalytic asymmetric processes, 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 photosensitisers, relied upon the formation of photoactive electron donor-acceptor (EDA) complexes **II**, arising from the ground state association of the electron-rich enamine **I** with electron-deficient alkyl bromides **2** (Figure 1).

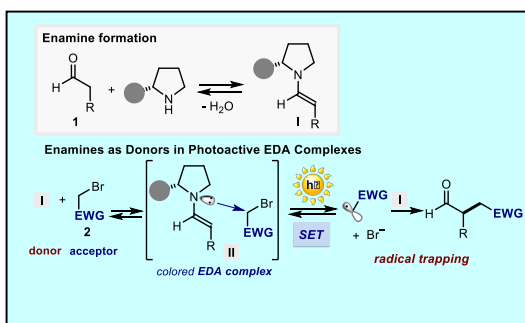


Figure 1. *The asymmetric photochemical  $\alpha$ -alkylation of aldehydes: enamines can drive the photochemical generation of radicals by inducing the formation of ground state, photoactive EDA complexes II; Nature Chem. 2013, 5, 750-756.*

Visible light irradiation of the colored EDA complex induced a single electron transfer (SET), allowing access to radical species under mild conditions. The strategy was used to develop a highly stereoselective light-driven  $\alpha$ -alkylation of aldehydes **1** with different classes of alkyl halides **2**, a synthetically useful catalytic transformation, which cannot be realised through thermal reactivity.

Recently, we demonstrated that the photochemical activity of chiral enamines and their potential for light-induced radical generation is not limited to the formation of ground-state EDA complexes. We unveiled the hidden ability of enamines **I**, generated by condensation of aldehydes **1** with a commercially available chiral secondary amine catalyst, to reach an electronically excited state (**I**<sup>\*</sup>) upon simple light absorption and then to act as effective photosensitizers. At the same time, such photochemical behavior conjugates with the enamine ability of stereoselectively intercepting the reactive radicals generated from the sensitization of organic halides (Figure 2). This novel photo-organocatalytic mechanism overcomes the need for an external photoredox catalyst. We used it to develop the enantioselective alkylation of aldehydes with bromo malonates **2c**.

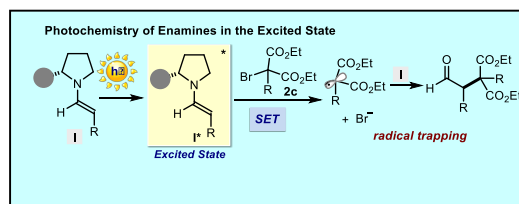


Figure 2. *Enantioselective  $\alpha$ -alkylation of aldehydes: enamines **I** can drive the photochemical generation of radicals by acting as a photoinitiator upon direct light excitation; J. Am. Chem. Soc. 2015, 137, 6120-6123.*

Recently, we further advanced the EDA complex activation concept to develop a visible-light driven enantioselective perfluoroalkylation of  $\beta$ -ketoesters **3** (Figure 3). The photo-organocatalytic process, which occurs at ambient temperature and utilizes readily available substrates and catalysts, is triggered by the photochemical activity of *in situ* generated electron donor-acceptor (EDA) complexes **IV**, arising from the association of chiral enolates **III** and perfluoroalkyl iodides **4**. From a synthetic perspective, the chemistry provides straightforward access to highly valuable chiral ketoester products **5** bearing a perfluoroalkyl-containing quaternary stereocenter. Since fluorine-containing functional groups can greatly alter the intrinsic properties of organic compounds, the catalytic production of

perfluoroalkyl-containing stereogenicity is a centrally important methodological goal. Conceptually, this study demonstrated that chiral enolates **III**, generated upon deprotonation of **3**, could serve as suitable donors for EDA complex formation.

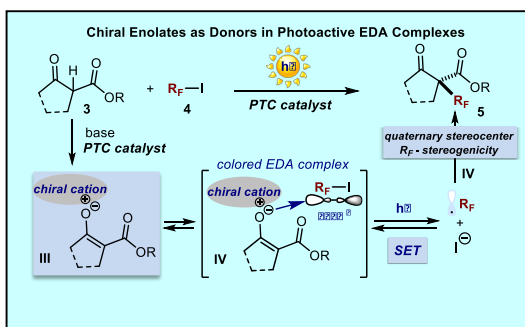


Figure 3. Photo-organocatalytic enantioselective perfluoroalkylation of  $\beta$ -ketoesters; *J. Am. Chem. Soc.* **2015**, *137*, 5678–5681.

Further exploiting the EDA complex activation strategy, we have also developed a straightforward method for the direct benzylation and phenacylation of substituted 1H-indoles **6**, which requires mild conditions in order to proceed (Figure 4). Evidence has been provided that the chemistry is driven by the photochemical activity of EDA complexes, easily formed upon mixing readily available indoles **6** and electron-accepting benzyl or phenacyl bromides **7**. In addition, the isolation and X-ray characterization of an EDA complex **V** relevant to the

photochemical alkylation accounted for additional mechanistic insights. This study establishes the potential of indoles to actively participate in the photo-excitation of substrates while promoting synthetically useful transformations.

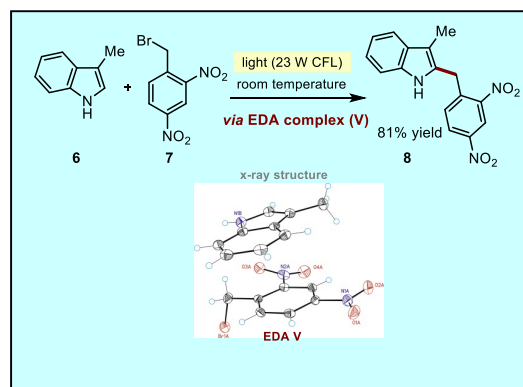


Figure 4 – EDA-activation strategy in the photochemical indole alkylation; *Angew. Chem. Int. Ed.* **2015**, *54*, 1485–1489.

We believe that our results corroborate the idea that the photochemistry of EDA complexes, formed upon aggregation of organic substrates, may provide a general reactivity framework for the design of unprecedented photochemical transformations, expanding the way chemists think about making chiral molecules.

## Articles

“X-Ray Characterization of an EDA Complex which Drives the Photochemical Alkylation of Indoles”

*Angew. Chem. Int. Ed.* (2015) *54*, 1485–1489  
Sandeep R. Kandukuri, Ana Bahamonde, Indranil Chatterjee, Igor D. Jurberg, Eduardo C. Escudero-Adán, Paolo Melchiorre

“Photochemical Direct Perfluoroalkylation of Phenols”

*Tetrahedron* (2015) *71*, 4535–4542  
Giacomo Filippini, Manuel Nappi, Paolo Melchiorre

“Computational Study with DFT and Kinetic Models on the Mechanism of Photoinitiated Aromatic Perfluoroalkylations”

*Org. Lett.* (2015) *17*, 2676–2679  
Victor M. Fernández-Alvarez, Manuel Nappi, Paolo Melchiorre, Feliu Maseras

“Photo-organocatalytic Enantioselective Perfluoroalkylation of  $\beta$ -Ketoesters”  
*J. Am. Chem. Soc.* (2015) *137*, 5678–5681  
Łukasz Woźniak, John J. Murphy, Paolo Melchiorre

“Enantioselective Organocatalytic Alkylation of Aldehydes and Enals Driven by the Direct Photoexcitation of Enamines”  
*J. Am. Chem. Soc.* (2015) *137*, 6120–6123  
Mattia Silvi, Elena Arceo, Igor D. Jurberg, Carlo Cassani, Paolo Melchiorre

“Diastereodivergent Organocatalysis for the Asymmetric Synthesis of Chiral Annulated Furans”  
*Chem. Sci.* (2015) *6*, 4242–4246  
Charlie Verrier, Paolo Melchiorre

“Light Opens Pathways for Nickel Catalysis”  
*Nature* (2015) *524*, 297–298 (*News & Views*)  
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