

Melchiorre Research Group



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Laboratory Engineer: Eva Raluy

Visiting Students: Alberto Vega / Bryan Matsuura

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Abstract

The group's research interests are broadly based on the use of *asymmetric organocatalysis* (which involves only organic elements in the active principle) to create new synthetic opportunities and conceptual perspectives for successfully attacking major challenges connected with the preparation of chiral molecules.

The main focus is on the discovery and mechanistic elucidation of new asymmetric 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 exciting 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, arising from the ground state association of the electron-rich enamine with electron-deficient alkyl bromides (Figure 1). 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 α -alkylation of aldehydes with different classes of alkyl halides, a synthetically useful yet challenging catalytic transformation, which cannot be realised through thermal reactivity.

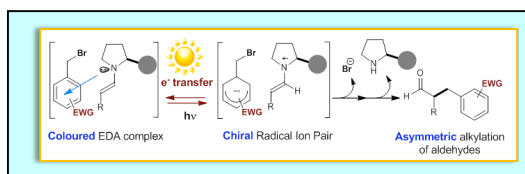


Figure 1 – *The asymmetric photochemical α -alkylation of aldehydes under enamine activation*; *Nature Chem.* **2013**, *5*, 750-756.

We then wondered if the catalytic principles inherent to the photochemical strategy depicted in Figure 1 could be successfully translated to ketonic systems, thereby providing an unreported catalytic method for their direct and enantioselective α -alkylation. Along this line, we successfully developed a direct methodology for the intermolecular asymmetric alkylation of cyclic ketones with alkyl bromides, leading to the formation of the α -alkylated products with high levels of regio-, diastereo-, and enantioselectivity (Figure 2). The process is catalyzed by a simple chiral primary amine and is photochemical in nature, since it requires light in order to proceed.

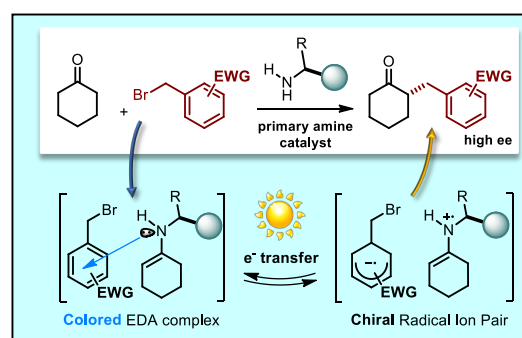


Figure 2 – *Enantioselective direct α -alkylation of cyclic ketones by means of photo-organocatalysis*; *Chem. Sci.* **2014**, *5*, 2438-2442.

Mechanistically, we found that the photochemical activity of in-situ generated chiral EDA complexes can drive the stereoselective intermolecular α -alkylation of ketones with alkyl halides. The success of this photochemical, metal-free asymmetric process (Figure 3) relied upon the formation of colored EDA complexes III. These are molecular aggregations, which occurred in the ground state upon association of the transiently generated electron-rich enamine II [the donor, formed from the condensation of a ketone 1 (R^1 = alkyl) and a chiral primary amine C (R = H)] with the electron-accepting alkyl bromide 2. Visible light irradiation of the colored EDA complex III induced an electron transfer to occur, which allowed access to open-shell reactive species under very mild conditions. Facile fragmentation of the bromide anion from the ion pair IV productively rendered the positively charged intermediate V, which brought two radicals within a geometrically restricted chiral space and in very close proximity. This condition facilitated a stereocontrolled radical combination within the solvent cage to form a new carbon-carbon bond while forging the α -carbonyl stereogenic center of the final product 3.

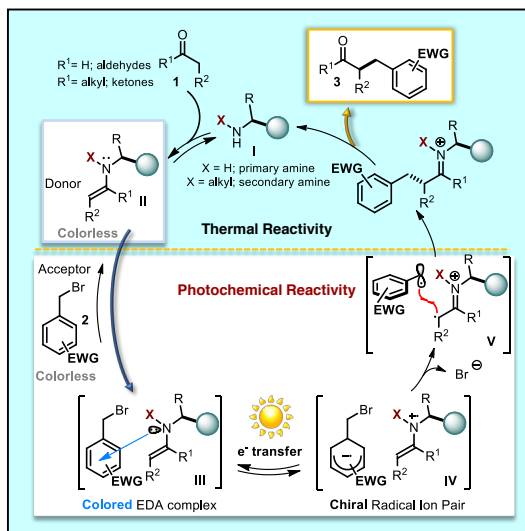


Figure 3 - Mechanistic proposal for the photochemical organocatalysed direct α -alkylation of ketones (R^1 = alkyl): exploiting the photochemical activity of the in-situ generated chiral EDA (electron donor-acceptor) complexes III to access radical reactivity patterns; EWG: electron withdrawing group; filled grey circles represent the chiral fragment of the aminocatalyst scaffold.

The EDA-complex activation strategy was also exploited to develop an operationally simple strategy for the direct aromatic perfluoroalkylation and trifluoromethylation of α -cyano arylacetates (Figure 4). The chemistry provides a very mild way to directly install a perfluoroalkyl fragment into aromatic compounds. This metal-free approach, which occurs at ambient temperature, in a relatively short period of time (4-12 hours), and under the visible light illumination of a household fluorescent bulb, is driven by the photochemical activity of in situ generated EDA complexes, formed by the interaction of transiently generated enolates and perfluoroalkyl iodides.

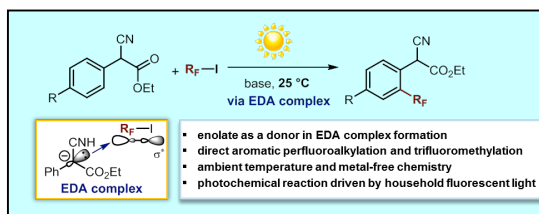


Figure 4 – Photochemical Aromatic Perfluoroalkylation of α -Cyano Arylacetates; *Angew. Chem. Int. Ed.* **2014**, *53*, 4921-4925.

Conceptually, this study establishes the possibility for enolates to work as suitable donors in EDA formation. 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 organic molecules.

Photo-organocatalysis and energy transfer

A major aim of our research program is to combine visible light photocatalysis and metal-free organocatalytic processes, powerful strategies of modern chemical research, to enable fundamental synthetic processes to be conducted in an environmentally respectful way. One specific area of photochemistry with great potential for synthetic innovations, in particular in conjunction with the reactivity of organic molecules, is photosensitisation. Although the utility of UV-absorbing organic chromophores as triplet photosensitisers has been well-established for decades, synthetic applications of triplet sensitisation induced by low-energy photons have found limited applications in synthetic chemistry so far.

We recently exploited the capability of simple organic molecules to act as triplet sensitisers, so as to efficiently realise fundamental transformations of organic chemistry. Specifically, we developed a methodology that allows the intermolecular atom transfer radical addition (ATRA) of a variety of haloalkanes onto olefins to be performed under unprecedentedly mild conditions.

Atom transfer radical addition to alkenes provides a clear demonstration of the utility of radical reactivity in organic synthesis. The chemistry, pioneered by Kharasch almost 70 years ago, has evolved to become an atom-economical and effective way to functionalise easily available olefinic substrates. The addition of an organic halide across a carbon-carbon double bond generates a new C-C and C-X bond (X = halogen) in a single operation. ATRA proceeds through a radical chain propagation mechanism (Figure 5a), and the formation of the radicals from alkyl halides classically requires stoichiometric amounts of initiators, such as triethyl borane, or potentially explosive oxidants, and high reaction temperatures. Recently, metal-mediated catalysis, including metal-based photoredox catalysis driven by light, has further expanded the potential of the ATRA technology. However, we still need a suitable approach for generating radical intermediates under mild reaction conditions which avoids expensive transition-metal catalysts or toxic reagents.

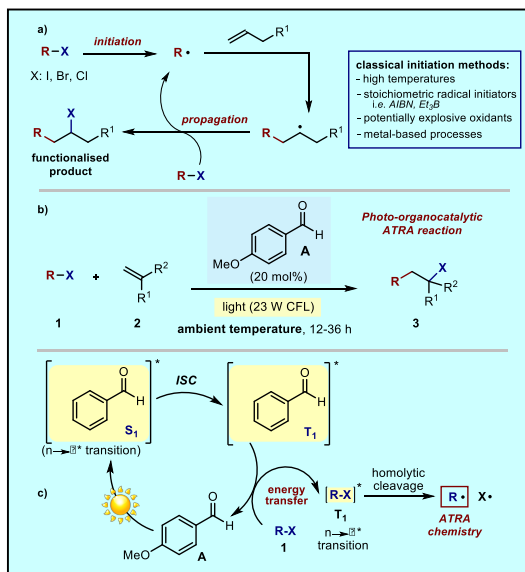


Figure 5 – The atom transfer radical addition (ATRA) technology. a) The classical radical chain mechanism of ATRA and typical harsh conditions required for radical generation. b) The discovered photochemical ATRA catalyzed by a simple organic molecule under mild conditions. c) The proposed triplet sensitization mechanism which drives the photo-organocatalytic ATRA reaction; *Angew. Chem. Int. Ed.* **2014**, *53*, 12064-12068.

Articles

“Synthesis of Cyclopropane Spirooxindoles by means of a Vinylogous Organocatalytic Cascade”

Asian J. Org. Chem. (2014) *3*, 466-469

R. César da Silva, I. Chatterjee, E. Escudero-Adán, M. Weber Paixao, P. Melchiorre

“Enantioselective Direct α -Alkylation of Cyclic Ketones by means of Photo-Organocatalysis”

Chem. Sci. (2014) *5*, 2438-2442

E. Arceo, A. Bahamonde, G. Bergonzini, P. Melchiorre

“Asymmetric Vinylogous Diels–Alder Reactions Catalyzed by a Chiral Phosphoric Acid”

Angew. Chem. Int. Ed. (2014) *53*, 2997-3000 X.

Tian, N. Hofmann, P. Melchiorre

We have found that an organic molecule as simple as p-anisaldehyde **A** efficiently catalyses the intermolecular atom transfer radical addition (ATRA) of a variety of haloalkanes onto olefins, one of the fundamental carbon-carbon bond-forming transformations of organic chemistry (Figure 5b). The reaction requires exceptionally mild conditions in order to proceed, since it occurs at ambient temperature and under illumination by a readily available fluorescent light bulb. Initial investigations support a mechanism whereby the aldehydic catalyst photochemically generates the reactive radical species by sensitization of the organic halides via an energy transfer pathway (Figure 5c). The sensitisation brings the alkyl halides **1** to the excited triplet, inducing an $n \rightarrow \sigma^*$ transition which would result in a rapid homolytic dissociation of the C-X bond in **1**.

The ability of a simple aldehyde to act as an effective triplet sensitizer under CFL light illumination can open new avenues for reaction design in the field of radical processes.

“Metal-Free Photochemical Aromatic Perfluoroalkylation of α -Cyano Arylacetates”

Angew. Chem. Int. Ed. (2014) *53*, 4921-4925 M.

Nappi, G. Bergonzini, P. Melchiorre

“Photo-Organocatalysis of Atom-Transfer Radical Additions to Alkenes”

Angew. Chem. Int. Ed. (2014) *53*, 12064-12068

E. Arceo, E. Montroni, P. Melchiorre