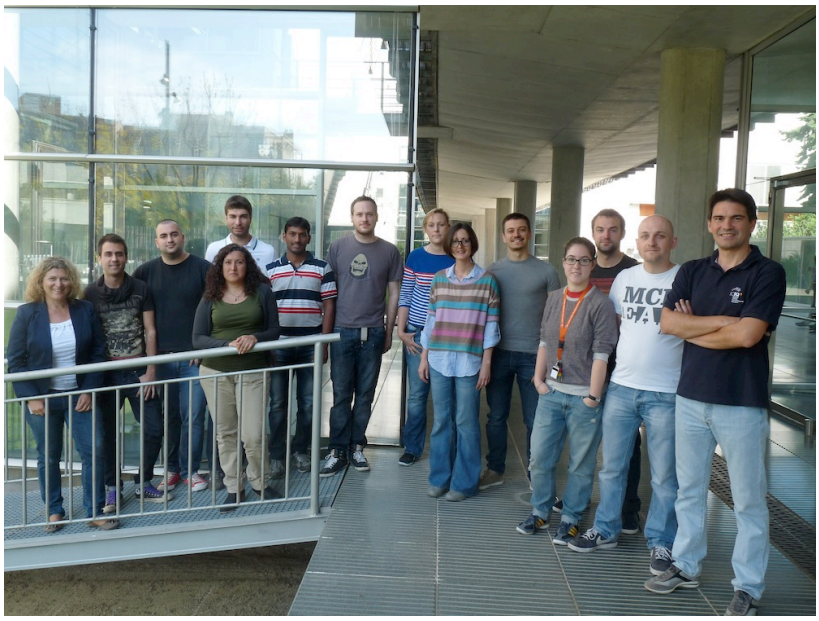
Melchiorre Research Group



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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.

Targeting Structural and Stereochemical Complexity by Cascade Catalysis

Finding cost-effective and sustainable synthetic ways to reproduce the rich structural diversity and complexity of natural molecules has always captured the attention of chemists, especially in relation to biologically active compounds.
The emerging field of organocatalytic cascade reactions has recently provided a way of achieving stereochemical and molecular complexity while addressing the requests for atom and step economy or protecting-group-free synthesis.
We recently developed a vinylogous cascade reaction for the one-step preparation of highly enantioenriched spirocyclopentane oxindoles (Figure 1). A crucial factor was the ability of a cinchona primary amine of type **A** to propagate the aminocatalytic activation modes through the conjugated π-system of β-substituted cyclic dienones **1** while transmitting the stereochemical information at distant positions. The cascade, which is based on a δ-addition/aldolization sequence, is initiated by a rare example of an organocatalytic 1,6-addition of a carbon-centered nucleophile. The inspiration for this approach arose from our previous studies (see *Angew. Chem. Int. Ed.* **2012**, *51*, 6439-6442) where we established that the cinchona-based primary amine **A** can condense with β-substituted cyclic dienones **1** facilitating the formation of an extended iminium ion intermediate **I**, with an enhanced electrophilic character at the δ-carbon atom. The resulting vinylogous iminium ion activation accounted for a highly δ-site- and enantioselective 1,6-addition of alkyl thiols. Expanding upon this precedent, we realized the cascade reaction in Figure 1 to assemble complex molecules in a single step while setting remote stereocenters.

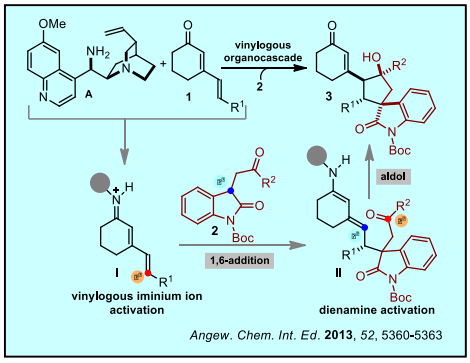

Fig. 1 - *Vinylogous organocascade catalysis: 1,6-addition/aldol sequence driven by vinylogous iminium ion/dienamine activation; Angew. Chem. Int. Ed.* **2013,** *52*, 5360-5363

Substrate **2**, which is characterized by a dichotomous reactivity profile, was key to realizing this design plan. The 3-substituted oxindole **2** was chosen because of its ability to first act as a carbon-centered nucleophile and then to develop, after the δ-site 1,6-addition, an electrophilic behavior. The pendant carbonyl moiety within the transiently generated nucleophilic dienamine intermediate **II**, drove an intramolecular aldol reaction resulting in a fast cyclization. The product of the vinylogous cascade reaction was a complex spirocyclopentane oxindole **3**, bearing four contiguous stereocenters and a preserved α,β-unsaturated carbonyl system. Highly substituted carbocyclic spirooxindole units are featured in a large number of natural products as well as medicinally relevant compounds with important biological activities.
Our study has been published in *Angew. Chem. Int. Ed.* **2013**, 52, 5360–5363.
Building upon the concept of vinylogous reactivity, we have developed another aminocatalytic triple vinylogous cascade reaction, yielding valuable spiro-oxindolic cyclohexane derivatives. The three-component domino process proceeds by way of an aminocatalyzed Michael addition/1,6-addition/vinylogous aldolization sequence which combines two intermolecular and one intramolecular bond-forming event while forging six contiguous stereogenic centers with high fidelity. Key to this study was the ability to control the δ-site selectivity of an asymmetric 1,6-addition to linear 2,4-dienals, which was achieved by positioning a steering group within the β-dienal architecture (Figure 2).

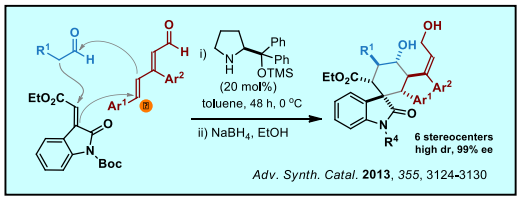

Fig. 2 - *The vinylogous triple cascade, which combines two intermolecular and one intramolecular bond-forming event to forge six contiguous stereocenters*

Following our desire to streamline the synthesis of nature-inspired complex chiral molecules, we have developed a novel aminocatalytic vinylogous cascade reaction, yielding valuable tetrahydrofuran spirooxindole derivatives (Figure 3). At the heart of our study was the use of dioxindole (3-hydroxy-2-oxindole, **4**), a simple molecule that we recently found as characterized by a strong nucleophilic behavior (see *Angew. Chem. Int. Ed.* **2012,** *51*, 971–974).

The chemistry is based on a rare example of asymmetric 1,6-addition to linear 2,4-dienals proceeding with high δ-site and stereo-selectivity. Spectroscopic conformational analyses were crucial to understanding how the structural features of the 2,4-dienal substrate **5** could be modulated to encode for a given molecular topology of the transient vinylogous iminium ion intermediate, formed upon condensation with the chiral aminocatalyst. This was critical to the rational design of an optimal linear dienal, which allowed for the development of a highly regio- and stereoselective 1,6-addition/*oxa*-Michael cascade with dioxindole **4**, directly leading to tetrahydrofuran spirooxindole derivatives **6.** In addition, we have used the trimethyl silyl moiety as a traceless directing group to achieve δ-site selectivity, providing a formal 1,6-addition of geometrically unbiased, linear dienals (Fig. 3d).

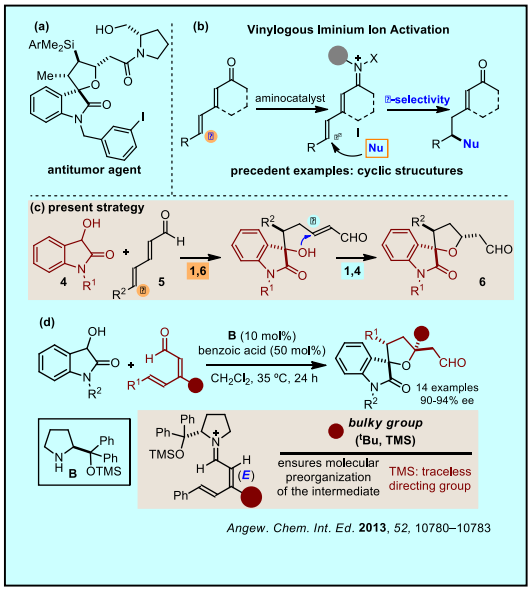

Fig. 3 - *a) A biologically active tetrahydrofuranyl spirooxindole; Ar: anisyl. (b) The vinylogous iminium ion strategy; X = H or alkyl. (c) The proposed design plan for vinylogous organocascade catalysis: 1,6-addition/oxa-Michael sequence driven by vinylogous iminium ion/iminium ion activation. (d) The developed system; Angew. Chem. Int. Ed.* **2013,** *52,* 10780 –10783.

Synthetically, this strategy addresses a problem of fundamental importance in enantioselective reaction design, namely the formation of multiple stereogenic centers remote from the catalyst's point of action. From a conceptual point of view, we further highlight how mechanistic studies are key to reaction development. Our study was published in *Angew. Chem. Int. Ed.* **2013,** *52,* 10780–10783.

Asymmetric Catalysis of Photochemical Reactions Driven by Visible Light

Recently, we have started a programme directed toward the use of solar energy to drive synthetically useful organic processes. Specifically, we have addressed a sought-after problem in the realm of enantioselective photochemistry, providing an unprecedented yet simple strategy to bias the stereochemical outcome of catalytic photochemical reactions driven by visible light. To achieve this, we demonstrated for the first time that chiral enamines, key intermediates of organocatalytic asymmetric processes in the ground state, have the potential to actively participate in the photo-excitation of substrates, without the need for an external photosensitiser. 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 4). Our approach could be used to enable transformations that, with thermal mechanisms, are extremely difficult; for example, forging all-carbon quaternary stereocentres with high fidelity, or targeting remote stereocentres. This demonstrates that the chemistry could provide a general reactivity framework for conceiving other enantioselective catalytic photoreactions.

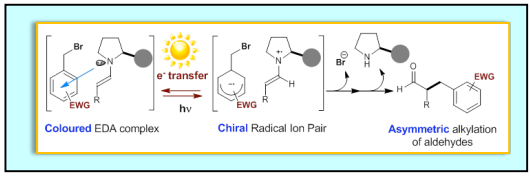

Fig. 4 – *The asymmetric photochemical a-alkylation of aldehydes under enamine activation; Nature Chem.* **2013,** *5,* 750-756.

Mechanistically, we found that the photochemical activity of in-situ generated chiral electron donor-acceptor (EDA) complexes can drive the stereoselective intermolecular α-alkylation of unmodified aldehydes with alkyl halides. The success of this photochemical, metal-free asymmetric process (Figure 5) 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 an aldehyde **1** (R^1= H) and a chiral secondary amine **C** (R = alkyl)] 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**.

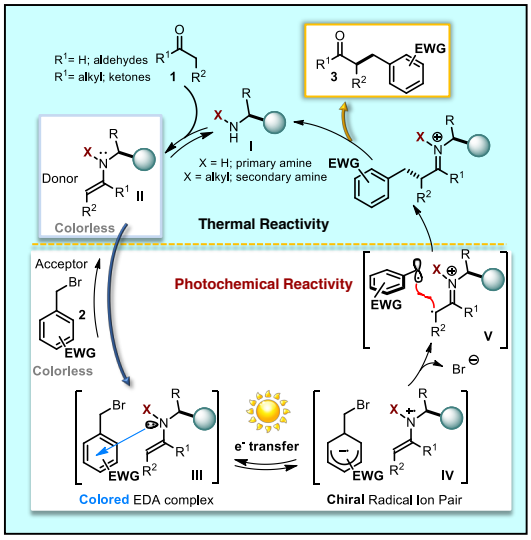

Fig. 5 - *Mechanistic proposal for the photochemical organocatalyzed direct α-alkylation of aldehydes (R^1= H): exploiting the photochemical activity of the in-situ generated chiral EDA (electron donor-acceptor) complexes **III** to access radical reactivity patterns; EWG: electron withdrawing group; filled grey circles represent the chiral fragment of the aminocatalyst scaffold.*

From a general perspective, we have found a bridge (donor-acceptor interactions) to connect two powerful fields of molecule activation: asymmetric organocatalysis and photochemistry, challenging the current perception that photochemistry is too unselective to parallel the impressive levels of efficiency reached by the asymmetric catalysis of thermal reactions. Our strategy differs from but complements the approach of photoredox catalysis, a fast developing area of modern chemical research. On this basis, our findings have the potential to immediately impact the organic chemistry community, particularly when considering the universal need for more sustainable and environmentally responsible chemical processes

Articles

"Asymmetric Vinylogous Aldol Reaction via H-Bond-Directing Dienamine Catalysis"
Org. Lett. (**2013**), *15,* 220–223
D. Bastida, Y. Liu, X. Tian, E. Escudero-Adán, P. Melchiorre

"Synthesis of 9-amino(9-deoxy)epi cinchona alkaloids, general chiral organocatalysts for the stereoselective functionalization of carbonyl compounds"
Nature Protocols (**2013**), *8,* 325-344
C. Cassani, R. Martín-Rapún, E. Arceo, F. Bravo, P. Melchiorre

"When Asymmetric Aminocatalysis Meets the Vinylogy Principle"
Chem. Commun. (**2013**), *49,* 4869-4883
I. Jurberg, I. Chaterjee, R. Tannert, P. Melchiorre

"Control of Remote Stereochemistry in the Synthesis of Spirocyclic Oxindoles by Means of Vinylogous Organocascade Catalysis"
Angew. Chem. Int. Ed. (**2013**), *52,* 5360–5363
X. Tian, P. Melchiorre

"Controlling the Molecular Topology of Vinylogous Iminium Ions by Logical Substrate Design: Highly Regio- and Stereoselective Aminocatalytic 1,6-Addition to Linear 2,4-Dienals"
Angew. Chem. Int. Ed. (**2013**), *52,* 10780-10783
M. Silvi, I. Chatterjee, Y. Liu, P. Melchiorre

"A Mechanistic Rationale for the 9-Amino(9-deoxy)epi Cinchona Alkaloids Catalyzed Asymmetric Reactions via Iminium Ion Activation of Enones"
J. Am. Chem. Soc. (**2013**), *135*, 9091-9098
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“Vinylogous Organocatalytic Triple Cascade Reaction: Forging SixStereocenters in Complex Spiro Oxindolic Cyclohexanes”
Adv. Synth. Catal. (**2013**), *355,* 3124–3130
I. Chatterjee, D. Bastida, P. Melchiorre

“Photochemical activity of a key donor–acceptor complex can drive stereoselective catalytic α-alkylation of aldehydes”
Nature Chem. (**2013**), *5*, 750-756
E. Arceo, I. D. Jurberg, A. Álvarez-Fernández, P. Melchiorre