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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 organocatalysis and visible light photocatalysis, two powerful strategies of modern chemical research with great 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 Organocatalysis in the Excited State

Our research aims at using visible light to promote synthetically useful synthetic 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 reactivity of electronically excited molecules differs fundamentally from that in the ground state. The '*excited state reactivity*' could provide unexplored possibilities for developing processes that cannot be realised using thermal activation.

A central theme of modern stereoselective chemistry is the identification of strategies for exploring the unexpressed potential of enantioselective photocatalysis. In this context, our laboratory recently introduced a unique strategy based on the ability of chiral organocatalytic intermediates to actively participate in the photoexcitation of substrates. This approach uses a chiral organic catalyst to transiently form a photoactive intermediate that, on excitation, can activate substrates without the need for an external photocatalyst. At the same time, the chiral organocatalytic intermediate can provide effective stereochemical control over the ensuing bond-forming process. In this strategy, stereoinduction and photoactivation conjugate in a sole chiral organocatalyst

In this vein, we recently established that chiral iminium ions can unveil a rich photochemistry upon light excitation (Figure 1). A crucial aspect is that the condensation of the chiral amine catalyst **1** with aromatic enals **2** converts an achromatic substrate into a coloured iminium ion **I**. Selective excitation with a violet-light-emitting diode (LED) brings this electron-poor intermediate into an electronically excited state (**I***). This turns a merely electrophilic species into a strong oxidant, which can trigger the formation of radicals through SET oxidation of organic silanes **3**. The latter event furnishes the chiral 5π-electron β-enaminyl radical intermediate **II** along with the neutral radical **III**, which is generated upon irreversible fragmentation of the carbon–silicon bond. A stereocontrolled intermolecular coupling of the chiral β-enaminyl radical **II** and **III** then forges the stereogenic centre within the β-functionalised aldehyde product **4**. Importantly, the employed organic trimethylsilane reagents **3** are non-nucleophilic substrates, which are recalcitrant to classical conjugate addition manifolds. Thus, the excitation of chiral iminium ions enables transformations that could not be realised within the framework of conventional catalytic asymmetric methodologies.

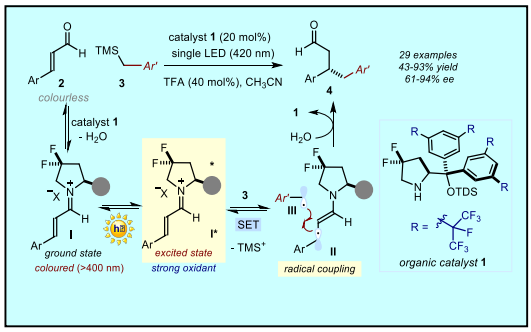

Figure 1. *Exploiting the direct photoexcitation of transiently generated chiral iminium ions **I** to enable stereocontrolled β-alkylation of enals with non-nucleophilic alkyl silanes **3**; the chiral β-enaminyl radical **II**, emerging from the SET reduction of the excited iminium ion **I***, which acts as a strong oxidant, governs the stereocontrolled radical coupling to afford products **4**. SET = single electron transfer; TMS: trimethylsilyl; the grey circle represents the chiral organic catalyst scaffold.*
Nature Chem. ***2017****, 9, 868-873.*

We have then used the photochemistry of iminium ions for the direct stereoselective installation of alkyl fragments at the β-carbon of enals (Figure 2). The direct introduction of sp^3 carbon fragments at the β position of α,β-unsaturated aldehydes is generally complicated by competing 1,2-addition manifolds. Previous catalytic enantioselective conjugate addition methods, based on the use of organometallic reagents or ground-state iminium ion activation, could not provide general and efficient solutions. We have used the light excitation of chiral iminium ions, which turns them into strong oxidants, to generate C(sp^3)-centered radicals from 4-alkyl-1,4-dihydropyridines **5**. The ensuing stereocontrolled radical pathway directly installs alkyl fragments exclusively at the β-carbon of enals providing adducts **6**.

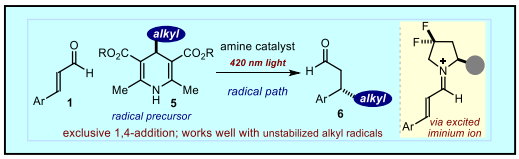

Figure 2. *Radical-based strategy for the direct and stereoselective installation of alkyl fragments at the β-carbon of enals via excited iminium ion catalysis. SET: single-electron transfer. ACS Catal. DOI: 10.1021/acscatal.7b03788.*

Conceptually, this study further demonstrate how the light excitation of organic molecules can unlock unconventional reactivity manifolds, switching on novel functions that are unavailable to ground-state reactivity. In this case, absorption of violet light turns chiral iminium ions, which are primarily understood as electrophiles in their ground state, into strong oxidants. We used this photochemical behavior to trigger a stereocontrolled radical pathway.

Recently, we have found that the light excitation of 4-alkyl-1,4-dihydropyridines (alkyl-DHPs) **7** can unlock unconventional reactivity manifolds. Alkyl-DHPs are primarily understood as hydride sources in their ground state. We found that, by directly exciting them with a violet LED, they become strong reducing agents that can activate reagents via single-electron transfer manifolds while undergoing a homolytic cleavage to generate C(sp^3)-centered radicals. This light-triggered dual-reactivity profile was integrated into a nickel catalytic cycle to enable C(sp^2)–C(sp^3) cross-coupling reactions without the need for an external photoredox catalyst (Figure 3).

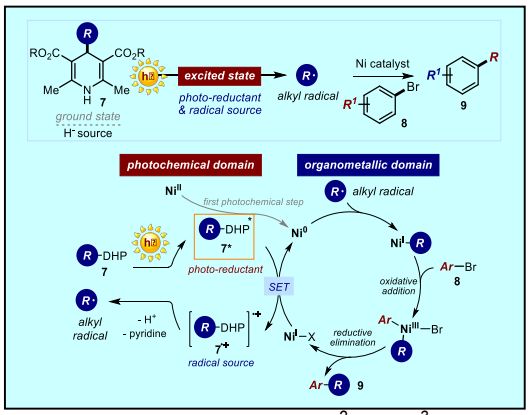

Figure 3. *Nickel-catalyzed C(sp^2)–C(sp^3) cross-coupling process enabled by the photochemical activity of alkyl-DHPs **7** and the proposed mechanism.*
*Angew. Chem. Int. Ed. **2017**, 56,15039–15043.*

In a different study, we evaluated the light excitation of 2-alkyl-benzophenones **10** to afford transient hydroxy-*o*-quinodinomethanes **A** (Figure 4). This is a historical photochemical process established in 1961. Here, we have used the high reactivity of **A** and its propensity to engage in an intermolecular aldol process facilitated by a readily available chiral amido-thiourea catalyst. This light-triggered organocatalytic strategy has allowed the desymmetrization of achiral 2-fluoro substituted cyclopentane-1,3-diketones **11**. Key for success is the ability of the catalyst to choose between enantiotopic carbonyl groups of **11**, facilitating a dissymmetric intermolecular aldol process. The resulting symmetry-breaking process generates two stereocenters simultaneously, and forges a C-F stereogenic unit far from the reaction site.

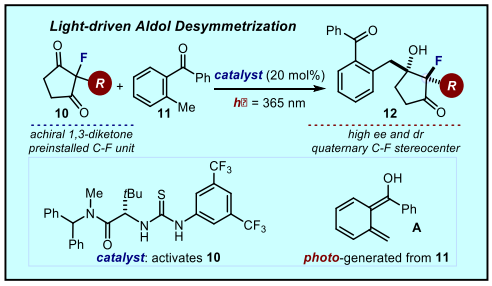

Figure 4. *Photochemical organocatalytic desymmetrization aldol process.*
*Angew. Chem. Int. Ed. **2017**, 56, 1875–11879.*

From a synthetic perspective, the chemistry provides unprecedented and straightforward access to highly valuable chiral 2-fluoro-3-hydroxycyclopentanones **12**. Since fluorine-containing functional groups can greatly alter the intrinsic properties of organic compounds, the catalytic production of fluorine-containing stereogenicity is a centrally important methodological goal. Conceptually, this study documents a novel catalytic strategy to stereoselectively construct fluorine-containing quaternary stereocenters, demonstrating that the desymmetrization of centrosymmetric compounds can be used for this purpose.

Articles

"Visible-Light Excitation of Iminium Ions Enables the Enantioselective β-Alkylation of Enals"
Nature Chem. (**2017**) *9,* 868–873
Mattia Silvi, Charlie Verrier, Yannick Rey, Luca Buzzetti, Paolo Melchiorre

"Studies on the Enantioselective Iminium Ion Trapping of Radicals Triggered by an Electron-Relay Mechanism"
J. Am. Chem. Soc. (**2017**) *139,* 4559-4567
Ana Bahamonde, John J. Murphy, Marika Savarese, Erik Bremond, Andrea Cavalli, Paolo Melchiorre

"Radical-based C-C Bond-Forming Processes Enabled by the Photoexcitation of 4-Alkyl-1,4-dihydropyridines"
Angew. Chem. Int. Ed. (**2017**) *56*, 15039–15043
Luca Buzzetti, Alexis Prieto, Sudipta R. Roy, Paolo Melchiorre

"Forging Quaternary Fluorine Stereocenters by a Light-driven Organocatalytic Aldol Desymmetrization Process"
Angew. Chem. Int. Ed. (**2017**) *56*, 11875–11879
Sara Cuadros, Luca Dell'Amico, Paolo Melchiorre

"Enantioselective Formal α-Methylation and α-Benzylation of Aldehydes by Means of Photo-Organocatalysis"
Angew. Chem. Int. Ed. (**2017**) *56*, 4447–4451
Giacomo Filippini, Mattia Silvi, Paolo Melchiorre

"Light-Driven Enantioselective Organocatalytic β-Benzylation of Enals"
Angew. Chem. Int. Ed. (**2017**) *56*, 3304–3308
Luca Dell'Amico, Victor M. Fernández-Alvarez, Feliu Maseras, Paolo Melchiorre

"Light-triggered Enantioselective Organocatalytic Mannich-type Reaction"
Synthesis (**2017**) *49,* 76-86
Hamish B. Hepburn, Giandomenico Magagnano, Paolo Melchiorre