NOVEL PHOTOCATALYTIC APPROACHES FOR ECO-SUSTAINABLE SYNTHESIS

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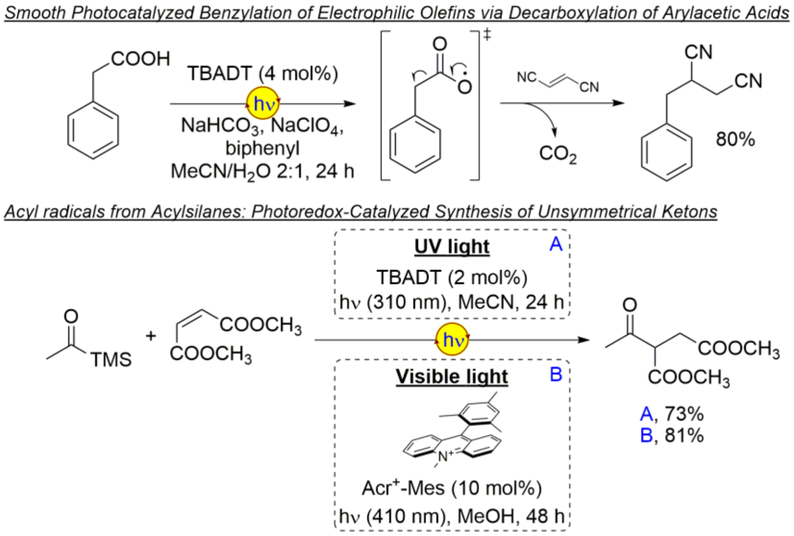
Over the past decades, photochemical synthesis, *i.e.* organic synthesis that uses light as source of energy to break and forge bonds, has vehemently re-emerged as an eco-sustainable methodology in organic chemistry. Thanks to the possibility to excite a single component in a complex reaction mixture and the peculiar reactivity of the so-formed excited states, photochemistry is very attractive for researchers from both academia and industry. An added value to this activation manifold is represented by photo*catalysis*: in these reactions, the substrate does not absorb light directly, instead low-energy light is absorbed by a purposely added molecule (photocatalyst, PC) that exploits this energy for the activation of an organic substrate. This activation step can occur via three different mechanisms: Single-Electron Transfer (SET), Hydrogen-Atom Transfer (HAT) or Energy Transfer (ET). During my three years of Ph.D. I decided to explore the potentialities of each approach for the generation of highly reactive intermediates under extremely mild conditions and the ensuing development of novel eco-sustainable synthetic protocols.

Photocatalysis via Single-Electron Transfer (SET).

During my first year of Ph.D. I mainly focused on photocatalysis via SET. In one study, I hypothesized that α-arylacetic acids could serve as precursors of benzyl radicals (upon photocatalyzed mono-electronic oxidation) to achieve the benzylation of electron-poor olefins (see Chart 1, top).[1] Accordingly, I decided to test a well-known tungsten-based photocatalyst, TBADT (tetrabutylammonium decatungstate, $(n\text{-Bu}_4\text{N})_4[\text{W}_{10}\text{O}_{32}]$) under UV light irradiation (λ_{exc} = 310 nm). My decision was based on the fact that the excited state of TBADT owns a remarkably high redox potential (~ +2.4 V vs SCE), which makes it prone for the photocatalytic oxidation of organic compounds.[2] To further promote the oxidation of α-arylacetic acids, we found that the addition of a mild base ($NaHCO_3$) to generate *in situ* the corresponding carboxylates, as well as the use of a salt ($NaClO_4$) to increase the ionic strength of the solution, were beneficial. Finally, we discovered that the addition of a co-catalyst (biphenyl) to prevent an otherwise-fast back electron transfer between the deactivated photocatalyst and the radical intermediate was a godsend in terms of reactivity and yield. This approach tolerates several substituents on the aromatic ring (whether electron-donating or electron-withdrawing) and can be successfully extended to heteroaromatic analogues, as well as to the NSAIDs (nonsteroidal anti-inflammatory drugs) ibuprofen and flurbiprofen.[1]


Smooth Photocatalyzed Benzylation of Electrophilic Olefins via Decarboxylation of Arylacetic Acids

Acyl radicals from Acylsilanes: Photoredox-Catalyzed Synthesis of Unsymmetrical Ketons

Chart 1

In another study, I designed a methodological approach for the use of acylsilanes as a source of acyl radicals under photocatalytic conditions (see Chart 1, bottom): being complementary to studies already present in the literature, our protocol allowed to smoothly generate aliphatic acyl radicals both under UV and visible light irradiation, as well as under flow and solar conditions.[3] The potentialities of this approach are highlighted also by the fact that it stands as a rare example of photocatalytic *umpolung* of the carbonyl group. As a matter of facts, while acylsilanes are markedly electrophilic in nature, the photogenerated acyl radicals are quite strong nucleophiles, as corroborated by their tendency to react with Michael acceptors in a radical addition reaction. Accordingly, we decided to exploit this reactivity: the obtained acyl radicals were trapped by electrophilic olefins to afford unsymmetrical ketones in high yields and without additives.

Photocatalysis via Hydrogen Atom Transfer (HAT).

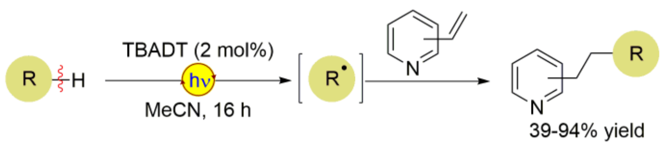
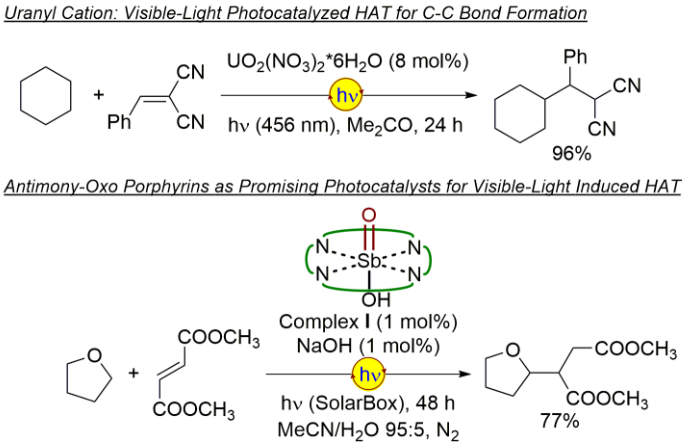

Vinylpyridines as Building Blocks for the Photocatalyzed Synthesis of Alkylpyridines

Chart 2

During my second year of Ph.D. I mainly focused on photocatalysis via HAT for the generation of C-centered radical via direct cleavage of C-H bonds. One of the most performing photocatalyst for such a reactivity is (again) TBADT: its excited state is also known to cleave homolytically (in a high chemo- and regioselective fashion) C-H bonds in a variety of organic derivatives (R-H) through a HAT process.[4]

The addition of radicals onto vinylaromatics to form homobenzyl derivatives is a challenging task, mainly due to competitive polymerization. A photocatalytic approach could bring about an intrinsic advantage, since it could hamper such undesired processes due to the efficient interception of the radical adduct. Accordingly, I embarked on a study to design a versatile strategy for the functionalization of vinylaromatics via Giese reaction to form alkylpyridines (Chart 2),[5] valuable compounds in several industrial and commercial applications. As an example, the present methodology allowed to synthesize derivatives responsible for the umami flavor, as well as an intermediate for the synthesis of the antihistamine drug pheniramine.


Uranyl Cation: Visible-Light Photocatalyzed HAT for C-C Bond Formation

Antimony-Oxo Porphyrins as Promising Photocatalysts for Visible-Light Induced HAT

Chart 3

Although I could appreciate the importance of photocatalyzed HAT as a versatile synthetic methodology, I could not ignore one of the main restrictions limiting the expansion of this strategy as an activation manifold in photocatalysis, namely the scarcity of catalysts compatible with cheap and versatile visible-light irradiation systems.

Accordingly, I decided to begin the search for novel photocatalysts for C-H to C-C bond conversion via visible-light HAT. Pleasingly, I found that the uranyl cation (UO_2^{2+}) performs well under irradiation at 456 nm in such process.[6] In particular, the excited state of the uranyl cation cleaves efficiently C(sp^3)- and C(sp^2)-H bonds to afford C-centered radicals, which are in turn trapped by electrophilic styrenes in high yields according to the Giese reaction (see Chart 3, top). Remarkably, different classes of substrates, ranging from cycloalkanes to aldehydes, from ethers, to amides and acetals were amenable to this reaction. A deep understanding of the reaction mechanism required dedicated isotope labeling and electrochemical experiments that also allowed to unveil the nature of the photocatalyst regeneration step.[6]

In a second moment, I came across a publication by Prof. Günther Knör from JKU in Linz (Austria),[7] which shows that antimony-oxo porphyrin complexes are potential photocatalysts via HAT under visible light irradiation. One such complex has been selected as a photocatalyst for the activation of tetrahydrofuran via HAT and the so-obtained radical was trapped with electrophilic olefins (see Chart 3, bottom). To the best of our knowledge, this is the first time that a metal-oxo porphyrin is used for a photocatalytic C-H to C-C bond conversion. Trapping experiments with the radical scavenger TEMPO and cross-over experiments showed the radical nature of the process and the KIE value was found to be in accordance for a rate-determining HAT step. To fully elucidate the behavior of the excited state of the photocatalyst, our collaborators at JKU are currently carrying out a thorough spectroscopic investigation.

Photocatalysis via Energy Transfer (ET).

During my third and last year of Ph.D., I decided to spend a visiting period at the University of Wisconsin-Madison, in Prof. Tehshik P. Yoon's research group, to study the potentialities of photocatalytic Energy Transfer as a synthetic methodology in organic chemistry. This group has studied in depth the use of triplet excited states of transition-metal complexes (TMCs) for visible-light sensitization in organic reactions.[8] One of the most promising reactions was the [2+2] photocycloaddition to prepare cyclobutanes.

We reasoned that, given the importance of these compounds in natural molecules with different biological activities, the possibility of late-stage diversification of this core would be extremely desirable. Accordingly, we started looking for a compatible and versatile synthetic handle to be introduced in the substrate that could bear conditions for the photocatalyzed [2+2] cycloaddition and we selected the class of vinylboronate esters. In particular, I contributed to explore the scope of intramolecular photocycloadditions between styrenes and vinylboronate esters to achieve cyclobutylboronates (see Chart 4). With the hypothesis that these products could serve as branching points for the rapid diversification of these novel scaffolds in medicinal chemistry campaigns, we are currently attempting chemical manipulation of the boronate functionality.

Visible Light promoted [2+2] Cycloadditions of Vinyl Boronate Esters

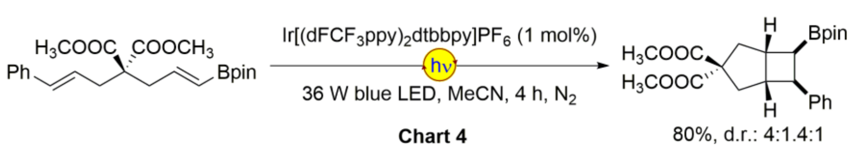


Chart 4

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