Clean and Easy Photochemistry

Claire-Lise Ciana and Christian G. Bochet*

Abstract: In this paper we try to convince you that the usual prejudices against photochemistry are not always well founded, supported by examples from the literature and from our own work. In fact, photochemistry can be a very powerful tool, for example in some elegant total syntheses which use key photochemical steps. Furthermore, the exploitation of chromatic orthogonality which allows wavelength-selective reactions, and recent strategies opening the possibility of enantioselective catalysis in photochemical reactions, expand the scope of this versatile synthetic tool. Finally, state-of-art LED-technology has allowed the development of small and easy-to-use photoreactors.

Keywords: Asymmetric reactions · Chromatic orthogonality · Organic photochemistry · Protecting groups · Synthesis

Introduction

Photochemistry is a powerful tool for the synthesis of organic molecules. As the electron distribution in the electronically excited state is usually very different from that of the electronic ground state, so is the reactivity of photochemically excited molecules. It is for this reason that photochemistry is a natural complement to standard thermal chemistry; unprecedented atomic connectivities can be accessed, or reactions of otherwise inert functional groups can occur. Extremely elegant and efficient syntheses of natural products have been achieved this way, such as Oppolzer's longifolene,[1] Pirrung's isocomene,[2] Wender's cedrene,[3] Winkler's ingenol[4] or, more recently, Corey's pentacycloanammoxic acid[5] (Scheme 1).
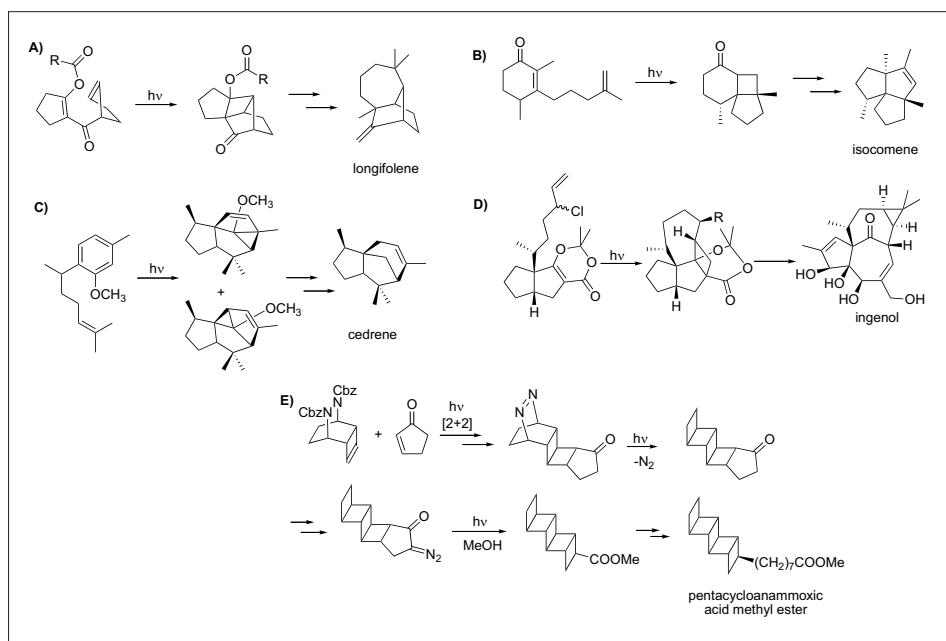
Scheme 1. Natural product syntheses containing a photochemical key step. A) Longifolene by Oppolzer and Godel,[1] B) isocomene by Pirrung,[2] C) cedrene by Wender and Hobwert,[3] D) ingenol by Winkler and coworkers,[4] E) pentacycloannamoxic acid by Mascitti and Corey.[5]

Additional attractive features of photochemical reactions are:
i) a relatively low cost, because no other reagents than photons are needed,
ii) simple workup procedures (essentially evaporation of the solvent), and
iii) atom-economy.

In view of these obvious advantages of photochemical reactions, the legitimate question should arise: *why are these steps not more often included in complex synthetic planning?* Playing the devil's advocate, here are a few commonly claimed drawbacks:

i) *Unpredictability* (which should not be confused with poor reproducibility): It is indeed true that small changes in the structure of a photochemically well-behaved substrate can sometimes dramatically modify the outcome or even inhibit the reaction completely.

ii) *Poor selectivity:* It is not uncommon that the expected product is formed together with significant amounts of isomers and/or degradation products.

iii) *Cumbersome experimental procedures:* Although simple on paper, photochemical reactions can be somewhat impracti-

Correspondence: Prof. Dr. C.G. Bochet
University of Fribourg
Department of Chemistry
Chemin du Musée 9
CH-1700 Fribourg
Tel.: +41 26 300 87 58
Fax: +41 26 300 97 38
E-Mail: christian.bochet@unifr.ch

cal. The venerable Hanovia immersion mercury lamp requires special glassware, a high-voltage power supply and adequate protection for the user. The introduction of the Rayonet® series made the operation much safer, but at high cost, due to the limited lifetime of the lamps and the need for a full set for each of the four available wavelengths.

iv) *No possibility for enantioselective catalysis:* Diastereoselective photochemical reactions are relatively common, but real asymmetric catalysis is indeed still a rarity.

It is the purpose of this article to show, by a few selected examples from literature or our own work, that, although the unrealistic promises which were made in the 60s about the panacean character of photochemical processes were obviously not fulfilled, and although Ciamician's dream[6] has remained a vision, many of the alleged drawbacks have since found solutions.

Unpredictability

Most of the reactions – thermal or photochemical – generating simultaneously many bonds and stereocenters are subject to numerous constraints in terms of substituents, steric and electronic environment and with compatibility with other functional groups (a notable exception being the Diels-Alder reaction). In fact, this wealth of parameters constitutes an inherent source of unpredictability. On the other hand, simple basic re-actions such as the acetylation of an alcohol or the reduction of a carbonyl group with a metal hydride are quite insensitive to perturbations by the environment. In a similar perspective, we have optimized very robust photochemical reactions, such as the photoacylation of nucleophiles to form amides, carbamates and esters.[7–9] Thus we found that, on irradiation N-acylnitroindolines transfer acyl groups to sufficiently strong nucleophiles, even at the relatively harmless wavelength of 405 nm (Scheme 2).

The nature of the side chain R^1 has very little influence on the reactivity; even ester-containing chains or highly conjugated and potentially photoactive carotenoids are compatible.[10] Heteroatoms are also tolerated; this allowed us to introduce three reagents capable of transferring Cbz, Fmoc and, to a more modest extent, Boc groups to amines[9] (Scheme 3). We emphasize once again the very mild conditions required, and the absence of additional aggressive additives such as acids, bases or even nucleophilic catalysts such as DMAP.

Protecting groups constitute a painful necessity in organic synthesis, but the pain is alleviated if the protection/deprotection steps are simple and efficient. Photolabile protecting groups are advantageous because their cleavage requires no reagents other than light and most are stable toward common chemical reagents. Compounds such as NVOC,[11] NPOC[12] and 5-bromo-7-nitro-indoline[13] have been shown on numerous occasions to be photocleavable without significant interference from most functional groups, substrates and solvents (Fig. 1).

This reliability has been further confirmed by the automated lithographic synthesis of oligonucleotides in DNA chips (immobilized oligonucleotides probes)[14] (Scheme 4).

Photoremovable protecting groups have also been used in total synthesis of natural products. As an example, *o*-nitrobenzyl protecting group was used in the total synthesis of Calicheamicin γ_1^I. The stability of *o*-nitrobenzyl ether toward most chemical reagents allowed an early introduction and a clean photodeprotection in 82% yield[15] (Scheme 5).

Poor Selectivity

A photochemical reaction is invariably initiated by the absorption of a photon of the wavelength matching the energy gap between the ground and an excited state of the reacting functional group (the chromophore) or the sensitizer, according to Planck's law $\Delta E = h\nu$. Irradiation of a polyfunctional substrate with polychromatic light, such as the one generated by a medium- or low-pressure mercury lamp, will excite all chromophores simultaneously, with a probability proportional to their individual absorption coefficients, ε. The situation is actually not as disastrous as it may seem, because rapid internal en-
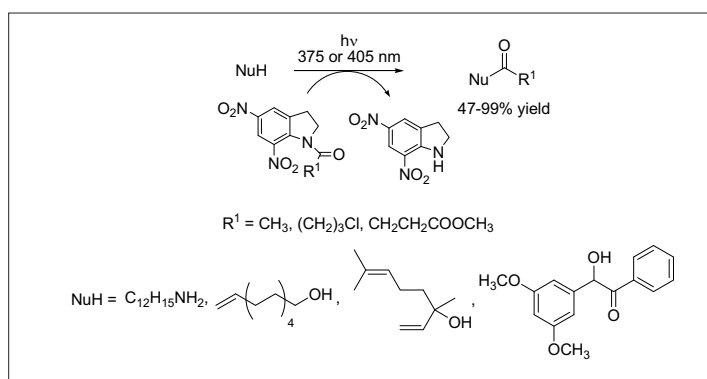
Scheme 2. Photoacylation of nucleophiles

Fig. 1. Photolabile protecting groups
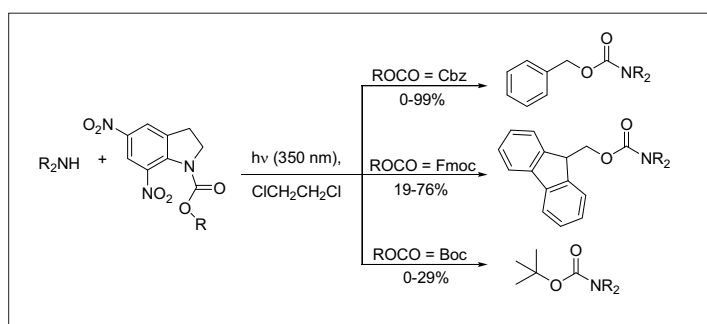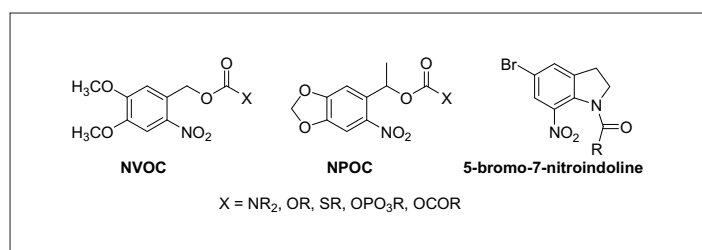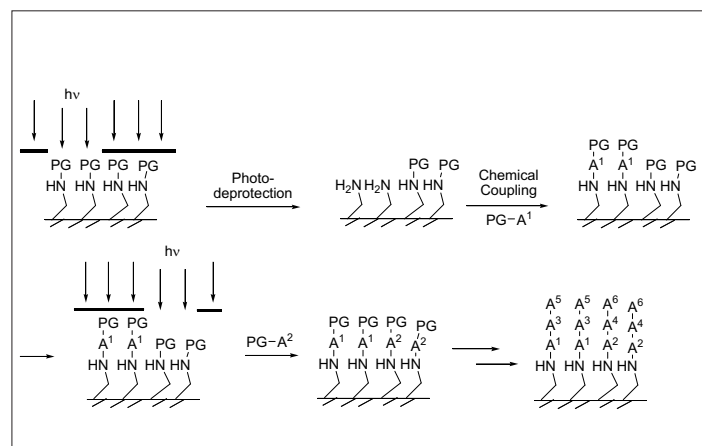

Scheme 3. Photochemical protection of amines with Cbz, Fmoc and Boc groups

Scheme 4. Concept of light-directed oligonucleotide synthesis

ergy conversion will normally funnel all excitations to the lowest lying excited state of the entire molecule (*Kasha rule*). This rule is, however, by no means a law, and we have uncovered many examples where it is not followed.[16] In these cases, the use of monochromatic light carefully tuned to the excitation wavelength of the desired chromophore or molecule is essential in order to increase the chances for a selective process.[17] Then, the group to be cleaved can be selected by changing the irradiation wavelength; a property that we have named *chromatic orthogonality*. For example, the diesters **1** and **2** can be photolyzed selectively and with good yield at the 'western' or 'eastern' termini depending on which wavelength is used[18] (Scheme 6A). Thus, the sequential photocleavage of the NVOC and *t*-butyl ketone moieties present in **2** were exploited in a sequential solid phase peptide synthesis[19] (Scheme 6B).

This concept of chromatic orthogonality can also be put to good use in other types of processes, for example by combining the acyl transfer reaction shown earlier with the cleavage of a protecting group (Scheme 7A). In Scheme 7B, both the introduction and the removal of the protecting groups are performed photochemically, but with light of different wavelengths.[10]

Supramolecular catalysis has also been used as an efficient tool for regioselective photoreactions. For example, the regioselectivity of olefin [2+2] photodimerization has been improved by Bassani and coworkers[20] by using supramolecular catalysis. The substrate bears a molecular recognition unit which binds non-covalently (H-bonds) to a template (barbituric acid derivative) in order to be oriented during the cycloaddition (Scheme 8A). Indeed, irradiation (350 nm) of cinnamate ester derivative in the presence of barbituric acid template enhanced the rate of formation of three products (out of eleven possible isomers), the major one being the *syn* head-to-head dimer (Scheme 8B).

## *Cumbersome Experimental Procedures*

It is clear that if the condition for a selective reaction is to have access to relatively monochromatic light, the old-fashioned high-pressure mercury lamps are not very useful sources (a narrow band filter has the double inconvenience of high cost and low photonic output and cutoff filters do not produce monochromatic light), in contrast to low-pressure mercury lamps which produce almost monochromatic 254 nm light. Rayonet® reactors are efficient but not very convenient for everyday synthesis. Fortunately, recent developments in UV-LED technology are offering a solution to these problems, as nowadays LEDs emitting down to 254 nm are commercially available.
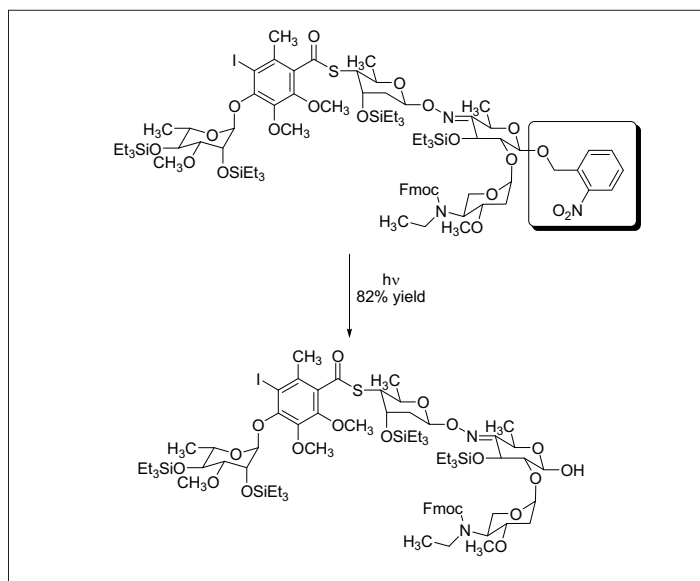
Scheme 5. The photodeprotection step in the total synthesis of Calicheamicin γ_1^I
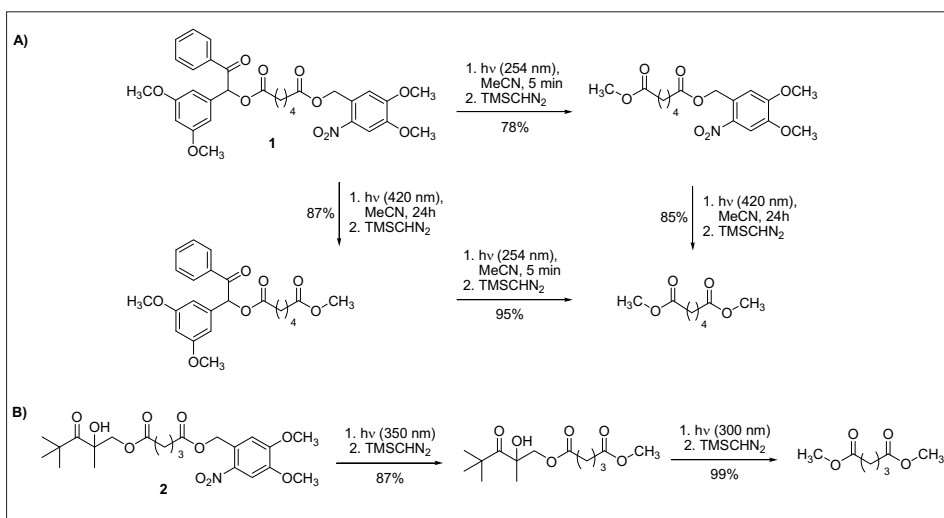
Scheme 6. Orthogonality of photolabile protecting groups
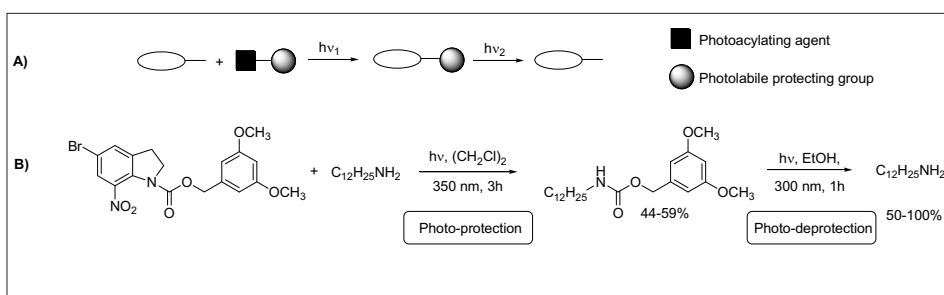
Scheme 7. Photochemical protection followed by photochemical deprotection of an amine

To date, the modest intensity of this devices is still an issue for the lower end of the spectrum (between 255 and 350 nm), but it is already sufficient for investigative-scale reactions (typically to convert less than 100 mg of a substrate).[7] In collaboration with a startup company, Atlas photonics, we have developed a compact photoreactor based on

UV-LEDs (the LUMOS reactor shown in Fig. 2), which allows the irradiation of samples in simple test or NMR tubes. As an example, the acylations of the alcohols shown in Scheme 2 were carried out with such a reactor. Another example, taken from the literature, is the Paterno-Büchi condensation of benzaldehyde and furane, which gives a
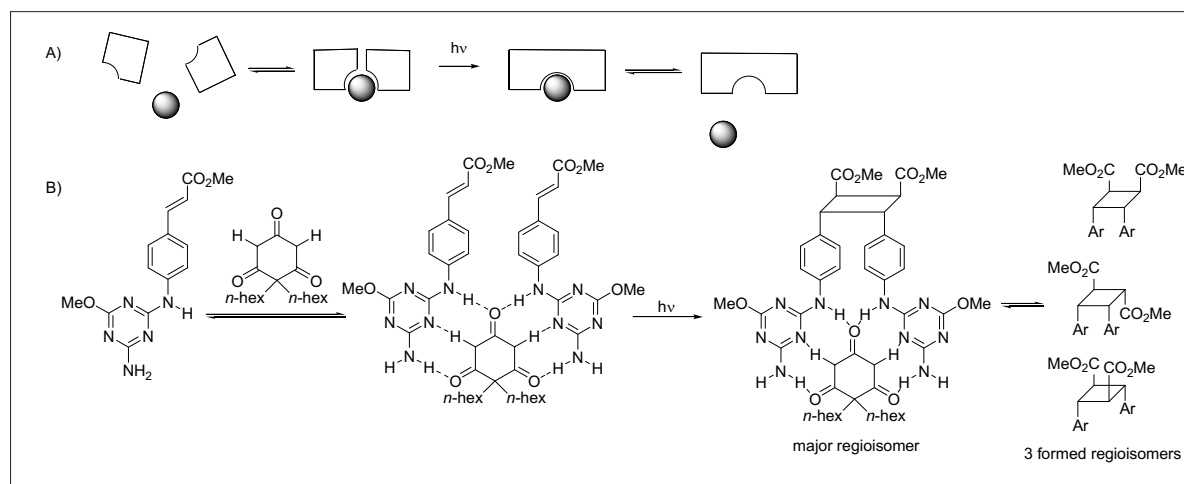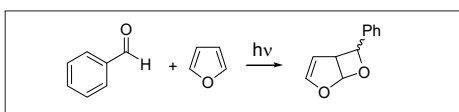
Scheme 8. Supramolecular control of [2+2] photodimerization

54% yield after 16 h irradiation at 375 nm, without any precautions other than using a commercially available 18 mm quartz test-tube[21] (Scheme 9).

Fig. 2. LUMOS reactor

Scheme 9. Paterno-Büchi reaction using UV-LEDs

UV-LED based microreactors open new horizons for photochemical syntheses. Of the few applications that were reported until now,[22] we choose as an illustration the photosensitized oxidation of citronellol by singlet oxygen (Scheme 10), which is used to produce rose oxide for the perfume industry. Meyer and coworkers[23] compared a normal batch-reactor with a microreactor in order to evaluate both reactors' efficiency. A slight advantage of microreactor over batch reactor was found concerning the space-time-turn-overs and the photonic efficiencies.

Enantioselective Catalysis

The importance of asymmetric synthesis must no longer be demonstrated. The development of asymmetric photoreactions would be advantageous compared to their organometallic counterparts, for example

in the synthesis of pharmaceutical compounds, because it avoids transition metal residues that may be difficult to eliminate. Several strategies have been (and are being) developed to obtain chiral selectivity in photoreactions. The main approaches are
i) reactions in confined chiral media (zeo-lite, calixarene, crystals),
ii) sensitization by chiral sensitizer and
iii) templated induced photoreactions.[24]

In terms of chiral economy, it is preferable to use a substoichiometric quantity of the chiral agent. In order for this to work the photoreaction should fulfil two conditions:
i) the energy transfer has to occur in a chiral micro-environment,
ii) the substrate must not react in the absence of the chiral source.

The following examples represent recent breakthroughs in this domain. Krische

and coworkers[25] described the use of a catalytic quantity of a chiral agent containing sensitizer and complexation units for the enantioselective catalysis of [2+2] cycloadditions. The concept is to bind the substrate to the chiral sensitizer *via* H-bonds. After excitation of the sensitizer, energy transfer occurs preferentially to the closer substrate (the complexed one) and cycloaddition afforded enantiomerically enriched **4** with modest *ee* (19% *ee* at −70 °C using 25 mol% of **6**) (Scheme 11A). Performing the reaction at room temperature or using a catalyst without H-bonding sites did not lead to any enantiomeric excess. In a similar vein, Bach and coworkers[26] developed a photoinduced electron transfer (PET) catalyzed conjugated addition of α-amino alkyl radicals to enones (Scheme 11B). The catalyst is made up of an electron accepting
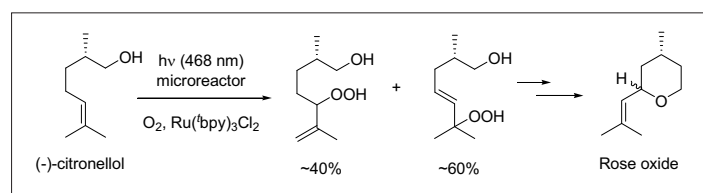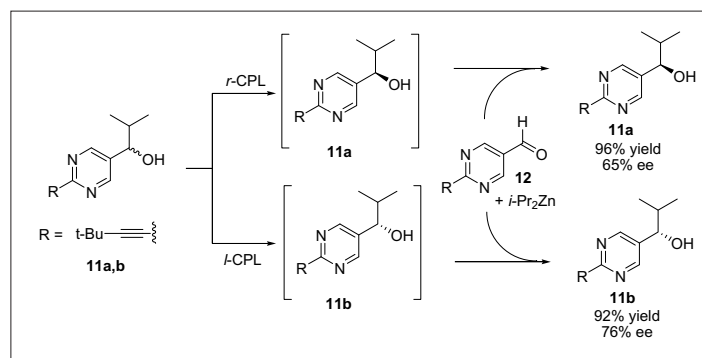

Scheme 10. Oxidation of citronellol by singlet oxygen
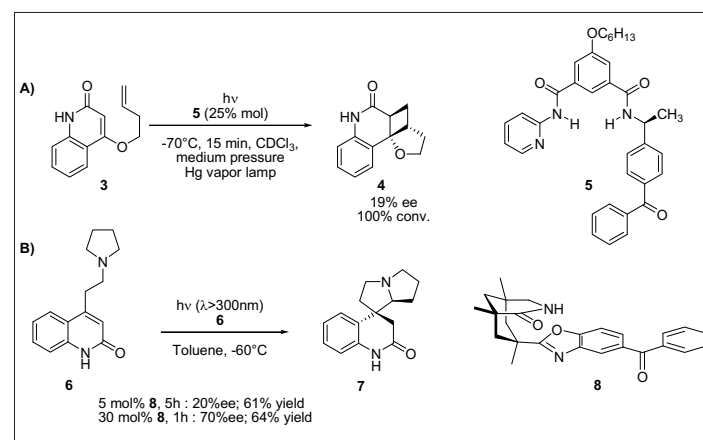
Scheme 11. A) Krische's asymmetric catalyzed [2+2] cycloaddition. B) Bach's PET-catalyzed conjugated addition of amine to enone.
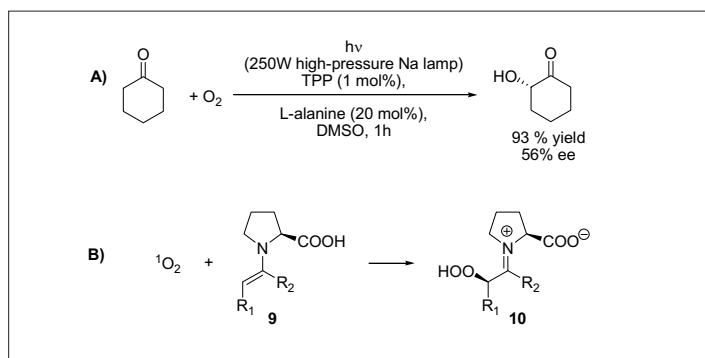
Scheme 12. A) Amino acid catalyzed asymmetric α-oxidation of cylohexanone with molecular oxygen. B) Catalytic enamine mechanism.

Scheme 13. CPL irradiation followed by asymmetric autocatalysis

group (benzophenone) and a lactam moiety which interacts with the substrate through hydrogen bonding. Significant *ee*s are obtained even with 5 mol% catalyst.

Córdova and coworkers[27] published the amino acid catalyzed asymmetric α-oxidation of ketones and aldehydes with molecular oxygen or air and a porphyrine sensitizer (TPP) (Scheme 12A). Several amino acids are able to catalyze this reaction with high yield, good *ee* and regioselectivity, for example L-alanine catalyzed oxidation of cyclohexanone with 93% yield and 56% *ee*. The reaction occurs *via* a catalytic enamine mechanism to afford peroxide intermediate **10** (Scheme 12B).

Finally, right (*r*) or left (*l*) circularly polarized light (CPL) was used in direct asymmetric photochemistry.[28] The principle is that two enantiomeric ground state reactants do not absorb the same amount of CPL. As the difference (Δε) is generally small, only slight *ee* are possible without amplification. Soai and coworkers[29] published several articles on the asymmetric autocatalytic addition of dialkylzinc reagents to aromatic aldehydes. Photodecomposition of racemic pyrimidyl alkanol **11a,b** by *r*- or *l*-CPL induced a slight *ee* which is amplified by autocatalysis in the addition of diisopropylzinc to pyrimidyl aldehyde **12** affording **11a** in 65% *ee* (*r*-CPL) and **11b** 76% *ee* (*l*-CPL) (Scheme 13). After three rounds of consecutive autocatalysis near enantiopure (>99.5% *ee*) **11a** and **11b** were obtained.

Conclusion

Photochemical reactions occur from excited states which have very different chemical properties than ground states. It would be a waste not to benefit from this unique reactivity. Even if photochemistry is like a 'naughty child' because excited molecules are often 'misbehaved', many problems have already been solved. Some examples of promising results and efficient methods have been presented here. Photochemistry is a fascinating and complex research field

that only demands to be explored and understood.

Received: July 17, 2007

[1] W. Oppolzer, T. Godel, *J. Am. Chem. Soc.* **1978**, *100*, 2583.

[2] M. C. Pirrung, *J. Am. Chem. Soc.* **1981**, *103*, 82.

[3] P. A. Wender, J. J. Hobwert, *J. Am. Chem. Soc.* **1981**, *103*, 688.

[4] a) J. D. Winkler, M. B. Rouse, M. F. Greaney, S. J. Harrison, Y. T. Jeon, *J. Am. Chem. Soc.* **2002**, *124*, 9726; b) J. D. Winkler, E. C. Y. Lee, L. I. Nevels, *Org. Lett.* **2005**, *7*, 1489.

[5] V. Mascitti, E. J. Corey, *J. Am. Chem. Soc.* **2004**, *126*, 15664.

[6] G. Ciamician, *Science* **1912**, *36*, 385, "On the arid lands there will spring up industrial colonies without smoke and without smokestacks; forests of glass tubes will extend over the plains and glass buildings will rise everywhere; inside of these will take place the photochemical processes that hitherto have been the guarded secret of the plants, but that will have been mastered by human industry which will know how to make them bear even more abundant fruit than nature, for nature is not in a hurry and mankind is".

[7] J.-L. Debieux, A. Cosanday, C. Helgen, C. G. Bochet, *Eur. J. Org. Chem.* **2007**, 2073.

[8] C. Helgen, C. G. Bochet, *Synlett* **2001**, 1968.

[9] C. Helgen, C. G. Bochet, *J. Org. Chem.* **2003**, *68*, 2483.

[10] C. Helgen, Ph.D. Thesis, University of Geneva No. 3482, **2003**.

[11] A. Patchornik, B. Amit, R. B. Woodward, *J. Am. Chem. Soc.* **1970**, *92*, 6333.

[12] A. C. Pease, D. Solas, E. J. Sullivan, M. T. Cronin, C. P. Holmes, S. P. Fodor, *Proc. Natl. Acad. Sci.* **1994**, *91*, 5022.

[13] B. Amit, D. A. Ben-Efraim, A. Patchornik, *J. Am. Chem. Soc.* **1976**, *98*, 843.

[14] a) G. H. McGall, A. D. Barone, M. Diggelmann, S. P. A. Fodor, E. Gentalen, N. Ngo, *J. Am. Chem. Soc.* **1997**, *119*, 5081; b) S. P. A. Fodor, J. L. Read, M. C. Pirrung, L.

Stryer, A. T. Lu, D. Solas, *Science* **1991**, *251*, 767.

[15] K. C. Nicolaou, C. W. Hummel, M. Nakada, K. Shibayama, E. N. Pitsinos, H. Saimoto, Y. Mizuno, K. U. Baldenius, A. L. Smith, *J. Am. Chem. Soc.* **1993**, *115*, 7625.

[16] A. Blanc, C. G. Bochet, *J. Am. Chem. Soc.* **2004**, *126*, 7174.

[17] T. Bally, *Chimia* **2007**, *61*, 645.

[18] a) C. G. Bochet, *Angew. Chem.* **2001**, *40*, 2071; b) A. Blanc, C. G. Bochet, *J. Org. Chem.* **2002**, *67*, 5567.

[19] M. Kessler, R. Glatthar, B. Giese, C. G. Bochet, *Org. Lett.* **2003**, *5*, 1179.

[20] a) D. M. Bassani, *Chimia* **2006**, *60*, 175; b) D. M. Bassani, V. Darcos, S. Mahony, J.-P. Desvergne, *J. Am. Chem. Soc.* **2000**, *122*, 8795.

[21] a) Atlas Photonics, Application sheet 7: Paterno-Büchi; b) A. G. Griesbeck, S. Stadtmueller, *Chem. Ber.* **1990**, *123*, 357.

[22] a) H. Ehrich, D. Linke, K. Morgenschweis, M. Baerns, K. Jahnisch, *Chimia* **2002**, *56*, 647; b) R. Gorges, S. Meyer, G. Kreisel, *J. Photochem. Photobiol. A* **2004**, *167*, 95.

[23] S. Meyer, D. Tietze, S. Rau, B. Schaefer, G. Kreisel, *J. Photochem. Photobiol. A* **2007**, *186*, 248.

[24] 'Chiral Photochemistry', Vol. 11, Mol. Supramol. Photochem. Ed. Y. Inoue, V. Ramamurthy, Marcel Dekker, New York, **2004**.

[25] D. F. Cauble, V. Lynch, M. J. Krische, *J. Org. Chem.* **2003**, *68*, 15.

[26] A. Bauer, F. Westkaemper, S. Grimme, T. Bach, *Nature* **2005**, *436*, 1139.

[27] a) H. Sunden, M. Engqvist, J. Casas, I. Ibrahem, A. Cordova, *Angew. Chem.* **2004**, *43*, 6532; b) A. Cordova, H. Sunden, M. Engqvist, I. Ibrahem, J. Casas, *J. Am. Chem. Soc.* **2004**, *126*, 8914.

[28] a) B. L. Feringa, R. A. Van Delden, *Angew. Chem.* **1999**, *38*, 3418; b) Y. Inoue, *Chem. Rev.* **1992**, *92*, 741.

[29] a) K. Soai, I. Sato, T. Shibata, *Chem. Rec.* **2001**, *1*, 321; b) T. Kawasaki, M. Sato, S. Ishiguro, T. Saito, Y. Morishita, I. Sato, H. Nishino, Y. Inoue, K. Soai, *J. Am. Chem. Soc.* **2005**, *127*, 3274.