

Conference Report

41th CUSO Summer School in Organic Chemistry,
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‘Unconventional Methods in Organic Synthesis’

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The 41th CUSO Summer School in Organic Chemistry took place in picturesque Villars-sur-Ollon, a village embedded in the mountains of the Villars-Gryon region that is famous for its vineyards. The lectures were chaired by *Christian Bochet* from the University of Fribourg, and had unconventional methods in organic synthesis as the central theme.

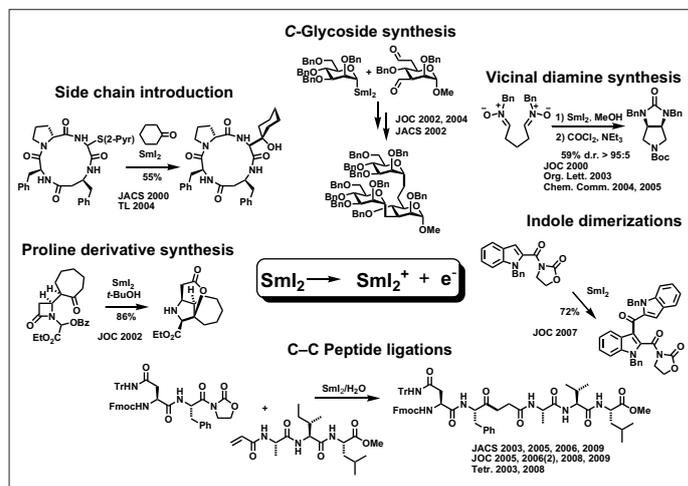


The invited speakers presented on one hand established methods like photo- and radical chemistry that have been used for over 100 years, but pointed out their current and growing importance in modern synthesis. On the other hand, new techniques such as microwave-assisted synthesis (and the underlying controversy on the origin of its rate acceleration) and the use of microreactors were discussed. Five speakers and forty-six PhD and postdoctoral students participated.



Prof. **Troels Skrydstrup** from the University of Aarhus, Denmark, opened the conference with a general introduction on radical chemistry in organic synthesis. Although Moses Gomberg, one of the pioneers, already mentioned in 1900 that he “wished to reserve the field [of radical chemistry] for himself”,^[1] there is a wide and free range of opportunities not just in classical polymerizations but also in the construction of

complex molecules. After a primer in stability and reaction rates of radicals, Skrydstrup pointed out the various options for removing halogen-, nitro-, amine- and carboxyl groups even in complex molecules, using tributylstannane (Bu₃SnH). Tin-free conditions for decarboxylation and functionalization were also presented. As the most important application, the formation of C–C bonds was



Prof. Troels Skrydstrup reviewed the use of single electron reducing agents, such as samarium diiodide (SmI₂), for the creation of C–C bonds in a variety of systems.

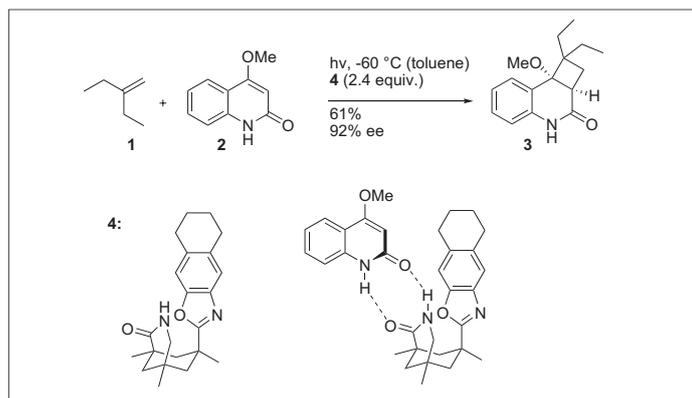
the main part of his lecture, with a particular emphasis on ring formation by cascade reactions.

In the following hours, Skrydstrup shared with the audience his passion for samarium diiodide. After some basic considerations in terms of structure, additives/cosolvents and in particular the preferable preparation of SmI₂ by the Kagan’s method, he explained multiple functional group transformations by reduction. Stereoselective reduction of a ketone in the synthesis of Epothilone,^[2] or the reaction of α -heteroatom carbonyl derivatives in complex molecules like Taxol were quite impressive examples of the use of samarium diiodide in synthesis.^[3]

Another synthetic application outlined by the speaker was the use of SmI₂ for C–C bond formation, as an alternative to the classical Grignard, Reformatsky or pinacolic reactions, as well as in intramolecular carbonyl-alkene couplings or sequential reactions like the impressive formation of a Paeonilactone B precursor.^[4] As part of an intramolecular radical cascade reaction involving an aldehyde, a methylenecyclopropene and an alkyne, two cycles are formed and a ketone is reduced stereoselectively to an alcohol. Finally, Skrydstrup showed further impressive applications of radical chemistry in the synthesis of different biomolecule analogues.



In four very informative and didactic lectures, Prof. **Thorsten Bach** from the University of Munich gave an excellent overview of organic photochemistry. After a general introduction on photophysics, including absorption and transition mechanisms, radiative and non-radiative energy transfer processes (El-Sayed’s rules for intersystem crossing and Kasha’s rule for internal conversion) he continued with the photochemistry of carbonyl compounds by presenting the Norrish-type I and II reactions and their different variations such as



Prof. Thorsten Bach showed how to control the enantioselectivity in photochemical reactions by using the chiral template **4** and its coordination with the substrate **2** (*J. Am. Chem. Soc.* **2000**, *122*, 11525).

the Norrish-Yang cyclization and γ -, δ -, ϵ -hydrogen abstraction. In the second part of this lecture, he dealt with the formation of oxetanes by the Paternò-Büchi reaction and detailed in several examples how to predict its regio- and stereoselectivity.

Bach continued with a lecture on α,β -unsaturated carbonyl compounds. Also starting with basics, such as the electronic states, mechanisms in photocycloadditions and selectivity rules, he showed some spectacular examples like the synthesis of (+)-penta-cycloammonox acid (a molecule with its overall structure resembling a flight of stairs)^[5] and the total synthesis of (+)-Meloscin. The latter includes an elegant intramolecular rearrangement for building up a functionalized cyclopentane, and was published by his group in 2008.^[6] As an example of his latest research in this area, he showed a very interesting example how a cyclization can be enantioselectively controlled by using a chiral Lewis acid.^[7]

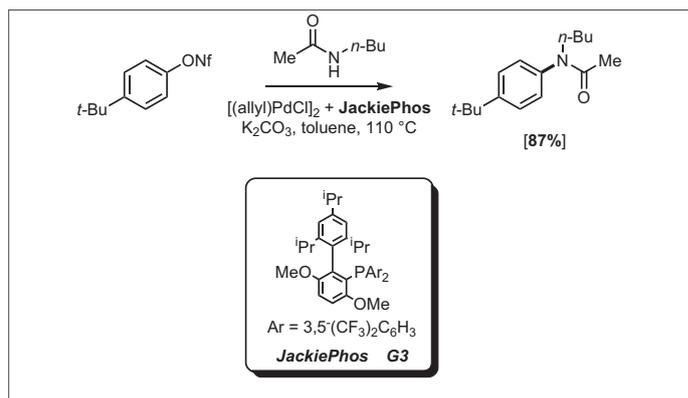
As another point of interest, Bach discussed the De Mayo reaction that is used in several natural product syntheses. The reaction product does however not look like a photocycloadduct; after an initial [2+2] cycloaddition of an olefin with an enolisable β -diketone, the intermediate cyclobutane undergoes immediately a cleavage by a retro-aldol reaction, leading to a 1,5-diketone.

In his last lecture, Bach showed many examples that helped to understand the intramolecular [2+2] cycloadditions and their stereoselectivity, [4 π] and [6 π] cyclizations of alkenes as well as the photochemistry of arenes.

After Bach finished presenting all the tools to solve difficult synthesis problems by photochemistry, he tested whether the audience had listened carefully or was already dreaming about the afternoon leisure activities organized by Christian Bochet's group. Therefore, he had prepared 40 multiple-choice questions for a quiz show. The audience was split into two teams, which had to compete against each other. After one team had given an answer, the quiz-master revealed the correct solution and gave further explanations before then the second team had to answer the next question. This really helped to improve the understanding and to translate the previously learned rules into practical problems.



The lectures in 'New synthetic methods' given by Prof. **Alan Spivey** from the Imperial College, London, were divided in two main parts. The first dealt with stereoelectronic effects in synthesis and the second reviewed (hetero-)aromatic functionalization. After a very informative and well-structured introduction about orbital interactions and conformation of hydrocarbons/functional groups, Spivey spent



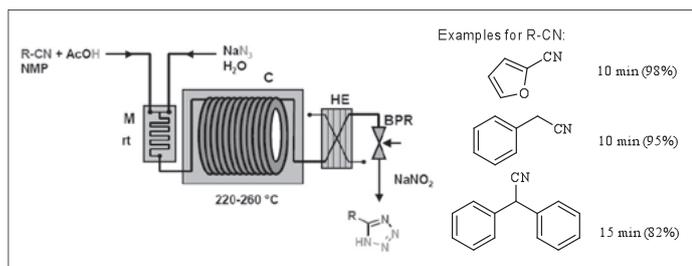
Prof. Alan Spivey detailed modern cross-coupling methods, such as the Pd-catalyzed coupling of *sec*-amides with aryl sulfonates, using JackiePhos as a ligand (Buchwald *et al.* *J. Am. Chem. Soc.* **2009**, *131*, 16720).

one hour on thermodynamically/kinetically controlled reactions, ionic 1,2-rearrangements like the Wagner-Meerwein, Pinacol, and Bayer-Villiger rearrangements, and about ionic fragmentations like the Beckmann, Grob or Eschenmoser fragmentations. Even though the material was known for some of the students, he accomplished the difficult task to keep the audience interested with his suspenseful talk and interesting examples. For instance, he showed how it is possible to identify the relative configuration in rigid alkaloids containing nitrogen by infrared spectroscopy, exploiting the anomeric effect of the C–H bonds anti-periplanar to the nitrogen lone pair (the so-called Bohlmann bands, now often forgotten). In the following part about functionalization, Spivey first dealt with the formation of C–N and C–O bonds by showing different Pd, Ni, Cu and Fe catalyst systems. He then discussed metallation reactions by halogen-metal exchange and deprotonation including directed ortho metallation (DoM). Some examples like the halogen-Zn exchange of ethyl-4-iodobenzoate with Et₂Zn and a phosphazine base, or the DoM used for the synthesis of Efavirenz were most interesting. Spivey finished up by giving an overview about methods of catalytic C–H activation reactions.



A poll in the audience showed that about two-thirds of the participants had already used, at least once, microwaves for synthesis. Microwave technology is known since 1946 and is nowadays used in nearly every kitchen for heating food. Its existence in organic chemistry is still modest, but the number of publications in this field is increasing very rapidly. Therefore the participants of the CUSO summer school were very happy to be able to hear the lectures of Prof. **C. Oliver Kappe** from the University of Graz, Austria, who tried to bring some light into the myths of this new technology.

In his first talk he explained the basics of microwaves, illustrating that the microwave (MW) energy is too low for breaking bonds, and that it is rather the electromagnetic waves that are responsible for heating the medium. Dipolar molecules try to follow an oscillating field by rotation, hence creating frictions that result in the heat (dipolar polarization mechanism).^[8] Ions in solution also move by the applied electric field (ionic conduction mechanism). The heat produced from the latter mechanism is greater than that arising from the dipolar polarization mechanism. It is the dissipation factor (loss tangent: $\tan \delta$) that defines the ability of materials to convert electromagnetic energy into heat at a given frequency and temperature. For most solvents,



Prof. C. Oliver Kappe used a combination of microwave and micro reactor technology to minimize the risk of using toxic and explosive HN_3 by their preparation *in situ* in very small amounts (B. Gutmann, J.-P. Roudit, D. Roberge and C.O. Kappe, *Angew. Chem. Int. Ed.* **2010**, *49*, 7101).

this value drops with increase of temperature, which is not the case for the ionic liquids. Mobilization capacity of the molecules is also important for the heating mechanisms as he demonstrated that ice cannot be heated by MW because the water molecules are fixed; there is thus no movement, no friction, therefore no heating.^[9] Metals can be heated by MW if they are in a powder form or in small particles. Kappe then pointed out the drawback of the low penetration of the waves that can be critical to the scale-up. There is also a general problem of uneven field distribution that can become a major issue when reproducing reactions.

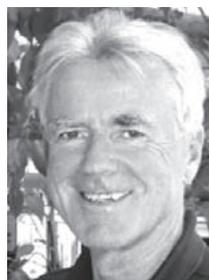
In the literature, several publications report on reactions which proceed in a microwave oven but not when using the same conditions with the 'classical oil bath technique', and thus propose a kind of 'non thermal' effect. Kappe spent a lot of effort in repeating these reactions under both types conditions to find out whether there is any difference.

The main difficulties when repeating these reactions are a) to have the same rapid heating in an oil bath and b) to have a proper temperature control in a microwave oven. As it is not possible to use normal thermometers, the temperature has to be measured from outside *via* IR sensors or with fiber optics. Kappe found out that reactions giving higher yields in microwaves just benefit from the higher pressure and the higher temperature that have been measured incorrectly. Common methods like IR sensors just measure the cold glass surface of the reaction tube and the temperature inside the reaction can be 20 to 30 °C higher. All reactions studied therefore showed no difference between oil bath and microwave. Kappe pointed out that it is probably easier and safer to reach harsh conditions in a microwave than in an oil bath.

Another common issue is the low absorbance of solvents like hexane that precludes their use in microwave chemistry. As a new invention, Oliver Kappe presented reaction vessels in silicon carbide that strongly absorb microwaves, and have an extremely high thermal conductivity. With them it was possible to carry out reactions with higher yields and higher temperature.^[10] Kappe also investigated the 'cooling while heating' method that is said to improve yields in some cases, but no evidence for this hypothesis could be found. Experiments with accurate temperature control gave the same results, irrespective of the heating method (oil/microwave/microwave with cooling).^[11]

The last lecture dealt with the scaling-up of microwave chemistry using microreactor technology. After describing problems with catalyst leaching when trying Heck reactions under flow conditions, he showed a very interesting example of direct tetrazole synthesis from cyanides. The required reagent hydrazoic acid, a highly toxic and explosive chemical, is prepared *in situ* in the reactor under flow conditions, and directly reacts with the cyanide. This method avoids any risks, since only small amounts of HN_3 emerge out of the reactor and can directly be quenched.

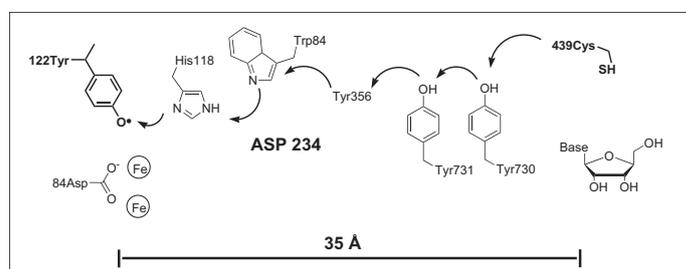
The fascinating lectures of Prof. Kappe showed that there are many reasons to use microwaves not just as a last resort, and that it is a perfect addition in normal laboratory equipment.



The evening talk of the CUSO summer school was given by Prof. **Bernd Giese** from the University of Fribourg, entitled 'enzymes that go radical'. He began by citing again Moses Gomberg, and noticed the fact that nature seems to have reserved radical chemistry for its greatest chemical challenges, for example in several radical enzymes like the *cytochrome P₄₅₀*, a powerful metabolic machinery, *ribonucleotide*

reductase or the *photolyase* that can repair thymine dimers. It can also help form C–C bonds like in *Thauera aromatica*. The precursor of radicals in our body is SAM (S-adenosylmethionine). Giese insisted on the important role played by the photolyase to repair DNA and the experiments which lead to the conclusion that an electron acts as a catalyst for this reaction (it can repair more than one thymine dimer). Then experiments carried out to study ribonucleotide reductase (RNR) were discussed. This enzyme catalyzes the formation of deoxyribonucleotides from ribonucleotides, which are then used in the synthesis of DNA. It regulates the synthesis of DNA and catalyzes a reaction that proceeds through a free radical mechanism. From the experiments studying RNR, Giese concluded that enzyme reactions are often driven by general acid/base catalysis and that water as a solvent was important.

The summer school ended on Thursday noon, as it should be: sitting with the newly made friends outside on the hotel terrace in the warm sun and having a last, delicious buffet.



Prof. Bernd Giese explained the mechanism of electron hopping and tunneling in proteins with the ribonucleotide reductase (B. Giese, M. Graber, M. Cordes, *Curr. Opin. Chem. Biol.* **2008**, *12*, 755).

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