Professor Manfred Schlosser

A Tribute



Dedicated to Prof. Manfred Schlosser in honor of his scientific achievements within his career

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Manfred Schlosser was born on June 12, 1934 in Ludwigshafen on Rhine in Rhineland-Palatinate (Germany), an industrial city whose importance increased hand in hand with chemical companies such as BASF. During the Second World War, he spent his childhood in Bavaria, while attending the Oberrealschule Schrobenhausen high school until June 1952. Between 1952 and 1957, he studied Chemistry and, to a lesser extent, medicine at the famous Universität Heidelberg (University of Heidelberg), where he was awarded the "Diplom-Chemiker" (comparable with M.Sc.). In 1957, Manfred Schlosser started his thesis work under the supervision of Prof. Georg Wittig, and received his doctorate in May 1960, thus becoming "Doctor rerum naturarum" (comparable with Ph.D.) at the University of Heidelberg. The neo-doctor Manfred Schlosser spent one year in Brussels (Belgium) as a Research Fellow with the European Research Associates, sponsored by Union Carbide Co, before he achieved the status of "Doctor habilitus" (coupled with the conferment of the "venia legendi") at the University of Heidelberg in 1966. After his Habilitation, Manfred Schlosser accepted in 1967, the position of "Oberarzt" (Senior Physician) becoming the head of a group of scientists at the German Cancer Research Center in Heidelberg, where he initiated a program for the synthesis of novel cytostatics, while maintaining contact with the Heidelberg Faculty of Science as a "Privat-Dozent" (comparable with Assistant Professor). In October 1971, Manfred Schlosser was appointed as successor to Prof. Jiři Sicher (second chair of organic chemistry) at the University of Lausanne (Switzerland) where he held regular class courses on Reaction Mechanisms, Stereochemistry, Organic Synthesis and Organometallic Reactivity. In 1983, together with Prof. Jean Tirouflet, he organized the second IUPAC Symposium on Organometallic Chemistry Oriented

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Toward Organic Synthesis (OMCOS II). Later, he organized a series of workshops on “Organometallic Reactivity” (1995) and "Organofluorine Chemistry: Synthesis and Bioapplication" (1997). For several years, he was a member of the Organizing Committee of the Conferences on Stereochemistry held annually in Bürgenstock (Switzerland, Lucerne) where, in 2003, he organized as a chairman, the International Symposium on “Fluorine in the Life Sciences”. As a visiting professor, Manfred Schlosser gave lectures in several Universities around the world: in Italy (Università di Perugia in 1985 and Università di Firenze in 1989), in Germany (Technische Universität Berlin in 1986), in Hungary (Budapest), in the USA (California IBM Research Center of San Jose in 1981 and University of California at Santa Barbara in 1998), and in Japan (University of Kyoto, 1984).



Figure 1. Manfred with his collaborators in Lausanne (1982).



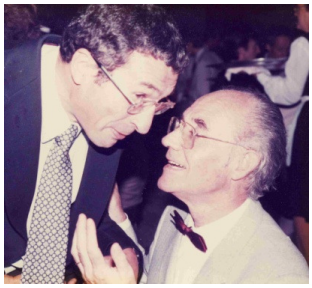




Figure 2. Manfred at OMCOS-II, Dijon (France), summer 1983 (above: Jean Tirouflet talking to him, drinking a jumbo glass of wine).

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In the summer 2004, Manfred Schlosser obtained the status of "Professor Emeritus" of the EPFL (Ecole Polytechnique Fédérale de Lausanne) and, as such, he was able to devote himself entirely to research.



Figure 3. Manfred (left) with his friends in Italy, visiting Grotte Frasassi (1984).



Figure 4. Manfred's lecture at ISCC-9, Palazzo Vecchio, Florence (Italy), July 2010.

A significant part of Manfred Schlosser's research activity was aimed at a deeper understanding of chemical reactivity in general and the behaviour of organometallic species in

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particular. His research studies in fields such as organophosphorus, organofluorine and organometallic chemistry combined both novel mechanistic insight and synthetic applications. He contributed to ca. 400 publications and gave about 300 plenary lectures. His concepts and findings are summarized in several review articles. He was editor of several books on organometallic chemistry, and the third edition of a very famous one was recently published (*Organometallics in Synthesis: A Manual*, Wiley, Chichester, **2013**).



Figure 5. Manfred in his office, Lausanne (September 2010).

Among the many contributions of Manfred Schlosser to organic chemistry we wish to cite his stereoselective olefination procedures ("Schlosser modifications of the Wittig reaction"), developed in Heidelberg,[1,2] the copper-catalyzed alkylation of organomagnesium compounds ("Fouquet-Schlosser coupling"),[3] the development and use of mixed-metal bases such as the LICKOR superbase,[4,5] and intense efforts to rationalize substituent effects on the behaviour of substrates in reactions.[6]

Manfred Schlosser made a remarkable contribution to improve the stereoselectivity of the Wittig reaction[1] with the development of the so-called "Schlosser Modification of the Wittig Reaction". The latter has been used broadly in organic synthesis for the stereoselective formation of alkenes with non-stabilized ylides, allowing the *E*-configured olefins to be prepared in more than 99% purity, which makes it one of the most stereoselective reactions reported in literature.[2,7] By introducing different electrophiles to the α-deprotonation intermediate (Schlosser termed it "betaine ylide"), Manfred Schlosser and E. J. Corey, independently, developed a new approach to trisubstituted ethylenic compounds (the so-called "SCOOPY reaction" or "three-dimensional Wittig reaction").[8] In addition, Manfred Schlosser contributed significantly to the mechanistic studies of Wittig and related reactions. He reported a series of elegant experiments aimed at trapping the betaine intermediates by incubating β-hydroxy phosphonium salts with acid at low temperature, and nicely explained the pronounced effect of lithium salts on the stereochemistry of Wittig reactions.[1,9]

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He also developed an efficient method to enhance the *cis*-selectivity of olefination with semistablized ylides,[10,11] as well as the "instant ylide" approach to promote the use of the Wittig reaction in large scale synthesis and the pharmaceutical industry.[12]

In the field of the polar organometallic chemistry, the use of bimetal bases allows 'synergic' reactions that cannot be reproduced by the corresponding monometal reagents. The contribution of Manfred Schlosser to this field was huge, in particular with the development of alkali metal-alkali metal mixed superbases such as LICKOR, a mixture of butyllithium and potassium *tert*-butoxide, and their application to organic synthesis.[4,5] He used drawings to depict the behavior of the main alkali metal bases. In his "zoo", the shark and workhorse are LICKOR and LICNaOR, respectively, whereas simple butyllithium (LIC) and its chelate with TMEDA (LICMEDA) are the snail and duck.

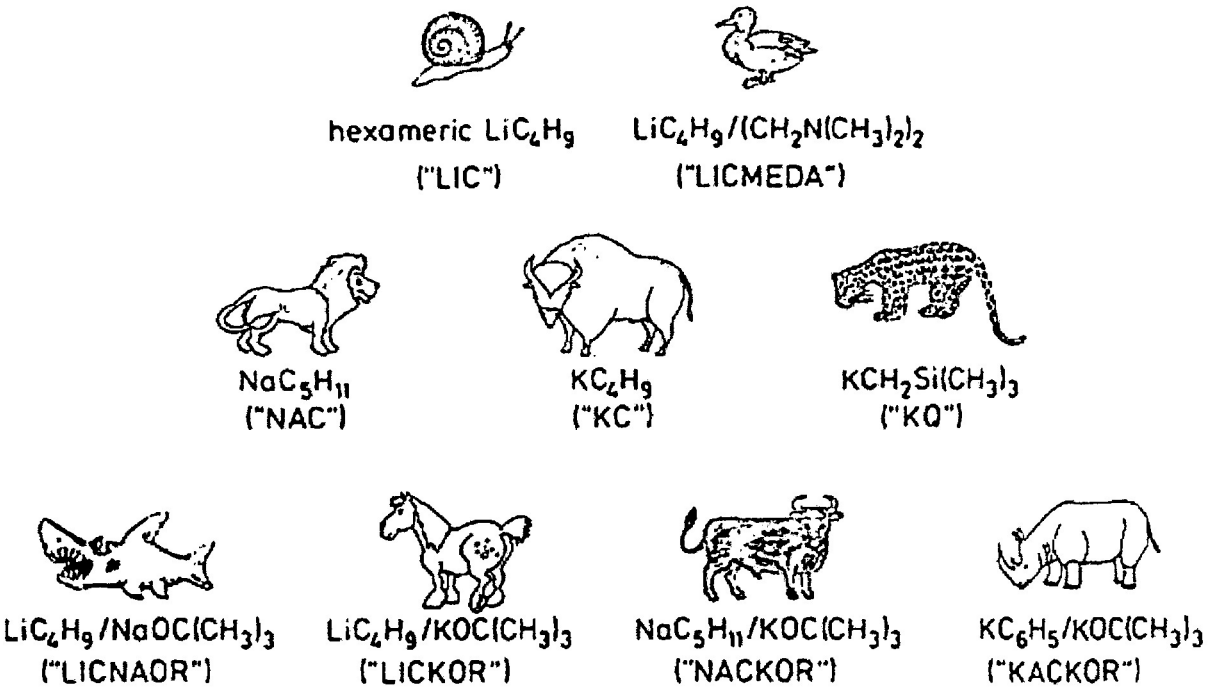


Figure 6. Manfred's zoo.[5]

More recently, the goal was to attain building blocks with uncommon substituent patterns available for research work in the life science area (fluorine-containing compounds, azines and diazines, azoles…) through selective deprotometalation and subsequent functionalization.[13-15] These efforts culminated in the concept of optional site selectivity and the development of a 'toolbox of organometallic methods for regiochemically exhaustive functionalization'.[16] The general goal was to convert simple aromatics, including heterocyclics, into all possible polar organometallic regioisomers, through a judicious choice of base, solvent and possibly ligand, as well as a better knowledge of the factors governing reactivity and regioselectivity, in order to afford a large range of functionalized scaffolds to achieve 'rational and maximal structure proliferation'.

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The last remarkable scientific contribution of Manfred Schlosser in collaboration with his Italian friends was made to physical organic chemistry with the rationalization and parametrization of the steric requirements of the most common organic substituents. The so-called B-factor arising from this collaboration is becoming a viable alternative to the already well-known A-factor.[17,18]

We could write much more about the scientific stature of Manfred Schlosser, but little is known about his human qualities, except in a superficial way. His scientific rigor, often accompanied with erudite citations and anecdotes referring to famous historical figures, intimated a vast humanistic, as well as scientific knowledge. As a teacher, his severe and sometimes provocative remarks at first seemed at least irritating but, after a deep reflection, such harshness became positive stimuli and valuable advice. His outward harsh temper hid, indeed, a very simple heart and a certain loftiness of feeling and great dignity at the same time. The adherence to own principles, generous willingness and, above all, reliability are the three main qualities that best represent the moral caliber of Manfred Schlosser.



Figure 7. Elsbeth Schlosser (center, deceased in 2004) at OMCOS-II, Dijon (France), summer 1983.

Unfortunately, the proverbial passion of Manfred Schlosser for–mountains, to which he devoted at least one day per week with hiking and perhaps, hazardous climbing, proved fatal for him. He disappeared during a hike in the Swiss mountains on June 26, 2013.

Those who had the chance of knowing Manfred Schlosser well, have lost a great teacher and a brotherly friend. This commemorative issue features the contributions of former collaborators, colleagues and friends of Manfred Schlosser. It is a testimony of the respect that we all have for him and the contribution of lasting value he made to the community.

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Figure 8. Manfred with friends in Italy on the occasion of the 2nd International Symposium on Organofluorine Compounds "Perugia Fluorine Days" (left: Trasimeno lake, right: Spoleto, 2010).

Prof. Florence Mongin
Chimie et Photonique Moléculaires
Institut des Sciences Chimiques de Rennes
UMR 6226, CNRS-Université de Rennes 1
Bâtiment 10A, Case 1003, Campus de Beaulieu
35042 Rennes, France
E-mail: florence.mongin@univ-rennes1.fr

Prof. Renzo Ruzziconi
Dipartimento di Chimica, Biologia e Biotecnologie
Università di Perugia
Via Elce di Sotto, 8
06123 Perugia / Italy

Prof. Qian Wang
Department of Chemistry and Biochemistry
University of South Carolina
631 Sumter Street
Columbia, SC 29208, USA

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