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Professor Samir Z. Zard

A tribute

This special issue of Arkivoc is dedicated to Professor Samir Z. Zard, on the occasion of his new status as Emeritus researcher and in recognition of his outstanding contribution to synthetic organic chemistry

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Prof. Samir Z. Zard was born in 1955 in Ife, Nigeria, of Lebanese parents who had left their home country eight years before, soon after their wedding. They had decided to join Sam's father's elder brother in Africa and to work with him in the cocoa business. At age six, Sam was sent to Lebanon to attend the Collège des Frères Maristes in Jounieh, a coastal town located about 15 km to the north of Beirut.

When he was about ten, he received a box for Christmas that contained a chemistry experimental set. It is this gift that triggered his passion for chemistry. Over the next few years, he ran a number of variously hazardous experiments, generally outside the frame of the educational system. The effects of a couple of these unsupervised trials were quite noticeable. In particular, a spectacularly loud explosion must have caused stupor and alarm in a wide neighborhood. It occurred in a deserted area, and may have remained a local mystery. Indeed, the perpetrator was never caught, having made sure he would be far away at the moment of the blast, sitting quietly in his classroom.

At the age of 18, Sam was admitted to the American University of Beirut (AUB), where he studied chemistry. He had nearly completed his BSc when the dangerous situation caused by the outbreak of the Lebanese civil war forced him to interrupt his studies and eventually leave the country in November 1975. After a few weeks of uncertainty, he was admitted to Imperial College London in January 1976. Two years later, he graduated with First Class Honours and was offered a position by Professor Sir Derek Barton to undertake a PhD under his supervision. Professor Barton informed him that he was about to become the new director of the *Institut de Chimie des Substances Naturelles* (ICSN) in Gif-sur-Yvette, France, and asked if he would be ready to follow him.

Thus, Samir Zard moved to France. He was supervised by Dr William B. Motherwell, who had noticed him during laboratory sessions at Imperial College. At the ICSN and under the guidance of such great chemists, Sam benefitted from a very stimulating environment and learned to follow a scientific approach for which he was certainly already prepared. This approach is based on curiosity (one of Sam's many qualities), rational thinking and the exploitation of unexpected results, with special attention to the understanding of reaction mechanism.

Sam defended his PhD in 1983, after very fruitful work dealing mostly with problems in steroid chemistry. Quite remarkably, he became a permanent researcher in the French "Centre National de la Recherche Scientifique" (CNRS) as an "attaché de recherche" while he was still a graduate student. He continued working with Prof. Barton at the ICSN until 1986, when the latter reached the age of retirement in France and consequently decided to move to Texas A&M University.

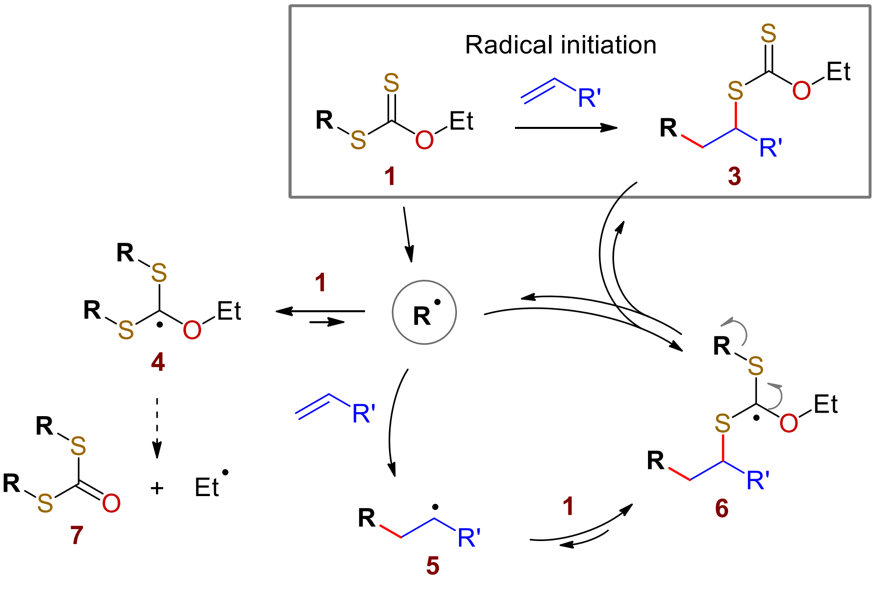
Sam then joined the Department of Chemistry of École Polytechnique, Palaiseau, to begin his independent career. In 1993, following a proposal by Prof. Pierre Potier, who was then the director of the ICSN, he took over laboratory space in Gif-sur-Yvette and started a long collaboration with Dr Béatrice Sire, a very important co-worker and a fine experimenter, whose supervisor, Dr Stéphane Géro, had just retired. She was given by the students in Sam's group, the affectionate nickname "la maman du labo", i.e. the mother of the laboratory. Indeed, on top of her research work with Sam, she took care of many of the practical problems associated with running the group, with kindness, enthusiasm and dedication, until her retirement in 2017.

For seven years, Sam's research activities were then conducted at École Polytechnique, as well as at the ICSN, which are located a few kilometers apart. His time was thus divided between the two sites, until he successfully obtained a full professorship at École Polytechnique, in the year 2000, and moved his ICSN team there. Since then, he has unwaveringly continued to devote his extraordinary energy and enthusiasm to the progress of organic chemistry, with special care to identify and solve important synthetic problems.

Scientific achievements

Sam's most famous, and perhaps most important contribution is the whole new branch of radical chemistry he discovered and explored, based on xanthates and related dithiocarbonyl derivatives such as trithiocarbonates, dithioesters, and dithiocarbamates. Most of the studies were conducted on xanthate radical precursors **1** (Scheme 1), in which the group of interest is located at a sulfur atom of the dithiocarbonate, rather than at the oxygen atom, as in xanthates **2** employed in the Barton-McCombie deoxygenation reaction (see Scheme 2).

Sam's curiosity and eagerness to understand led him to realise the potential of these molecules when he carefully analysed some unexpected results observed in the Barton group.[1] This thinking resulted in the introduction of a new, general carbon-carbon bond-forming radical reaction, in which the starting xanthate **1** undergoes the formal insertion of a non-activated olefin to produce a new xanthate **3** (Scheme 1).[6,7,13,20] According to the simplified mechanistic picture shown, the radical $R^\bullet$, which can be conveniently generated using simple initiation systems, such as dilauroyl peroxide (DLP)/heating or triethylborane/oxygen, reacts reversibly with the starting xanthate **1** to produce the highly stabilised and poorly reactive radical species **4**. The effect of this process is to "store" $R^\bullet$ in the form of this semi-persistent radical **4**. This considerably reduces the concentration of $R^\bullet$ in solution, thereby limiting unwanted radical-radical interactions and giving it sufficient time to participate in comparatively sluggish events, such as the addition onto non-activated olefins.[7] The resulting radical **5** can then be trapped by the starting xanthate **1**, in the same manner as the radical $R^\bullet$. This is a reversible reaction. However, when $R^\bullet$ is more stabilised than radical **5**, fragmentation of the ensuing radical **6** preferentially leads to the xanthate adduct **3** and the regeneration of $R^\bullet$, to effectively propagate the radical chain.



Scheme 1. The radical addition of xanthates **1** onto non-activated olefins.[6,7,13,20]

A conceivable side reaction of radical **4** would be the alternative cleavage of the ethyl-oxygen bond to give the carbonyl derivative **7** and an ethyl radical. This is disfavoured by the higher strength of this C-O bond, compared to a C-S bond, as well as by the production of a non-stabilised primary radical. Consequently, **4** plays the role of a stabilised reservoir of $R^\bullet$ particularly efficiently, with unwanted side reactions seldom occurring.

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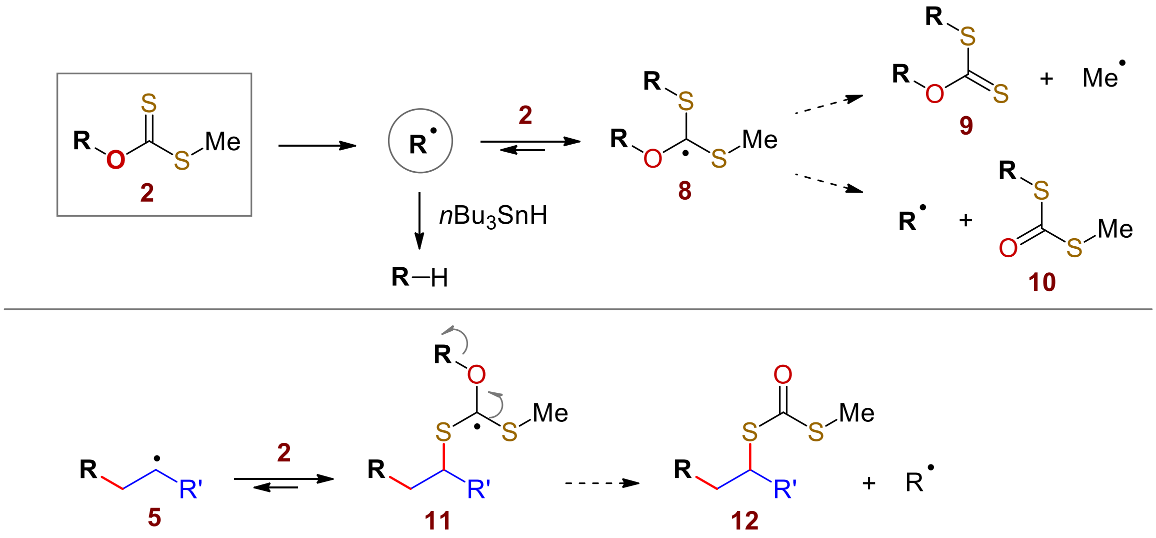
Importantly, the xanthate product **3** can play a similar role to **1** in the capture of free radicals and their storage in stabilised forms. This ensures that the semi-persistent radical effect is preserved all along, as the starting xanthate **1** is gradually converted into **3**.

It is interesting to compare this situation with the behaviour of xanthates **2** employed in the Barton-McCombie reaction. Indeed, although this reaction is a valuable tool for the production of deoxygenated products, it cannot be extended to more difficult intermolecular processes. One reason is that unwanted side-reactions of the highly stabilised radical **8**, which is analogous to **4**, are more likely to occur than in the case of the latter (Scheme 2, top). In particular, irreversible cleavage of the R-O bond, although it does regenerate the R• radical, represents a net conversion of **2** into the compound **10**, which is not a xanthate and cannot play a role in the generation of stabilised radical species. Other problems for a hypothetical addition reaction onto a non-activated alkene lie in the final propagation step and in the nature of the product **12** (Scheme 2, bottom). Indeed, release of the latter from the intermediate **11** requires C-O bond cleavage, which is comparatively more difficult. Moreover, just like **10**, the addition product **12** would not be able to participate in the indirect reversible storage of active free radicals. The semi-persistent radical effect, would thus be lost progressively, along with the consumption of the starting xanthate **2**.



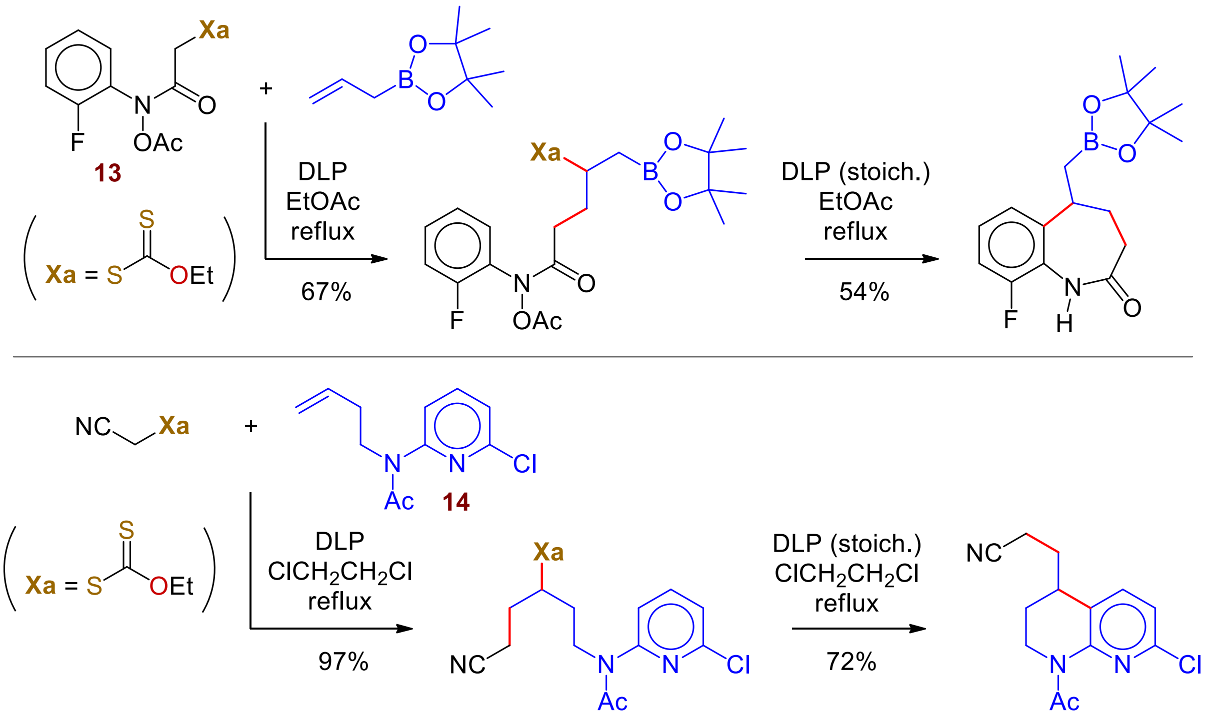
Scheme 2. Some aspects of the reactivity of xanthates **2** used in the Barton-McCombie deoxygenation reaction.

To summarise these considerations, the seemingly minor change of using xanthates **1** rather than **2** dramatically widens the range of reactions that can be performed: all sorts of kinetically demanding transformations can be achieved, which would give poor results starting from xanthates of type **2**.

If desired, simple reduction of the radical R• by hydrogen atom abstraction remains possible and efforts have been devoted to carry out this reaction under tin-free conditions. One particularly attractive solution consists of using isopropanol as the hydrogen atom donor which, incidentally, also works starting from Barton xanthates.[7,10]

Over the years, countless examples of intermolecular radical additions of xanthates onto olefins (as in Scheme 1) have been reported by Sam's group,[13] as well as by others. These involve various molecules and functional groups. In this respect, Sam has demonstrated the utility of his reaction for the introduction of a wide range of valuable chemical functions, such as amino groups[10,13] and boronic esters.[10,17,19] Overall, a complete toolbox for the construction of organic skeletons and the expedient introduction of functional groups was developed.

The possibilities offered by this chemistry include cyclisation processes with remote unsaturated functions which, typically, are C=C double bonds or aromatic groups. Successful examples include Minisci-type radical additions onto nitrogen-containing heteroaromatic compounds.[15] All these cyclisation reactions can be combined with earlier intermolecular radical additions, in order to assemble a suitable cyclisation precursor. This can be done in two ways: the aromatic moiety participating in the final cyclisation can be located on the same molecule as the initial xanthate reactant, e.g. **13**,[14] or it can be attached to the olefin partner, e.g. **14** (Scheme 3).[15]



Scheme 3. Examples of xanthate addition-cyclisation sequences, illustrating two modes of assembly of the xanthate precursor for the cyclisation step.[14,15]

The utility of these methods has been demonstrated by several expedient syntheses of natural products, such as (±)-cinnamolide,[6] (±)-methylenolactocin,[7] (±)-lepadin B,[13,23] (±)-10-norparvulenone,[13] (±)-*O*-methylasparvenone, xestamines C, E, and H,[20] as well (±)-hirsutic acid.

Among intermolecular transformations, particularly interesting carbon-carbon bond-forming processes involving sequential radical addition and β-fragmentation steps were developed, to achieve net allylation or vinylation of the starting organic fragment bearing the xanthate group. Several suitable reactants were identified for allylation reactions, such as allyl sulfones or allyl diphenylphosphine oxides.[13,20,23] A particularly powerful variation relies on the use of fluoropyridinyloxy derivatives of allylic alcohols, e.g. **15** (Scheme 4).[13,16] Concerning vinylation reactions, 2,2-dichlorovinyl ethyl sulfone was shown to be a valuable partner, with the gem-dichlorovinyl moiety offering attractive possibilities of further functionalisation, for example through its conversion into an alkyne by the Corey-Fuchs reaction.[13,20,23]

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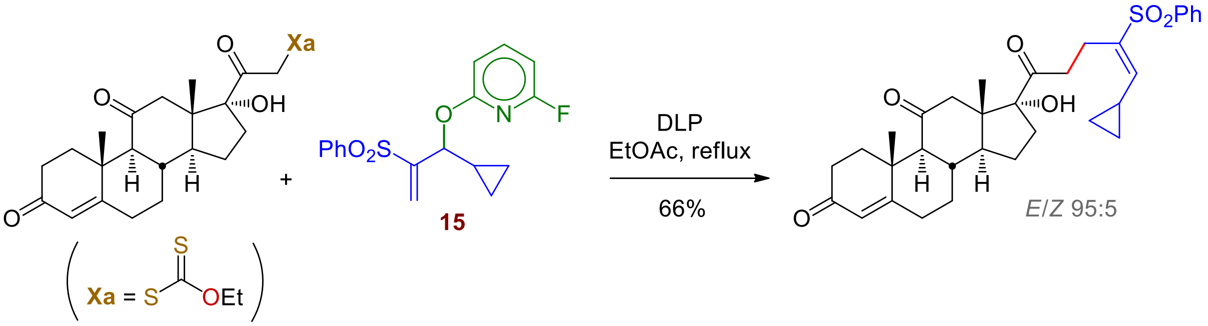
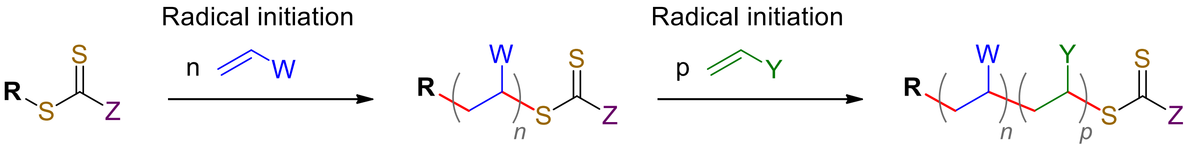


Scheme 4. Example of radical allylation of a xanthate with a fluoropyridinyloxy derivative.[16]

Sam's radical addition of xanthates onto olefins has also found applications in polymer chemistry. Indeed, the product of this transformation is also a xanthate. The addition reaction can thus be used as a propagation step in the free-radical chain polymerization of an olefin. Investigations in this direction gave birth to the RAFT-MADIX process. They established that the living polymers thus obtained have a low polydispersity index and can be used to prepare block copolymers in a controlled fashion (Scheme 5).[22] This technology has become extremely popular, as shown by the innumerable publications and patents that have appeared on the topic, as well as by various industrial applications.



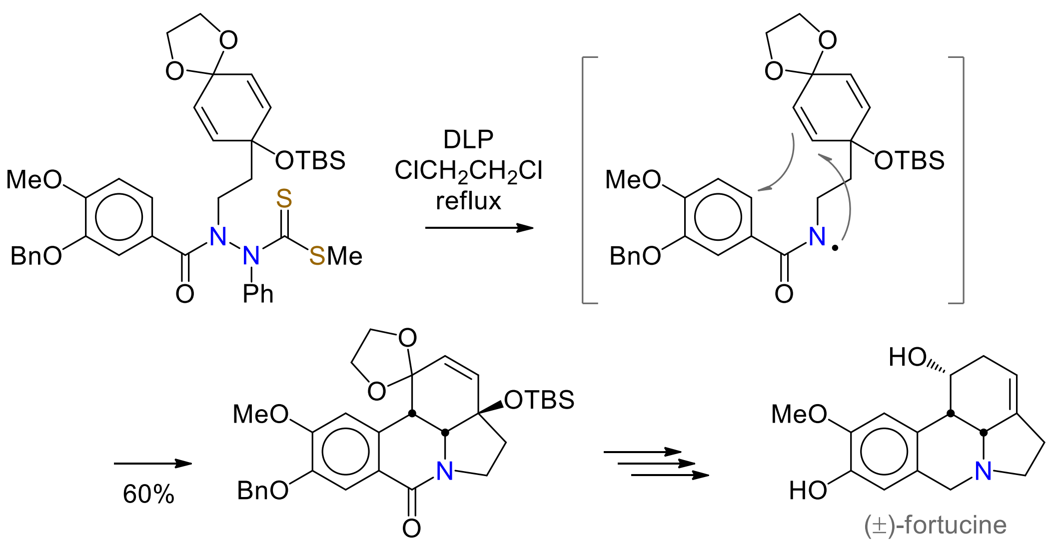
Z = Ar, CR^1_3, OR, SR, NR^1R^2,

Scheme 5. The RAFT-MADIX polymerisation process.[22]

It should be mentioned that Sam's group also devoted significant efforts to the study of the non-radical chemistry of xanthates. *S*-Propargyl xanthate derivatives proved especially interesting. Their reactivity formed the basis for the introduction of an original and advantageous alternative to the Mitsunobu reaction.[21]

However, these outstanding findings and developments in xanthate chemistry should not overshadow a remarkable sum of contributions in various other areas, of which only a few can be presented here.

First, to go back to free radical chemistry, extensive work has been carried out by Sam and his co-workers to develop methods for the generation and capture of nitrogen-centred radicals, in particular iminyls and amidyls. These investigations have led to the total syntheses of several complex natural products: (−)-dendrobine, *γ*-lycorane, (±)-13-deoxyserratine,[8,11] (±)-aspidospermidine[11] and (±)-fortucine (Scheme 6).[12] These add up to the already mentioned total syntheses completed using the radical chemistry of xanthates.



Scheme 6. Total synthesis of (±)-fortucine.[12]

In an entirely different field, the Barton-Zard reaction, which Sam would rather see called the Schöllkopf-Barton-Zard reaction, in recognition of previous work by the late Ulrich Schöllkopf, has become a popular method for the preparation of pyrroles, especially useful as building blocks in the synthesis of porphyrins (Scheme 7, top).[2] This particular achievement is in the context of wider efforts devoted to the exploration of the chemistry of nitro compounds. In this respect, the use of ethylenediamine and its congeners as efficient catalysts for the condensation of nitromethane with hindered or unreactive ketones, as well as the [2,3] sigmatropic rearrangement of allylic nitro derivatives to give ultimately allylic alcohols (Scheme 7, second transformation),[5] are especially noteworthy. Another major contribution is a new general synthesis of alkynes, which proceeds by nitrosation of 5-isoxazolinones, in the presence of iron(II) sulfate (Scheme 7, third transformation).[3,9] The development of this reaction originates from intriguing literature results reported by Sharon L. Abidi. Careful investigation led to an understanding of the mechanisms at play and to the design of a truly practical and reliable method. Another example of a reaction that was developed by the rational analysis of previous results is a valuable and popular new synthesis of trifluoromethyl ketones. It is based on the generation of a pyridinium betaine from an acyl chloride, followed by trapping with trifluoroacetic anhydride (Scheme 7).[4] Finally, going back to the Barton years, and often within the framework of collaboration with industry, Sam and his co-workers have contributed to solving several important problems in steroid chemistry.

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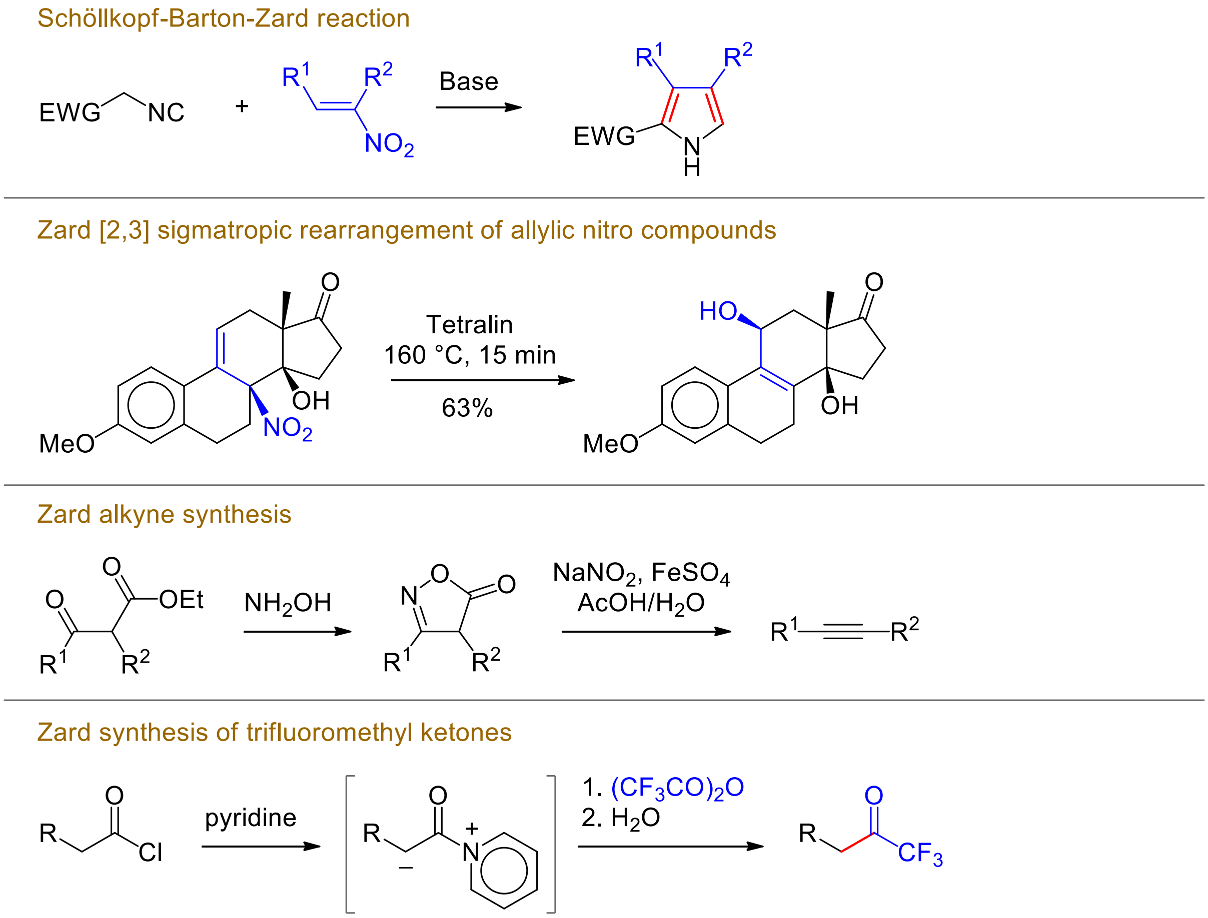

Scheme 7. Selected reactions developed by Prof. Samir Zard and his co-workers.

Retrospective information and prospects

Through hard work fuelled by enthusiasm and creativity, Prof. Samir Zard has achieved important contributions in several areas, of which only a glimpse is presented in the preceding paragraphs. To date, his work has led to over 385 publications and 40 patents. Sam has given more than 660 invited lectures and seminars, including around 80 plenary lectures at national and international events. He was the President of the Department of Chemistry of École Polytechnique for 14 years, from 2000 to 2014, and served as a regional Editor of *Tetrahedron Letters* for 12 years, from 2004 to 2016.

His achievements have also been recognised by a number of academic awards and honours, including the Silver medal of the CNRS in 2007, the presidency of the Bürgenstock conference in the same year, the Grignard-Wittig Award of the German Chemical Society in 2008, the Chair of the organising committee of the 10th Tetrahedron Symposium in Paris in 2009, which gathered over 1000 participants from 60 countries and a memorable choice of invited speakers, the Woodward Distinguished Lectureship at Harvard University in 2010, the Grand Prix Joseph-Achille Le Bel of the French Chemical Society in 2012, the inaugural Barton Distinguished Lectureship in Creativity in Organic Synthesis at Imperial College in 2012, the Arthur Birch Lecture 2015 at the Australian National University in Canberra, and the Liversidge Lecture 2015 at the University of Sydney.

Prof. Samir Zard received the “Croix de chevalier dans l’ordre de la Légion d’Honneur” in 2007. He was elected Foreign Corresponding Member of the Academy of Sciences of Lisbon in 2015 and was awarded a *honoris causa* doctorate of the American University of Beirut in 2016.

Sam is now an emeritus Director of Research, exceptional class, in the CNRS and an emeritus professor at École Polytechnique. This means he has now stopped his teaching activities and cannot supervise PhD students any longer. Nevertheless, he remains fully involved in his research projects and everyone at the LSO laboratory can testify that he has lost none of his enthusiasm, energy and curiosity.

Outside the laboratory

Sam met his wife Lydia Valente, a chemist herself, during the early Barton years in Gif-sur-Yvette. They have been married for 42 years. Highly supportive, open, generous, and as full of energy as Sam, she is also an outstanding cook, always ready to experiment with new recipes and to share the marvellous fruits of her efforts with family and friends. They have two children. Michael (born 1983) obtained an MBA from the *Institut Européen d'Administration des Affaires* (INSEAD) and is an engineer in computer sciences. Emilie (born 1987) is a practicing medical doctor. A part of Sam's family still lives in Lebanon and he makes a point to travels there as often as possible, especially to visit his elderly mother who lives in the suburbs of Beirut. After each trip, he invariably treats his colleagues in the laboratory with delicious Lebanese pastries. Now and then, he also generously offers seed packets of original vegetables from the Near East, such as Lebanese cucumbers.

Sam and Lydia share a passion for gardening. In spring, their house is surrounded by a symphony of colours and scents, coming from the harmonious arrangement of all sorts of shrubs, flowers and trees. Their garden is unquestionably one of the most beautiful in the area. Sam has learnt to master the technique of layering, to multiply roses or fig trees. He is especially keen on growing vegetables and is informally in charge of this particular task. His approach is reminiscent of his scientific work, relying on an interplay of literature analysis, daring experimentation and careful observation. Various "starting materials": seeds or seedlings of beans, green peas, cucumbers, courgettes, pumpkins, tomatoes, including original or rare varieties, are employed. Different techniques and conditions are explored as well, although unlike in the laboratory, some parameters cannot be fully controlled, the most obvious one being the weather.

Prof. Samir Zard also enjoys very much listening to music and reading, in particular non-fiction essays dealing with History, Geopolitics or Politics. However, these quiet activities often have to be left aside when, to their delight, his young grandchildren come over to Sam and Lydia's place.

To finish, it is worth pointing out that Prof. Samir Zard is a widely respected person, not only for his scientific achievements but also for his kindness and generosity, as well as for the inconspicuous support he has continuously provided to a number of colleagues in the world, especially young researchers (including myself, some years ago). This recognition could be measured by the very warm messages I received from several contributors of this special issue when I first contacted them.

Prof. Samir Zard and just a few of his numerous former students, together with Dr Béatrice Sire, during the barbecue party organized in Summer 2022, on the occasion of Sam's retirement from his teaching activities.
First row, from left to right: Nicolas Legrand, Stéphanie Seguin, Béatrice, Jérôme Cassayre.
Second row, from left to right: Gilles Ouvry, Sam, Frédérique Bertrand-Wendeborn, Benoît Sortais.

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