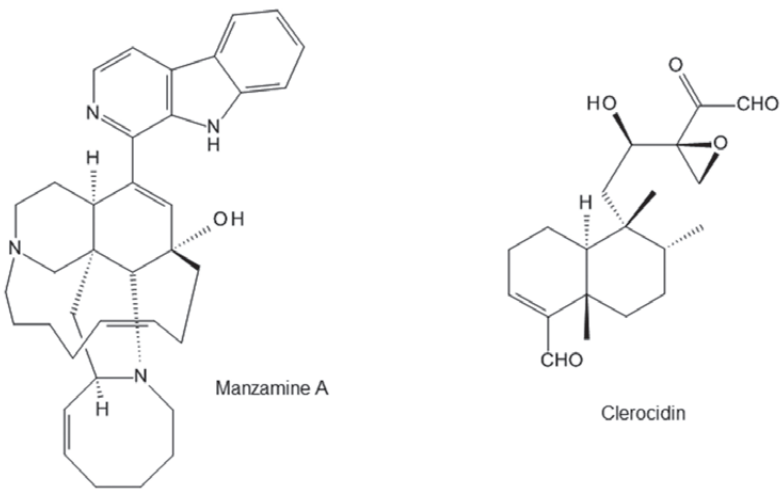
Raphaël DUMEUNIER
Rue de Fluh, 68220 Leymen, France,
e-mail: raphael.dumeunier@gmail.com

A personal selection of Pr I.E. Markó's Contributions and Achievements in Organic Chemistry

It is by no means an easy task to summarize the scientific achievements of Istvan E. Markó's *group*, but one thing is quite certain: that he would have been happy with this phrasing. Indeed, Markó did always put the group and its individuals into the light, whenever he was given the chance to. Even though it was clear to everyone where the brilliant ideas came from, he always made a point to highlight how great were the achievement of the students, as well as their own intellectual and, obviously, experimental contributions. It is also relatively safe to say that such contributions spanned over a huge breadth of organic chemistry, and that Markó's interests have always been extremely varied. In this paper, we will see indeed that Markó has never hesitated exploring any areas where his interest had been risen, regardless how subjectively "less conventional" they may have seemed at first sight. Very high pressure reactions, pyrolysis, electrochemistry, the use of super-critical CO_2 as solvent or freshly cut pieces of vegetables as catalysts into reactions were indeed considered as important and received equal attention as the more classical (but obviously still very innovative) methodologies and total syntheses of the group.

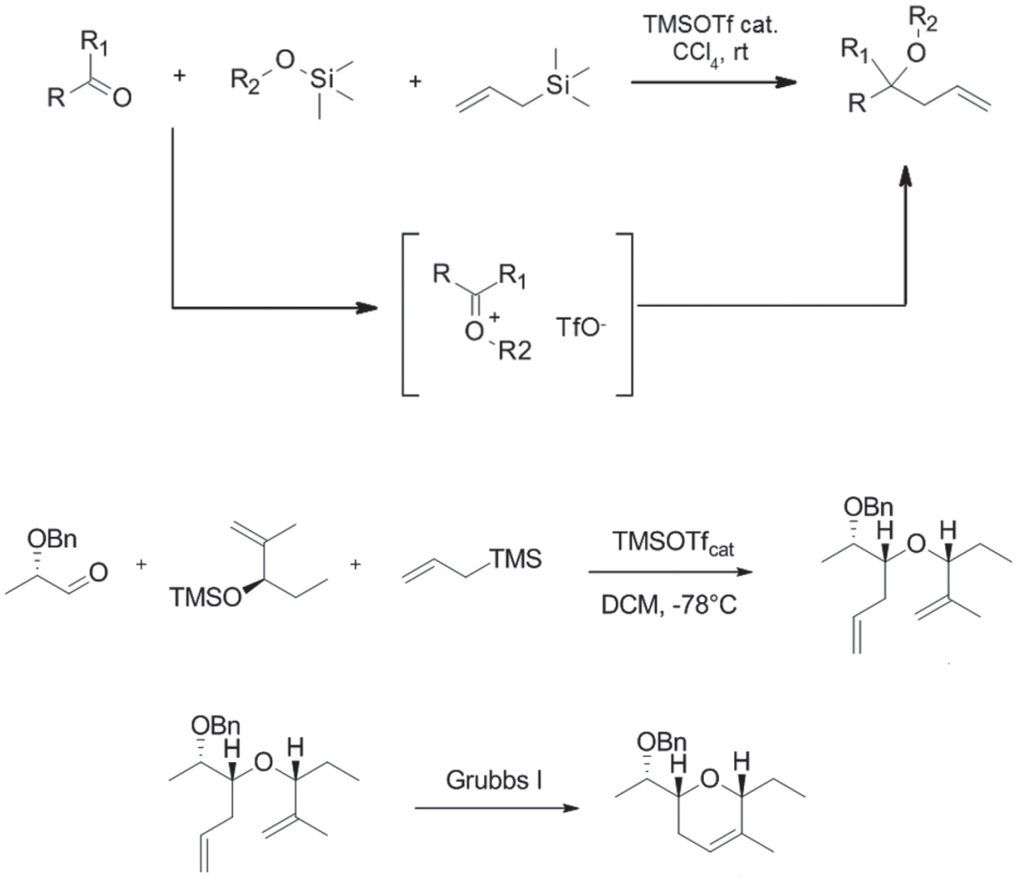
As an independent group leader and lecturer based in Sheffield, UK, Markó's initial interests lied at once into the development of novel methodologies to be used in total syntheses. From his very first publications in 1990, one can immediately learn indeed about novel methods based on radical mediated oxidations, but also read about initial advances towards the total syntheses of Manzamine [1] and Clerocidin [2] (scheme 1).



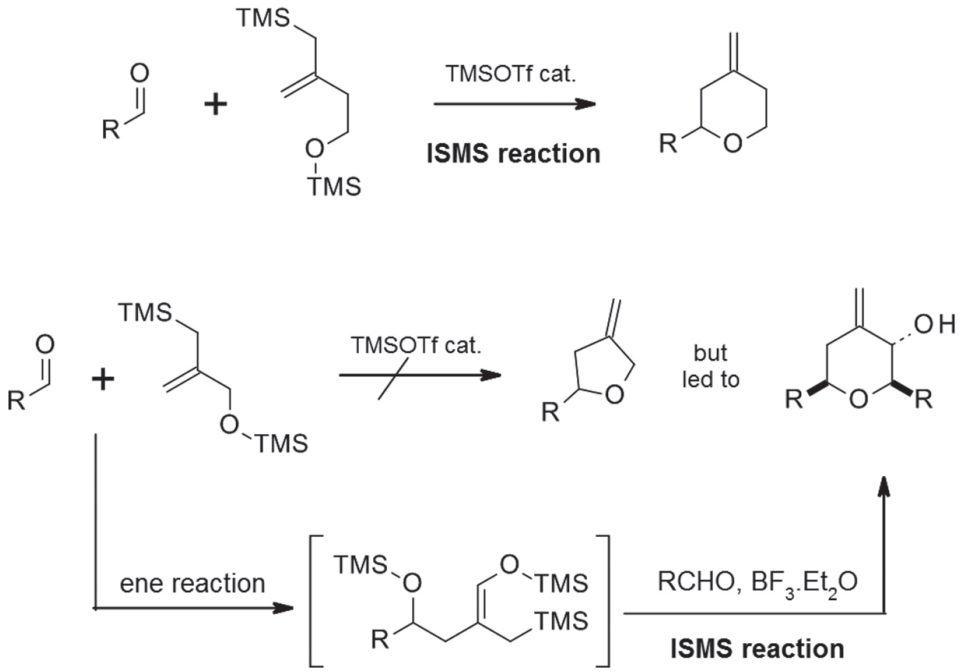
Scheme 1 – Very first targets of the Group, Manzamine A and Clerocidin

Clerocidin has potent antibiotic activities, essentially against gram-positive bacteria, and also some anticancer activities. If Markó's first foray into its synthesis was still undeniably influenced by his post-doctoral studies with B. Sharpless (epoxidations); the target remains nonetheless a quite complex molecule bearing many reactive functional groups (an α-keto-aldehyde, an epoxide, an α,β-unsaturated aldehyde). Manzamine A exhibits also many interesting biological activities, such as anti-inflammatories, anti-malarial, insecticidal, anti-bacterial and anti-tumor activities. It also has a more complicated architecture, displaying unique features; a complex target to start an academic career, one might say, but not a surprising one to those who knew Markó's admiration for the syntheses of alkaloids of R.B. Woodward. In Markó's own words [3] indeed, he acknowledged having been "fascinated by the elegancy, the conciseness and the apparent simplicity of the synthesis of Reserpine by R. B. Woodward", whom he called a "great master" and qualified his synthesis "simply magnificent". Markó would keep studying organic chemistry in a "classical" way, through total syntheses and the development of novel, useful and widely applicable transformations, but from the very start also, his complementary taste for less conventional approaches would already show up, for example by the use of triorganothallium reagents to convert acid chlorides into ketones in a single step, at room temperature [4, 5].

Shortly after those articles, Markó published the work of his very first PhD student, Dr Abdelaziz Mekhalfia, displaying a new transformation which would yet accompany many generations of students, namely, the silyl modified Sakurai (SMS) multicomponent reaction (scheme 2).



Scheme 2 - The SMS reaction, a catalytic, one-step, formation of homoallylic ethers from carbonyl derivatives, and its application in a fragment synthesis of (+)-Ambruticin [6].



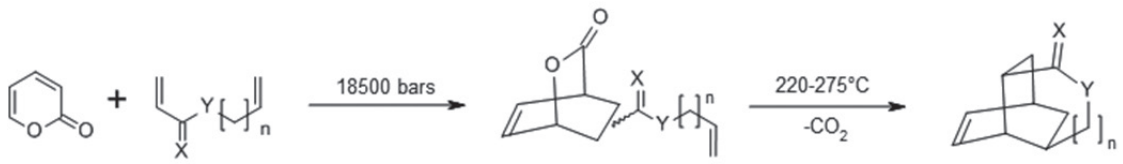
Scheme 3 – The seminal ISMS [8], its failed application to the synthesis of *exo*-methylene-furans at the origin of the discovery of a tandem ene/ISMS [9].

The SMS reaction rapidly evolved across the years, and its major variation remains today the ISMS Cyclisation (Intramolecular Silyl Modified/Mediated Sakurai Cyclisation), also called the IMSC (Intramolecular Sakurai Cyclisation) depicted in scheme 3. The ISMS itself was in turn at the origin of further unexpected findings. Indeed, trying to prepare *exo*-methylene-furans derivatives by ISMS led to the serendipitous discovery of a tandem "ene reaction/ISMS", also utilized later on as a novel methodology in the group for various total syntheses (Polycavernoside A, Amphidinol, Pseudomonic Acid, Milbemycin β3 or Methyl Monate C, etc.) [7].

Once again, in the early nineties, while new methodologies were already being developed and applied to natural product syntheses, Markó would keep walking less trodden paths, like for example by assessing very high pressure reactions affected by changes in the entropy of activation (scheme 4).

This research led part of the group into the field of Tandem Pericyclic Reactions (TPR), later used for the syntheses of gibberellic acid and the zizaenes [11], or into the study of radical-initiated rearrangements of bicyclo-[2,2,2]-lactones [12], followed by Pd-catalyzed rearrangements towards the oxa-triquinane core structure [13].

It would now fall well beyond the scope of this paper to review comprehensively the group achievements, as the research went on to cover quickly most major fields of organic chemistry (organo-metallic catalysis and organocatalysis, radical chemistry, cationic, radicals or pericyclic rearrangements, novel oxidations and reductions, polycyclisations, hydrosilylations,



Scheme 4 [10] - An ultra-high pressure Diels-Alder reaction followed by tandem decarboxylation / Intramolecular Diels-Alder reaction at high temperature.

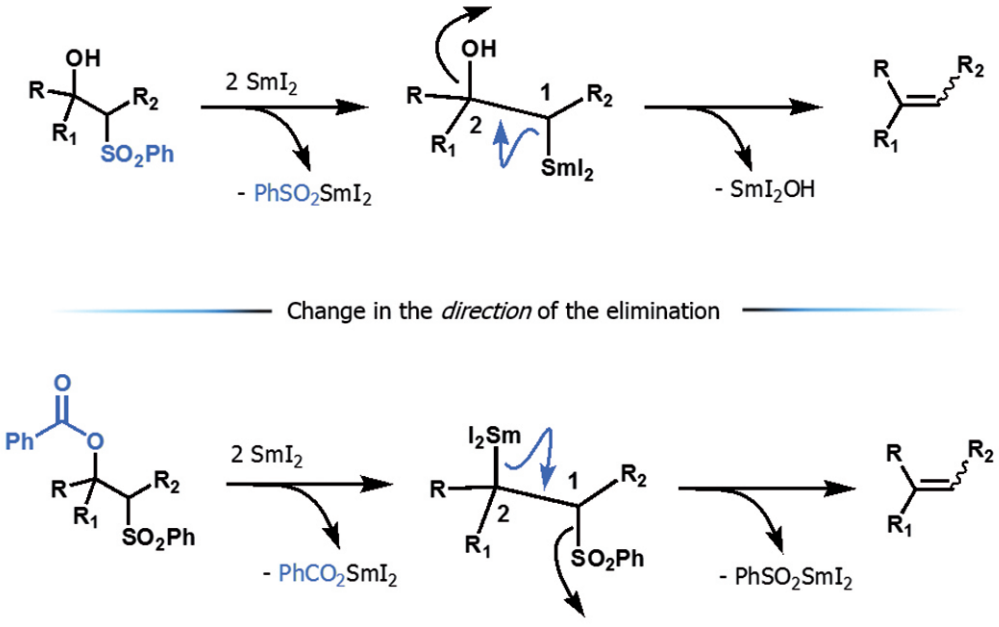
electrochemistry, hydroaminations, development of new catalysts and ligands, heterocyclic chemistry, novel olefinations or deoxygenations, enzymatic catalysis using plant extracts, etc.).

After having shown the initial steps of Markó's research, only a few of the important reactions he further discovered will be highlighted, as well as something close to his heart, namely the understanding of reaction mechanisms, and the gaining of mechanistic insights through carefully chosen, targeted investigations. We will also show how Markó could make use and create value out of chance findings, recognizing humbly while staying true in the telling, the key importance of serendipity in discovering new transformations.

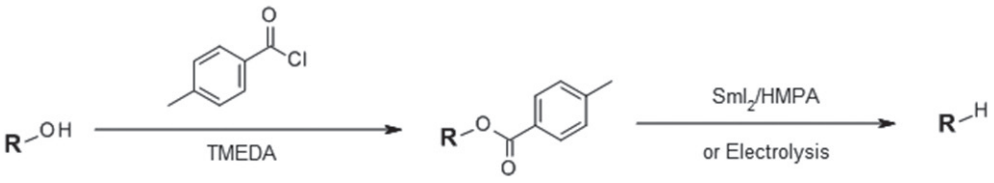
Markó had a gift to notice "odd" experimental results and would propose immediately a correct hypothesis. For example, already in 1997, Markó noticed that an alcohol function present in a catalyst of a Baylis-Hillman reaction would increase the rate of the reaction [14]. Instead of accepting contemporary explanations [15], he hypothesized about the potential role of *any* alcohol, external to the catalyst, which would actually ease the rate determining step (RDS) by shuttling protons through Hydrogen-bonds, which RDS he then speculated to be the prototropy occurring in any Baylis-Hillman reaction. Both remarkable intuitions were actually to be confirmed close to 10 years later, the one on the Rate Determining Step by McQuade [16], and the one on the effect of alcohols on the rate of reaction, by Aggarwal [17].

This example shows Markó's huge power of intuition, backed up by a dedicated attention to experimental observations, and a humble behavior regarding serendipitous findings. But as telling as the Baylis-Hillman example may be, it would not give a fair representation on how Markó built on such experimental findings. Usually indeed, much more work would stem from those unexpected observations, numerous ideas would quickly branch out, as their fruits would be passed on many times, from the hands of a generation of students to another.

In that respect, one of the important breakthroughs made within the group was about the reductions of β-sulfoxy-benzoates by single electron reducing agents. If the expected products were obtained easily (the corresponding olefins, from the well-known Julia-Lythgoe olefination); by using SmI_2(/HMPA) as reducing agent, Markó discovered that *the mechanism of the reaction may not have been the same* [18]. From the careful observations of different reduction rates between analogous β-hydroxy-



Scheme 5 – The different mechanisms hypothesis for the synthesis of alkenes by using SmI_2(/HMPA)



Scheme 6 – The Markó–Lam deoxygenation

and β-benzoate-sulfones, it was surmised that if in the first case the sulfone was reduced (conventional mechanism), in the second case it might have been that the benzoate group was reduced instead (scheme 5).

This observation led to many different studies later in the group, from its verification and generalization [19], to many variations, like the replacement of sulfones by sulfoxides (the development of a new variant of the Julia olefination) [20] and many applications in total syntheses (Polycavernoside A, Jerangolid D, (R)-(+)-goniothalamin) [21]. More practical also was the idea to avoid the use of sulfones/sulfoxides as leaving group and to simply deprotect esters [22], or to trap the intermediate radical [23] or even to "deoxygenate" alcohols by converting them to toluates and reducing them with SmI_2/HMPA [24]. Later on, reducing toluates by using electrolysis [25] finally led to the naming of this reaction, the "Markó–Lam deoxygenation" depicted in scheme 6.

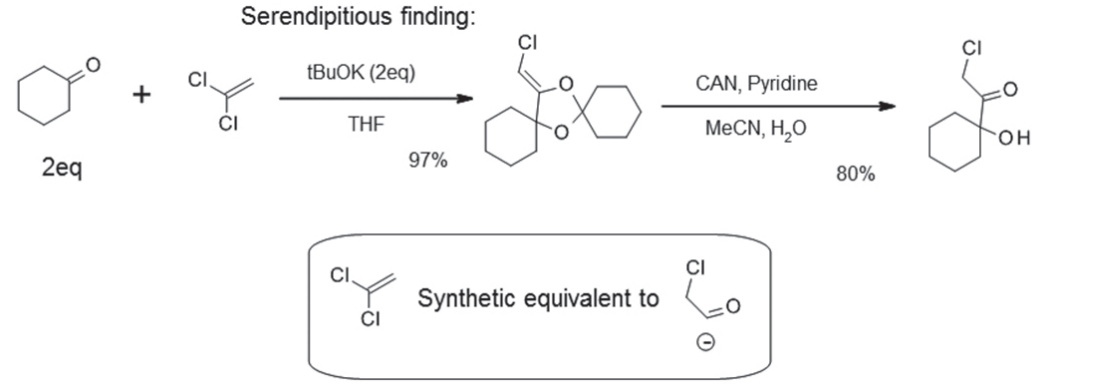
This evolution of an observation to a named reaction gives a rather typical example on how, within the lab, an initial experimental observation would lead to mechanistic hypotheses, understanding and verification; then to various developments in the group, from novel methodologies to natural product syntheses.

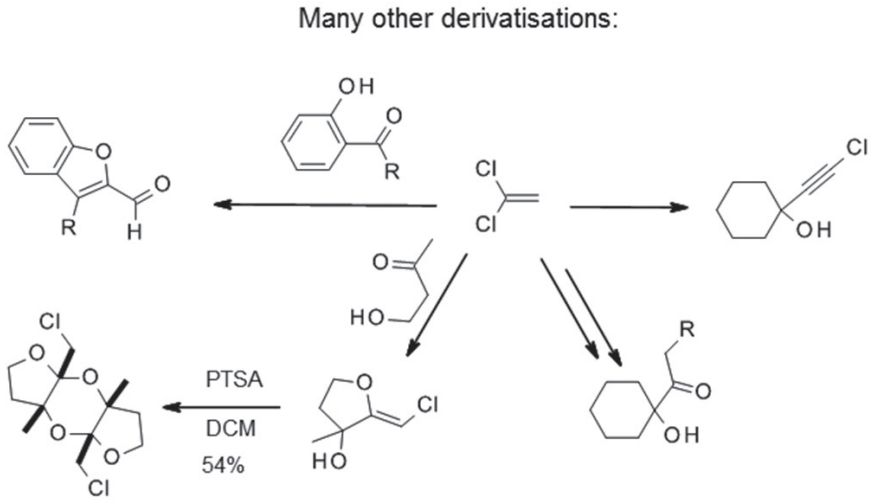
Other examples may be the serendipitous discovery (made once again while rationalizing odd experimental behaviors) that Et_2AlSPh reacts with aldehydes and regenerates them by simple hydrolysis [26]. This led to the development of a very useful method for the chemoselective reduction of ketones to alcohols in the presence of aldehydes [27]. A more recent case was the discovery that, while trying a Pd-catalyzed coupling between a ketone and 1,1-dichloroethylene, the latter was actually deprotonated twice by tBuOK before going through uncatalyzed reactions (addition and cyclisation) with the carbonyl derivative. After careful structure elucidation, this finding led, after mechanistic studies (NMR experiments, kinetic measurements, scope evaluation) [28] and rationale hypotheses, to the development of new methodologies, some even patented in collaboration with an external company [29] for the synthesis of kinase inhibitors (scheme 7).

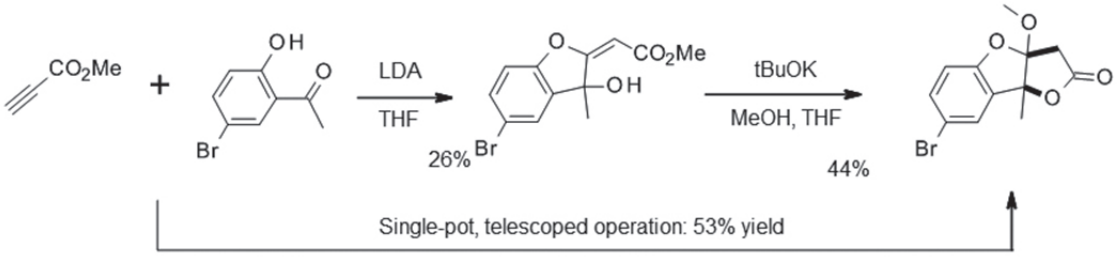
One could exemplify this over and over, but as a last example, nobody can describe this way of research better than Markó himself. Thankfully, we have indeed an enlightening, personal account of such development of a specific methodology, namely, the CAN deprotection of acetals under mild and neutral conditions, as an *account of chemical research* [30]. The fascinating "story of a synthetic venture" unfolds to the enthralled reader, from a humble start by a chance finding until the final acknowledgements to all the former co-workers who participated in the project, all carefully named throughout the story telling which Markó was so gifted at.

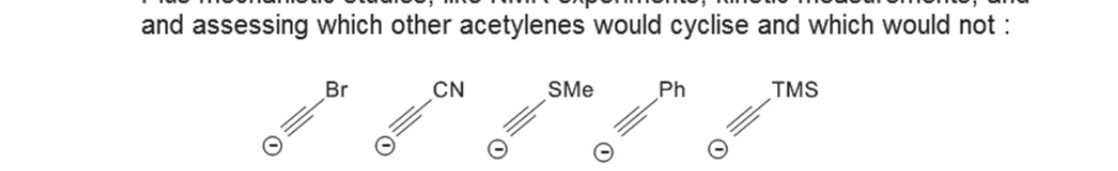
Before concluding, two major areas of research of the group cannot go without a special mention: first, the hydrosilylation [31], and second, the Cu catalyzed oxidation of alcohols to aldehydes and ketones [32]. The group contributions made to both methodologies were as important as to gain publication into *Science*; which is by itself a testimony to the talent of Markó.

Moreover, as conclusion, more minor papers – undeniably, as compared to S*cience* articles – do also deserve to be highlighted, as they are representative of a personality trait of Markó which





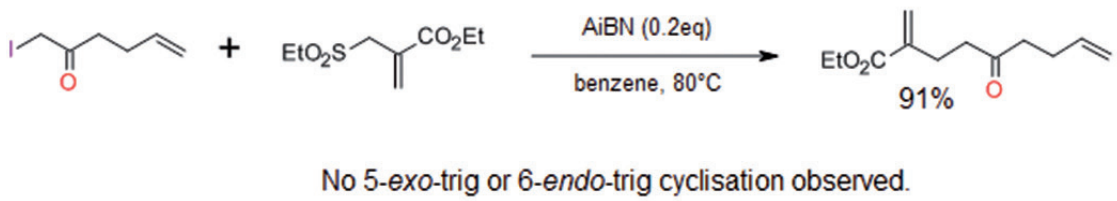




Scheme 7 – A typical use and development of a "chance" finding, made by careful experimental observations.

may not have appeared so far, but always did influence the way the research had been managed in the group. Anyone who ever met Markó would indeed have quickly noticed, the truly honest pleasure that he took when challenging the commonly accepted knowledge. Almost as a game, but always seriously, Markó would indeed initiate many discussions, sometimes engage into (lively) debates, but all for a reason; *in fine*, to bring more knowledge to the area under scrutiny. In chemistry, so many challenges were made, by Markó to his students and group members, that it became part of the group culture to create one's own knowledge by keeping some distance, if not always questioning, what was learned, before finally gaining confidence into one's own abilities. It would then raise the confidence of each members of the laboratory by the sharing of such soundly acquired knowledge. It also happened sometimes, that similar thought-provoking statements would show outside of the group and be published in the literature, like for example the questionable use of unaffordable triflate Lanthanides as simple sources of triflic acid (in some cases, the overlooked actual catalytic species) [33], or in other areas like radical chemistry, the statement that free-radicals located in the α-position of ketones are actually nucleophilic, and would not, as expected, behave as electrophilic species (Scheme 8) [34].

Reaching the end of this highlight paper on Markó's contributions and achievements, the difficulty mentioned in the very first sentence pales down faced to the impossible task to write the final words. So much more would be worth mentioning. Out of the two hundreds and more publications of the group, obviously, but also out of an indeterminate amount of material left unpublished, unfortunately, stories now likely to stay forever untold. However, as much as Markó's contributions and achievements are, from a personal perspective, undeniably great, creative, innovative, when not plain bright, I may also take the liberty to end up with another personal note. As one of Pr Markó's former students, I would like to highlight one more major achievement he made: to give so many of us a chance, and to take us from naïve, ignorant chemists-to-be to, hopefully, educated scientists and researchers. He did so by teaching us so much, of course, but far more than that: by giving us the means and the taste, to never stop teaching ourselves.



No 5-*exo*-trig or 6-*endo*-trig cyclisation observed.

Scheme 8 – Demonstrating that a α-keto-radical would prefer to react intermolecularly with an electrophilic, electron deficient partner, rather than intramolecularly, with a more electron rich alkene, even though such radicals were believed to possess electrophilic properties.

Références

[1] Chesney, Antony; Markó, Istvan E. *Synthetic Communications* (1990), 20(20), 3167-80.

[2] Bailey, Mark; Markó, Istvan E.; Ollis, W. David; Rasmussen, Poul R. *Tetrahedron Letters* (1990), 31(31), 4509-12.

[3] Markó, Istvan E. *Actualite Chimique* (2003), (4-5), 143-144.

[4] Markó, Istvan E.; Southern, J. Mike *Journal of Organic Chemistry* (1990), 55(10), 3368-70.

[5] Personal note: It would have been interesting to display a Mendeleev table on the desk of I.E. Markó and to ask him to color every atom squares he had worked with already with the group. A very high proportion would have been colored at once, and knowing his curiosity, I might say without risk that, apart (maybe) from the transient and the radioactive elements, it would have given him the impetus to color all the rest, given a few more years.

[6] Markó, Istvan E.; Bayston, Daniel J. *Tetrahedron* (1994), 50(24), 7141-56 / Pospisil, Jiri; Kumamoto, Takuya; Markó, Istvan E. *Angewandte Chemie, International Edition* (2006), 45(20), 3357-3360.

[7] van Innis, Livia; Plancher, Jean Marc; Markó, Istvan E. *Organic Letters* (2006), 8(26), 6111-6114 / Markó, Istvan E.; Bailey, Mark; Murphy, Fiona; Declercq, Jean-Paul; Tinant, Bernard; Feneau-Dupont, Jeanine; Krief, Alain; Dumont, Willy *Synlett* (1995), (1), 123-6.

[8] Markó, Istvan E.; Mekhalfia, Abdelaziz; Bayston, Daniel J.; Adams, Harry *Journal of Organic Chemistry* (1992), 57(8), 2211-13.

[9] Markó, Istvan E.; Bayston, Daniel J. *Tetrahedron Letters* (1993), 34(41), 6595-8.

[10] Markó, Istvan E.; Seres, Peter; Swarbrick, Terry M.; Staton, Ian; Adams, Harry *Tetrahedron Letters* (1992), 33(38), 5649-52.

[11] Markó, Istvan E.; Seres, Peter; Evans, Graham R.; Swarbrick, Terry M. *Tetrahedron Letters* (1993), 34(45), 7305-8.

[12] Markó, Istvan E.; Warriner, Stuart L.; Augustyns, Benoit *Organic Letters* (2000), 2(20), 3123-3125.

[13] Liao, Jyh-Hsiung; Maulide, Nuno; Augustyns, Benoit; Markó, Istvan E. *Organic & Biomolecular Chemistry* (2006), 4(8), 1464-1467.

[14] Markó, Istvan E.; Giles, Paul R.; Hindley, Nigel J. *Tetrahedron* (1997), 53(3), 1015-1024.

[15] Drewes, Siegfried E.; Freese, Susan D.; Emslie, Neville D.; Roos, Gregory H. P. *Synthetic Communications* (1988), 18(13), 1565-72.

[16] Price, Kristin E.; Broadwater, Steven J.; Jung, Hyun M.; McQuade, D. Tyler *Organic Letters* (2005), 7(1), 147-150.

[17] Aggarwal, Varinder K.; Fulford, Sarah Y.; Lloyd-Jones, Guy C. *Angewandte Chemie, International Edition* (2005), 44(11), 1706-1708.

[18] Markó, Istvan E.; Murphy, Fiona; Dolan, Simon *Tetrahedron Letters* (1996), 37(12), 2089-92.

[19] Markó, I. E.; Murphy, F.; Kumps, L.; Ates, A.; Touillaux, R.; Craig, D.; Carballares, S.; Dolan, S. *Tetrahedron* (2001), 57(13), 2609-2619.

[20] Pospisil, Jiri; Pospisil, Tomas; Markó, Istvan E. *Organic Letters* (2005), 7(12), 2373-2376.

[21] Jourdain, Pierre; Philippart, Freddi; Dumeunier, Raphael; Markó, Istvan E. *Tetrahedron Letters* (2009), 50(26), 3366-3370. / Pospisil, Jiri; Markó, Istvan E. *Tetrahedron Letters* (2006), 47(33), 5933-5937 / Pospisil, Jiri; Markó, Istvan E. *Journal of the American Chemical Society* (2007), 129(12), 3516-3517.

[22] Lam, Kevin; Markó, Istvan E. *Organic Letters* (2009), 11(13), 2752-2755.

[23] Lam, Kevin; Markó, Istvan E. *Organic Letters* (2008), 10(13), 2773-2776.

[24] Lam, Kevin; Markó, Istvan E. *Tetrahedron* (2009), 65(52), 10930-10940.

[25] Lam, Kevin; Markó, Istvan E. *Chemical Communications* (2009), (1), 95-97 / Lam, Kevin; Markó, Istvan E. *Synlett* (2012), 23(8), 1235-1239.

[26] Leclercq, Cedric; Markó, Istvan E. *Tetrahedron Letters* (2005), 46(42), 7229-7233.

[27] Bastug, Gulluzar; Dierick, Steve; Lebreux, Frederic; Markó, Istvan E. *Organic Letters* (2012), 14(5), 1306-1309.

[28] Schevenels, Florian; Markó, Istvan E. *Chemical Communications* (2011), 47(11), 3287-3289 / Schevenels, Florian; Markó, Istvan E. *Organic Letters* (2012), 14(5), 1298-1301. / Schevenels, Florian; Tinant, Bernard; Declercq, Jean-Paul; Markó, Istvan E. *Chemistry - A European Journal* (2013), 19(13), 4335-4343. / Markó, Istvan E.; Schevenels, Florian T. *Beilstein Journal of Organic Chemistry* (2013), 9, 1319-1325, No. 148.

[29] Stensen, Wenche; Schevenels, Florian; Markó, Istvan E.; Svendsen, John Sigurd Mjoeen *PCT Int. Appl.* (2014), WO 2014198844 A1 20141218.

[30] Maulide, Nuno; Vanherck, Jean-Christophe; Gautier, Arnaud; Markó, Istvan E. *Accounts of Chemical Research* (2007), 40(6), 381-392.

[31] Markó, Istvan E.; Sterin, Sebastien; Buisine, Olivier; Mignani, Gerard; Branlard, Paul; Tinant, Bernard; Declercq, Jean-Paul *Science* (2002), 298(5591), 204-207.

[32] Markó, Istvan E.; Giles, Paul R.; Tsukazaki, Masao; Brown, Stephen M.; Urch, Chistopher J. *Science* (1996), 274(5295), 2044-2046.

[33] Dumeunier, Raphael; Markó, Istvan E. *Tetrahedron Letters* (2004), 45(4), 825-829.

[34] De Dobbeleer, Corinne; Pospisil, Jiri; De Vleeschouwer, Freija; De Proft, Frank; Markó, Istvan E. *Chemical Communications* (2009), (16), 2142-2144.