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Tribute

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Professor Léon Ghosez

A tribute

This special issue of Arkivoc is dedicated to Prof. Léon Ghosez in honor of his scientific contribution to organic chemistry

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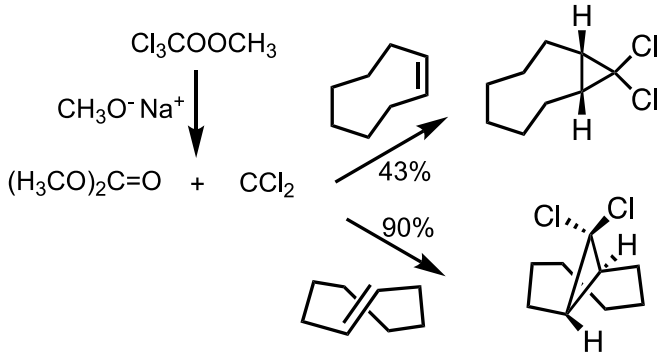
Prof. Léon Ghosez's life started in a French-speaking family in Aalst, a small city located in the Flemish part of Belgium. As Prof. Ghosez's father was a chemist, he probably passed on his genes coding for chemistry to his son, but he certainly had a definite influence on his career. Prof. Ghosez studied at the Catholic University of Leuven and, in 1955, he obtained his degree of "licencié en sciences chimiques" with "summa cum laude". After his degree, he joined Prof. Smets' group at the University of Leuven for a PhD on "kinetics of polymerization and co-polymerization of *N*-vinyl urethane",[1,2] which he was awarded in 1958 also with "summa cum laude". It seems that these two "summa cum laude" distinctions set up Dr L Ghosez's future career. As he was about to do his military service, he was integrated into a laboratory of the Royal Military School where he studied chemi-sorption on molecular layers of metals evaporated under high vacuum. However, after his training in polymers and in physical properties, he felt that he was more attracted to creating new molecules. Léon Ghosez needed to take a big step between the synthesis of polymers and the synthesis of small molecules, but he likes challenges. At that point in time, not many Belgium students were crossing the Atlantic to achieve a postdoctoral stay in the US but Léon Ghosez decided to complete his training by a postdoctoral internship in the US, and he joined Prof. Woodward's group in Harvard (who had not yet obtained the Nobel prize). His project in Woodward's group was to find a substitute "to the Edman's method to study the amino acid sequence in peptides which consisted in attaching hydrazino-acetic acid to a terminal NH_2 group in order to cleave at least two *N*-terminal amino-acids".

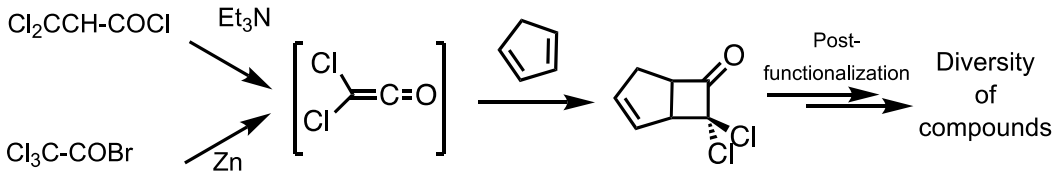
In 1961, back in Belgium at the University of Leuven, he decided to prepare his "thèse d'aggrégation" e.g. his habilitation. During, his habilitation, he decided to combine organic chemistry with mechanistic studies and to study carbenes. At that time, there was a big controversy about the spin states of carbenes and their reactivity. Léon Ghosez was able to show that a stereospecific cycloaddition of dichlorocarbene occurred on *cis*- and *trans*-cyclooctenes and these results strongly supported the absence of any 1,4-dipole or diradical intermediates in the cycloaddition. He proved that the two σ bonds were formed by a concerted mechanism[3,4] (Scheme 1).



Scheme 1. Stereospecific cycloaddition of dichlorocarbene to *cis*- and *trans*-cyclooctenes.

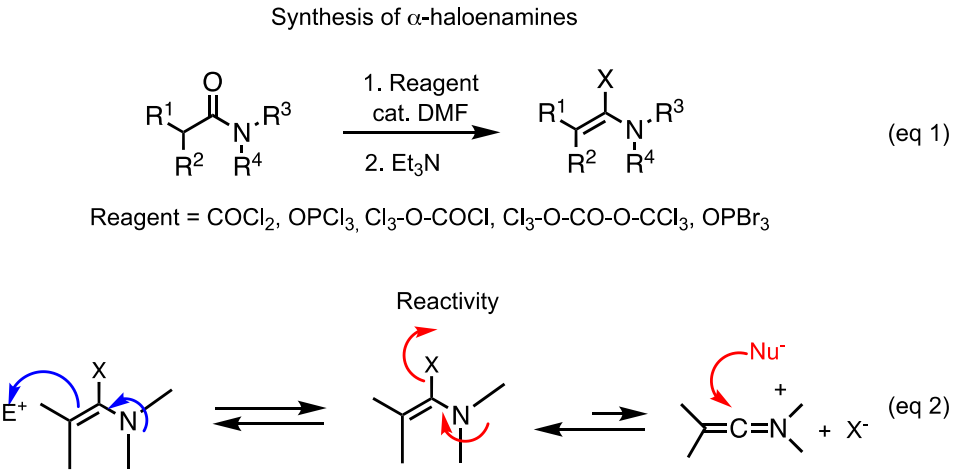
In 1973, Léon Ghosez moved to Louvain-la-Neuve, where he and his colleagues created a chemistry department in the new University. Léon Ghosez took the risk to generate carbenes from dichloroacetyl chloride with triethylamine and from trichloroacetyl bromide with zinc. When the carbenes are generated, in the presence of an alkene (e.g. indene, dihydropyran, cyclopentadiene, …), he observed the formation of cyclobutanones in a highly diasteroselective manner according to a [2+2]-cycloaddition process.[5] The potential of the obtained cycloadducts is enormous and a variety of interesting complex molecules were obtained. This risky project paid off as the generation of this dichloroketene in a very simple way opened many research doors

in his laboratory but also in other laboratories around the world (Scheme 2). This project was the first step on a long journey into the realm of ketenes and and cycloadditions.



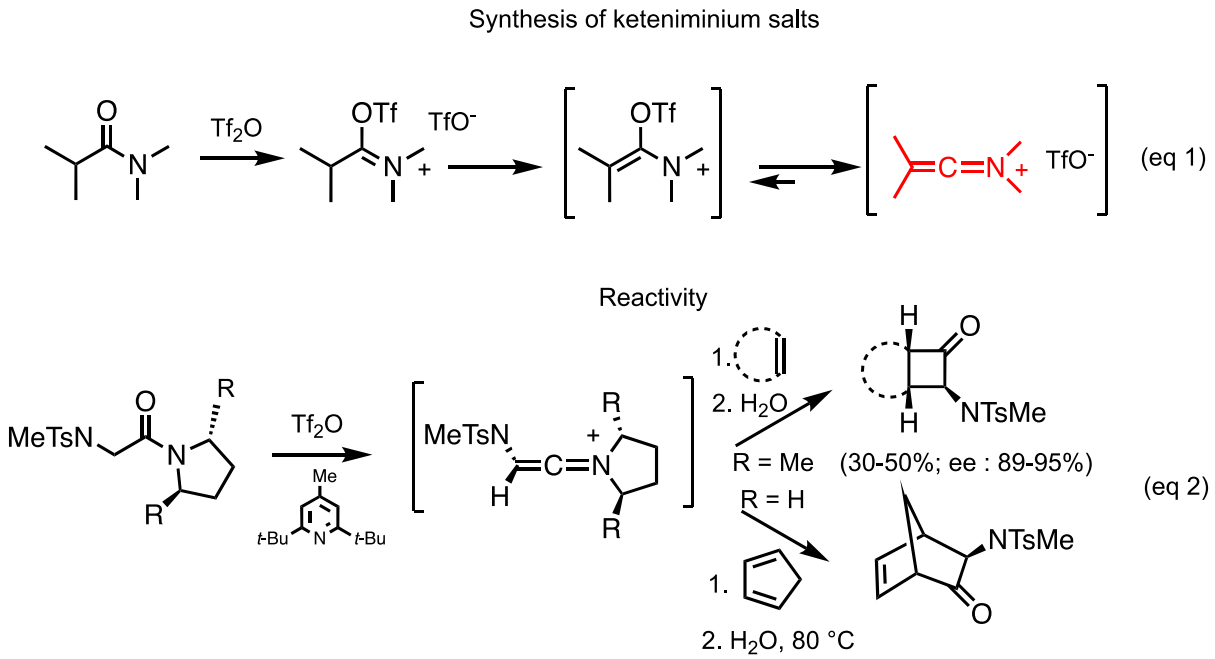
Scheme 2. [2+2]-cycloaddition of the dichloroketene to olefins.

Léon Ghosez was looking for reactive ketene equivalents and he reasoned that keteniminiums would be more electrophilic than the corresponding ketenes. After discussion with a good friend, Prof. Heinz Viehe who was professor at Louvain-la Neuve, he realized that α-haloenamines would be good precursors of keteiminiums salts and of ynamines.[6-9] Thus, Léon Ghosez prepared β-alkyl and β-aryl α-chloroenamines from tertiary amides[10,11] (Scheme 3, eq 1) and these α-chloroenamines showed a remarkable chemical behavior since they are nucleophiles at C2 and electrophiles at C1.[6-10,12,13] (Scheme 3, eq 2). Many applications have been derived from this discovery (Scheme 3).



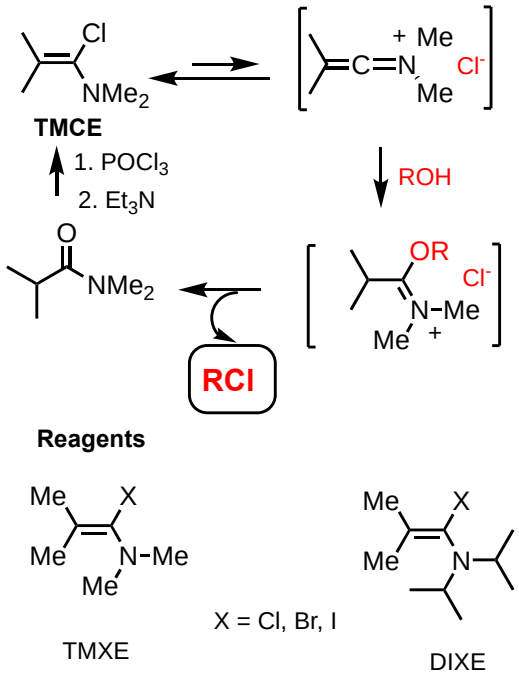
Scheme 3. Preparation of α-chloro- and α-bromoenamines and their ambiphilic reactivity.

As Léon Ghosez wanted to find a convenient source to access keteniminium salts, which could be used as activated ketenes, and involved in a [2+2]-cycloaddition with different unsaturation,[14-21] he treated tertiary amides with triflic anhydride which, after deprotonation, led to the desired keteniminium trifluoromethyl sulfonates[22] (Scheme 4, eq 1). The latter were then involved in intra- and intermolecular [2+2]- and [4+2]-cycloadditions with olefins and dienes. Given the synthetic potential of these reactions, a large number of chemists have used it (Charette, Maulide, Movassaghi, De Mesmaeker, Snider) and, even today, numerous applications are emerging from this research. A significant advantage of the keteniminium salts over ketenes resulted from the possibility of introducing chirality in the readily cleavable iminium functional groups. The first example of asymmetric [2+2]-cycloaddition of keteniminium salts was described by Léon Ghosez in 1982[23] which opened an enormous potential for the synthesis of complex molecules (Scheme 4, eq 2).



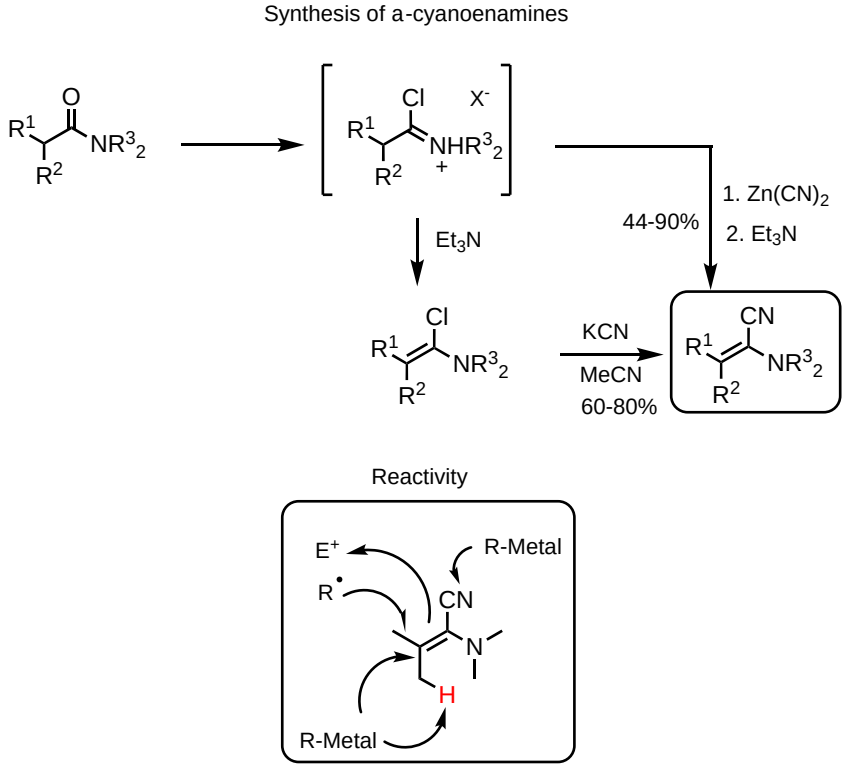
Scheme 4. Keteneiminium salts and [2+2]- and [4+2]-cycloadditions.

During these studies, Léon Ghosez discovered that tetramethyl-α-chloroenamine (TMCE) reacted with a variety of alcohols and carboxylic acids to produce the corresponding chlorides and acyl halides respectively. Thanks to his practical chemical sense, Léon Ghosez recognized that TCME could be useful to the synthetic organic community and hence this reagent, called the "Ghosez reagent", was commercialized. He also developed other reagents which differ by the halogen atom and the size of the alkyl groups on the nitrogen, (TMXE and DIXE reagents) DIXE being selective in the halogenation of polyhydroxylated molecules. (Scheme 5).



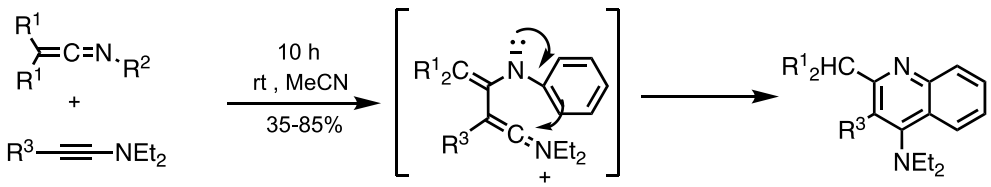
Scheme 5. Tetramethyl-α-chloroenamine (TMCE) and reagents TMXE and DIXE.

The synthetic potential of these α-haloenamines is important. For example, they can be transformed to α-cyanoenamines by nucleophilic substitution with a cyanide anion.[24] These α-cyanoenamines were transformed to a variety of compounds since they react with nucleophiles and electrophiles and even with radicals (Scheme 6).



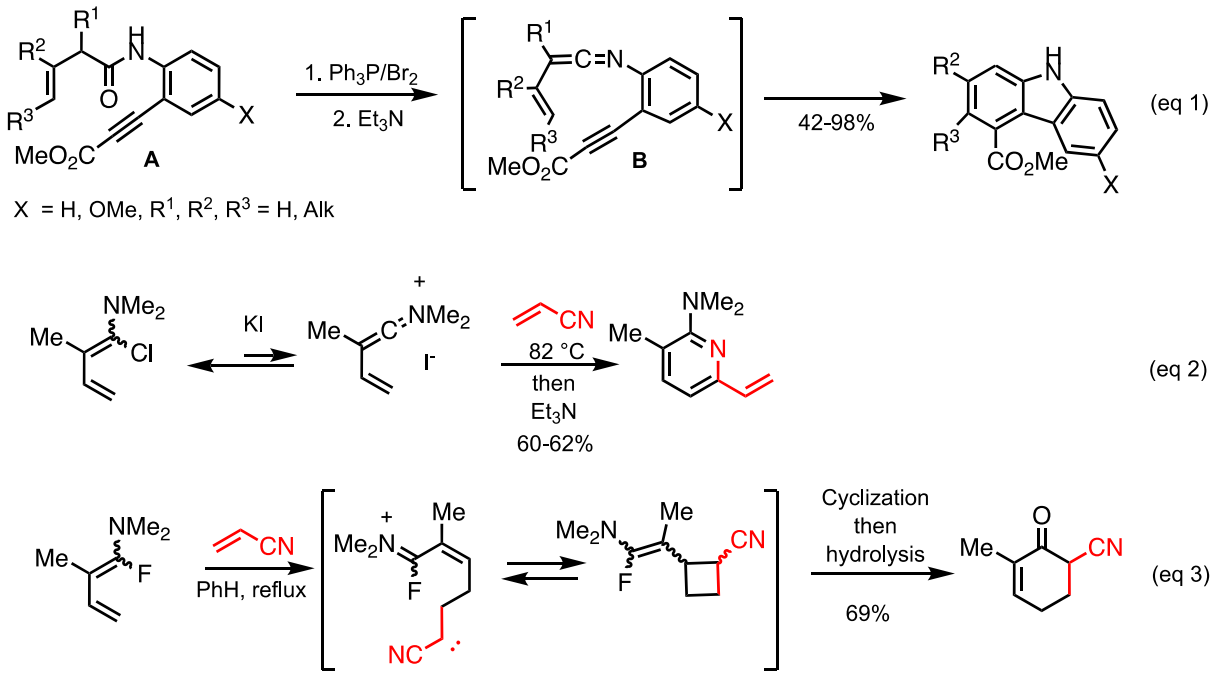
Scheme 6. Synthesis and reactivity of α-cyanoenamines.

Léon Ghosez is well-recognized for [2+2]-cycloadditions, and also for [4+2]-cycloadditions, e.g. Diels-Adler reactions. In 1971, he described the first example of a [4+2]-cycloaddition of ketenimines to ynamines.[25] He found that aryl substituted ketenimines were less reactive towards nucleophilic double bonds than the corresponding ketenes and keteniminium salts. Thus, new synthetic opportunities appeared as the obtained product was a formal adduct between the triple bond of the ynamine and the diene formed by the C=N bond of the ketenimine and the double bond of the aromatic ring (Scheme 7). Following this result, and after some thinking, Léon Ghosez decided to consider the reactivity of vinyl keteneimines.of vinyl ketenimines, vinyl keteniminium salts, 1- and 2-azadienes in [4+2]-cycloadditions (Scheme 7).



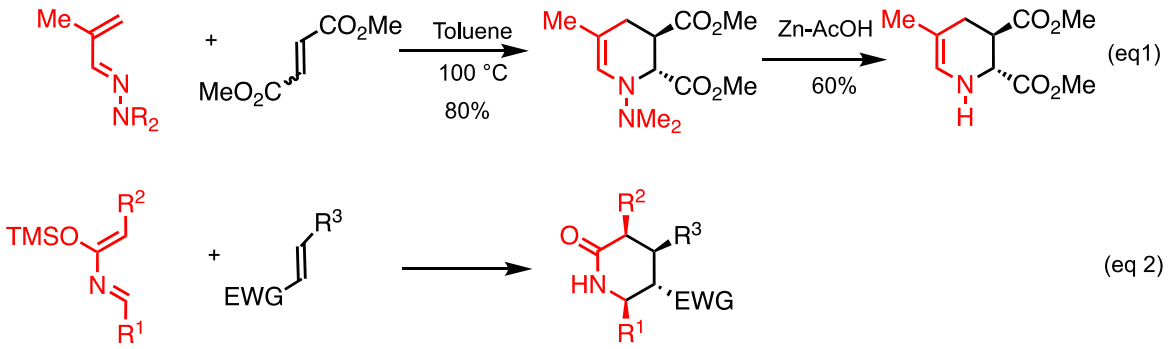
Scheme 7. [4+2]-Cycloaddition of keteneimines to ynamines.

By generating vinyl ketenimines **B** from β,γ-unsaturatured amides **A**, an intramolecular [4+2]-cycloaddition occurs to produce carbazoles[26] (Scheme 8, eq 1). Vinyl keteniminiums or vinyl iminiums can be obtained from α-haloenamines. When the halogen at C1 is a chloride atom, vinyl keteniminium salts can be generated and these latter react as electrophilic dienes and cycloadd to the C-N triple bond of acrylonitrile to produce, after aromatization, pyridines.[27] This reaction was accelerated by the presence of KI (Scheme 8, eq 2). When a fluorine atom is present, as in α-fluorodienamines, these dienamines behaved as nucleophilic dienes as they react with the double bond of acrylonitrile to produce cyclohexanones after hydrolysis[27] (Scheme 8, eq 3).



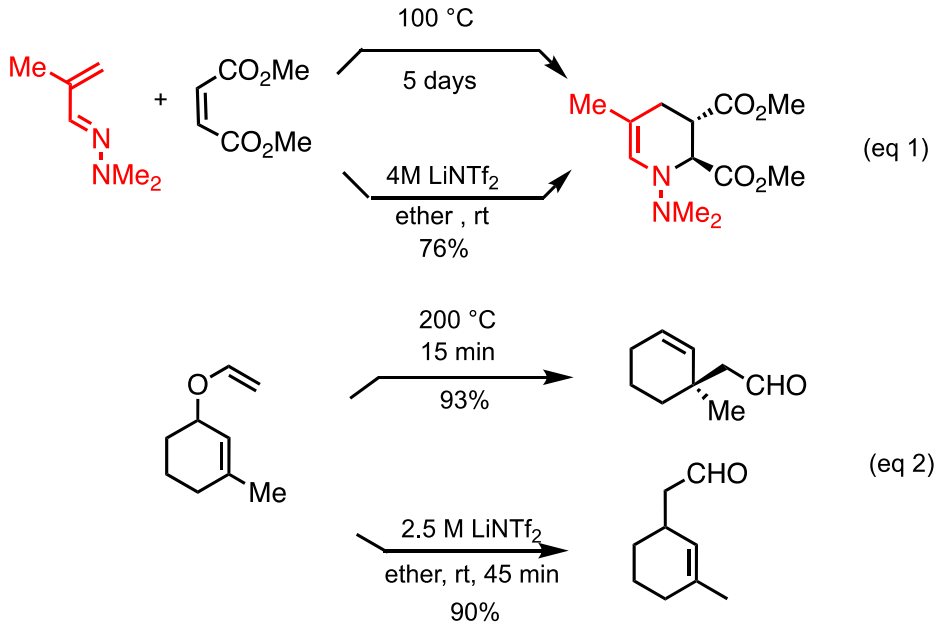
Scheme 8. Reactivity of vinyl ketenimines, vinyl keteniminiums and vinyl iminiums.

Léon Ghosez is a chemist who makes possible reactions that were considered difficult, not possible or even forbidden. In the context of Diels-Alder reactions, to access nitrogen-containing heterocycles, he examined the reactivity of 1-azadienes and found a way to stabilize these reactive substrates by synthesizing vinyl-hydrazones[28] (Scheme 9, eq 1). When these 1-azadienes were heated in the presence of olefins, substituted by electro-withdrawing groups, they led to a variety of nitrogen containing heterocycles (Scheme 9, eq 1). Of course, Léon Ghosez could not resist to study the reactivity of 2-azadienes in Diels-Alder reactions to access other nitrogen-containing heterocycles, and he was able to increase the reactivity of these substrates by introducing a silyl ether at the C3 position of 2-azadienes[12,29] (Scheme 9, eq 2). With these substrates, a facile Diels-Alder reaction occurs with a variety of electrophilic dienophiles, e.g. aldehydes, azido, *N*-oxide compounds, to produce a diversity of nitrogen-containing heterocycles (Scheme 9)



Scheme 9. Diastereoselective synthesis of nitrogen-containing heterocycles from 1-azadienes and 2-azadienes.

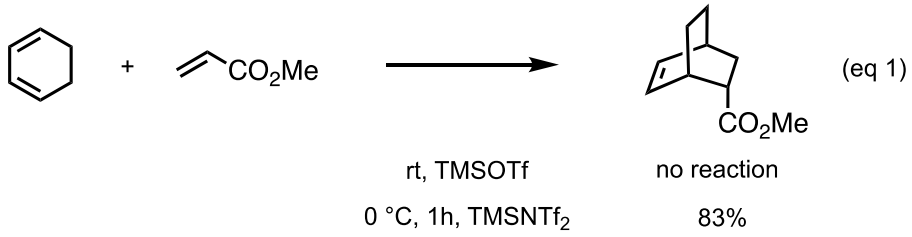
To accelerate the Diels-Alder reaction, Léon Ghosez was using $LiClO_4$ which is explosive. An electrochemist from the University of Montreal, M. Armand, suggested replacing $LiClO_4$ by lithium triflimide ($LiNTf_2$), a very popular salt among electrochemists. Thus, when Léon Ghosez looked at the Diels-Alder reaction of 1,1-dimethylamino hydrazine, derived from 2-methylpropenal, with dimethylfumarate in acetonitrile in the presence of $LiNTf_2$, the *trans*-cycloadduct product was obtained in 78% yield at rt, whereas when the reaction was realized without $LiNTf_2$, it takes 5 days at 100 °C to obtain the cycloadduct! (Scheme 10, eq 1). With this ionic solvent the difficult becomes possible.[30] Making possible the forbidden was also realized by Léon Ghosez as, when he explored the Claisen rearrangement, he found that the forbidden [1,3]-sigmatropic rearrangement occurred at rt when the reaction was conducted in the presence $LiNTf_2$ (Scheme 10, eq 2).



Scheme 10. Diels-Alder reactions and rearrangements without and with $LiNTf_2$.

Léon Ghosez's research is like a game of dominoes, a new result leads to a whole cascade of ideas. Working with $LiNTf_2$, Léon Ghosez anticipated that trialkylsilyl triflimide should be a stronger Lewis acid than the corresponding triflates as Si-N bonds are weaker than Si-O bonds. Thus, he prepared silylated triflimides and used them in Diels-Alder reactions. He showed the superiority of silylated triflimide catalysts over triflates, in the Diels-Alder reaction of cyclohexadiene with methyl acrylate. This reaction is sluggish or does not occur with

TMSOTf but, on the contrary, the reaction is very efficient with $TMSNTf_2$! Once again, the impossible becomes possible. In addition, some enantiopure silylated triflimides were prepared and these latter show a good asymmetric activity in Diels-Alder reactions[31,32] (Scheme 11)



Scheme 11.: Diels-Alder reaction in the presence of $TMSNTf_2$.

I have also to mention that besides all the methods that Léon Ghosez developed, he synthesized a number of scaffolds related to alkaloids, terpenoids, and analogs of natural products related to ottelione A and rhazilinam. He was involved in the synthesis of substituted penams, penems and carbapenems.[33-35] He also synthesized new selective ligands for the human glucocorticoid and progesterone receptors (treatment of allergic and inflammatory diseases), and one of the synthesized ligands turned out to be very potent in human A549 IL6 inhibition assays, being 10-fold more potent than prednisolone.[36,37] In addition, he synthesized new cationic oxidants, looked at the functionalization of C_{60} and made an excursion into the world of foldamers. This list is only a small part of what Léon Ghosez has achieved.

Léon Ghosez has had many industrial collaborations, and he trained an incredible number of PhDs and postdocs from all around the World (300). Besides his research, Léon Ghosez was involved in many committees. At the early stage of his career, he was one of the initiators of the chemistry department at the University of Louvain-la Neuve, and he is one of those who have contributed to the international recognition of this department. He was also at the origin of the European Institute of Chemistry and Biology (EICB) in Bordeaux (France). I should also mention that he is one of the initiators of a number of meetings in Belgium, among them, the famous *Belgium Organic Synthesis Symposium*, well known as the *BOSS meeting*, that takes place every two years and attracts the best organic chemists of the world. It is worth mentioning that he was one of the regional Tetrahedron editors for 32 years, and he is Member Emeritus of the "Académie Royale des Sciences, des Lettres & des Beaux-Arts de Belgique».

Léon Ghosez is creative, open-minded and passionate about chemistry with an enthusiasm that he knows how to pass on. He can be very proud of the synthetic methods he has developed, as they have been, and are still being used by the organic chemist community. His chemistry was, is and will be an inspiration for many chemists.

With consideration and great admiration,

Janine Cossy

Selected Publication

For more details on Prof. Ghosez's work and related publications see:

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