Young Career Focus: Prof. Vittorio Pace (University of Torino, Italy)

Background and Purpose. SYNFORM regularly meets young up-and-coming researchers who are performing exceptionally well in the arena of organic chemistry and related fields of research, in order to introduce them to the readership. This Young Career Focus presents Prof. Vittorio Pace (University of Torino, Italy).

Biographical Sketch

Prof. V. Pace

Vittorio Pace graduated in Pharmacy at the University of Perugia (Italy) in 2005 and received a PhD in Chemical Sciences from the Complutense University of Madrid (Spain) under the guidance of Prof. A. R. Alcántara and J. V. Sinisterra in 2010. In 2009 he also obtained a postgraduate MSc in Drug Design and Development from the University of Pavia (Italy). He realized three postdoctoral experiences at the University of Vienna (Austria; Prof. Holzer, 2010–2011 – Mach fellow), The University Manchester (UK; Prof. Procter, 2011–2013) and Stockholm University (Sweden; Prof. Olofsson, 2013–2014). Then he started his independent career at the University of Vienna in August 2014 as Group Leader in Synthetic Chemistry, receiving his Habilitation for Pharmaceutical Chemistry from the University of Vienna in 2016. After being promoted to tenure-track professor in Drug Synthesis in 2018, in 2020 Prof. Pace became Chair of Organic Chemistry at the University of Torino (Italy). He realized several placements as visiting scientist/professor at Perugia, Sassari, Palermo, Keio (Japan), Barcelona, and Thandavur (India) – among others.

During his career, Prof. Pace has been awarded several prizes including the Vincenzo Caglioti by the Accademia Nazionale dei Lincei, the Ciamician Medal by the Division of Organic Chemistry of the Italian Chemical Society, the Innitzer Award, the Young Investigator Award by the Faculty of Life Sciences of the University of Vienna, the La Roche–Hoffman Prize by the European Federation of Medicinal Chemistry, the Habilitation Award of the Austrian Chemical Society and the Thieme Chemistry Journals Award – among others. During his career, Prof. Pace has supervised 8 PhD theses and several postdoctoral associates, besides MSc and BSc students.

He has been a full professor of Organic Chemistry at the University of Torino since March 2020.

INTERVIEW

SYNFORM *What is the focus of your current research activity?*

Prof. V. Pace Since the launching of my research group in Vienna in 2014 we have been actively engaged with the development of homologation tactics for selectively introducing functionalized methylene (CH_2) fragments into a given organic array. To this end, we take advantage of the intrinsic nucleophilic behavior of the so-called lithium carbenoid reagents, which deliver the methylenic fragments with high efficacy and chemocontrol onto a proper carbon electrophilic platform. Furthermore, we became interested in designing synthetic transformations whose initial step is represented by the homologation event and, upon modulating the reaction conditions, rearrangement sequences may be effectively triggered. At the same time, the high significance of fluorinated scaffolds – as optimal modulators of physical–chemical properties – inspired us to undertake studies for the introduction of fluorine-containing carbanions in nucleophilic regime.

SYNFORM *When did you get interested in synthesis?*

Prof. V. Pace During my MSc in Pharmacy at the University of Perugia (Italy) I developed a strong interest in synthesis, which guided the orientation of my subsequent studies. I received my PhD at the Complutense University of Madrid (Spain) with Profs. Alcántara and Sinisterra, working on the synthesis of enantiopure haloketone precursors of biologically relevant structures. A short-term placement as a PhD visiting student in the laboratory of Prof. De Kimpe in Gent (Belgium) introduced me to the prototypal C1-synthon – diazomethane – and I would consider that my first touch with homologation chemistry. Later, I expanded my knowledge in synthesis during my postdocs at Vienna (Prof. Holzer), Manchester (Prof. Procter) and Stockholm (Prof. Olofsson). Together, these experiences provided me with the skills for starting my independent career in Vienna in 2014, culminating with the *Habilitation* in 2016 and the Chair in Organic Chemistry at the University of Torino in March 2020.

 Synform **2021/06**, A93–A95 • Published online: May 18, 2021 • DOI: 10.1055/s-0040-1720525

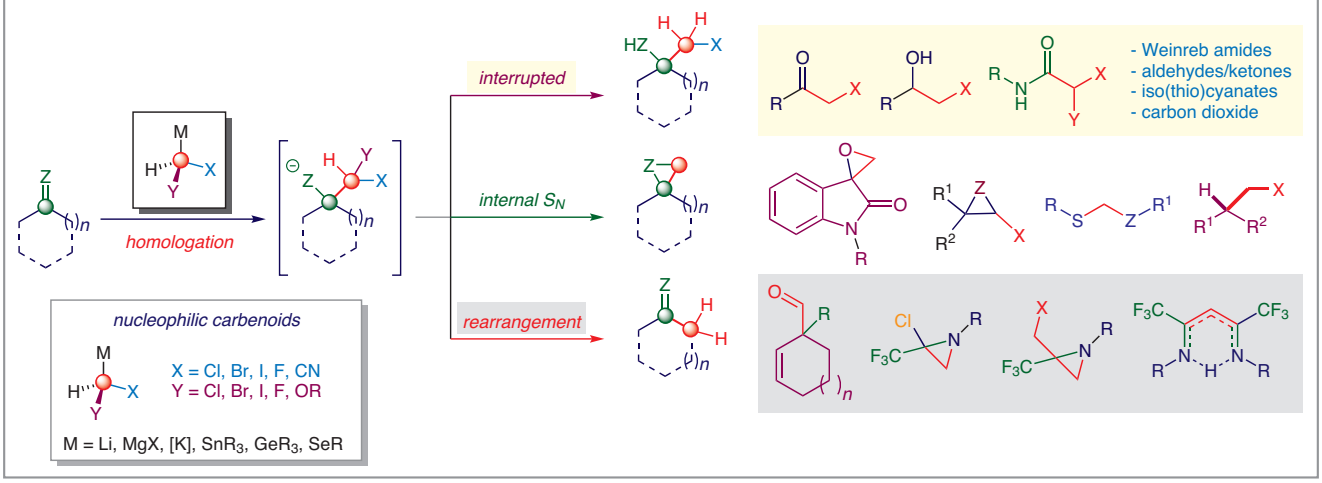
SYNFORM *What do you think about the modern role and prospects of organic synthesis?*

Prof. V. Pace Organic synthesis plays a central role in modern society: there is almost no field of our life that doesn't benefit from the contributions of the art of making molecules. This is particularly evident in biomedical research but also encompasses materials and agrochemical sciences, *inter alia*. Accessing optically active substances continues to fascinate chemists and, in my opinion, there is a huge need to implement strategies for this purpose: it would elevate the chemical lab towards the ideal lab, namely live organisms! Both systems are based on the same chemical rationale and, if we were able to fully understand and explain a biochemical cascade, why not attempt to emulate it *in vitro*? I am fully convinced that the canonical nucleophilic–electrophilic paradigm could still drive new directions of synthesis with a touch of fantasy added by scientists... As a chemist working with carbanions, I am excited to see complex syntheses solved with concepts introduced by Grignard more than a century ago. *In summa*, these are only a few of the seminal works directing our imagination and stimulating our research! Critical for the operator and his/her success is making them flexible to current needs. This is what I try to apply to my own work. *Nada más…*

SYNFORM *Could you tell us more about your group's areas of research and your aims?*

Prof. V. Pace As briefly mentioned above, we are interested in formally introducing single (functionalized) carbon atoms into an organic skeleton, using halocarbenoids as C1-delivery synthons (Scheme 1). Some crucial aspects of their reactivity are worth mentioning: a) they manifest ambiphilic reactivity (nucleophilic vs. electrophilic), tunable by properly selecting the metal, with lithium analogues having predominant carbanion-like features; b) the constitutive instability has historically represented the Achilles heel of these species and taming or eliminating it is often a critical part of our studies. For the sake of clarity, recent studies by others indicate that microfluidic techniques could prevent these degradative phenomena. Although the initial applications of carbenoids in synthesis date back to the 1960s, later searches for new elements of reactivity have focused mainly on the homologation of heteroatoms. The venerable Matteson reaction is one of the most beautiful examples, as recently documented in brilliant works by Aggarwal and Blakemore.

In this context, my group looks at developing new reactions of carbenoids with carbon electrophiles: previously, these species have been studied only marginally and thoroughly applied to intuitive transformations such as the carbonyl–epoxide conversion, the synthesis of α-haloketones from esters, *inter alia*. We recognized that a plethora of carbon-centered electrophilic manifolds could be reacted with carbenoids and, upon the proper modulation of the conditions, complex architectures could be accessed through a single synthetic operation. This is because, besides what we call the *interrupted homologation* – i.e. the final compound features the unmodified inserted fragment during the homologation event – the innate reactivity of a given CHXY motif represents an inspirational element for elaborate unusual rearrangements and sequential reactions. This is, at the moment, one of the hottest topics that we are pursuing.



Scheme 1

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In parallel, the group looks at some additional aspects of carbenoid-like reactivity: a) the implementation of the stability of halomethyl-type metal units through formal transmetalations to Sn, Se, Si or Ge (we refer to these as shuttle reagents); b) the use in nucleophilic mode of fluorinated elements, usually considered elusive species in preparative processes, being the commercially available and easy-to-manipulate liquid fluoroiodomethane (bp 52 °C), an excellent F-containing C1 source amenable for metalation, deprotonation or nucleophilic substitution; c) the outstanding performance of Weinreb amides as acylating placeholders for a wide series of functionalized organolithiums; we succeeded in isolating and characterizing for the first time the putative hemiaminal-type tetrahedral intermediates; d) the forging of (thio)amide linkages through nucleophilic additions of formal carbanions to heterocumulenes. Discovered by Gilman in the early 1920s, these processes provide extremely versatile strategies whose efficiency favorably compares with more sophisticated techniques, thus showing once again that the nucleophile–electrophile classical reactivity still drives the new horizons in synthesis!

Finally, I am delighted to edit for Wiley a book on the topic – *Homologation Reactions. Reagents, Applications and Mechanisms* – in which 25 world-leading chemists bring together the most recent advances on the exciting formal targeted delivery of single C1 atoms.

SYNFORM *What is your most important scientific achievement to date and why?*

Prof. V. Pace The merging of homologation events with conceptually distinct transformations is undoubtedly our most significant contribution to synthesis. I am referring to the operationally simple conversion of an unsaturated ketone to the corresponding homologated fully α-substituted aldehyde: indeed, the design of a chemical sequence constituted by three completely disconnected events (homologation – Meinwald rearrangement – aldenolate electrophilic trapping) enables the rapid access to complex motifs in just one pot. Also, we build up robust telescoped homologations on the reactivity of trifluoromethyl chloroimidates with carbenoids, establishing genuine chemoselective processes tunable at the operator's wish (nature of the halogen of the carbenoid): so, treating the same starting material with different carbenoids (or modulating the stoichiometry) results in different products, as a result of the diverse chemical pathways triggered by the conditions. In this section, I cannot forget to mention the first direct fluoromethylation tactic with fluoromethyllithium: in collaboration with my friend and colleague – Prof. Renzo Luisi, Univ. Bari (Italy) – we recognized how to lithiate ICH_2F and then played around with the delivery of nucleophilic CH_2F to several electrophiles. Indeed, that was the missing piece in lithium carbenoid chemistry: the preparative use of the fluorinated analogue for introducing the fluoromethyl fragment in a highly convenient and straightforward way. Having developed this concept means having removed *de facto* unnecessary operations: installation and removal of stabilizing elements on the F-carbanion.

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