Stereodivergent 1,3-Difunctionalization of Alkenes by Charge Relocation

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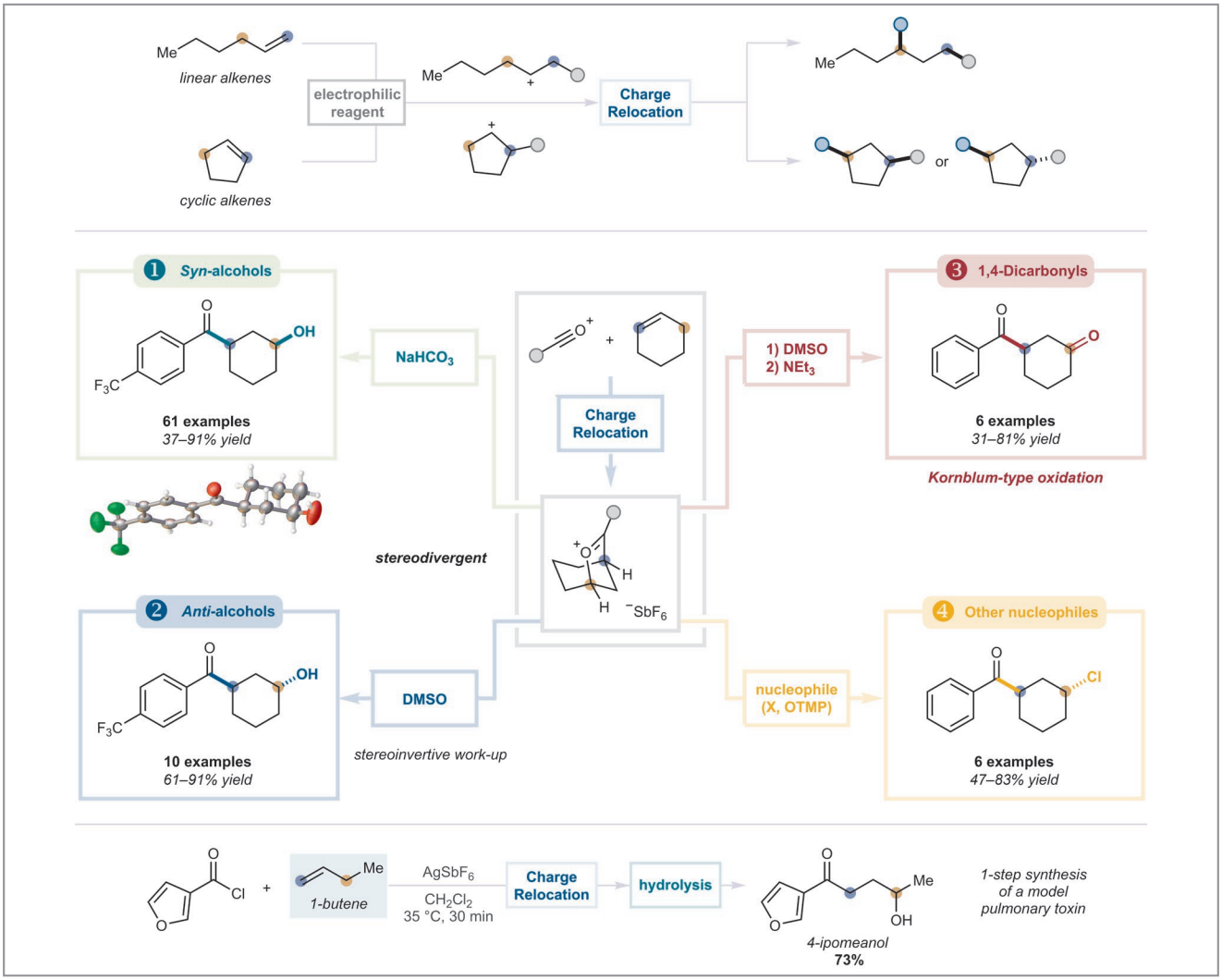
Alkenes are one of the most basic, crucial and ubiquitous functional groups in organic synthesis and, as such, have long been of immense commercial importance, finding applications in, among other things, petrochemistry and the production of pharmaceuticals and fragrances. Among the many reaction modes accessible to alkenes (e.g., cycloaddition, oxidation, polymerization, metathesis, and others), alkene difunctionalization is arguably the most intuitive paradigm, serving as a textbook example of alkene reactivity in organic chemistry curricula around the world. Within the realm of alkene difunctionalization, 1,2-addition across the double bond and allylic functionalization are the most widely encountered reaction classes. In contrast, difunctionalization at positions remote from one another has been reported considerably less



Scheme 1 Stereodivergent 1,3-difunctionalization of alkenes by charge relocation

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frequently, and typically relies on carefully crafted substrates with directing groups and/or stabilizing features, all of which control the final site of bond formation.

"While an extensive body of work on remote functionalization using transition-metal catalysis can be found in the literature, such methods rely on a directing group that can stabilize the reactive intermediate in order to prevent common side-reactions such as β-hydride elimination," said Professor Nuno Maulide, from the University of Vienna (Austria). "Our initial idea was born out of a consideration of the limitations of classical methods for alkene transformation. While the majority of known reactions only allow functionalization on the two alkene carbon atoms – or the allylic position – we sought to break this paradigm using the reactivity inherent to carbocationic species generated from the addition of electrophiles to alkenes."

"Firstly, one cannot speak about electrophilic additions to alkenes without mentioning the extensive body of research on Friedel–Crafts-type reactions of alkenes," continued Professor Maulide. "While Friedel–Crafts-type reactions have indeed been known to lead to a degree of functionalization at remote positions, a lack of regiocontrol for unbiased substrates invariably leads to a plethora of products and intractable mixtures – from elimination to mixtures of 1,2 and 1,3-functionalization products, resulting from unspecific addition of nucleophiles present in the reaction mixture."

Aiming to funnel reactivity towards a single product, Professor Maulide and co-workers turned to a non-coordinating and non-basic counter anion, hexafluoroantimonate (SbF_6^-). "Generating an electrophile in the presence of this anion led to a reagent that, after addition of the alkene, not only allows the resulting carbocation to persist, but enabled uninterrupted equilibration," explained Professor Maulide. "By choosing an acylium ion as the electrophile and hexafluoroantimonate as the counteranion, we were able to generate a scenario in which the resulting positive charge relocates, through a series of hydride shifts, to a defined position, at which it is intercepted by the carbonyl oxygen, forming an oxocarbenium ion – our key intermediate."

Professor Maulide outlined: "In exploring the possibilities for the synthesis of appealing products from the oxocarbenium intermediate, we relied on our experience with high-energy reactive intermediates, many of which we have similarly generated under mild conditions. Fortunately, we were able to identify a variety of complementary conditions that could be productively applied. While simple aqueous work-up leads to the formation of *syn*-configured 1,3-keto alcohols, we found dimethyl sulfoxide (DMSO) – in combination with tetrabutylammonium bromide (TBAB) – to be capable of affording the isomeric *anti*-configured keto alcohols. Replacing TBAB with triethylamine, we gratifyingly found Kornblum-type oxidation to take place, directly forming 1,4-dicarbonyls (Scheme 1)."

"The appeal of this methodology lies not only in its conceptual beauty and simplicity, but also in the synthetic possibilities it opens up," enthused Professor Maulide. He continued: "While established methods for alkene transformation require additional directing groups to enable selective reactions, our method works even with one of the simplest alkenes, 1-butene – a compound that was beyond the reach of all previous methods."

Professor Maulide concluded: "Moving forward, we will expand the applications of feasible electrophilic reagents for the functionalization of alkenes as well as further investigate the bioactivity of 4-ipomeanol and the library of analogues we produced in a biological context."

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Giulia Iannelli received her M.Sc. in pharmaceutical chemistry and technology in 2018 and her Ph.D. in 2022 from the University of Salerno (Italy) under the guidance of Professor Gianluca Sbardella and Professor Sabrina Castellano. Her doctoral work focused on the design, synthesis and biological evaluation of small-molecule modulators of epigenetic proteins. Currently, Giulia is a post-doctoral researcher in the laboratory of Professor Nuno Maulide in the University of Vienna (Austria), where she is working on the development of innovative synthetic transformations and the synthesis of complex structures with pharmaceutical relevance.

Dr. M. Riomet

Margaux Riomet studied chemistry at École Nationale Superieure de Chimie de Paris (France) where she completed her Engineer Degree and M.Sc. degree in 2015 in partnership with Université Pierre et Marie Curie. In 2018, she obtained her Ph.D. under the supervision of Dr. Frédéric Taran at CEA Saclay (France). Her work was dedicated to the chemistry of iminosydnones and their application in biology. After graduating, she joined the group of Professor Nuno Maulide at the University of Vienna (Austria) where she worked on the reactivity of short-lived carbocationic species. She then joined the team of Professor Thomas Poisson and Professor Philippe Jubault in Rouen (France), focusing her research on photo-mediated transformations.

Dr. D. Kaiser

Daniel Kaiser completed his M.Sc. at the University of Vienna (Austria) in 2013 and received his Ph.D. in 2018, completing his studies under the supervision of Professor Nuno Maulide (University of Vienna). After a post-doctoral stay with Professor Varinder K. Aggarwal at the University of Bristol (UK), he returned to Vienna in 2020 to assume a position as senior scientist in the Maulide group. His current research focusses on the chemistry of destabilized carbocations and related high-energy intermediates.

Professor N. Maulide

Nuno Maulide studied at the Instituto Superior Técnico (Portugal) and obtained his M.Sc. degree from the École Polytechnique (France). Following Ph.D. studies (Professor István Markó) at the Université catholique de Louvain (Belgium) in 2007, he moved to Professor Barry Trost's group (Stanford University, USA), before becoming Max-Planck Research Group Leader (MPI für Kohlenforschung, Germany) in 2009. In 2013, he moved to the University of Vienna (Austria), where he is Full Professor of Organic Synthesis and Adjunct PI at the Research Center for Molecular Medicine (CeMM) of the Austrian Academy of Sciences. His research involves unconventional reactivity in organic chemistry and the development of small-molecule tools for biochemical and medicinal applications.

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