Synlett M. van Gemmeren, M. Beller Cluster

Late-Stage C–H Deuteration of Organic Compounds via Ligand-Enabled Palladium-Catalyzed Hydrogen Isotope Exchange

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This article is part of the special issue on Isotopic Labeling.

Received: 30.05.2024
Accepted after revision: 30.05.2024
Published online: 15.11.2024 (Version of Record)
DOI: 10.1055/s-0043-1773498; Art ID: ST-2023-Z-01924-C

Manuel van Gemmeren was born in Madrid (Spain) and raised in both Spain and Germany. After studying chemistry at the Albert-Ludwigs University in Freiburg until 2010, he conducted his doctoral studies in the lab of Prof. Benjamin List and obtained his doctorate in 2014 (*summa cum laude*). Subsequently, he joined the group of Prof. Rubén Martín for postdoctoral studies. From 2016 onwards, he established his independent research group at the University of Münster. In 2022, he joined the Otto Diels Institute of Organic Chemistry at Kiel University as a tenured professor of organic chemistry. Research in the van Gemmeren lab focusses on the development of novel synthetic methods, typically based on Pd-catalyzed C–H activation, that enable challenging transformations to proceed with catalyst-controlled reactivity and selectivity.

Matthias Beller was born 1962 in Gudensberg (Germany) and studied chemistry at the University of Göttingen, Germany, where he completed his Ph.D. in 1989 in the group of Prof. L.-F. Tietze. As recipient of a Liebig scholarship, he subsequently spent one year studying with Prof. K. B. Sharpless at MIT, USA. From 1991 to 1995 he worked in industry. He then moved to the Technical University of München as a professor of inorganic chemistry. In 1998, he relocated to Rostock to head the Institute for Organic Catalysis, which in 2006 became the Leibniz Institute for Catalysis. The work of his group has been published in nearly 1150 original publications and reviews, and over 150 patent applications have been filed.

Key words isotopic labeling, late-stage functionalization, imaging, synthetic methods, catalysis

Isotopic labeling has long been recognized as a key technology in organic synthesis. Its importance stems from the diverse applications of the resulting labeled compounds, such as in ADMET (absorption, distribution, metabolism, elimination, toxicity) studies in drug development, diagnostics, biological research, spectroscopy, mechanistic studies, materials synthesis, and many more.[1] Depending on the desired application, a number of (comparably) stable isotopes are of particular interest, including deuterium, ^{13}C, ^{15}N, $^{17}O/^{18}O$, ^{32}P, and $^{34}S/^{35}S$. Likewise, the introduction of radioisotopes is highly attractive, e.g., tritium, $^{11}C/^{14}C$, ^{13}N, ^{15}O, and ^{18}F. Notably, the inclusion of isotopes in a desired organic compound often requires different reaction conditions, catalysts, etc. compared to the parent non-labeled product. It is thus imperative that there is continued interest in developing modern and efficient synthetic methods to introduce such labels into complex organic molecules. In this *Synlett* Cluster, novel synthetic methods developed by leading research groups in the field are presented. These are complemented by Accounts in which leading groups summarize key developments of their research programs from recent years.

As detailed above, various isotopes are of interest for labeling purposes. Undoubtedly, the introduction of ^{18}F is amongst the most sought-after technologies. In their report, Herth and colleagues describe a novel approach to the labeling of highly reactive tetrazines. By overcoming limitations of previous methodologies, the authors were able to access attractive [^{18}F]SuFEx reagents with significant application potential.[2]

Another key area of isotopic labeling is the introduction of heavy hydrogen isotopes. Such compounds are, for example, required in mechanistic or ADMET studies, and the influence of deuterium incorporation on the metabolic properties of bioactive compounds has recently led to the FDA approval of deuterium-containing compounds as novel drugs. Notably, these drugs specifically contain trideuteromethyl groups in place of methyl groups to control metabolic decomposition. The introduction of such trideuteromethyl groups is at the center of the report by Rueping and co-workers, who have developed an electrochemical cross-electrophile coupling between alkyl or (hetero)aryl bromides and trideuteromethyl-sulfonates as coupling

partners. The method features a broad scope that complements previous approaches for the introduction of trideuteromethyl groups.[3]

Besides trideuteromethyl groups, the regioselective introduction of deuterium instead of hydrogen into organic compounds is of great interest with a wide range of possible applications. A conceptually ideal approach for the introduction of deuterium, especially into complex organic molecules, is to use late-stage hydrogen isotope exchange (HIE), since this does not require the synthesis of substituted analogs using labeled precursors. However, regioselectivity in the labeling step is a prerequisite for this approach and requires the use of functional groups in the starting material as directing groups for the HIE process. In their report, Kerr and colleagues describe an iridium-catalyzed HIE using the carboxylate group in benzoic acids as a directing group to achieve *ortho*-selective labeling with deuterium gas as the deuterium source. The method developed as part of a long-running collaboration with researchers from Sanofi-Aventis proceeds under mild conditions and features a wide substrate scope, including the late-stage regioselective deuteration of pharmaceuticals.[4]

The above-mentioned collaboration between the Kerr lab and researchers from Sanofi-Aventis is also incorporated as part of an extensive Account by Sib and Derdau, who summarize industrial research on isotopic labeling conducted within their drug discovery program. This Account outlines the real-life importance of labeling methods and systematically covers various approaches to deuteration, tritiation, ^{14}C-labeling, the introduction of short-lived isotopes and concludes with some methods for late-stage functionalization resulting from their research program.[5]

The significant interest in isotopic labeling is further underscored by Dömling and colleagues, who summarize how multicomponent reactions can be harnessed to access complex, isotopically labeled scaffolds. This Account covers both labeling with stable isotopes as well as with the key radioactive isotopes required for imaging.[6]

Finally, Dey and van Gemmeren provide an Account on the van Gemmeren lab's research program towards palladium-catalyzed HIE reactions. Besides carboxylate-directed C(sp^3)–H deuterations, the authors detail the development of methods for the perdeuteration of (hetero)aromatic compounds. A common feature of the methods summarized in this Account is their suitability for a wide range of complex bioactive substrates.[7]

The above-mentioned contributions in the field of isotopic labeling highlight the continued importance of research in this field, both from an academic as well as an industrial point of view. Many attractive transformations remain to be developed in this area and are expected to serve as a platform for the discovery of novel concepts and catalysts in the future.

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October 2024

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