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Carbon and hydrogen isotopes have found important applications in diverse scientific domains, such as drug discovery, chemistry, or materials science.[1] Stable isotopes (deuterium and carbon-13) of these ubiquitous atoms are used to synthesize for example internal standards for LC-MS quantification or labelled metabolites for magnetic resonance imaging techniques.[2] On the other hand, radiolabelled compounds (containing tritium (^{3}H) or carbon-14 (^{14}C)) are still indispensable for investigating metabolic pathways and, more generally, the in vivo fate of substances within absorption, distribution, metabolism, and excretion (ADME) studies. Over the last decade, important breakthroughs have been realized in the context of hydrogen isotope exchange (HIE),[3] which can be eyed as the most fundamental C–H functionalisation process (Scheme 1). Progress in this field of research, facilitated by the compelling development of a wide variety of catalysts for selective C–H functionalisation, now provides straightforward access to deuterated or tritiated analogues. Using this well-established strategy, hydrogen isotope incorporation is nowadays possible on multiple positions, which is an essential feature for the preparation of internal standards for MS, and with impressive degrees of selectivity even on molecules of high complexity, such as pharmaceuticals.[3] However, ^{3}H-labelled compounds may undergo undesirable in vivo metabolic degradation by enzymatic reactions and/or isotopic exchange with surrounding water, which can lead to ^{3}H-label loss. This explains the complementary need for ^{14}C-labelled compounds. Indeed, imbedding the ^{14}C isotope into the structural core of compounds is a highly recommended approach for tracing parent molecules and subsequent metabolites to elucidate their fate in vivo. Nevertheless, the preparation of ^{14}C-labelled molecules is often associated with high synthetic costs and the generation of significant amounts of radioactive intermediates and wastes, which need to be handled appropriately. These drawbacks are the result of the limited number of commercially available ^{14}C sources for its incorporation into substrates at an early stage of a multi-step radiosynthesis.[4] Conceptually, the development of a similar approach to HIE for carbon isotopes, that is, carbon isotope exchange (CIE), might be naturally considered as a cornerstone for access to ^{13}C- and ^{14}C-labelled molecules in a direct and more sustainable way. However, the development of selective catalytic C–C bond activation processes has attracted less attention compared to C–H activation technologies. This lag is mainly due to the higher inertness of C–C σ-bonds compared to C–H bonds. Nonetheless, after significant progress in C–C bond activation with transition metals by oxidative addition over the last three decades,[5] the first examples of CIE have been recently described (Scheme 1). These pioneering and complementary methods, which rely on C–C bond decarboxylative carboxylation reactions carried out in the presence of selected transition metals and labelled carbon monoxide (CO) or carbon dioxide (CO_2), are discussed herein (Figure 1).

In late 2018, Gauthier and co-workers[6] (Figure 1 a) reported a procedure based on the use of a known dual-chamber system[7] with a labelled CO precursor to generate the gas in situ and achieve CIE under palladium catalysis. This process, which was applied to activated acid chlorides as the starting materials, provided access to a large scope of both aliphatic and aromatic labelled compounds with good isotope incorporations and yields, even for complex structures such as pharmaceuticals. In addition, for carboxylic acids bearing a stereocenter in α-position of the carbonyl group, the enantiopurity could be retained by fine-tuning of the experimental conditions and the nature of the phosphine ligands. The main limitations are the preactivation of the carboxylic acid moiety in its acyl chloride form and the use of [^{14}C]COgen, a reactant able to produce [^{14}C]CO in special glassware. Indeed, carbon-14 is generated in nuclear reactors as barium carbonate ([^{14}C]$BaCO_3$) and routinely converted into highly stable carbon dioxide ([^{14}C]CO_2). Then, the [^{14}C]COgen reagent is formed in three steps from [^{14}C]CO_2, increasing the number of synthetic steps and the amount of generated radiochemical waste. Nevertheless, its use is a safe

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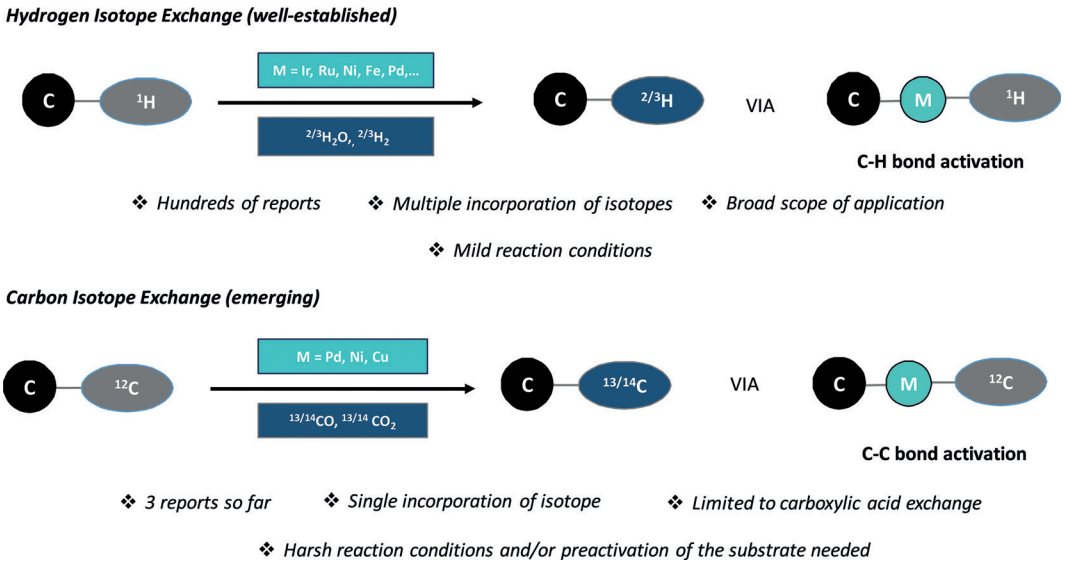

Scheme 1. Comparison of hydrogen and carbon isotope exchange.

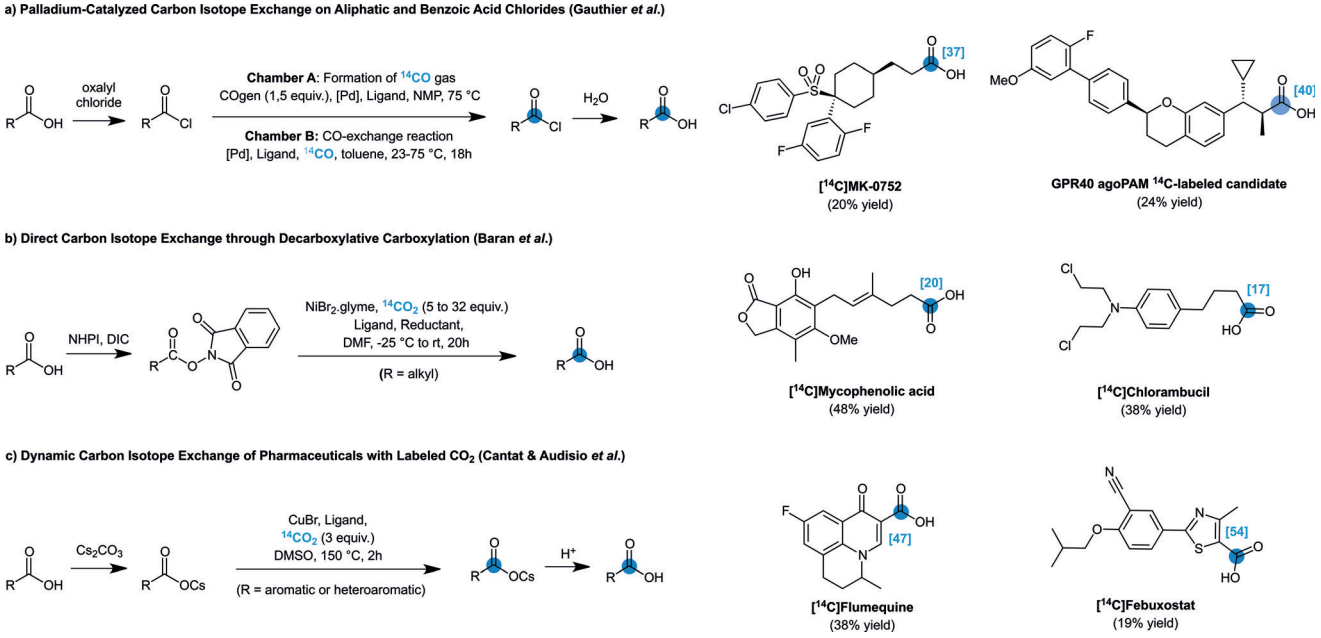

Figure 1. CIE reactions developed by the groups of Gauthier, Baran, and Cantat and Audisio, with examples of prepared ^{14}C-labelled compounds. The percentage of carbon-14 isotope incorporation is given in blue in square brackets, and the yields of the isolated labelled acids are given in black in parentheses.

and precise method for introducing controlled amounts of [^{14}C]CO gas (1.5 equiv) in a two-chamber reactor.

Using more convenient [^{14}C]CO_2 gas as the isotope source, a method to generate carbon-14 radiolabelled aliphatic acids has been developed by Baran[8] and co-workers (Figure 1b). This strategy is based on a nickel-mediated transformation of activated acids in the presence of an excess of [^{14}C]CO_2 (5–32 equiv). While *N*-hydroxyphthalimide redox-active esters had to be formed prior to the CIE reaction, this process afforded a range of labelled complex alkyl carboxylates, with sufficient isotope incorporations for ADME studies, under mild conditions at room temperature.

Cantat, Audisio,[9] and co-workers also used [^{14}C]CO_2 gas as the isotope source for a CIE reaction on aromatic and heteroaromatic carboxylic acids (Figure 1c). They reported that aromatic carboxylates undergo thermal CO_2 extrusion in the presence of a copper salt, which is followed by the reaction of the organometallic intermediates with labelled gas to yield the corresponding ^{14}C-labelled acids. This CIE procedure was carried out on cesium salts of the carboxylic acids with 3 equiv [^{14}C]CO_2 in only 2 hours but at a high reaction temperature (150 °C). Several biologically active carboxylic acids were successfully labelled in this one-step process with excellent specific activities. These examples

clearly show the advantages of these CIE methods over traditional multi-step approaches.

In summary, we have highlighted the emerging concept of carbon isotope exchange, which will pave the way to an easier and more sustainable access to molecules labelled with carbon isotopes. There is no doubt that numerous future research works will be dedicated to the discovery of novel CIE reactions in order to broaden the scope of applications and to allow multiple isotope incorporation. Further utility for carbon-11 labelling of in vivo imaging radiotracers[10] could be foreseen because of the late-stage and high isotopic enrichment assets of this promising CIE approach. Beyond applications in the field of labelling, the development of such reactions is also important for fundamental research in chemistry because these transformations can be considered as the most fundamental C–C functionalisation processes, giving crucial information on the feasibility of catalytic C–C bond activation.

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Conflict of interest

The authors declare no conflict of interest.

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