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Classical and Modern Methods for Carbon Isotope Labeling

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Abstract: Isotope labeling of small molecules is a crucial tool for drug discovery and understanding biochemical processes. Expanding the toolbox of a radiochemist with methods that allow late-stage labeling is therefore important. Of the methods that have been developed, the use of isotopically-labeled *C (* = 14, 13, 11) precursor is among the most useful platforms for installing isotopically-labeled carbon into the molecule. While this area has undergone a tremendous amount of development in recent years, the preparation of *C-labeled molecules (* = 14, 13, 11) remains difficult and time-consuming, with established methods involving label incorporation at an early stage of synthesis. On the other hand, the development of chemical reactions based on the reversible cleavage of C-C bonds would offer new opportunities in the preparation of *C-labeled molecules (* = 14, 13, 11). This review aims to provide a short survey on the classical and recent methods that provide effective opportunity for late-stage labeling.

Keywords: *Isotope labeling; carbon isotope; *C-labeled molecules (* = 14, 13, 11)*

1. Introduction

There is increased pressure on the chemical industry and allied fields to produce compounds with less waste from non-toxic starting materials, while simultaneously reducing manufacturing costs. Synthetic methodology and homogeneous catalysis can offer solutions to these challenges (Blakemore *et al.*, 2018). Synthetic chemistry is the primary method used to produce and identify new medicines (Dias *et al.*, 2012). The development of new synthetic methods impacts the pharmaceutical industry in two different ways, first by increasing overall efficiency and second by enabling access to novel chemical matter (Lovato *et al.* 2021, Campos *et al.*, 2019). Discovering, developing, and designing new medical drugs is time-consuming and complex. It requires between 12 to 15 years to take a drug from project initiation to market, with costs of around $2.6 billion per new entity (Grygorenko *et al.* 2020, Horien *et al.*, 2017, Hughes *et al.*, 2011).

During various stages of drug discovery and development, several in vitro and in vivo studies are carried out to give a better understanding of ADME properties of the drug candidate (El Masaoudy

et al., 2023; Kaddouri et al., 2022). The Food and Drug Administration (FDA) (Korde *et al.*, 2022). recommends Phase 0 clinical trials to provide an alternative early drug development strategy by micro-dosing healthy volunteers with pharmaceuticals that are radiolabeled. The drug candidates can be synthesized with long-lived radionuclides (^{3}H or ^{14}C) and/or short-lived radionuclides (^{11}C or ^{18}F). Labeling the drug candidate with these radioisotopes enables the follow-up of the in vivo fate of the drugs, as these radioisotopes are traceless (Zhang *et al.*, 2020). The synthesis of radiolabeled compounds is a complex, time-consuming process and usually needs multistep synthesis, while taking into account that the labeling position must be introduced into a metabolically stable position. Therefore, there is a great demand and need for introducing and developing efficient methods to introduce isotopic labeling for the drug candidate to help with the drug discovery process. The selection of the stable isotope to incorporate in the drug molecules depends on several factors, including cost, commercial availability, and the synthetic methods available. Isotopic labeling of molecules with isotopes of carbon is important because labeling molecules with isotopes of carbon is sought widely in many disciplines (medicinal chemistry, agroscience, PET studies) (Babin *et al.* 2022, Marathe *et al.* 2004, Voges *et al.*, 2009, Hunter *et al.* 2011, Gehen *et al.*, 2019, Escher *et al.*, 2011, Löffler *et al.*, 2005). The use of carbon labels is often the ideal labeling approach because the molecule's scaffolds are not altered significantly (like they are with ^{18}F labels) and are not prone to wash out or metabolic shifting (like with ^{2}H or ^{3}H labels) (Krauser *et al.*, 2013).

This review will briefly discuss the classical and recent methods that allow for carbon isotope replacement by using isotopically-labelled building blocks. In addition, some representative examples of isotope replacement, by means of exchange strategies, will be discussed.

2. *C-Labeling of Organic Compounds [*C = ^{14}C, ^{13}C, or ^{11}C] via Classical Methods

2.1 $^{13/14}$C-Labeling of Organic Compounds

Dried sample of … These were also locally sourced. Carbon has 15 isotopes, from ^{8}C to ^{22}C, of which ^{12}C and ^{13}C are stable isotopes. The longest-lived radioisotope is ^{14}C, which has a half-life of 5730 years. The incorporation of ^{13}C and ^{14}C into the organic molecule via functional group transformation can be done by using isotopically-labeled building blocks.

Isotopically-labeled building blocks include metal [*C]cyanides (M = Na, K, Zn, Cu) (Derdau *et al.*, 2018), which are useful building blocks for introducing *****C [*C = ^{14}C, ^{13}C] into an organic molecule (**Figure 1a**). While these solids are easier to handle, many M*CN are hygroscopic and all are toxic; therefore, care must be taken when handling them. The second building block is the [$^{14}C_2$]acetylenes building block. For example, Elmore et al. reported the synthesis of triphenylsilyl [$^{14}C_2$]acetylene for the use in Sonogashira reaction (**Figure 1b**) (Dorff *et al.*, 2011). The third building block is the [^{14}C]cyanamide building block. For example, Murthy et al. reported the use of [^{14}C]H_2NCN to incorporate a C-14 label on the position of a pyrimidine ring, as shown in (**Figure 1c**) (Murthy *et al.*, 2009). The fourth building block is the [^{14}C]methyl iodide, which is one of the most frequently used building blocks, being the source of both electrophilic and nucleophilic one [*C] carbon synthons. An example of the use of [^{14}C]methyl iodide is the synthesis of [*S*-methyl-^{14}C]methionine (**Figure 1d**) (Melville *et al.*, 1947). Isotopically-labeled building blocks also include CO; an example of that is the synthesis of ^{14}C-carboxylic acid from the more complex substrate *o*-chloroaryl iodide to provide the product in 87% chemical yield and 32% overall radiochemical yield from barium [^{14}C]carbonate. The product is a key intermediate in the preparation of a series of labeled gonadotropin-releasing hormone agonist (GnRH agonist) of the amide type (**Figure 2a**) (Elmore *et al.*, 2003).

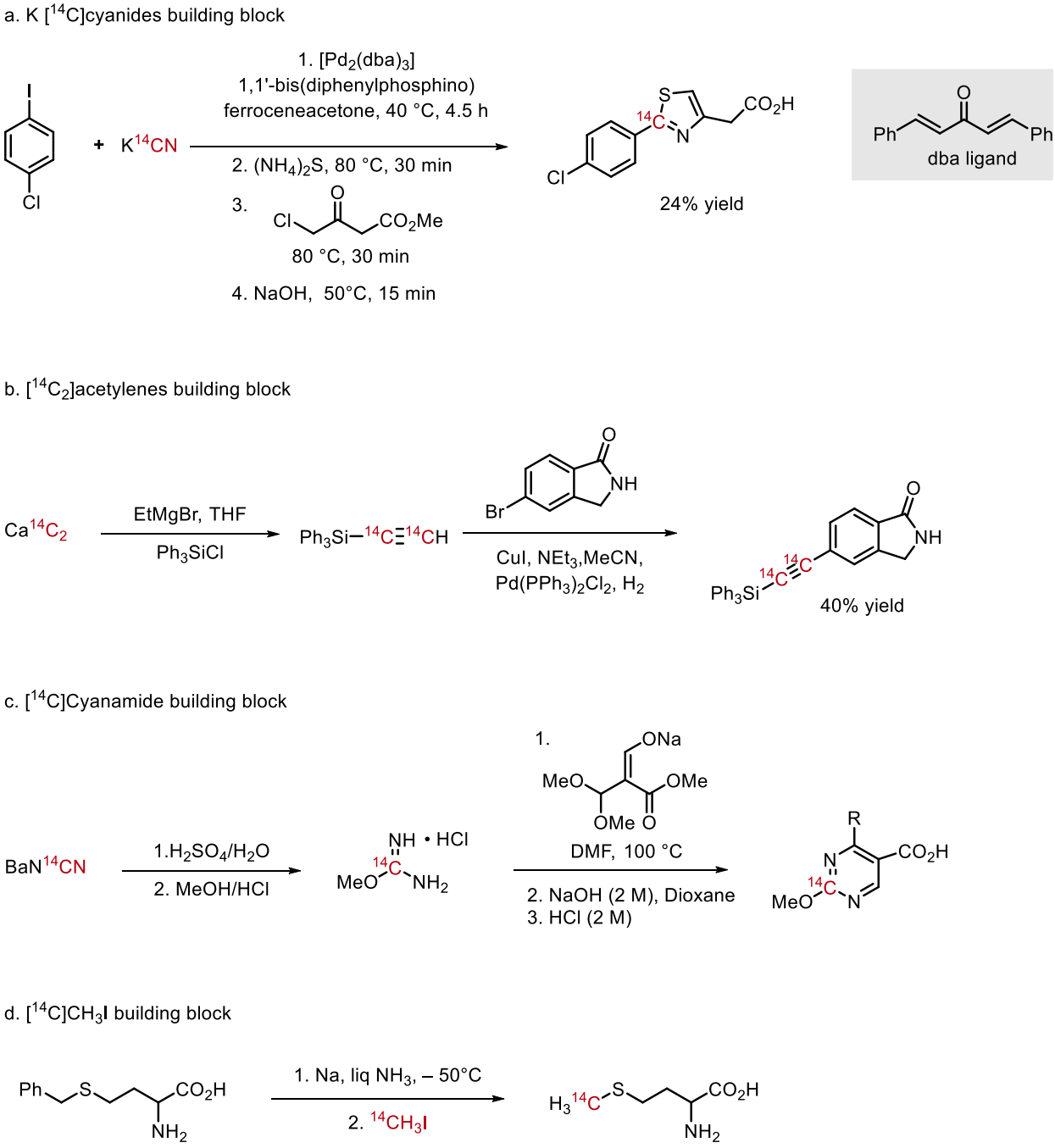

Figure 1. [13/14] C-Labeling of organic compounds with labeled building blocks: a. K[^{14}C]CN building block, b. [$^{14}C_2$]acetylenes building block, c. [^{14}C]cyanamide building block. d. [^{14}C]CH_3I building block

The [^{14}C]HCOOH building block, an example of which is the synthesis of 3-deaza[8-14C] adenosine derivative, which is a key intermediate in the synthesis of 3-deaza[8-14C] adenosine (**Figure 2b**); (Wheeler *et al.*, 1992) the [^{14}C]HCHO building block, an example of which is used for the synthesis of the corresponding alkenylamine provided *N*-benzyl[2,6-^{14}C]piperidin-4-ol, which served as a key intermediate to the CCR5 receptor antagonist [^{14}C]SCH 351125 (**Figure 2c**); (Ren *et al.*, 2007) and the [^{14}C]CH_3NO_2 building block, an example of which is used for the synthesis of [2-^{1}C]ketoglutaric acid, which was used for investigations in the biosynthesis of cephalosporins (**Figure 2d**) (Baldwin *et al.*, 1989). In addition to all the previously-mentioned building blocks is the isotopically-labeled carbon dioxide building block, *CO_2 [*C = ^{14}C, or ^{13}C], which can be introduced via carboxylation of organometallic compounds and coupling with organomagnesium or organolithium

reagent. These traditional methods need harsh conditions and have poor functional group tolerance; therefore, the installation of the labeled carbon occurs at an early stage of the synthesis. An example of this is the synthesis of a potent and selective adenosine A_{2a} antagonist by Hesk *et al.* (**Figure 3**) (Hesk *et al.*, 2017).

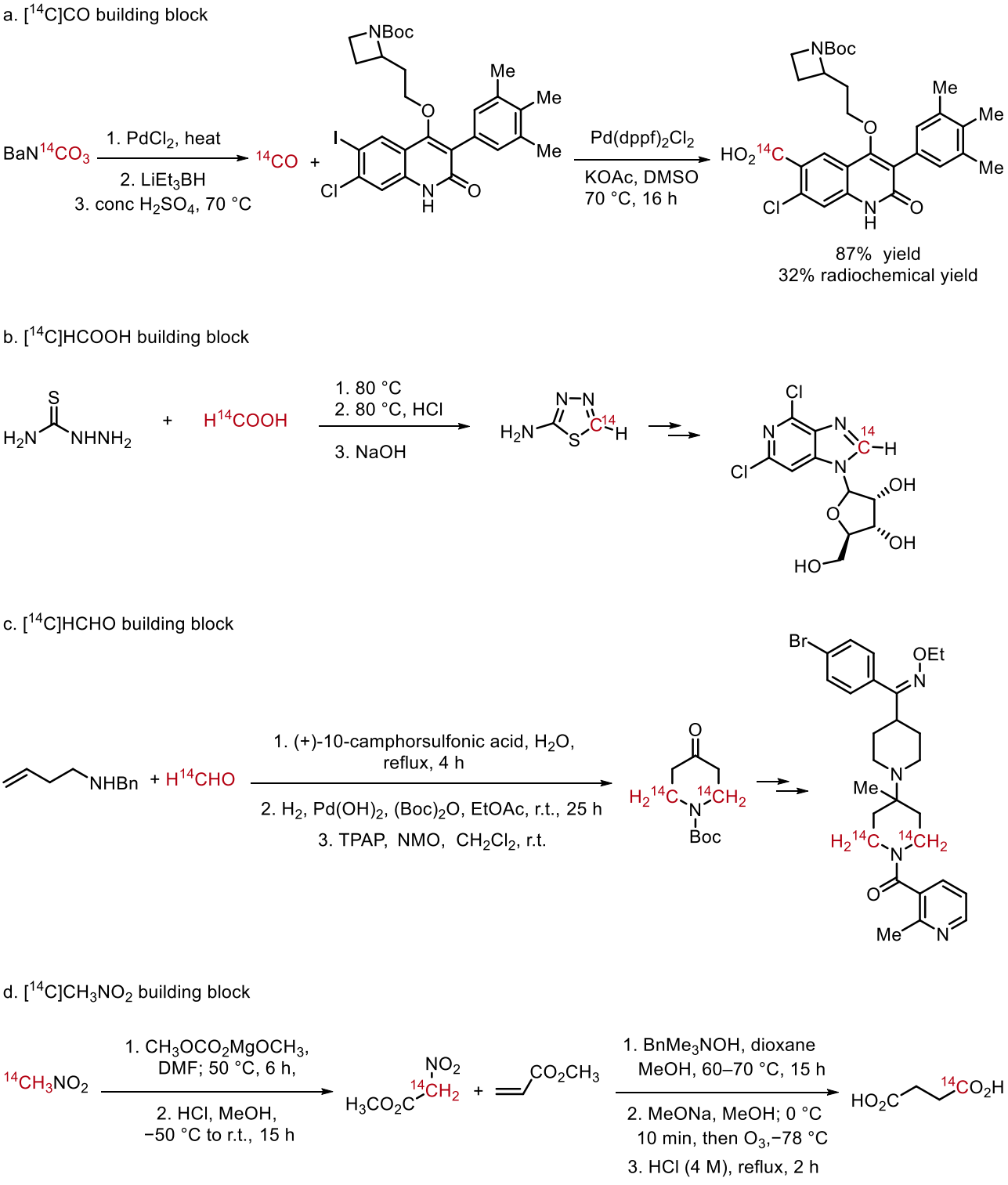

Figure 2. [13/14] C-Labeling of organic compounds with labeled building blocks: a. [^{14}C]CO building block, b. [^{14}C]HCOOH building block, c. [^{14}C]HCHO building block, d. [^{14}C]CH_3NO_2 building block.

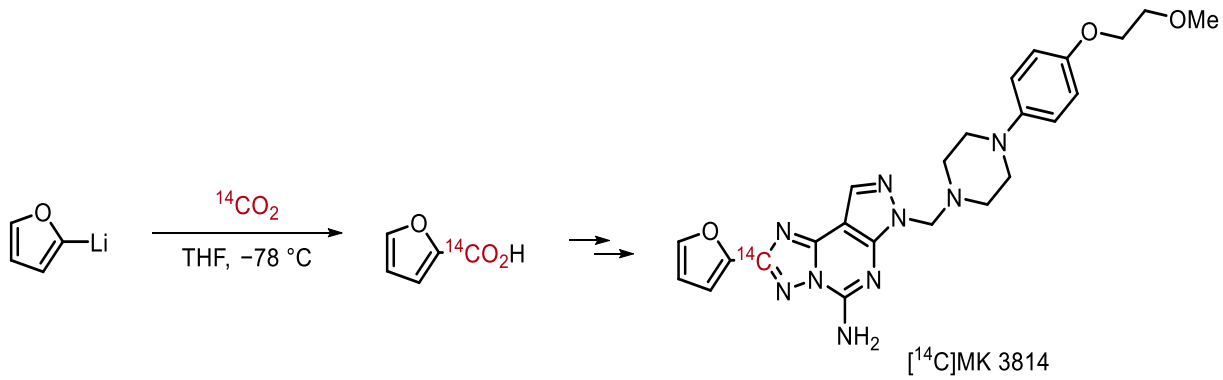

Figure 3. Carboxylation of furan-2-yllithium route to [^{14}C]MK3814.

2.2 ^{11}C-Labeling of Organic Compounds

Carbon-11 has a half-life of 20.3 min. Carbon-11 is generally prepared via a cyclotron by proton bombardment of nitrogen gas. Carbon-11 labels are used as a radionuclide for positron emission tomography studies (Löffler *et al.*, 2005). Incorporation of $^{13/14}$C into the organic molecule via functional group transformation can be done by using isotopically-labeled building blocks.

Isotopically-labeled building blocks include the [^{11}C]CH_3X (X = I or OTf) building block. [^{11}C]CH_3I is by far the most frequently used ^{11}C-labeling agent, an example of which is the nucleophilic substitution of [^{11}C]CH_3X (X = I or OTf) to generate ^{11}C-methyl heteroatomic (N, O, or S) compounds. This simple and direct ^{11}C-methylating method has been well-applied in the synthesis of many ^{11}C-labeled tracers, including [^{11}C]PIB, [^{11}C]DASB, [^{11}C]flumazenil (**Figure 4a**) (Deng *et al.*, 2019), and the [^{11}C]CO building block. [^{11}C]CO is an established building block for the synthesis of ^{11}C-carbonyl labeled carboxylic acids, esters, amides, ketones, and aldehydes via transition-metal mediated carbonylation reactions. An example of this building block is the Pd-mediated transmetalation preceding ^{11}C-carbonylation with [^{11}C]CO. Representative examples include a retinoid compound, [^{11}C]Am80, and [^{11}C]aspirinobtained from the corresponding boronates (**Figure 4b**) (Takashima-Hirano *et al.* 2012, Ishii *et al.*, 2019). Metal [^{11}C]cyanides building block (M = Na, K, Zn, Cu) are useful building blocks to introduce ^{11}C into an organic molecule. An example of that is the use of K[^{11}C]CN, as shown in **Figure 4c** (Derdau *et al.*, 2018), and the [^{11}C]CO_2 building block. [^{11}C]CO_2 is the feedstock virtually for all ^{11}C chemistry and can be converted readily to other synthons in high RCYs and high specific activity. An example of the use of this building block is when Riss and Pike et al. developed a novel strategy to synthesize ^{11}C-labeled carboxylic acids and derivatives from boronic esters in the presence of a copper catalyst in high RCYs and high specific activity (**Figure 4d**) (Riss *et al.*, 2012).

3. Isotopic Labeling Via Exchange Reactions

*3.1 ^{12}C/*C Exchange of Organic Compounds [*C = ^{14}C, ^{13}C, or ^{11}C]*

The incorporation of isotopically-labeled carbon via functional group transformation has some limitations. For example, some methods, like the carboxylation of organometallic compounds and coupling with organomagnesium or organolithium reagent, need harsh conditions and have poor functional group tolerance; therefore, the installation of the labeled carbon occurs at an early stage of the synthesis. Another approach for the incorporation of isotopically-labeled carbon is via exchange reactions, which give an advantage to the late-stage incorporation of isotopically-labeled carbon. Reports of direct non-enzymatic reversible CO_2-exchange of carboxylic acids are restricted to specialized substrate/mediator pairs (Häußermann *et al.*, 2012).

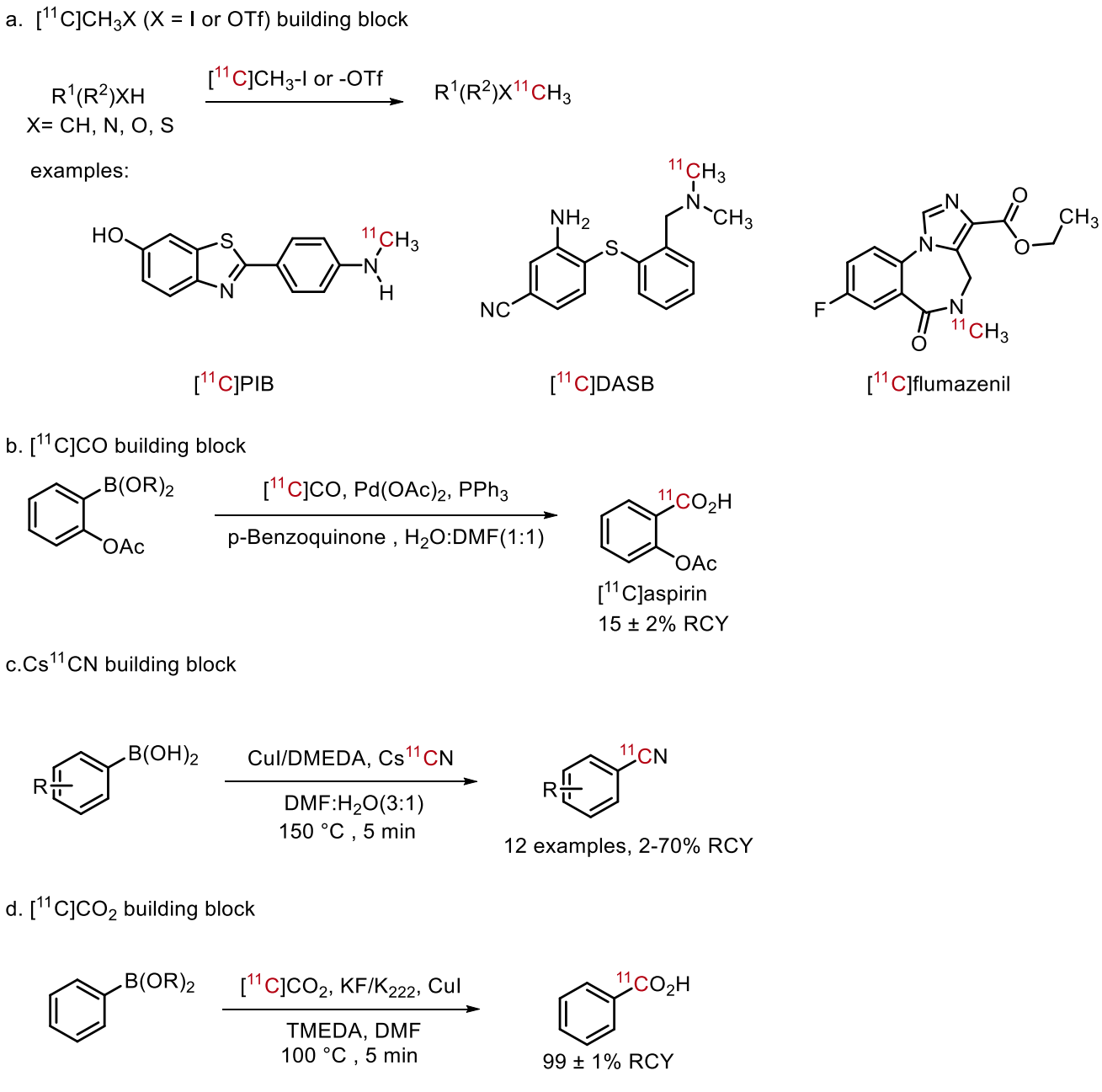

Figure 4. ^{11}C-Labeling of organic compounds with labeled building blocks: a. [^{11}C]CH_3X (X = I or OTf) building block. b. [^{14}C]CO building block. c. Cs[^{11}C]CN building block. d. [^{11}C]CO_2 building block.

An example of that is when Darensbourg et al. showed that the dimeric complex $[(Ph_3P)_2CuO_2CCH_2CN]_2$ can undergo a reversible decarboxylation/carboxylation reaction readily in the temperature range 30–50 °C, as evidenced by its exchange with [^{13}C]CO_2 in DME (**Figure 5a**) (Darensbourg *et al.*, 1993). The second method is the exchange of carboxylate groups in simple aliphatic acids with [^{14}C] CO_2, which has been documented but requires heating of neat substrates at 280–400 ºC (**Figure 5b**) (Szabolcs *et al.* 1974, Nakai *et al.*, 1959). The third method is the exchange of C(sp^2)-carboxylate groups. Destro et al. were inspired by HIE methods, which allow a radionuclide to be introduced on a previously synthesized drug in a single step. This methodology allows the direct exchange of C(sp^2)-carboxylate groups catalyzed by transition metals.

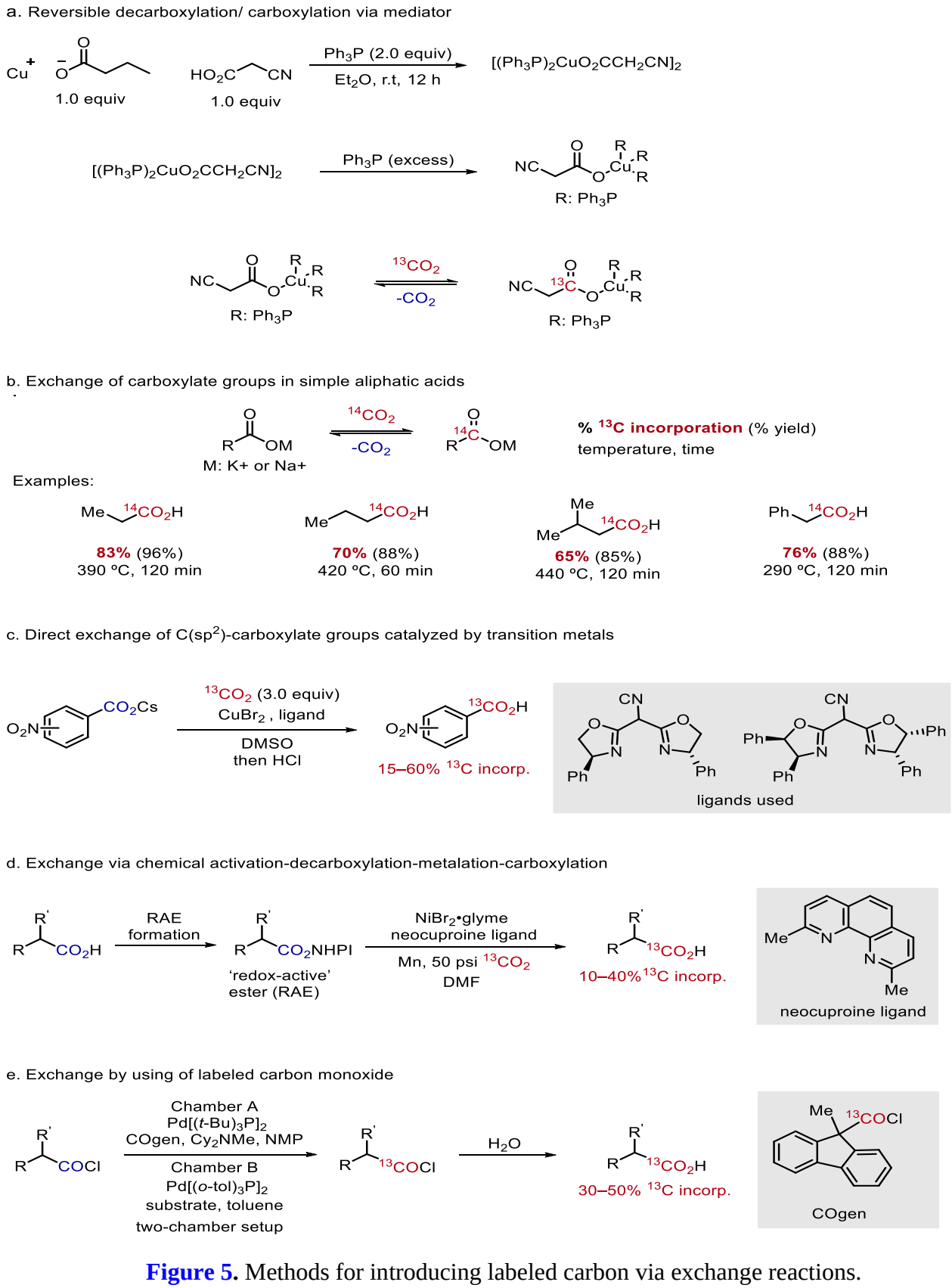

Figure 5. Methods for introducing labeled carbon via exchange reactions.

The reaction is limited to nitro- or sulfonyl-containing arenes or 2-heteroatom substituted electron-rich heterocycles at high temperature (≥150 ºC) (**Figure 5c**) (Destro *et al.*, 2018). The fourth method is by chemical activation-decarboxylation-metalation-carboxylation sequences mediated by transition metals (Hinsinger *et al.* 2019, Kingston *et al.*, 2019, Tortajada *et al.*, 2019). An example of this

approach is when Baran et al. reported the nickel-mediated decarboxylative carboxylation of alkyl carboxylic acids via redox-active ester formation (**Figure 5d**) (Kingston *et al.*, 2019). The fifth method of $^{12}C/^{*}C$ involves the use of labeled carbon monoxide in place of CO_2 (Tortajada *et al.* 2019, Ravn *et al.*, 2019). As an example of this method, Gauthier et al. have reported the use of COgen as a source for labeled carbon monoxide to promote palladium-catalyzed [^{13}C]CO and [^{14}C]CO exchange with activated aliphatic and benzoic carbonyls (**Figure 5e**) (Gauthier *et al.*, 2018). Among pharmaceutically active carboxylic acids, the Phenyl Acetic Acid (PAA) scaffold occupies a predominant place in Non-Steroidal Anti-Inflammatory Drugs (NSAID). In this context, in 2020, the groups of Lundgren and Audisio Lundgren reported two concomitant strategies for carboxylate isotope replacement. The group of Lundgren published a reversible decarboxylation of stable organic acids in a polar aprotic solvent (Kong *et al.*, 2020). This procudere was carried out form from potassium carboxylates in presence of excess of [^{13}C]CO_2 (1 atm) in DMF, which allowed it to obtain the isotopically-labeled carboxylic acids in high isotopic incorporation, in a single step.

The direct reversible decarboxylation of stable organic acids in a polar aprotic solvent process enables access to isotopically-labeled carboxylic acids. An overview of the scope examples is provided in **Figure 6**. (hetero)arylacetic acid salts with anion-stabilizing groups can undergo carboxylate exchange at moderate temperatures, whereas arylacetates with a strongly electron-donating OMe group required higher temperatures at 100 to 115 ºC and benefitted from the addition of 18-C-6. Alkyl and aryl substitution adjacent to the carboxylate was tolerated, including examples of disubstituted arylacetic acid salts and trisubstituted, non-enolizable arylacetic acid salts. The simplicity of the process enabled broad functional group compatibility, including tolerance to ketones, aldehydes, amides, esters, and potentially reactive heterocycles. They showed also that other classes of potassium carboxylates can undergo reversible decarboxylation, including malonate half-esters and cyanoacetates.

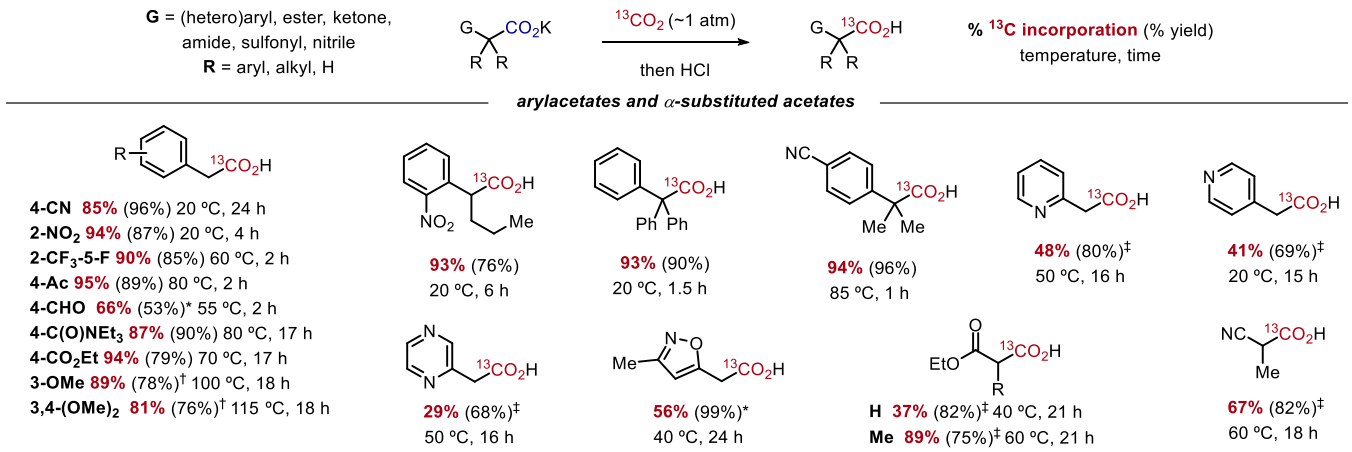

Figure 6. Carboxylate exchange scope**.** Unless noted yields are of isolated material. *Calibrated ^{1}H NMR spectroscopy yield using 1,3,5-trimethoxybenzene as an internal standard. †1.0 Equivalent 18-C-6 added. ‡%^{13}C Incorporation and yield determined by analysis of the corresponding methyl or benzyl ester.

Independently, in the same year, Audisio and co-workers developed isotopic exchange of carboxylate groups in cesium arylacetic acid salts with $^{*}CO_2$ ($^{*}C = ^{14}C$, ^{13}C, or ^{11}C) in DMSO at 80–190 ºC (**Figure 7**). The reactivity of this reaction is restricted to nitro- or sulfonyl-containing arenes or certain classes of heterocycles at high temperature (≥150 ºC) (Destro *et al.*, 2020). Despite their importance, labeled amino acids remained essentially unexplored by modern CIE until recently, when the groups of Lundgren and Rotstein published a novel method to access these compounds, based on a

biomimetic approach involving the decarboxylation/carboxylation of imino acids (Bsharat *et al.*, 2022, Doyle *et al.*, 2024). (±)-[C_1-^{13}C]phenylalanine could be obtained with 75% ^{13}C incorporation and 84% yield when ~8 equivalents of [^{13}C]CO_2 are supplied in the presence of 20 mol% 4-anisaldehyde and 40 mol% Cs_2CO_3 in DMSO at 70 ºC. Aldehyde catalyzed carboxylate exchange is amenable to labeling a diverse range of unprotected α-amino acids, including most proteinogenic substrates (**Figure 8**).

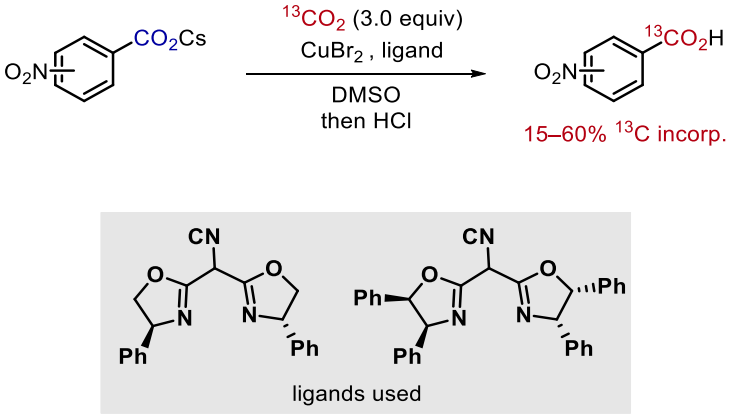

Figure 7. Direct exchange of C(sp^2)-carboxylate groups catalyzed by transition metals.

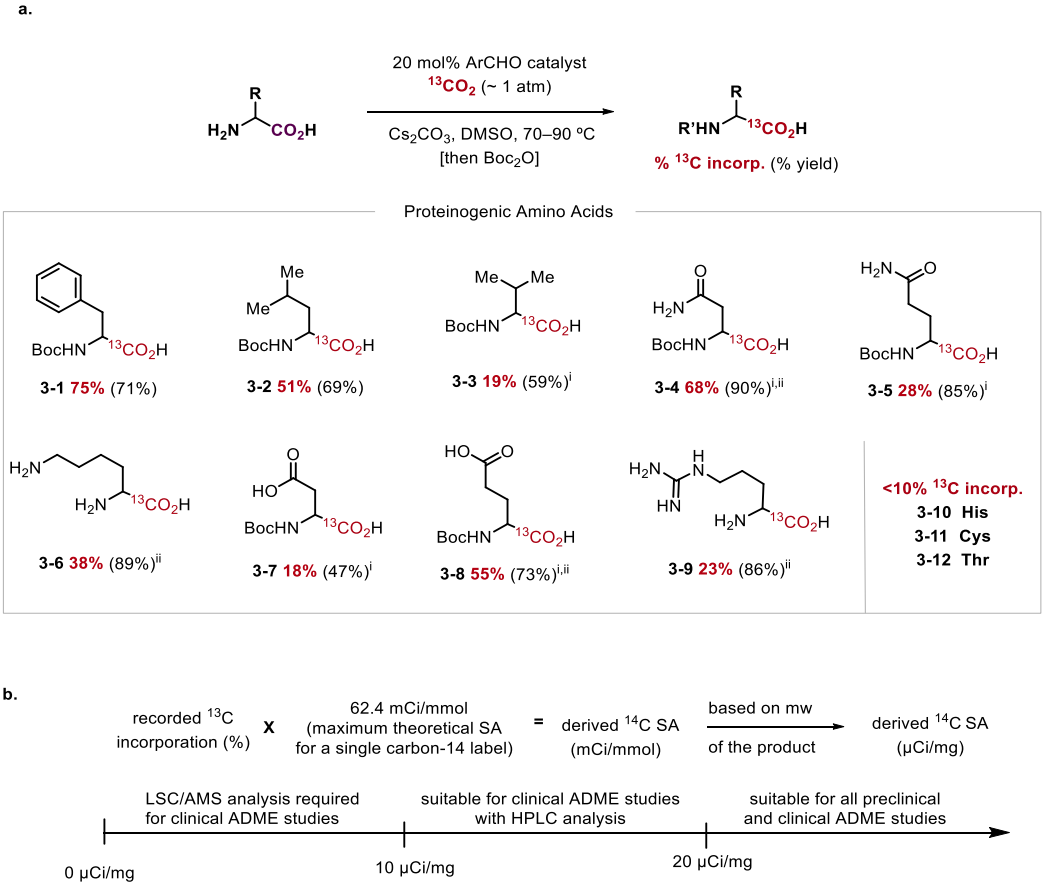

Figure 8a. Aldehyde-catalyzed carboxylate exchange of proteinogenic α-amino acids with [^{13}C]CO_2. [i] Yield determined by ^{1}H NMR spectroscopy, [ii] 75 mol% catalyst, 100% Cs_2CO_3, 0.017 M, **b.** Translation of ^{13}C incorporation to ^{14}C specific activity.

Aliphatic and aromatic α-amino acids can be labelled in 31–75% ^{13}C-incorporation with >50% yield (±)-phenylalanine, (±)-leucine. In most cases, products were isolated as the corresponding *N*-tert-butyloxycarbonyl products for convenience. β-Branched aliphatic and cyclic substrates, such as (±)-valine (19%) were labeled to a lower extent under modified conditions. Acidic or basic side-chain

groups generally were well-tolerated to give 23–55% incorporation of label. To gauge the potential application of the methodology for carbon-14 preclinical and clinical ADME studies, the observed [^{13}C]CO_2 incorporations can be converted to the theoretical specific activities that would result from using [^{14}C]CO_2. This is done by translation of ^{13}C incorporation to ^{14}C theoretical specific activity as shown in **Figure 8b**. In general, higher incorporations of ^{14}C (≥20 μCi/mg) are required for all preclinical and clinical ADME studies (Kingston *et al.*, 2019).

Conclusion

After decades of low-key innovation, the field of isotopic labeling with isotopically-labeled carbon has recently explored new alternative methods. The shortcoming of radiochemistry with long-lived isotopes and high prices of starting materials has motivated chemists to discover and develop alternative methods for labeling which can implement a late-stage of incorporation of the radiolabeled isotope. A promising method was recently provided by CIE technology, which implement the selective of ^{12}C-drivied functional group (i.e. COOH, CN) with its radiolabeled in one step operation. CIE technology depends on the reversible C-C bond cleavage to incorporate easily accessible C-labeled building blocks. The aim of this review is to highlight the range of classical and modern methods that involve CIE technology that have been explored. Although important methods have been reported with CIE of carboxylic acids and nitrile derivatives, the avenue is still open for further development. Some of these methods have scope and they are limited to specific scaffolds such as phenyl acetic acids. In addition to that, the implementation of enantioselective variants still remains difficult to achieve.

Disclosure statement: *Conflict of Interest:* The authors declare that there are no conflicts of interest.
Compliance with Ethical Standards: This article does not contain any studies involving human or animal subjects.

References

Babin, V., Taran, F. and Audisio, D. (2022). Late-stage carbon-14 labeling and isotope exchange: emerging opportunities and future challenges. *JACS Au*, *2*(6), 1234-1251.

Baldwin, J.E., Adlington, R.M., Russell, M.A., Schofield, C.J. and Wood, M.E. (1989). Syntheses of [2-13C] and [1, 2-13C] labelled α-ketoglutaric acid. *J. Label. Compd. Radiopharm.*, 27(9), 1091-1099.

Blakemore, D.C., Castro, L., Churcher, I., Rees, D.C., Thomas, A.W., Wilson, D.M. and Wood, A. (2018). Organic synthesis provides opportunities to transform drug discovery. *Nat. Chem.*, 10(4), 383-394.

Bsharat, O., Doyle, M.G., Munch, M., Mair, B.A., Cooze, C.J., Derdau, V., Bauer, A., Kong, D., Rotstein, B.H. and Lundgren, R.J. (2022). Aldehyde-catalysed carboxylate exchange in α-amino acids with isotopically labelled CO_2. *Nat. Chem.*, *14*(12), 1367-1374.

Campos, K.R., Coleman, P.J., Alvarez, J.C., Dreher, S.D., Garbaccio, R.M., Terrett, N.K., Tillyer, R.D., Truppo, M.D. and Parmee, E.R. (2019). The importance of synthetic chemistry in the pharmaceutical industry. *Science*, 363(6424), p.eaat0805. https://doi.org/10.1126/science.aat0805

Darensbourg, D.J., Longridge, E.M., Holtcamp, M.W., Klausmeyer, K.K. and Reibenspies, J.H. (1993). Reversible decarboxylation of phosphine derivatives of Cu (I) cyanoacetate. Mechanistic aspects germane to catalytic decarboxylation of carboxylic acids. *J. Am. Chem. Soc.*, *115*(19), 8839-8840.

Deng, X., Rong, J., Wang, L., Vasdev, N., Zhang, L., Josephson, L. and Liang, S.H. (2019). Chemistry for positron emission tomography: recent advances in 11C-, 18F-, 13N-, and 15O-labeling reactions. *Angew. Chem. Int. Ed.*, 58(9), 2580-2605.

Derdau V. (2018) New trends and applications in cyanation isotope chemistry, *J. Label. Comp. Radiopharm.*, 61(14), 1012-1023.

Destro, G., Horkka, K., Loreau, O., *et al.* (2020). Transition-metal-free carbon isotope exchange of phenyl acetic acids. *Angew. Chem. Int. Ed.*, *132*(32), 13592-13597.

Destro, G., Loreau, O., Marcon, E., Taran, F., Cantat, T. and Audisio, D. (2018). Dynamic carbon isotope exchange of pharmaceuticals with labeled CO2. *J. Am. Chem. Soc.*, *141*(2), 780-784.

Dias, D.A., Urban, S. and Roessner, U. (2012). A historical overview of natural products in drug discovery. *Metabolites*, *2*(2), 303-336.

Dorff, P.N., Powell, M.E. and Elmore, C.S. (2011). Synthesis of [13C5] and [carbonyl-14C]-5-chlorofuran-2-carboxylic acid. *J. Label. Comp. Radiopharm.*, *54*(3), 123-125.

Doyle, M.G., Mair, B.A., Sib, A., Bsharat, O., Munch, M., Derdau, V., Rotstein, B.H. and Lundgren, R.J. (2024). A practical guide for the preparation of C1-labeled α-amino acids using aldehyde catalysis with isotopically labeled CO_2. *Nat. Protoc*, 1-33.

El Masaoudy Y., Tabti K., Koubi Y., Maghat H., Lakhlifi T., Bouachrine M. (2023) In silico design of new pyrimidine-2,4-dione derivatives as promising inhibitors for HIV Reverse Transcriptase-associated RNase H using 2D-QSAR modeling and (ADME/Tox) properties, *Mor. J. Chem.*, 14(2), 300-317. https://doi.org/10.48317/IMIST.PRSM/morjchem-v11i2.35455

Elmore, C.S., Dean, D.C., DeVita, R.J. and Melillo, D.G. (2003). Synthesis of two non-peptidyl GnRH receptor antagonists via [14C] carbonylation. *J. Label. Compd. Radiopharm.*, 46(10), 993-1000.

Escher, B.I. and Fenner, K. (2011). Recent advances in environmental risk assessment of transformation products. *Environ. Sci. Technol.*, *45*(9), 3835-3847.

Gauthier Jr, D.R., Rivera, N.R., Yang, H., Schultz, D.M. and Shultz, C.S., (2018). Palladium-catalyzed carbon isotope exchange on aliphatic and benzoic acid chlorides. *J. Am. Chem. Soc.*, *140*(46), 15596-15600.

Gehen, S., Corvaro, M., Jones, J., Ma, M. and Yang, Q. (2019). Challenges and opportunities in the global regulation of crop protection products. *Org. Process Res. Dev.*, *23*(10), 2225-2233.

Grygorenko, O.O., Volochnyuk, D.M., Ryabukhin, S.V. and Judd, D.B. (2020). The symbiotic relationship between drug discovery and organic chemistry. *Chem. Eur. J.*, *26*(6), 1196-1237.

Häußermann, A., Rominger, F. and Straub, B.F. (2012). CO_2 on a Tightrope: Stabilization, Room-Temperature Decarboxylation, and Sodium-Induced Carboxylate Migration. *Chem. Eur. J.*, *18*(44), 14174-14185.

Hesk, D., Borges, S., Dumpit, R., Hendershot, S., Koharski, D., McNamara, P., Ren, S., Saluja, S., Truong, V. and Voronin, K. (2017). Synthesis of 3H, 2H4, and 14C-MK 3814 (preladenant). *J. Label. Comp. Radiopharm.*, 60(4), 194-199.

Hinsinger, K. and Pieters, G., (2019). The emergence of carbon isotope exchange. *Angew. Chem. Int. Ed.*, *58*(29), 9678.

Horien, C. and Yuan, P., (2017). Focus: drug development: drug development. *Yale. J. Biol. Med.*, *90*(1), 1.

Hughes, J.P., Rees, S., Kalindjian, S.B. and Philpott, K.L. (2011). Principles of early drug discovery. *Br. J. Pharmacol.*, *162*(6), 1239-1249.

Hunter, R.P., Shryock T.R., Cox B.R., Butler R.M., Hammelman J.E. (2011) Overview of the animal health drug development and registration process: an industry perspective. *Future Med. Chem.*, *3*(7), 881-886.

Ishii, H., Minegishi, K., Nagatsu, K. and Zhang, M.R. (2015). Pd (0)-mediated [11C] carbonylation of aryl and heteroaryl boronic acid pinacol esters with [11C] carbon monoxide under ambient conditions and a facile process for the conversion of [carbonyl-11C] esters to [carbonyl-11C] amides, *Tetrahedron*, *71*(10), 1588-1596.

Kaddouri Y., Abrigach F., Yousfi El B., Hammouti B., El Kodadi M., Alsalme A., Al-Zaqri N., Warad I. and Touzani R. (2021), New Heterocyclic Compounds: Synthesis, Antioxidant Activity and computational Insights of Nano-Antioxidant as Ascorbate Peroxidase Inhibitor by Various Cyclodextrin as Drug Delivery Systems, *Current Drug Delivery*, 18(3), 334-349. https://doi.org/10.2174/1567201817999201001205627

Kingston, C., Wallace, M.A., Allentoff, A.J., deGruyter, J.N., Chen, J.S., Gong, S.X., Bonacorsi Jr, S. and Baran, P.S. (2019). Direct carbon isotope exchange through decarboxylative carboxylation. *J. Am. Chem. Soc.*, *141*(2), 774-779.

Kong, D., Moon, P.J., Lui, E.K., Bsharat, O. and Lundgren, R.J. (2020). Direct reversible decarboxylation from stable organic acids in dimethylformamide solution. *Science*, 369(6503), 557-561.

Korde, A., Mikolajczak, R., Kolenc, P., *et al.* (2022). Practical considerations for navigating the regulatory landscape of non-clinical studies for clinical translation of radiopharmaceuticals. *EJNMMI Radiopharmacy and Chemistry*, 7(1), 18.

Krauser, J.A. (2013). A perspective on tritium versus carbon-14: ensuring optimal label selection in pharmaceutical research and development. *J. Label. Comp. Radiopharm.*, *56*(9-10), 441-446.

Löffler, D., Römbke, J., Meller, M. and Ternes, T.A. (2005). Environmental fate of pharmaceuticals in water/sediment systems. *Environ. Sci. Technol.*, 39(14), 5209-5218.

Lovato, K., Fier, P.S. and Maloney, K.M. (2021). The application of modern reactions in large-scale synthesis. *Nat. Rev. Chem.*, *5*(8), 546-563.

Marathe, P.H., Shyu, W.C. and Humphreys, W.G. (2004). The use of radiolabeled compounds for ADME studies in discovery and exploratory development. *Curr. Pharm. Des.*, *10*(24), 2991-3008.

Melville, D.B., Rachele, J.R. and Keller, E.B. (1947). A synthesis of methionine containing radio-carbon in the methyl group. *J. Biol. Chem.*, 169, 419-426.

Murthy, A. and Ullas, G. (2009). Synthesis of [14C] labeled 2-methoxypyrimidine-5-carboxylic acid. *J. Label. Comp. Radiopharm.*, 52(4), 114-116.

Nakai, R., Sugii, M. and Nakao, H. (1959). Isotopic tracer studies of the ketonic pyrolysis of sodium carboxylates. *J. Am. Chem. Soc.*, *81*(4), 1003-1006.

Ravn, A.K., Vilstrup, M.B., Noerby, P., Nielsen, D.U., Daasbjerg, K. and Skrydstrup, T. (2019). Carbon isotope labeling strategy for β-Amino acid derivatives via carbonylation of Azanickellacycles. *J. Am. Chem. Soc.*, *141*(30), 11821-11826.

Ren, S., McNamara, P., Royster, P., Lee, J., Saluja, S.S., Koharski, D., Hendershot, S. and Truong, V. (2007). Synthesis of 14C-labeled piperidines and application to synthesis of [14C] SCH 351125, a CCR5 receptor antagonist. *J. Label. Compd. Radiopharm.*, 50(7), 643-648.

Riss, P.J., Lu, S., Telu, S., Aigbirhio, F.I. and Pike, V.W. (2012). Cu (I)-catalyzed 11C-carboxylation of boronic acid esters: a rapid and convenient entry to 11C-labeled carboxylic acids, esters and amides. *Angew. Chem. Int. Ed.*, *51*(11), 2698.

Szabolcs, A., Szammer, J. and Noszkó, L. (1974). A new method for the preparation of carboxyl-labelled aliphatic carboxylic acids. *Tetrahedron*, *30*(19), 3647-3648.

Takashima-Hirano, M., Ishii, H. and Suzuki, M. (2012). Synthesis of [11C] Am80 via novel Pd (0)-mediated rapid [11C] carbonylation using arylboronate and [11C] carbon monoxide. *ACS Med. Chem. Lett.*, 3(10), 804-807.

Tortajada, A., Duan, Y., Sahoo, B., Cong, F., Toupalas, G., Sallustrau, A., Loreau, O., Audisio, D. and Martin, R. (2019). Catalytic decarboxylation/carboxylation platform for accessing isotopically labeled carboxylic acids. *ACS Catal.*, *9*(7), 5897-5901.

Voges, R., Heys, J.R. and Moenius, T. (2009). *Preparation of compounds labeled with tritium and carbon-14*. John Wiley & Sons.

Wheeler, W.J. and Blanchard, W.B. (1992). The synthesis of 1, 3, 4-thiadiazol-2-ylcyanamide sodium, a potentially useful anti-influenza agent and its [5-14C] and [UL-13C3] isotopomers *J. Label. Compd. Radiopharm*, 31(7),.495-504.

Zhang, Z., Qiu, C., Xu, Y., Han, Q., Tang, J., Loh, K.P. and Su, C. (2020). Semiconductor photocatalysis to engineering deuterated N-alkyl pharmaceuticals enabled by synergistic activation of water and alkanols. *Nat. Commun.*, *11*(1), 4722.