Direct Carbon Isotope Exchange of Pharmaceuticals via Reversible Decyanation

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ABSTRACT: The incorporation of carbon-14 allows tracking of organic molecules and provides vital knowledge on their fate. This information is critical in pharmaceutical development, crop science and human food safety evaluation. Herein, a transition-metal-catalyzed procedure enabling carbon isotope exchange on aromatic nitriles is described. Utilizing the radiolabeled precursor $Zn([^{14}C]CN)_2$, this protocol allows the insertion of the desired carbon tag without need of structural modifications, in a single step. Reducing synthetic costs and limiting the generation of radioactive waste, this procedure will facilitate the labeling of nitrile containing drugs and accelerate ^{14}C-based ADME studies supporting drug development.

Humans are surrounded by a dazzling array of synthetic organic molecules. Their impact on improving life quality and lifestyle is beyond doubt. Thus, it is of fundamental importance to accurately detect and quantify the fate of organic compounds and provide a precise risk/benefit assessment before they reach the market and large public exposure. The seemless incorporation of carbon-14 tracer (^{14}C, β^- emitter, $t_{1/2}$ = 5730 years) is a technology recognised as the gold standard.[1,2]

^{14}C radiolabeling is indeed a unique tool that, in association with ▨-counting and ▨-imaging technologies, provides vital knowledge on the fate of synthetic organic molecules.[3,4] This information is critical to assess potential issues affecting human health and is required worldwide by regulatory agencies for: *i)* crop science and environmental fate studies, *ii)* human food safety evaluation and *iii)* human and veterinary pharmaceutical development to unveil drug absorption, distribution, metabolism and excretion (ADME) and pharmacokinetic properties of novel pharmaceuticals (Fig 1A).[5] A rapid and straightforward synthetic access to carbon radiolabeled organic molecules is a strict requirement for accelerating research in these societal impacting fields. However, carbon radiosynthesis surprisingly still represents a major bottleneck and a fundamental problem. The energetic barrier required for carbon-carbon bond formation and the rare ^{14}C-bulding blocks available are major obstacles.[6,7] ^{14}C-

building blocks are classicaly used in a multi-step fashion and the radioactivity is incorporated into the chemical scaffold at an early stage of the synthesis (Fig. 1C).[8] This approach is marred by several drawbacks: *i)* the generation of radioactive waste (extremely difficult and expensive to dispose of); *ii)* the multi-step, time-consuming nature of such approaches mandates the development of a specific route in line with the radio-synthetic requirements and safety regulations; *iii)* high resource-demanding: the price for 37 GBq of Ba[^{14}C]CO$_3$ (ca. 3.3 g), the cheapest source of ^{14}C is 25 k€. Other starting materials require additional synthetic steps and costs increase dramatically with each additional step.

Recent examples of late-stage ^{14}C incorporation allow insertion of the label in the last-step of the synthesis, but they require the elaboration of functionalized precursors.[9] Isotope exchange is a promising concept. The selective replacement of molecular moieties into organic molecules, by reversible deconstruction/reconstruction in presence of an appropriate radiolabeled moiety, enables the access to labeled compounds in a single operation, directly from the end-use molecules. Isotope exchange has only recently emerged for carbon radiolabeling[10] and it is thus far limited to carboxylic acids using [^{14}C]CO$_2$[11,12,13,14] and [^{14}C]CO.[15] Herein, we propose a solution for fast radiolabeling that is based on a reversible decyanation/cyanation procedure to enable nitrile (^{14}CN) incorporation into pharmaceuticals by means of transition-metal catalysis.
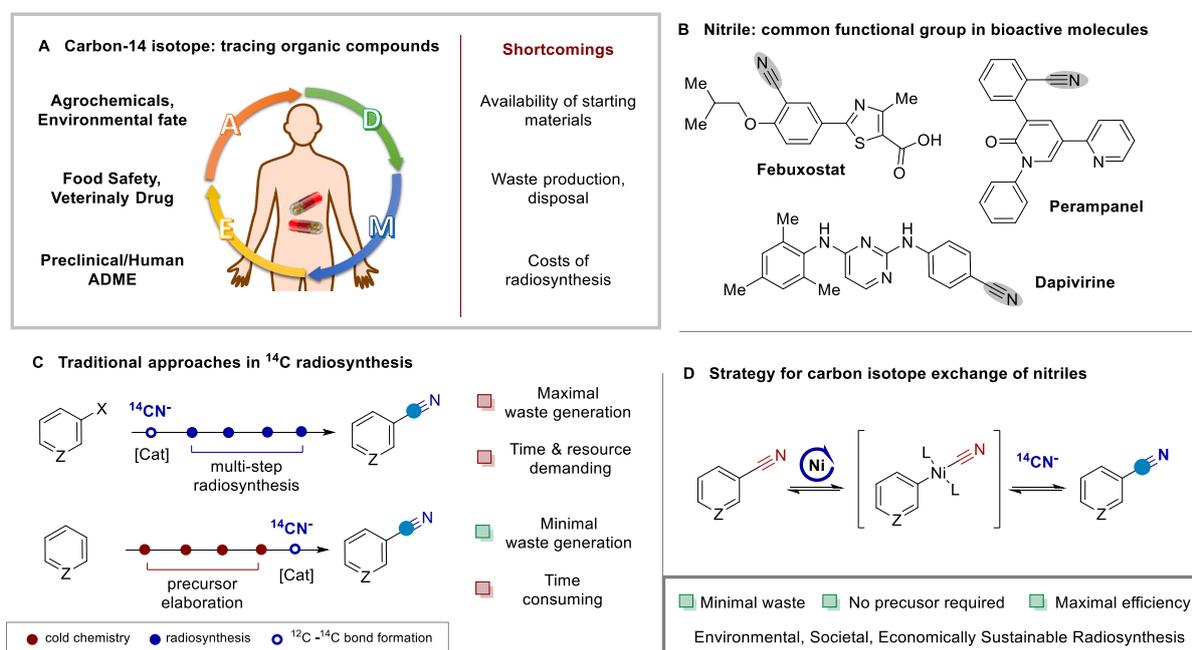

Fig. 1. Development of nitrile carbon isotope exchange. (A) societal field impacted by routine ^{14}C-radiosynthesis of organic compounds. (B) representative examples of bioactive molecules bearing nitrile moieties. (C) Multi-steps approaches commonly utilized to insert ^{14}C-nitriles into biologically relevant molecules. (D) Nitrile carbon isotope exchange. The blue colored circles denote the positions of the labeled carbon atoms.

Nitriles are versatile synthetic intermediates, precursors to amines, carboxylic acids, carboxamides, aldehydes, ketones and alcohols.[16] Besides its malleability as a functional group, the nitrile moiety is present on a number of natural products and pharmaceuticals[17] thus representing a valuable and yet versatile architectural element for labeling (Fig 1B).[18] Metal [14C]cyanides (M = Na, K, Zn) are among the most versatile reagents in ^{14}C synthesis. They are available commercially at reasonable price or can be prepared with relative ease. Their easier manipulation, compared to gaseous sources such as [14C]CO$_2$ and [14C]CO, makes [14C]cyanides the most utilized building blocks in ^{14}C radiosynthesis. [6,18]

We recognised that access to a late-stage, functional group tolerant carbon isotope exchange (CIE) reaction of (hetero)aryl nitriles would be attractive and increase the chemical space available for direct ^{14}C-labeling. Such technology would enable straightforward access to ^{14}C-nitrile radiotracers and a more sustainable radiocarbon synthesis. To bridge this gap, one would need to selectively break a stable [12]C-[12]CN bond (C-CN bond dissociation energy ~130 kcal/mol)[19] and create a new [12]C-[14]CN bond with a radiolabeled source of nitrile.

In contrast to the activation of aryl halides, routinely performed under palladium catalysis, the oxidative addition of C-CN bonds often required the use of low-valent nickel species.[20,21] On the other hand, metal cyanides are known to transmetalate on organometallic metal species (with Ni, Pd and Pt).[22,23] Based on these precedents, the hypothesis of nitrile CIE seemed reasonable and should allow isotopic nitrile metathesis in presence of suitable labeled CN$^-$ sources.[24]

Based on this hypothesis, preliminary studies conducted on model nitrile **1**, rapidly confirmed that isotope exchange proceeded successfully (Fig. 2A). In presence of Ni(COD)$_2$ (40 mol%), trimethylphosphine PMe$_3$ (2 equiv.) and DMAP (1.3 equiv.) in refluxing toluene, cyanide metathesis was optimal with stable Zn([13C]CN)$_2$ (0.65 equiv. corresponding to 1.3 equiv. of [13C]CN$^-$) as isotopic source. Labeled nitrile **[13C]1** was isolated in 90% yield and 55% isotope enrichments, which is in line with the maximal value expected under dynamic conditions.[25] Variation from the standard conditions afforded either minimal isotope incorporation and inferior isolated yield of **[13C]1a** (Fig. 2A, and SI). Alternative cyanide sources proved ineffective (Fig. 2A, entries 1 and 2) and the use of trimethyl phosphine and DMAP were crucial for the optimal cyanide incorporation (Fig. 2A, entries 4 to 6). Lower catalyst loading provided minimal isotope incorporation suggesting catalyst poisoning under the reaction conditions (Fig. 2A, entry 7)..[26] When the reaction was performed at lower temperature poor isotope enrichment was obtained (Fig. 2A, entry 8).

On the basis of these results, we sought to evaluate the generality of the cyanide exchange (Fig. 2B). Variation of substituents on the aromatic group revealed that presence of electron-rich methoxy substituents in ortho, meta and para position are compatible, affording the desired products in 78 to 90% yield and good isotope incorporation. The presence of substituted amines (**6, 7**), alcohol (**8**) and poly aromatic derivative (**11-13**) were tolerated.
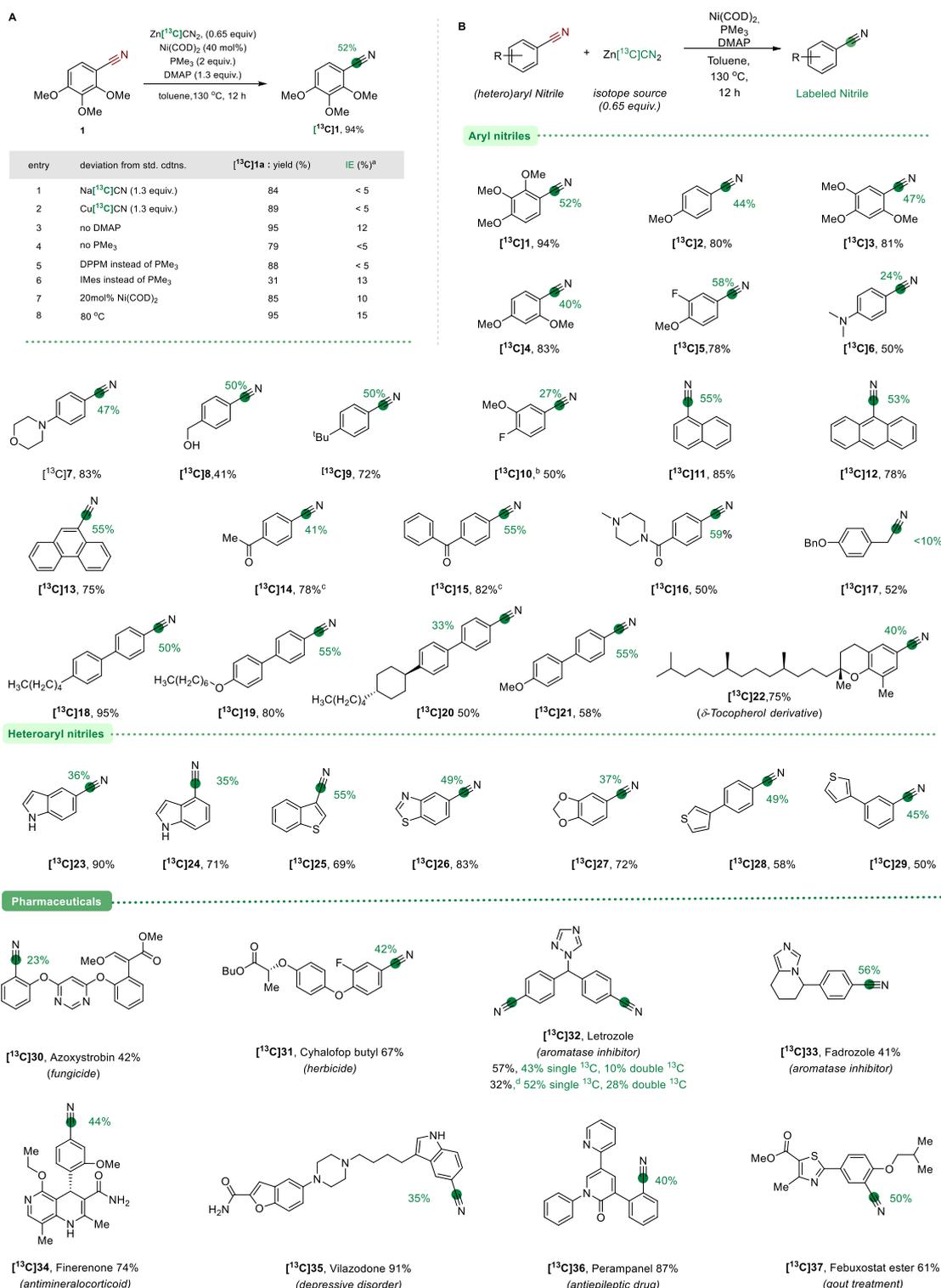
A

Zn[¹³C]CN₂, (0.65 equiv)
Ni(COD)₂ (40 mol%)
PMe₃ (2 equiv.)
DMAP (1.3 equiv.)
toluene,130 °C, 12 h

1 → **[¹³C]1**, 94% (52%)

entry	deviation from std. cdtns.	[¹³C]1a : yield (%)	IE (%)[a]
1	Na[¹³C]CN (1.3 equiv.)	84	< 5
2	Cu[¹³C]CN (1.3 equiv.)	89	< 5
3	no DMAP	95	12
4	no PMe₃	79	<5
5	DPPM instead of PMe₃	88	< 5
6	IMes instead of PMe₃	31	13
7	20mol% Ni(COD)₂	85	10
8	80 °C	95	15

B

(hetero)aryl Nitrile + Zn[¹³C]CN₂ (isotope source, 0.65 equiv.)

Ni(COD)₂, PMe₃, DMAP
Toluene, 130 °C, 12 h
→ Labeled Nitrile

Aryl nitriles

[¹³C]1, 94% 52%
[¹³C]2, 80% 44%
[¹³C]3, 81% 47%
[¹³C]4, 83% 40%
[¹³C]5, 78% 58%
[¹³C]6, 50% 24%

[¹³C]7, 83% 47%
[¹³C]8, 41% 50%
[¹³C]9, 72% 50%
[¹³C]10,[b] 50% 27%
[¹³C]11, 85% 55%
[¹³C]12, 78% 53%

[¹³C]13, 75% 55%
[¹³C]14, 78%[c] 41%
[¹³C]15, 82%[c] 55%
[¹³C]16, 50% 59%
[¹³C]17, 52% <10%

[¹³C]18, 95% 50%
[¹³C]19, 80% 55%
[¹³C]20 50% 33%
[¹³C]21, 58% 55%
[¹³C]22, 75% 40%
(δ-Tocopherol derivative)

Heteroaryl nitriles

[¹³C]23, 90% 36%
[¹³C]24, 71% 35%
[¹³C]25, 69% 55%
[¹³C]26, 83% 49%
[¹³C]27, 72% 37%
[¹³C]28, 58% 49%
[¹³C]29, 50% 45%

Pharmaceuticals

[¹³C]30, Azoxystrobin 42% 23%
(fungicide)

[¹³C]31, Cyhalofop butyl 67% 42%
(herbicide)

[¹³C]32, Letrozole 57%
(aromatase inhibitor)
57%, 43% single ¹³C, 10% double ¹³C
32%,[d] 52% single ¹³C, 28% double ¹³C

[¹³C]33, Fadrozole 41% 56%
(aromatase inhibitor)

[¹³C]34, Finerenone 74% 44%
(antimineralocorticoid)

[¹³C]35, Vilazodone 91% 35%
(depressive disorder)

[¹³C]36, Perampanel 87% 40%
(antiepileptic drug)

[¹³C]37, Febuxostat ester 61% 50%
(gout treatment)

Fig. 2. Carbon Isotope exchange with nitriles. (A) Deviation from standard conditions. [a] Isotopic enrichments (IE) were determined by mass spectrometry (see SI for details). Gernal reaction conditions: benzonitrile (0.10 mmol, 1.0 equiv.), Ni(COD)₂ (0.040 mmol, 40 mol%), trimethylphosphine (1.0 M solution in toluene, 0.2 mmol, 2.0 equiv.), 4-dimethylaminopyridine (0.13 mmol, 1.3 equiv.), Zn(¹³CN)₂ (0.065 mmol, 0.65 equiv.), tolene (0.4 mL), 130 °C, 12 h. **(B) Scope of the reaction.** The colored circles (green) and numbers denote the positions of the carbon atoms labeled and the percent incorporation of the carbon isotope. [b] reaction temperature, 120 °C, reaction time 6 h. [c] reaction time 8h. [d] benzonitrile (0.10 mmol, 1.0 equiv.), Ni(COD)₂ (0.080 mmol, 80 mol%), trimethylphosphine (1.0 M solution in toluene, 0.4 mmol, 4.0 equiv.), 4-dimethylaminopyridine (0.26 mmol, 2.6 equiv.), Zn(¹³CN)₂ (0.13 mmol, 1.3 equiv.), toluene (0.2 mL), 130 °C, 12 h.

While ketone derivatives were tolerated (**14, 15**) with no formation of corresponding cyanohydrins, substrate **10** with electron-poor fluoride in para position was ineffective under standard conditions. The requirement of milder temperature conditions allowed to isolate **[13C]10** in 50% yield and 27% IE. Commonly used nematic liquid crystal **[13C]18** was successfully obtained in high yield and 50% IE.[27] The procedure was also successfully applied to the natural product δ- tocopherol derivative **[13C]22**.

To test the relevance of this procedure, the labeling of important substructures in pharmaceuticals was tested. It was found that the presence of nitrogen-, oxygen- and sulphur-containing heterocycles was tolerated and substrates **23-29** could be labeled in fair to good enrichment. Next, a series of pharmaceuticals and agrochemicals were labeled in a single step using the nitrile CIE with good IE (Fig. 2). Esters (**[13C]30-31, [13C]37**) worked satisfyingly, as did primary amide (**[13C]34**). Pleasingly, a variety of additional heterocycles was compatible, such as 1,2,4-triazole **[13C]32**, pyridine **[13C]41**, pyrimidines **[13C]30** and 2-pyridone **[13C]28**.

Among current CIE technologies based on CO_2 and CO exchange, none would be suitable for these bioactive compounds and, in the case of ester derivatives **30** and **31**, they would require a series of additional saponification/esterification. The benefit is even more striking compared to traditional cyanating reactions, where the synthesis of the halogenated precursor is required.
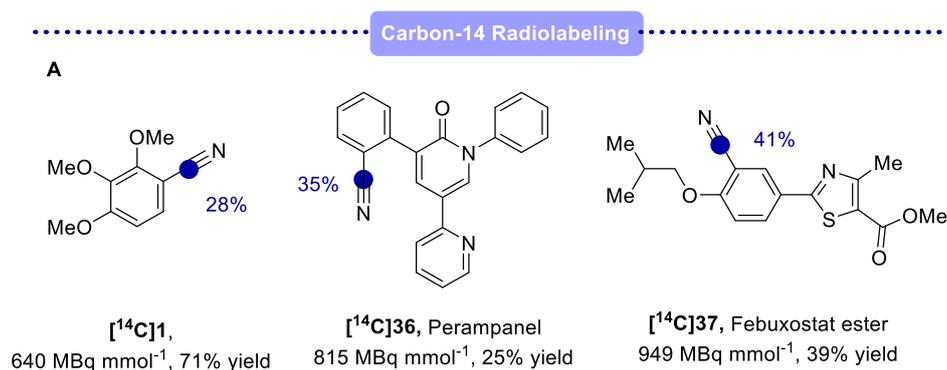

Fig 3. : Ni-catalyzed carbon-14 labeling.

To assess the utility of the nickel-catalyzed CIE over existing multistep methods, representative compounds were labeled using $Zn[^{14}C]CN_2$ (Fig. 3). Model substrate **[14C]1**, was obtained in 71% yield and molar activity of (A_m) 640 MBq mmol^{-1}. To widen its practicability, air-sensitive Ni(COD)$_2$ was used in stoichiometric amounts avoiding requirement for radioactive-glovebox facilities. Perampanel **[14C]36**, an antiepileptic drug, was obtained with a A_m of 815 MBq.mmol^{-1} and 25% yield. Febuxostat methyl ester **[14C]37** was labeled on the nitrile position with a molar activity of 949 MBq.mmol^{-1}, illustrating the complementarity of this method to the previously described CIE with $[^{14}C]CO_2$.[12] Vilazodone **[14C]35**, a medication used to treat depressive disorders, was obtained with a molar activity of 540 MBq.mmol^{-1}. Finerenone is a nonsteroidal anti-mineralocorticoid agent for the treatment of chronic kidney diseases, whose full metabolic profile in dogs, rats and humans was recently disclosed by Bayer. ^{14}C-Finerenone was labeled at the nitrile position by a multi-step procedure with an A_m

of 117 MBq.mmol^{-1}.[28] By means of this nickel-catalyzed CIE, **[^{14}C]34** was synthesized in a ten time higher A$_m$ of 1032 MBq.mmol^{-1} in a single step from its unlabeled isotopomer.

Based on previous literature on C-CN bond cleavage, we suggest a catalytic cycle whereby, after an initial coordination of the metal to the nitrile, activation of benzonitrile occurs through oxidative addition onto a zerovalent Ni species, followed by nitrile isotope exchange. Subsequent reductive elimination delivers the desired labeled aromatic nitrile.

In summary, a nickel-catalysed nitrile isotope exchange procedure has been discovered. This reversible decyanation/cyanation technology bridges a gap in the state of the art, thus allowing for direct ^{13}C and ^{14}C-labeling of nitrile derivatives. We anticipate that this methodology will accelerate access to new radiotracers suitable to support ADME studies and drug development.[29]

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