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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. By utilizing the radiolabeled precursor Zn([14C]CN)2, this protocol allows the insertion of the desired carbon tag without the need for structural modifications, in a single step. By reducing synthetic costs and limiting the generation of radioactive waste, this procedure will facilitate the labeling of nitrile containing drugs and accelerate 14C-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 (14C, β– emitter, t1/2 = 5730 years) is a technology recognized as the gold standard. (1,2)

14C radiolabeling is indeed a unique tool that, in association with β-counting and β-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 (Figure 1A). (5) A rapid and straightforward synthetic access to carbon radiolabeled organic molecules is a strict requirement for accelerating research in these 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 14C-building blocks available are major obstacles. (6,7)14C-building blocks are classically used in a multistep fashion, and the radioactivity is incorporated into the chemical scaffold at an early stage of the synthesis (Figure 1C). (8) This approach is marred by several drawbacks: i) the generation of radioactive waste (extremely difficult and expensive to dispose of); ii) the multistep, time-consuming nature of such approaches mandates the development of a specific route in line with the radio-synthetic requirements and safety regulations; and iii) high resource-demanding: the price for 37 GBq of Ba[14C]CO3 (ca. 3.3 g), the cheapest source of 14C is 25 k€. Other starting materials require additional synthetic steps, and costs increase dramatically with each additional step.

Recent examples of late-stage 14C incorporation allow insertion of the label in the last step of the synthesis, but they require the elaboration of functionalized precursors. (9−11) Isotope exchange is a promising concept. The selective replacement of molecular moieties into organic molecules, by reversible deconstruction/reconstruction in the 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, (12) and it is thus far limited to carboxylic acids using [14C]CO2 (13−19) and [14C]CO. (20) Herein, we propose a solution for radiolabeling that is based on a reversible decyanation/cyanation procedure to enable nitrile (14CN) incorporation into pharmaceuticals by means of transition-metal catalysis. Nitriles are versatile synthetic intermediates, precursors to amines, carboxylic acids, carboxamides, aldehydes, ketones, and alcohols. (21) Besides its malleability as a functional group, the nitrile moiety is present on a number of natural products and pharmaceuticals, (22) thus representing a valuable and yet versatile architectural element for labeling (Figure 1B). (23) Metal [14C]cyanides (M = Na, K, Zn) are among the most versatile reagents in 14C synthesis. They are available commercially at a reasonable price or can be prepared with relative ease. Their easier manipulation, compared to gaseous sources such as [14C]CO2 and [14C]CO, makes [14C]cyanides the most utilized building blocks in 14C radiosynthesis. (6,23)

We recognized 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 14C-labeling. Such technology would enable straightforward access to 14C-nitrile radiotracers and a more sustainable radiocarbon synthesis. To bridge this gap, one would need to selectively break a stable 12C–12CN bond (C–CN bond dissociation energy ∼130 kcal/mol) (24) and create a new 12C–14CN 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. (25−29) On the other hand, metal cyanides are known to transmetalate on organometallic metal species (with Ni, Pd, and Pt). (30,31) Based on these precedents, the hypothesis of nitrile CIE seemed reasonable and should allow isotopic nitrile metathesis in the presence of suitable labeled CN– sources. (32−34)

Based on this hypothesis, preliminary studies conducted on model nitrile 1 rapidly confirmed that isotope exchange proceeded successfully (Figure 2A). In the presence of Ni(COD)2 (40 mol %), trimethylphosphine PMe3 (2 equiv), and DMAP (1.3 equiv) (35,36) 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 the isotopic source. Labeled nitrile [13C]1 was isolated in 94% yield and 52% isotope enrichments, which is in line with the maximal value expected under dynamic conditions. (37) Variation from the standard conditions afforded either minimal isotope incorporation or inferior isolated yield of [13C]1a (Figure 2A and the SI). Alternative cyanide sources proved ineffective (Figure 2A, entries 1 and 2), and the use of trimethylphosphine and DMAP was crucial for the optimal cyanide incorporation (Figure 2A, entries 4–6). Lower catalyst loading provided minimal isotope incorporation suggesting catalyst poisoning under the reaction conditions (Figure 2A, entry 7). (38) When the reaction was performed at lower temperature, poor isotope enrichment was obtained (Figure 2A, entry 8).

On the basis of these results, we sought to evaluate the generality of the cyanide exchange (Figure 2B). Variation of substituents on the aromatic group revealed that the presence of electron-rich methoxy substituents in ortho, meta, and para positions is compatible, affording the desired products in 78–94% yield and good isotope incorporation. The presence of substituted amines (6 and 7), alcohol (8), and polyaromatic derivatives (11–13) was tolerated.

While ketone derivatives were tolerated (14 and 15) with no formation of corresponding cyanohydrins, substrate 10 with electron-poor fluoride in the para position was ineffective under standard conditions. The requirement of milder temperature conditions allowed isolation of [13C]10 in 50% yield and 32% IE. Commonly used nematic liquid crystal [13C]18 was successfully obtained in high yield and 50% IE. (39) The procedure was also successfully applied to the natural product δ-tocopherol derivative [13C]22. It is informative to note that in some reactions the formation of the protodecyanation byproduct was observed. In terms of limitations, benzyl nitrile 17 proved recalcitrant to isotope exchange and also in the presence of Lewis acid BPh3, and the presence of bromide and chlorides was not tolerated. (35)

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 sulfur-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 (Figure 2). Esters ([13C]30–31, [13C]37) worked satisfyingly, as did a primary amide ([13C]34). Pleasingly, a variety of additional heterocycles were compatible, such as 1,2,4-triazole [13C]32, pyridine [13C]34, pyrimidines [13C]30, and 2-pyridone [13C]36.

Among current CIE technologies based on CO2 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.

To assess the utility of the nickel-catalyzed CIE over existing multistep methods, representative compounds were labeled using Zn[14C]CN2 (Figure 3A). Model substrate [14C]1 was obtained in 71% yield and molar activity of (Am) 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 an Am 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 [14C]CO2. (15) 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 antimineralocorticoid agent for the treatment of chronic kidney diseases, whose full metabolic profile in dogs, rats, and humans was recently disclosed by Bayer. 14C-Finerenone was labeled at the nitrile position by a multistep procedure with an Am of 117 MBq·mmol–1. (40) By means of this nickel-catalyzed CIE, [14C]34 was synthesized in a ten times higher Am of 1032 MBq·mmol–1 in a single step from its unlabeled isotopomer. The versatility of selected labeled nitriles was showcased with representative examples of nickel-catalyzed [4 + 2]cycloadditions (Figure 3B). Following the procedure of Ogoshi and co-workers, (41) pyridines [13C]39 and 40 were obtained starting from the corresponding nitrile and 1,3-diene 38. 13C-Labeled 42 was obtained under mild conditions in the presence of alkyne 41 in agreement with the report by the Louie group. (42)

Looking for evidence supporting the reaction mechanism, we investigated a series of stoichiometric experiments (Figure 3C). When [12C]1 was reacted with 1 equiv of Ni(0) and 2 equiv of P(Et)3, a smooth oxidative addition took place at 80 °C to deliver the Ni(II) complex [12C]-int in 76% yield. 31P NMR shows a resonance's signal corresponding to the trans phosphines (singlet at 19.0 ppm), and its square planar geometry was confirmed by single-crystal X-ray analysis. (43−48) When [12C]-int was refluxed in toluene, reductive elimination occurred, and [12C]1 was recovered, highlighting the reversibility of this step. Next, we looked into the putative nitrile isotope metathesis. In the presence of Zn([13C]CN)2 (0.65 equiv), [12C]-int (1 equiv), and DMAP (1.3 equiv) in refluxing toluene, the formation of labeled [13C]1 was observed. To observe cyanide exchange on the nickel complex, milder temperature was applied. At 40 °C in DCM, 13CN– incorporation was observed by 31P NMR spectroscopy, as a resonance doublet corresponding to the cis-P,C coupling constant (d, δ = 19.0 ppm, JP–C = 30 Hz) appeared. (49,50) Under these conditions, isotope exchange peaked at 35% after 5 h (see the SI, for details). While performing the 14C-labeling experiments, we noticed the formation of a second 14C-active spot by radio-TLC, which was assigned to an isotopically 14CN– species. Subsequently, its structure was assigned to a (PMe)xNiCNy by 1H, 13C, and 31P NMR and MS. Slow evaporation of a DCM/heptane solution delivered two distinct orange and yellow crystal forms, which were elucidated by single-crystal X-ray diffraction as a trigonal bipyramidal Ni complex (43) and trimeric unit (44, see the SI). (51) When utilized in the CIE procedure, it was shown that these complexes are catalytically inactive (52) and unable to perform isotope exchange. The role of DMAP appears to be critical in the nitrile exchange step. As reported by Liu and co-workers, coordination of DMAP to Zn(CN)2 might facilitate the transmetalation step. (35,36) In addition, its role as a coligand in nickel catalyzed transformation has also been recently claimed. (53−55) Attempts to highlight these intermediates in the nitrile CIE have thus far been unsuccessful.

In light of this evidence and 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-catalyzed 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 13C- and 14C-labeling of nitrile derivatives. We anticipate that this methodology will accelerate access to new radiotracers suitable to support ADME studies and drug development. (56,57)

REFERENCES

(1) Kamen, M. D. Early History of Carbon-14. Discovery of thissupremely important tracer was expected in the physical sense but notin the chemical sense. Science 1963, 140, 584−590

(2) Isin, E. M.; Elmore, C. S.; Nilsson, G. N.; Thompson, R. A.;Weidolf, L. Use of Radiolabeled Compounds in Drug Metabolism andPharmacokinetic Studies. Chem. Res. Toxicol. 2012, 25, 532−542.

(3) Penner, N.; Klunk, L. J.; Prakash, C. Human radiolabeled massbalance studies: objectives, utilities and limitations. Biopharm. DrugDispos. 2009, 30, 185−203.

(4) Maxwell, B. D.; Elmore, C. S. In ADME-Enabling Technologies inDrug Design and Development; John Wiley & Sons, Inc.: Hoboken,2012; pp 461−472, DOI: 10.1002/9781118180778.ch30.

(5) Elmore, C. S. The Use of Isotopically Labeled Compounds inDrug Discovery. Annu. Rep. Med. Chem. 2009, 44, 515−534.

(6) Voges, R.; Heys, J. R.; Moenius, T. Preparation of CompoundsLabeled with Tritium and Carbon-14; John Wiley & Sons: 2009;DOI: 10.1002/9780470743447.

(7) 14C is generated as Ba[14C]CO3 , routinely converted to carbondioxide [14C]CO2 , as the primary source, see: Zwiebel, N.; Turkevich,J.; Miller, W. W. Preparation of Radioactive CO2 from BaCO 3 . J. Am.Chem. Soc. 1949, 71, 376−377. Other CO2 -derived primary buildingblocks are K14CN and 14CH 3I.

(8) Atzrodt, J.; Derdau, V.; Loewe, C. In Drug Discovery andEvaluation: Methods in Clinical Pharmacology; Hock, F. J., Gralinski,M. R., Eds.; Springer International Publishing: Cham, 2017; pp 1−19,DOI: 10.1007/978-3-319-56637-5_12-1.

(9) Donslund, A. S.; Pedersen, S. S.; Gaardbo, C.; Neumann, K. T.;Kingston, L.; Elmore, C. S.; Skrydstrup, T. Direct Access toIsotopically Labeled Aliphatic Ketones Mediated by Nickel(I)Activation. Angew. Chem., Int. Ed. 2020, 59, 8099−8103.

(10) Del Vecchio, A.; Caillé, F.; Chevalier, A.; Loreau, O.; Horkka,K.; Halldin, C.; Schou, M.; Camus, N.; Kessler, P.; Kuhnast, B.;Taran, F.; Audisio, D. Late-Stage Isotopic Carbon Labeling ofPharmaceutically Relevant Cyclic Ureas Directly from CO2 . Angew.Chem., Int. Ed. 2018, 57, 9744−9748.

(11) Pipal, R. W.; Stout, K. T.; Musacchio, P. Z.; Ren, S.; Graham,T. J. A.; Verhoog, S.; Gantert, L.; Lohith, T. G.; Schmitz, A.; Lee, H.S.; Hesk, D.; Hostetler, E. D.; Davies, I. W.; MacMillan, D. W. C.Metallaphotoredox aryl and alkyl radiomethylation for PET liganddiscovery. Nature 2021, 589, 542−547.

(12) Hinsinger, K.; Pieters, G. The Emergence of Carbon IsotopeExchange. Angew. Chem., Int. Ed. 2019, 58, 9678−9680.

(13) Kingston, C.; Wallace, M. A.; Allentoff, A. J.; deGruyter, J. N.;Chen, J. S.; Gong, S. X.; Bonacorsi, S.; Baran, P. S. Direct CarbonIsotope Exchange through Decarboxylative Carboxylation. J. Am.Chem. Soc. 2019, 141, 774−779.

(14) Tortajada, A.; Duan, Y.; Sahoo, B.; Cong, F.; Toupalas, G.;Sallustrau, A.; Loreau, O.; Audisio, D.; Martin, R. CatalyticDecarboxylation/Carboxylation Platform for Accessing IsotopicallyLabeled Carboxylic Acids. ACS Catal. 2019, 9, 5897−5901.

(15) Destro, G.; Loreau, O.; Marcon, E.; Taran, F.; Cantat, T.;Audisio, D. Dynamic Carbon Isotope Exchange of Pharmaceuticalswith Labeled CO 2. J. Am. Chem. Soc. 2019, 141, 780−784.

(16) Destro, G.; Horkka, K.; Loreau, O.; Buisson, D.-A.; Kingston,L.; Del Vecchio, A.; Schou, M.; Elmore, C. S.; Taran, F.; Cantat, T.;Audisio, D. Transition-Metal-Free Carbon Isotope Exchange ofPhenyl Acetic Acids. Angew. Chem., Int. Ed. 2020, 59, 13490−13495.

(17) Kong, D.; Moon, P. J.; Lui, E. K. J.; Bsharat, O.; Lundgren, R. J.Direct reversible decarboxylation from stable organic acids indimethylformamide solution. Science 2020, 369, 557−561.

(18) Babin, V.; Talbot, A.; Labiche, A.; Destro, G.; Del Vecchio, A.;Elmore, C. S.; Taran, F.; Sallustrau, A.; Audisio, D. A PhotochemicalStrategy for Carbon Isotope Exchange with CO2 . ACS Catal. 2021,11, 2968−2976.

(19) Kong, D.; Munch, M.; Qiqige, Q.; Cooze, C. J. C.; Rotstein, B.H.; Lundgren, R. J. Fast Carbon Isotope Exchange of CarboxylicAcids Enabled by Organic Photoredox Catalysis. J. Am. Chem. Soc.2021, 143, 2200−2206.

(20) Gauthier, D. R.; Rivera, N. R.; Yang, H.; Schultz, D. M.; Shultz,C. S. Palladium-Catalyzed Carbon Isotope Exchange on Aliphatic andBenzoic Acid Chlorides. J. Am. Chem. Soc. 2018, 140, 15596−15600.

(21) Science of Synthesis; Murahashi, S.-I., Ed.; Georg Thieme Verlag:Stuttgart, Germany, 2004; Vol. 19.

(22) Fleming, F. F.; Yao, L.; Ravikumar, P. C.; Funk, L.; Shook, B. C.Nitrile-Containing Pharmaceuticals: Efficacious Roles of the NitrilePharmacophore. J. Med. Chem. 2010, 53, 7902−7917.

(23) Derdau, V. New trends and applications in cyanation isotopechemistry. J. Labelled Compd. Radiopharm. 2018, 61, 1012−1023.

(24) Tobisu, M.; Chatani, N. Catalytic reactions involving thecleavage of carbon−cyano and carbon−carbon triple bonds. Chem.Soc. Rev. 2008, 37, 300−307. For comparison, the C−Br bonddissociation energy is ∼80 kcal/mol

(25) Nakao, Y. C−C Bond Activation. In Catalytic C−CN BondActivation; Topics in Current Chemistry; Dong, G., Ed.; Springer:Berlin, Heidelberg, 2014; Vol. 346, DOI: 10.1007/128_2013_494.

(26) Nakao, Y. Metal-mediated C−CN Bond Activation in OrganicSynthesis. Chem. Rev. 2021, 121, 327−344.

(27) Nájera, C.; Sansano, J. M. Asymmetric IntramolecularCarbocyanation of Alkenes by C-C Bond Activation. Angew. Chem.,Int. Ed. 2009, 48, 2452–2456.

(28) Wen, Q.; Lu, P.; Wang, Y. Recent advances in transition-metal-catalyzed C–CN bond activations. RSC Adv. 2014, 4, 47806–47826.

(29) Bonesi, S. M.; Fagnoni, M. The Aromatic Carbon–Carbonipso-Substitution Reaction. Chem. - Eur. J. 2010, 16, 13572–13589.

(30) Anbarasan, P.; Schareina, T.; Beller, M. Recent developmentsand perspectives in palladium-catalyzed cyanation of aryl halides:synthesis of benzonitriles. Chem. Soc. Rev. 2011, 40, 5049–5067.

(31) Jones, L. H.; Summerhill, N. W.; Swain, N. A.; Mills, J. E.Aromatic chloride to nitrile transformation: medicinal and syntheticchemistry. MedChemComm 2010, 1, 309–318.

(32) For examples of transfer hydrocyanation, see refs 32–34:Bhawal, B. N.; Morandi, B. A Reversible, Transfer HydrocyanationManifold. Trends Chem. 2020, 2, 1034–1035.

(33) Bhawal, B. N.; Reisenbauer, J. C.; Ehinger, C.; Morandi, B.Overcoming Selectivity Issues in Reversible Catalysis: A TransferHydrocyanation Exhibiting High Kinetic Control. J. Am. Chem. Soc.2020, 142, 10914–10920.

(34) Yu, P.; Morandi, B. Nickel-Catalyzed Cyanation of ArylChlorides and Triflates Using Butyronitrile: Merging Retro-hydro-cyanation with Cross-Coupling. Angew. Chem., Int. Ed. 2017, 56,15693–15697.

(35) Zhang, X.; Xia, A.; Chen, H.; Liu, Y. General and Mild Nickel-Catalyzed Cyanation of Aryl/Heteroaryl Chlorides with Zn(CN)2 :Key Roles of DMAP. Org. Lett. 2017, 19, 2118–2121.

(36) Kartal, Z.; Ş ahin, O. The synthesis of heterolepticcyanometallate aminopyridine complexes and an investigation intotheir structural properties with various spectroscopic methods. J. Mol.Struct. 2021, 1227, 129514.

(37) At equilibrium, theoretically the ratio [13CN]:[12 CN] = 1.3:1,in a reaction system.

(38) When higher amounts of Zn[13C]CN 2 were utilized, we did notobserve improvement in the isotope enrichment. On the other hand,the efficiency of the reaction decreases. This results in further supportof the hypothesis of catalyst poisoning. See the SupportingInformation for details.

(39) Tsuei, M.; Shivrayan, M.; Kim, Y.-K.; Thayumanavan, S.;Abbott, N. L. Optical “Blinking” Triggered by Collisions of SingleSupramolecular Assemblies of Amphiphilic Molecules with Interfacesof Liquid Crystals. J. Am. Chem. Soc. 2020, 142, 6139–6148.

(40) Gerisch, M.; Heinig, R.; Engelen, A.; Lang, D.; Kolkhof, P.;Radtke, M.; Platzek, J.; Lovis, K.; Rohde, G.; Schwarz, T.Biotransformation of Finerenone, a Novel Nonsteroidal Mineralo-corticoid Receptor Antagonist, in Dogs, Rats, and Humans, In Vivoand In Vitro. Drug Metab. Dispos. 2018, 46, 1546–1555.

(41) Ohashi, M.; Takeda, I.; Ikawa, M.; Ogoshi, S. Nickel-CatalyzedDehydrogenative [4 + 2] Cycloaddition of 1,3-Dienes with Nitriles. J.Am. Chem. Soc. 2011, 133, 18018–18021.

(42) McCormick, M. M.; Duong, H. A.; Zuo, G.; Louie, J. A Nickel-Catalyzed Route to Pyridines. J. Am. Chem. Soc. 2005, 127, 5030–5031.

(43) For pioneering studies on oxidative addition to Csp 2−CNbonds, with nickel, see refs 43−48: Garcia, J. J.; Jones, W. D.Reversible Cleavage of Carbon−Carbon Bonds in Benzonitrile UsingNickel(0). Organometallics 2000, 19, 5544−5545.

(44) Garcia, J. J.; Brunkan, N. M.; Jones, W. D. Cleavage ofCarbon−Carbon Bonds in Aromatic Nitriles Using Nickel(0). J. Am.Chem. Soc. 2002, 124, 9547−9555.

(45) García, J. J.; Arévalo, A.; Brunkan, N. M.; Jones, W. D. Cleavageof Carbon−Carbon Bonds in Alkyl Cyanides Using Nickel(0).Organometallics 2004, 23, 3997−4002.Journal of the American Chemical Society pubs.acs.org/JACS Communicationhttps://doi.org/10.1021/jacs.1c01923J. Am. Chem. Soc. 2021, 143, 5659−56655664

(46) Ateş in, T. A.; Li, T.; Lachaize, S.; Brennessel, W. W.; García, J.J.; Jones, W. D. Experimental and Theoretical Examination of C−CNand C−H Bond Activations of Acetonitrile Using Zerovalent Nickel. J.Am. Chem. Soc. 2007, 129, 7562−7569.

(47) Ateşin, T. A.; Li, T.; Lachaize, S.; García, J. J.; Jones, W. D.Experimental and Theoretical Examination of C−CN BondActivation of Benzonitrile Using Zerovalent Nickel. Organometallics2008, 27, 3811−3817.

(48) Tauchert, M. E.; Warth, D. C. M.; Braun, S. M.; Gruber, I.;Ziesak, A.; Rominger, F.; Hofmann, P. Highly Efficient Nickel-Catalyzed 2-Methyl-3-butenenitrile Isomerization: Applications andMechanistic Studies Employing the TTP Ligand Family. Organo-metallics 2011, 30, 2790−2809.

(49) Nielsen, D. U.; Lescot, C.; Gøgsig, T. M.; Lindhardt, A. T.;Skrydstrup, T. Pd-Catalyzed Carbonylative α-Arylation of ArylBromides: Scope and Mechanistic Studies. Chem. - Eur. J. 2013, 19,17926−17938.

(50) Partridge, M. G.; Messerle, B. A.; Field, L. D. Signs andMagnitudes of Heteronuclear Coupling Constants in OctahedralRhodium Complexes by High-Resolution 2D NMR. Organometallics1995, 14, 3527−3530.

(51) Meier, P.; Merbach, A. E.; Dartiguenave, M.; Dartiguenave, Y.Solution structure and ligand exchange in the five-coordinatemolecular complexes NiX 2(PMe3)3 . J. Am. Chem. Soc. 1976, 98,6402−6403.

(52) Patra, T.; Agasti, S.; Akanksha; Maiti, D. Nickel-catalyzeddecyanation of inert carbon−cyano bonds. Chem. Commun. 2012, 49,69−71.

(53) Xiao, Y.-L.; Min, Q.-Q.; Xu, C.; Wang, R.-W.; Zhang, X. Nickel-Catalyzed Difluoroalkylation of (Hetero)Arylborons with Unactivated1-Bromo-1,1-difluoroalkanes. Angew. Chem., Int. Ed. 2016, 55, 5837−5841.

(54) Tamang, S. R.; Singh, A.; Unruh, D. K.; Findlater, M. Nickel-Catalyzed Regioselective 1,4-Hydroboration of N-Heteroarenes. ACSCatal. 2018, 8, 6186−6191.

(55) Zhang, S.; Li, L.; Li, X.; Zhang, J.; Xu, K.; Li, G.; Findlater, M.Electroreductive 4-Pyridylation of Electron-deficient Alkenes withAssistance of Ni(acac)2 . Org. Lett. 2020, 22, 3570−3575.

(56) This work was first posted as a preprint on February 18, 2021:Feng, M.; De Oliveira, J.; Sallustrau, A.; Destro, G.; Thuéry, P.; Roy,S.; Cantat, T.; Elmore, C. S.; Blankenstein, J.; Taran, F.; Audisio, D.Direct Carbon Isotope Exchange of Pharmaceuticals via ReversibleDecyanation. ChemRxiv. 2021; Preprint. https://chemrxiv.org/articles/preprint/Direct_Carbon_Isotope_Exchange_of_Pharmaceuticals_via_Reversible_Decyanation/14049896 (accessed2021-04-04), DOI: 10.26434/chemrxiv.14049896.v1.

(57) While this work was submitted, an analogous study wasuploaded as a preprint (February 8, 2021): Reilly, S.; Lam, Y.-H.; Ren,S.; Strotman, N. Late-Stage Carbon Isotope Exchange of Aryl Nitrilesthrough Ni-Catalyzed C–CN Bond Activation. ChemRxiv. 2021,Preprint. https://chemrxiv.org/articles/preprint/Late-Stage_Carbon_Isotope_Exchange_of_Aryl_Nitriles_through_Ni-Catalyzed_C_CN_Bond_Activation/13724023 (accessed 2021-04-04), DOI: 10.26434/chemrxiv.13724023.v2.Journal of the American Chemical Society pubs.acs.org/JACS Communicationhttps://doi.org/10.1021/jacs.1c01923J. Am. Chem. Soc. 2021, 143, 5659−56655665

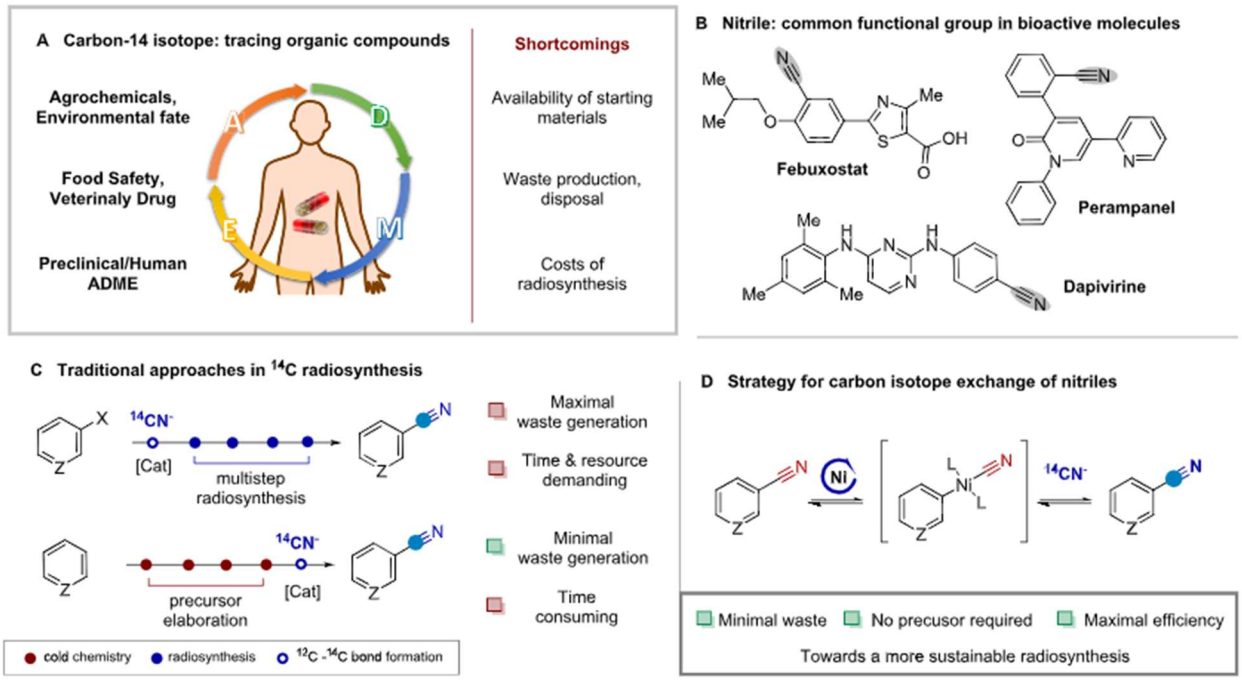

Figure 1. Development of nitrile carbon isotope exchange. (A) Societal field impacted by routine ^{14}C-radiosynthesis of organic compounds. (B) Representative examples of bioactive molecules bearing nitrile moieties. (C) Multistep approaches commonly utilized to insert ^{14}C-nitriles into biologically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

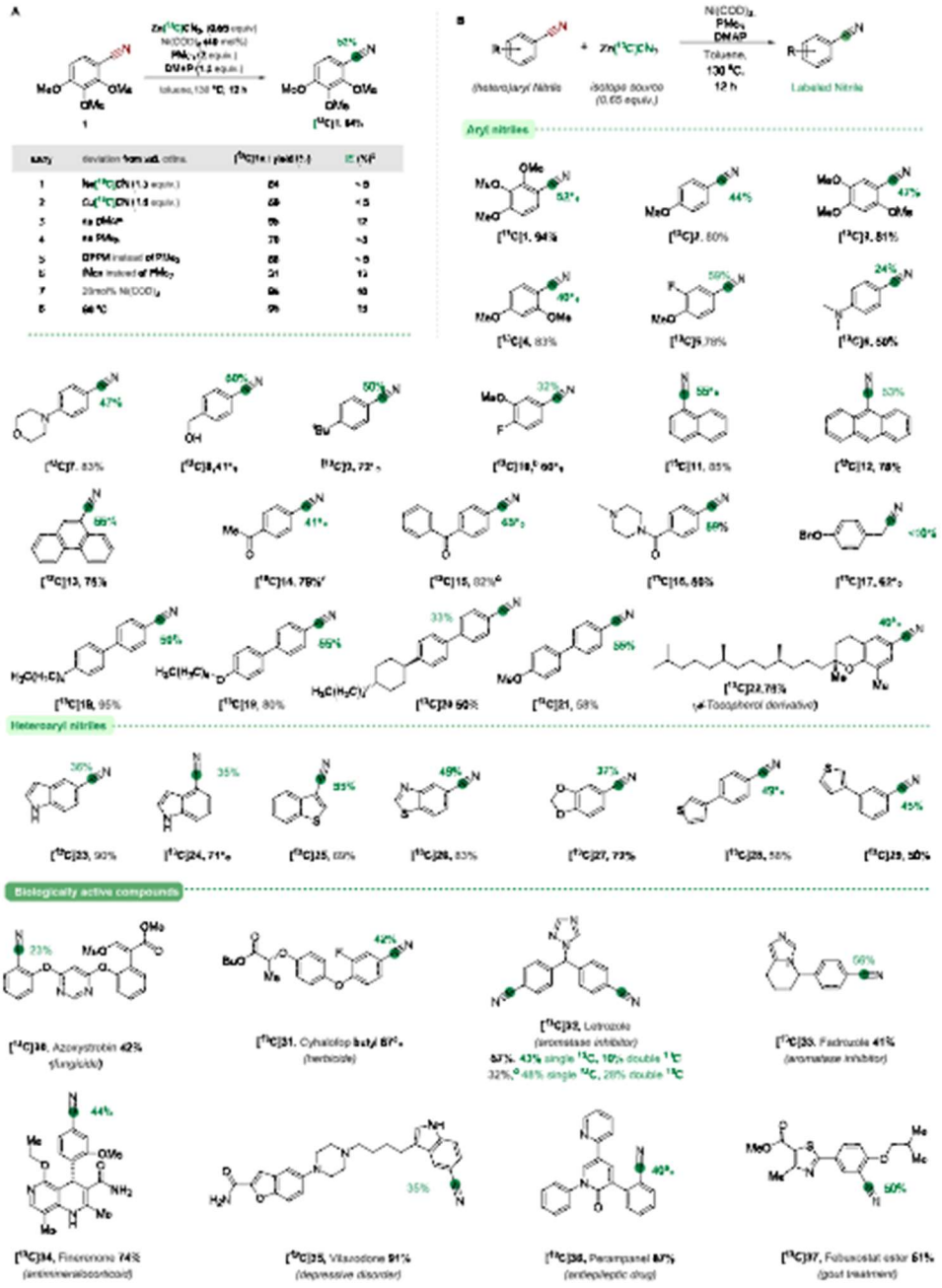

Figure 2. Carbon isotope exchange with nitriles. (A) Deviation from standard conditions. [a]Isotopic enrichments (IEs) were determined by mass spectrometry (see the SI for details). General reaction conditions: benzonitrile (0.10 mmol, 1.0 equiv), $Ni(COD)_2$ (0.040 mmol, 40 mol %), trimethylphosphine (1.0 M solution in toluene, 0.2 mmol, 2.0 equiv), 4-dimethylaminopyridine (0.13 mmol, 1.3 equiv), $Zn(^{13}CN)_2$ (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 8 h. [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), $Zn(^{13}CN)_2$ (0.13 mmol, 1.3 equiv), toluene (0.2 mL), 130 °C, 12 h.

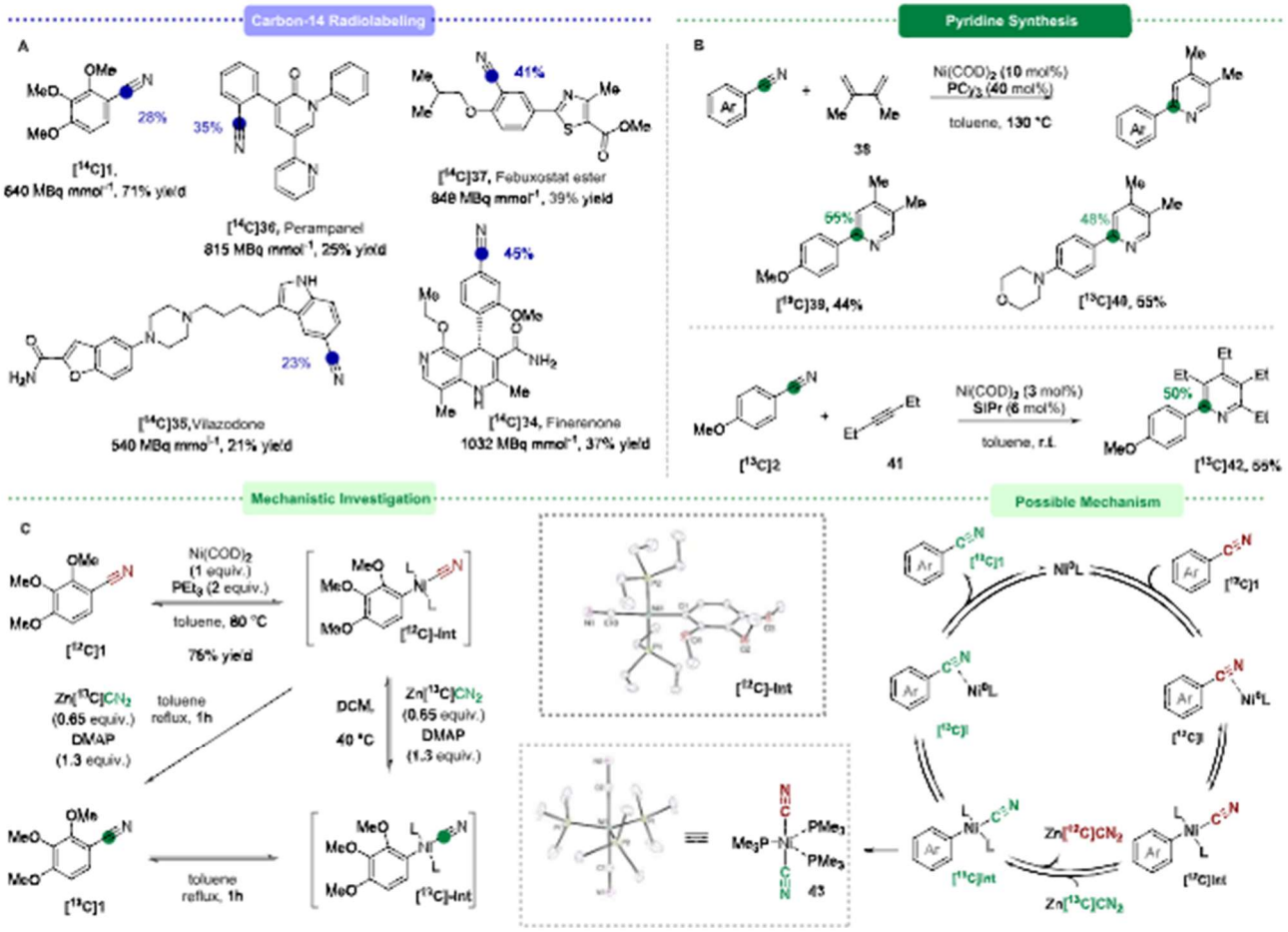

Figure 3. (A) Ni-catalyzed carbon-14 labeling. (B) Synthesis of labeled pyridine by [4 + 2]cycloaddition reactions. (C) Mechanistic investigation on the nitrile isotope exchange and preliminary mechanistic proposal.