Communication

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Donald R. Gauthier, Jr., Nelo R Rivera, Haifeng Yang, Danielle M Schultz, and C. Scott Shultz

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Palladium-Catalyzed Carbon Isotope Exchange on Aliphatic and Benzoic Acid Chlorides

Donald R. Gauthier, Jr.,* Nelo R. Rivera, Haifeng Yang, Danielle M. Schultz and C. Scott Shultz

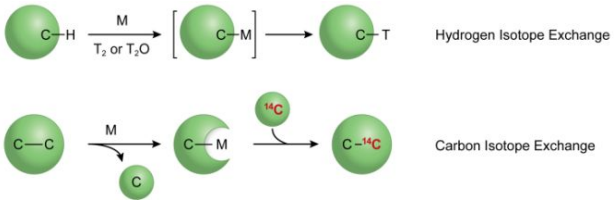
Department of Process Research and Development, Merck & Co., Inc., Rahway, New Jersey 07065, United States

Supporting Information Placeholder

ABSTRACT: An operationally simple protocol for a Palladium-catalyzed ^{13}CO and ^{14}CO exchange with activated aliphatic and benzoic carbonyls is presented. Several ^{13}C and ^{14}C building blocks, natural product derivatives, and pharmaceuticals have been prepared to showcase the method for late-stage carbon isotope incorporation and its functional group compatibility.

Radiolabeled pharmaceutical compounds, typically featuring tritium and carbon-14, provide vital knowledge of drug metabolism and disposition.[1] During early phases of pharmaceutical discovery, the radioisotope selection process must weigh the benefits and liabilities incurred by labeling with either tritium or ^{14}C. Hydrogen isotope exchange performed directly on the target molecule offers inexpensive, rapid access to tritiated compounds;[2] however, the sites of tritiation often coincide with sites of metabolism, thus rendering these strategies unproductive. On the other hand, the metabolic stability engendered by imbedding ^{14}C firmly into the carbon framework of the molecule is attractive. Despite this important advantage, the synthesis of ^{14}C tracers can be prohibitively difficult and expensive, often requiring de novo synthetic routes structured around the limited collection of commercially available ^{14}C raw materials.[3] Furthermore, these methods involve handling and purification of radioactive intermediates that result in significant amounts of long-lived radiocarbon waste ($T_{1/2}$ 5730 years). Nonetheless, ^{14}C radiotracers are essential to the clinical development of a drug candidate.[4] Therefore, the concept of late-stage isotope exchange, routine for swapping isotopes of hydrogen, would be highly valuable as a carbon labeling strategy to address these challenges.[5]

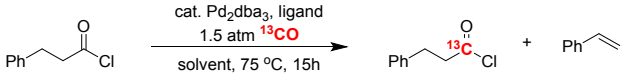
Hydrogen isotope exchange relies on C-H activation, often metal catalyzed,[6] followed by tritiation of a metal complex, typically utilizing T_2 gas or tritiated water as the source of tritium (Scheme 1). Extending this strategy to ^{14}C is expected to be more challenging as the breaking of a C-C bond is generally much higher in energy than that of a C-H bond. Premised on well-established metal catalyzed carbonylation[7] and recent reports demonstrating palladium catalyzed carbonyl exchange by Arndtsen[8] and Morandi,[9] we envisaged facile $^{12}CO/^{14}CO$ exchange could occur with a suitably activated carboxylic acid derivative under a partial atmosphere of ^{14}CO. Moreover, the use of carboxylic acids and their derivatives comprise one of the most important structural motifs in pharmaceuticals, agrochemicals and organic materials and are often selected as targets for radiocarbon labeling.[10,11,12] Herein we report a general carbon isotope exchange method for substrates containing carboxylic acids utilizing ^{13}CO and ^{14}CO, readily available sources of isotopically labeled carbon.[13]



Scheme 1. Hydrogen and Carbon Isotope Exchange.

Initial studies were focused on looking at an array of Pd-ligand complexes in 1.5 atm of ^{13}CO (as a surrogate for precious ^{14}CO) with dihydrocinnamoyl chloride as the activated acid (Table 1). Significant ^{13}CO incorporation was observed by LCMS analysis with several ligands including XantPhos, tBuXPhos, and P(*o*-tol)$_3$; however, competitive β-hydride elimination from the presumed [Pd-alkyl] intermediate to liberate styrene was observed as a significant byproduct under many conditions. Fortunately, this side reaction was minimized in toluene using the P(*o*-tol)$_3$ ligand.

Table 1. ^{13}CO Exchange in Dihydrocinnamoyl Chloride Using Pd-Catalysis.

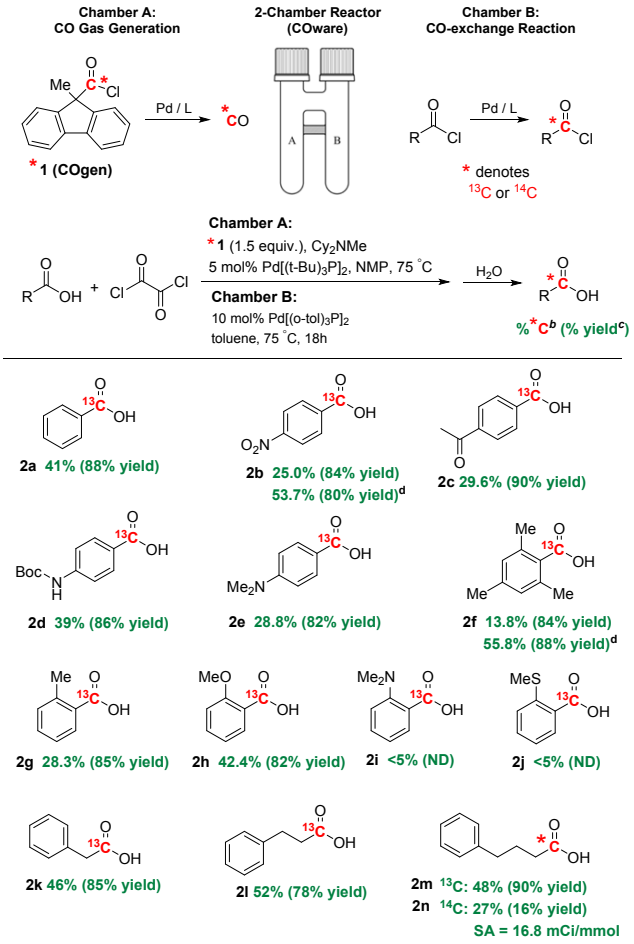


Ligand	1,4-doxane M+1	1,4-doxane Prod/Styrene[b]	toluene M+1	toluene Prod/Styrene[b]
DPPF (1,1'-Ph_2P-Ferrocene)	9%	7.4	10%	1.4
DIPPF (1,1'-(iPr)$_2$P-Ferrocene)	8%	5.0	9%	1.2
DPPP	9%	1.7	9%	1.5
DPPB	12%	2.7	12%	1.3
DPEPHOS	13%	3.2	20%	1.0
XantPhos	75%	2.8	85%	1.7
JosiPhos (R)-(S)-cy_2PF-PtBu_2	10%	3.2	9%	1.2
CataCXium PtB: N-Ph-2-(tBu)$_2$P-pyrrole	43%	10.0	33%	0.9
tBuXPhos	55%	5.7	70%	1.0
Cy_3P-HBF_4	12%	2.5	13%	2.0
(o-Tol)$_3$P	77%	3.2	100%	11.4

[a]Microscale screen conditions: 10 mol% Pd_2dba_3, 10 mol% bidentate ligand or 20 mol% monodentate ligand, pressurized with ^{13}CO gas using a regulator, 0.25M, 75 °C, 15 h, then aqueous LiOH. [b]^{13}C incorporation and acid/styrene ratios as determined by UPLC-MS at 210 nm.

Having demonstrated proof of concept in our initial screening we sought to explore the scope of this chemistry. As a result, we turned to the use of $^{13}COgen$ or $^{14}COgen$, developed by Skrydstrup,[14] as a convenient and precise method for introducing ^{13}CO or ^{14}CO gas into the reaction.[15] The sealed two chamber system (COware) allowed for accurate dispensing of 1.5 equivalents COgen into one chamber, making the liberated CO gas available for Pd-catalyzed exchange in the connecting chamber. In contrast to our catalyst screening study that used a large excess of ^{13}CO gas, we aimed to minimize the labeled COgen due to the high cost of carbon-14 reagents. Therefore, the percent enrichment is limited by the equivalents of COgen. In the present study, we chose 1.5 equivalents COgen as it can provide up to 60% isotope enrichment if the system reaches equilibrium[16] by distributing the label equally amongst the free CO gas and the acid chloride substrate. Since carbon-14 is detectable at very low concentrations, often high specific activity (SA)[17] compounds are diluted with the unlabeled compound to meet dosimetry requirements;[18] therefore, even modest levels of enrichment can be suitable for in vivo studies. In our initial assessment using Pd[(o-tol)$_3$P]$_2$ as catalyst, substituted aromatic and primary aliphatic acid chlorides were observed to perform with the highest levels of isotopic exchange (Table 2). Secondary aliphatic acid chlorides exchanged to a lesser degree than primary. These conditions failed with tertiary acid and *N*-protected α-amino acid chlorides with the primary observation being recovery of unlabeled starting material. In general, exchange was not significantly affected by the benzoyl chloride substitution patterns; however, exchange was attenuated by strong chelating o-substituents (Table 2, entries **2i** and **2j**).

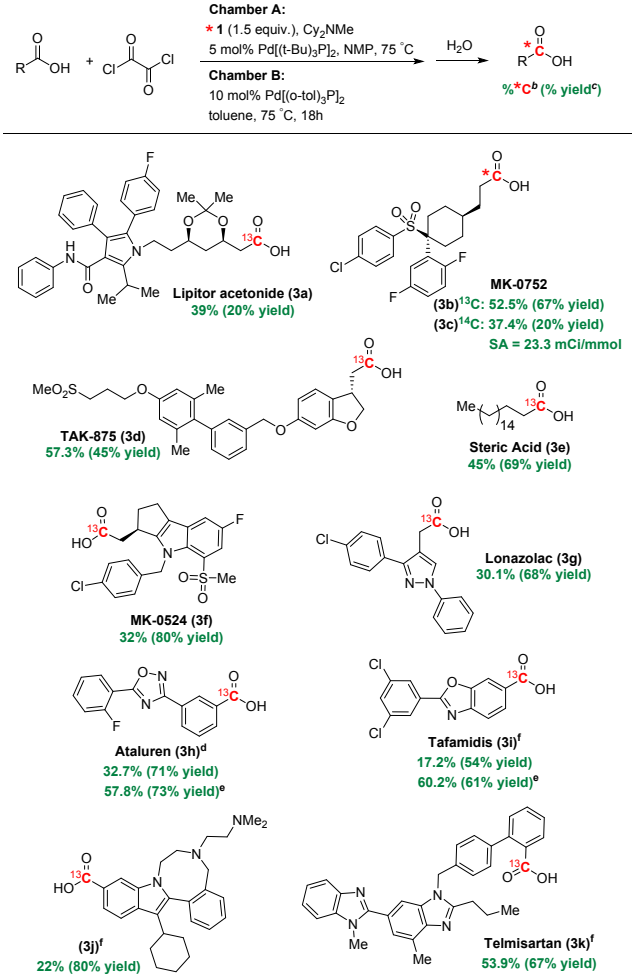
Table 2. Exchange Scope: Benzoic and Aliphatic Acids[a]



[a]Conditions: Chamber A: 1.5 equiv. COgen, 5 mol% Pd[(t-Bu)$_3$P]$_2$, 3 equiv. Cy$_2$NMe, 0.5M NMP, 75 °C; Chamber B: 0.1 – 0.3 g of substrate, 10 mol% Pd[(o-tol)$_3$P]$_2$, 0.25M toluene, 75 °C, 18h. [b]Percent carbon isotope enrichment. [c]Isolated yield of *C enriched acid. [e]Used Pd[(t-Bu)$_3$P]$_2$ as catalyst in Chamber B.

To further demonstrate the utility of the labeling method, we performed both ^{13}C and ^{14}C labeling on a set of biologically active substrates (Table 3). The method proved effective on the penultimate precursor to Lipitor (**3a**), yielding 39% ^{13}C incorporation with 1.5 equiv. ^{13}CO. This concise labeling strategy highlights the simplicity and power of the transformation compared to previous approaches.[19] A diverse series of pharmaceuticals containing primary aliphatic acids and substituted benzoic acids likewise underwent smooth exchange, including gamma secretase inhibitor MK-0752,[20] GPR40 agonist TAK-875,[21] steric acid, prostaglandin D2 receptor antagonist MK-0524,[22] Lonazolac, Ataluren, Tafamidis, HCV polymerase inhibitor **3j**,[15a] and Telmisartan.

Table 3. Exchange on Biologically Active Substrates[a]



[a]Conditions: Chamber A: 1.5 equiv. COgen, 5 mol% Pd[(t-Bu)$_3$P]$_2$, 3 equiv. Cy$_2$NMe, 0.5M NMP, 75 °C; Chamber B: 0.1 – 0.3 g of substrate, 10 mol% Pd[(o-tol)$_3$P]$_2$, 0.25M toluene, 75 °C, 18h. [b]Percent carbon isotope enrichment. [c]Isolated yield of *C enriched acid. [d]Substrate in 1,4-dioxane. [e]Pd[(t-Bu)$_3$P]$_2$ as catalyst in Chamber B. [f]Substrate in NMP.

Having demonstrated the applicability of this methodology on pharmaceutically relevant compounds containing aromatic and primary aliphatic acids, we sought to understand why secondary and tertiary acids had variable performance under the Pd/P(*o*-tol)$_3$ catalyzed conditions. A mechanism to describe the exchange is displayed in Figure 1 (**A** to **F**) and is related to carbonylation/decarbonylation studies for acyl group isomerization with palladium complexes.[23,24] Based on literature precedent, we suspected that either decarbonylation (**A** to **C**) or C-Cl reductive elimination (**F** to product) is turn-over limiting and that the employment of bulky and electron rich ligands could potential facilitate both processes. Specifically, work by Sanford has shown that the use of BrettPhos can greatly accelerate decarbonylative processes by allowing more facile generation of an unsaturated Pd^{II} species.[25] Moreover, Arndtsen has reported that P^{t}Bu$_3$ greatly accelerates C-Cl reductive elimination from Pd-benzoyl(chloride) complexes due to the ligand providing both an electron rich and hindered environment but also an empty coordination site for CO association.[8,26,27]

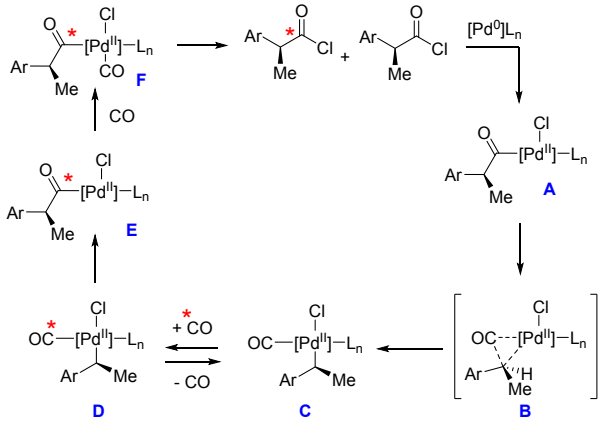
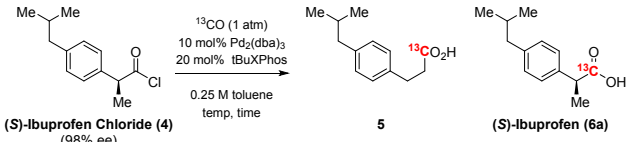


Figure 1. Proposed Pd-cat. CO-Exchange Mechanism

We then performed a second round of screening focusing on bulky and electron-rich ligands that would facilitate both CO exchange and C-Cl reductive elimination (step **A** to **F**), utilizing (*S*)-ibuprofen chloride (**4**) as a model chiral benzylic acid that gave negligible exchange under the Pd/P(*o*-tol)$_3$ conditions. To our delight, several bulky and electron rich catalysts were shown to promote CO exchange at 75 °C; however, it was determined that the product had completely isomerized to unbranched acid **5**. Performing the exchange at 50 °C gave predominantly the desired branched acid **6a** albeit with diminished enantiopurity (Scheme 2). We suspect that the observed isomerization at elevated temperatures can be attributed to β-hydride elimination/re-insertion pathway either through **A** or **C/D** (Figure 1).[20a] Remarkably, running the reaction at ambient temperature resulted in high incorporation of ^{13}CO with no isomerization or loss in %ee observed.[28] While we do not have a complete understanding of this observation we hypothesize that benzylic acid chlorides allow facile decarbonylation through stabilization of the developing negative charge on the alkyl group by the adjacent aromatic ring (Figure 1, B).

Scheme 2. CO Exchange Optimization for (*S*)-Ibuprofen

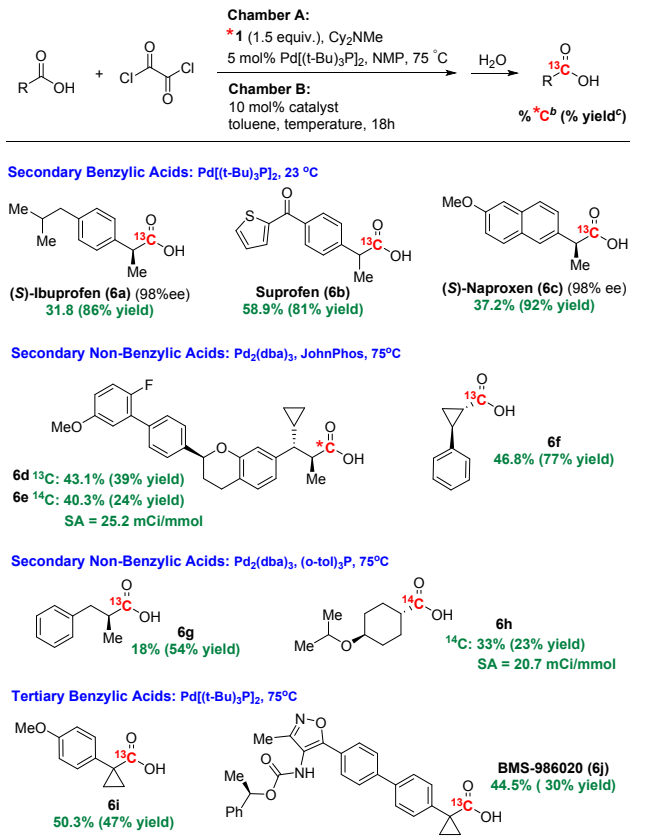


temp, time	ratio 5:6a
75 °C, 18h	100 : 0
50 °C, 18h	1 : 3 (70% ee)
23 °C, 18h	0 : 100 (98%ee)

Transition of these conditions to the dual chambered system with ^{13}COgen and Pd[(t-Bu)$_3$P]$_2$ as catalyst provided ^{13}C-labeled (*S*)-Ibuprofen (**6a**), Suprofen (**6b**) and (*S*)-Naproxen (**6c**) in high yield (Table 4) with >30% ^{13}C incorporation.[14] Bulky electron rich catalysts also proved highly effective for non-benzylic secondary acids, providing GPR40 agoPAM candidate (**6d,e**)[29] and phenylcyclopropyl acid **6f** both in good yield with high isotopic enrichment. α-Methylhydryocinnamic acid (**6g**) gave only β-methylstyrene products using bulky electron rich ligands; however, (o-tol)$_3$P minimized decarbonylation and furnished **6g** with 18% ^{13}C without loss of enantiopurity. In general, tertiary acid chlorides were resistant to exchange; however, benzylic cyclopropyl acid **6i** was found to exchange with a high degree of isotopic enrichment. These conditions were also successfully applied to BMS-986020.[30] In addition, we also compared the performance of Pd[(t-Bu)$_3$P]$_2$ with

benzoyl chlorides that gave modest exchange with Pd[(o-tol)$_3$P]$_2$ and found significant improvement, nearing or attaining perfect 60% ^{13}C enrichment (Table 2: **2b** and **2f**, Table 3: **3h** and **3i**).

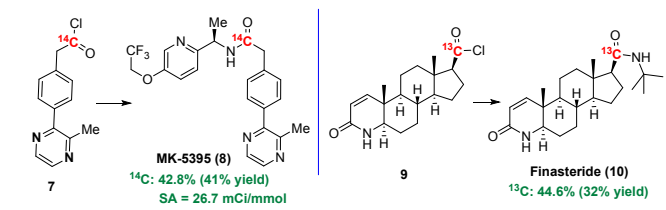
Table 4. Exchange on Secondary and Tertiary Acids[a]



[a]Conditions: Chamber A: 1.5 equiv. COgen, 5 mol% Pd[(t-Bu)$_3$P]$_2$, 3 equiv. Cy$_2$NMe, 0.5M NMP, 75 °C; Chamber B: 0.1 – 0.3g of substrate, 10 mol% catalyst, 0.25M toluene, indicated temp., 18h. [b]Percent carbon isotope enrichment. [c]Isolated yield of *C enriched acid.

Subsequent to the carbon isotope exchange, the labeled acid chloride product can serve as a versatile intermediate. For example, after exchange with ^{14}CO on acid chloride **7**, [^{14}C]MK-5395 was prepared by simple addition of the requisite amine (Scheme 3). In a similar manner, [^{13}C]finasteride (**10**) was prepared in with 44.6% ^{13}C incorporation.

Scheme 3. Extended Substrate Scope for CO Exchange: Pharmaceuticals Containing Amides



In summary, late stage carbon isotope exchange significantly enhances the ability to produce metabolically stable tracers that aid in the development and understanding of the interplay of pharmacophores with biological systems. As such, we have developed a straightforward approach that allows late stage carbon isotope incorporation using a dual chamber system where labeled CO is generated and exchanged under a Pd-catalyzed process. The utility of this method is highlighted by the ability to carry out incorporation of ^{13}C and ^{14}C into substrates bearing primary, secondary, tertiary and aromatic acid chlorides. A series of structurally diverse pharmaceutical agents were also successfully labeled with no isomerization or racemization detected. Work is ongoing to expand the scope using other carbonyl exchange conditions, and to explore further the application of carbon isotope exchange in the development new radiolabeling methods.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

Experimental proceedure and compound characterization (PDF)

AUTHOR INFORMATION

Corresponding Author

*donald_gauthier@merck.com
ORCID
Donald R. Gauthier, Jr.: 0000-0003-2825-0530

Notes

The authors declare no competing financial interests.

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(Word Style "TF_References_Section"). References are placed at the end of the manuscript. Authors are responsible for the accuracy and completeness of all references. Examples of the recommended formats for the various reference types can be found at http://pubs.acs.org/page/4authors/index.html. Detailed information on reference style can be found in The ACS Style Guide, available from Oxford Press.

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