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Letter

Rapid Access to Carbon-Isotope-Labeled Alkyl and Aryl Carboxylates Applying Palladacarboxylates

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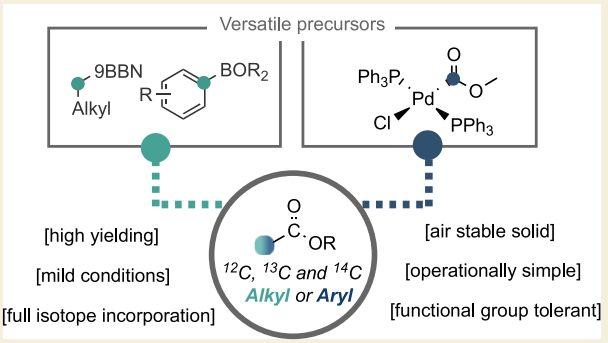
ABSTRACT: Herein, we report a strategy for the formation of isotopically labeled carboxylic esters from boronic esters/acids using a readily accessible palladium carboxylate complex as an organometallic source of isotopically labeled functional groups. The reaction allows access to either unlabeled or full ^{13}C- or ^{14}C-isotopically labeled carboxylic esters, and the method is characterized by its operational simplicity, mild conditions, and general substrate scope. Our protocol is further extended to a carbon isotope replacement strategy, involving an initial decarbonylative borylation procedure. Such an approach allows access to isotopically labeled compounds directly from the unlabeled pharmaceutical, which can have implications for drug discovery programs.



KEYWORDS: *isotope labeling, carbon-14, pharmaceuticals, organic acids, palladium*

Carboxylic acids and esters are a central motif in drug discovery programs and constitute versatile synthetic intermediates en route to active pharmaceutical ingredients (APIs).[1] Pharmacokinetic studies of these APIs, however, are costly to perform, as they require isotope enrichment of the API for adsorption, metabolism, elimination (ADME) studies.[2] Often, staple synthetic techniques used in process or medicinal chemistry to access carboxylic acids and esters do not transfer to isotope labeling programs due to stringent limitations in efficiently incorporating the valuable radiolabel. The synthesis of isotopically labeled compounds differs from traditional organic synthesis due to (1) the scarcity of isotopically labeled reagents, (2) the high cost of these reagents, and (3) the production of dangerous radioactive waste, which therefore requires new synthetic routes to be devised.[3] Radiochemists therefore aim to incorporate the radiolabel in high radiochemical yields at the latest stage possible in a synthetic route in order to minimize cost and hazardous waste.

Of the radiolabeled motifs, accessing carbonyl containing compounds are among the most valuable with three carbonyl containing functional groups (amides, carboxylic acids, and esters) among the most prevalent in bioactive molecules.[4] Furthermore, these methods often utilize feedstock radiolabels that originate from $Ba^{14}CO_3$, which is the source of all radioactive carbon-14 containing compounds and liberates isotopically labeled carbon dioxide (Scheme 1).[5]

From this stage the CO_2 can be used directly or reduced to afford a variety of one carbon synthons such as CO. Most commonly utilized strategies for the synthesis of isotopically labeled carboxylic acids include nitrile substitution followed by hydrolysis or direct carboxylation from organomagnesium or -lithium reagents.[6−8] However, both of these approaches suffer from harsh reaction conditions and poor functional group compatibility, which limits their applicability en route to functional group dense molecules often found within drug discovery programs. Modern carboxylation or alkoxycarbonylation strategies relevant to isotope labeling have been developed from aryl halides,[9−11] pseudohalides,[12,13] and boronic esters derivatives[14−17] using palladium, nickel, or copper catalyzed/mediated processes with superior substrate compatibility. However, these methods require the use of gaseous reagents as radiolabels, which have specific drawbacks, including the requirement for specialized equipment and safety considerations. Furthermore, the radiolabel is often used in significant excess, which produces challenging to handle gaseous radioactive waste and storage of gaseous radiolabeled CO gas may undergo radiolysis. Alternative approaches that take advantage of functional group exchange have also been developed with recent dynamic carbon isotope exchange strategies developed by Audisio[18] and Lundgren[19] utilizing aryl carboxylate salts and by Baran[20] and Martin[21] using redox

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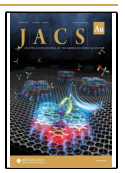

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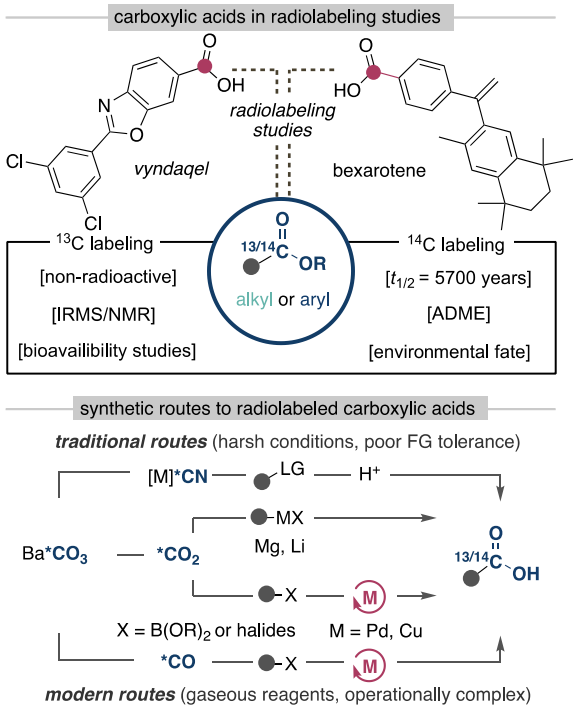
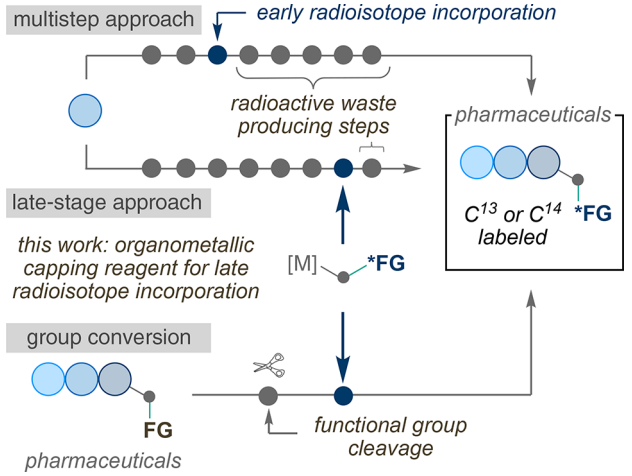
Scheme 1. Pharmaceuticals with Aryl Carboxylic Acid Functionalities and Traditional Synthetic Routes for Isotope Incorporation



active alkyl esters. These dynamic exchange methods have emerged as atom efficient routes for isotope labeling, though have a generalized drawback with incomplete isotope incorporation occurring due to the presence of an equilibrium of labeled to unlabeled compound.

Considering these challenges, our group has aimed to develop isotope labeling reagents that can readily incorporate carbonyl motifs and be compatible with late-stage functionalization and functional group interconversion technologies (Scheme 2). Imagining general and robust reagents, we envisioned an efficient synthesis toward an organometallic species bearing an isotopically labeled carbonyl functional group may serve as "organometallic capping reagents". In line with this objective, our group recently reported a procedure for

Scheme 2. Approaches to Radiolabeling and Carboxylate Labeling Reagent



the carbon isotope labeling of aliphatic esters from alkyl iodides using a nickel mediated approach.[22] We initially designed this approach through the *in situ* formation of an isotopically labeled nickel(II) carboxylate species (Ni^{II}-*COOMe), which could react with an open-shell alkyl species. However, our mechanistic investigations suggested an alternative pathway was operative, involving alkyl-radical addition to a metal ligated CO species to generate a nickel-acyl complex en route to the aliphatic ester. As such, we re-evaluated this approach and targeted well-defined complexes that could be accessed in a single, efficient step in high yields, and be isolated as an air-stable and readily weighed solid. If realized, this reagent could offer a complementary method to our previous report without the need for gaseous reagents or specialized equipment, and it would provide an operationally simple and robust method for the synthesis of isotopically labeled carboxylic esters and acids. We targeted our approach toward related, well-defined metallacarboxylate complexes, coupling these reagents to transmetalation reactions from boronic esters/acids offered an ideal scenario due to its robust nature and the stability of these reagents.[23,24] Boronic esters/acids are particularly attractive precursors due to the ability of boron to be installed at late-stages in a synthetic route, which merges well within the context of late-stage isotope incorporation.[25] Herein, we describe our efforts toward this goal using an isotopically labeled Pd-carboxylate complex.

We began our investigations by synthesizing metal carboxylate complexes, which could be accessed from simple commercially available starting materials, in high yielding and utilize low equivalents of CO or CO_2 as the carbon isotope label source. The resultant complex should also be easy to purify, store, and utilize in subsequent reactions. Surveying the literature of complexes that fit these criteria, we initially examined nickellacarboxylate complexes isolated utilizing low equivalence of one carbon synthons, (CO or CO_2) amenable to isotope labeling.[26] However, due to their multistep synthesis and the formation of reactive species en route to the final Ni(II)-COOR compounds, we began to investigate alternatives. The utilization of cobalt-carboxylates such as (salen)-Co(III)-*COOMe (salen = *N*,*N*′-Ethylenebis(salicylimine)) was initially promising as they could be accessed directly from (salen)Co(II), CO, and MeOH under oxidative conditions,[27,28] but we found these organometallic complexes were unreactive to standard coupling reagents.

Continuing our investigation, we synthesized $(PPh_3)_2$Pd-(Cl)(CO_2Me) **Pd-1** from an adapted procedure originally reported by Yamamoto et al.,[29] with **Pd-1** being accessed in a single step from commercial $(PPh_3)_4$Pd. After some optimization, a final procedure was developed that reacted $(PPh_3)_4$Pd with LiCl and O_2 along with near stochiometric CO released from SilaCOgen, to afford **Pd-1** as a white powder in a satisfactory 96% isolated yield (Scheme 3). The structure of **Pd-1** could be unambiguously determined by XRD as a square planar complex with trans-oriented PPh_3 ligands. We note the synthesis of **Pd-1** is in stark contrast to the synthesis from similar Pd(II) species $(PPh_3)_2PdCl_2$, which required pressures of 30 bar CO to proceed toward the carboxylate formation.[29] As anticipated, isotopically labeled analogs of **Pd-1** could be accessed using ^{13}CO or ^{14}CO applying either COgen (10% ^{14}C-labeled) or SilaCOgen reagents.[30] Importantly the ^{14}C-radiolabeled complex was found to be stable over a storage period of 6 months as both a solid and as a solution in dichloromethane at −32 °C seeing no loss in

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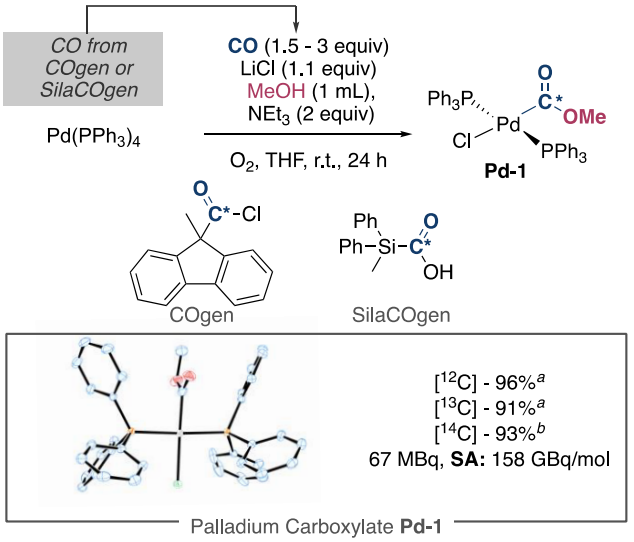
Scheme 3. Synthesis of Palladium-Carboxylate Complex



[a]^{12}C- or ^{13}C- SilaCOgen (1.5 equiv.). [b]^{14}C−COgen (3 equiv.).

radioactivity. In a similar nature to our desired reactivity, palladium(0) sources have been been utilized under oxidative conditions for the direct synthesis of esters from boronic ester/acids under atmospheric pressures of CO and were later applied to ^{11}C isotope labeling.[31−33]

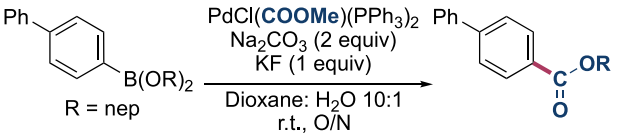
With **Pd-1** in hand, we turned to evaluating its reaction with boronic esters/acids (Table 1A). After some optimization, the reaction between the aryl neopentyl glycol ester and **Pd-1** at room temperature with KF and Na_2CO_3 in a dioxane/water mixture afforded the 4-phenyl−phenylboronic ester **1** in excellent yields (91%). Boronic acids showed similar reactivity to boronic esters (entry 2), and of the bases evaluated, the inorganic base Na_2CO_3 performed optimally (entries 3 and 4). Lower yields were found by replacing dioxane (entries 5 and 6), while comparable yields were found using H_2O or MeOH or heating the reaction (entries 7 and 8). The reaction components KF, H_2O and Na_2CO_3 were all found to be beneficial for the reaction outcome (entries 9−11). Furthermore, performing the reaction in air rather than an inert atmosphere only resulted in a slight reduction in yield (85%), highlighting the simplicity of the experimental setup.

To gain further information on the reaction, we monitored the standard reaction and performed a Hammett analysis (Table 1B). Monitoring the reaction of 4-biphenyl boronic acid with **Pd-1** under standard conditions, we observed full conversion within 4 h, while performing a Hammett analysis of phenyl boronic acids bearing *p*-OMe, *p*-^{t}Bu, *p*-Cl, and *p*-CN groups observed a σ value of −0.64, which supports the reaction kinetics being relatively insensitive to the electronic nature of the boronic acid.

Next, we turned to studying the generality of the protocol (Table 2). Gratifyingly, a range of electron-donating or electron-withdrawing aryl boronic esters delivered the targeted methyl esters **1**−**3** (R = OMe, *t*Bu, CN). Substrates containing free N−H or O−H bonds (**4**, **5**, **6**, and **9**) and those containing acrylates (**8**) and phenothiazine (**10**) groups were also amenable to the reaction conditions. Aryl bromide (**7**) could also be tolerated with the addition of $PhIOAc_2$ as an external oxidant which reacts with the Pd(0) species formed following transmetalation and reductive elimination. Derivatives of drug

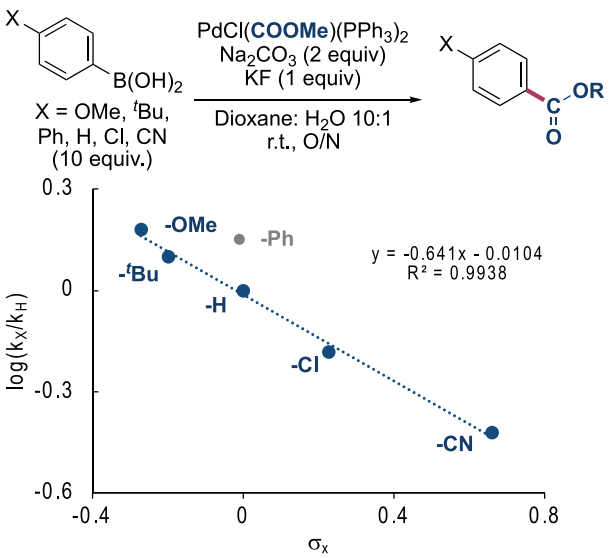
Table 1. Optimization and Hammett Analysis of the Reaction Conditions[a]

(A) Optimization of Reaction Conditions



Entry	Deviation	Yield (%)[a]
1	None	90 (91)[b]
2	$B(OH)_2$ i.o. $B(OR)_2$	82
3	K_3PO_4 i.o. Na_2CO_3	67
4	Et_3N i.o. Na_2CO_3	32
5	Toluene i.o. Dioxane	35
6	MeCN i.o. Dioxane	72
7	MeOH i.o. H_2O	89
8	60 °C i.o. r.t.	91
9	without KF	73
10	without H_2O	31
11	without Na_2CO_3	25
12	Air atmosphere	85

(B) Hammett Analysis of Reaction[c]



[a]**Pd-1** (0.1 mmol), 4-phenyl−phenylboronic ester (0.1 mmol), KF (0.1 mmol), Na_2CO_3 (0.2 mmol), dioxane/H_2O (5.4 mL/0.6 mL), r.t., 16 h. [b]isolated yield [c]**Pd-1** (0.025 mmol), boronic acid (0.25 mmol), KF (0.025 mmol), Na_2CO_3 (0.05 mmol), dioxane/H_2O (1.35 mL/0.15 mL), r.t..

compounds clofibrate (**11**) and indomethacin (**12**) were smoothly synthesized under the standard conditions. The synthesis of ^{14}C-labeled methyl esters was carried out using ^{14}C labeled material diluted with unlabeled ^{12}C material (approximately 10% ^{14}C, see the Supporting Information for details). The synthesis proceeded smoothly, with the standard biphenyl substrate (**13**) being synthesized in a 93% yield with >98% radiochemical purity and a radiochemical yield of 98%. ^{14}C-Labeling was extended to functionalities such as oxathianes (**14**), amides (**15**), or a drug derivative of fenofibrate containing ester and ketone functionalities (**16**), which were well tolerated in this method.

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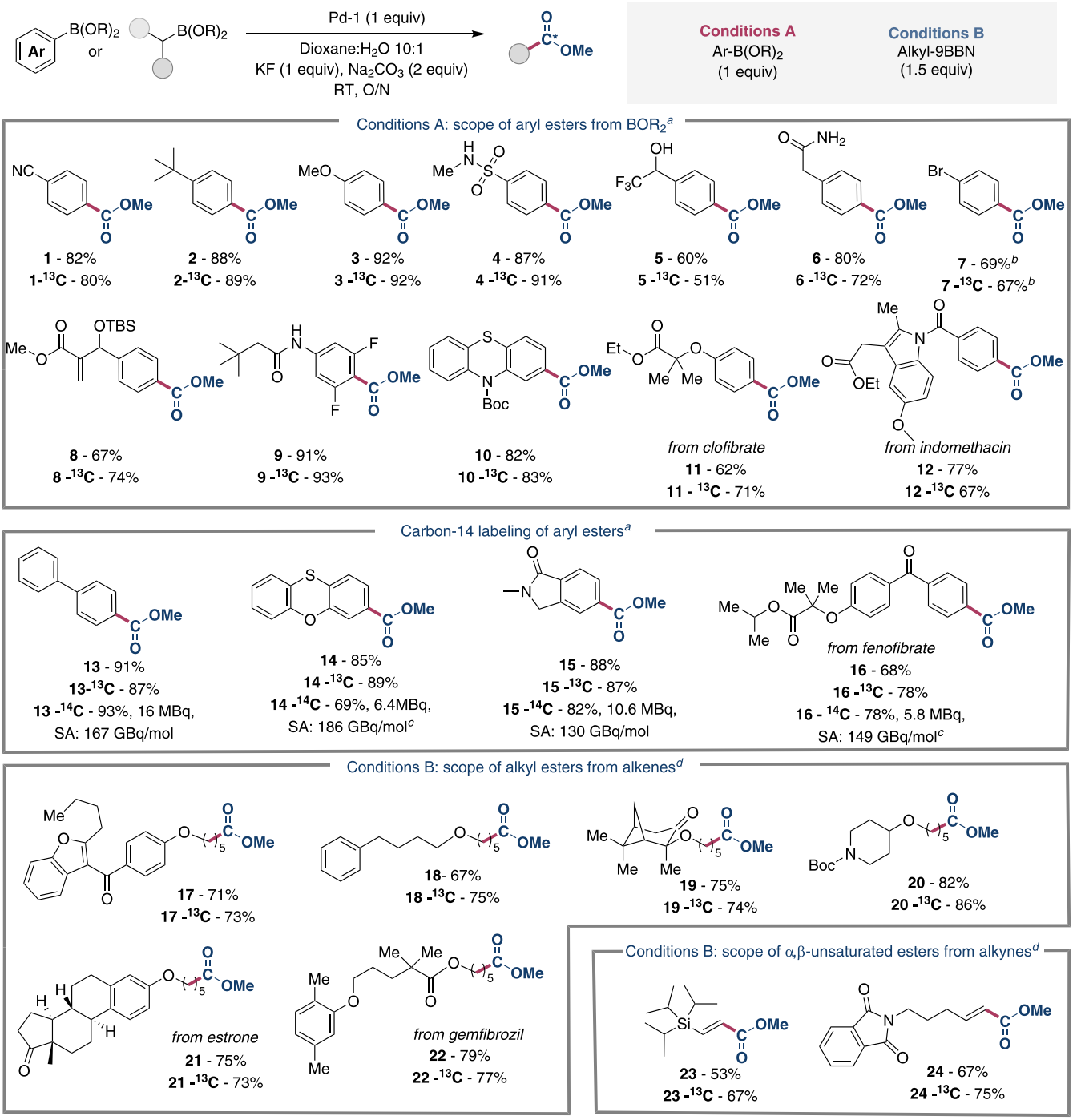
Table 2. Accessing Radiolabeled Methyl Esters[a,b]



[a]Reaction conditions A: as in Table 1, entry 1. [b]As in Table 1, entry 1, with 1 equiv. of $PhIOAc_2$ (0.15 mmol, 1.5 equiv.) [c]As in Table 1, entry 1, 0.05 mmol scale. [d]Reaction conditions B: alkene or alkyne (1.5 equiv.), 9-BBN dimer (0.75 equiv.), dioxane, 60 °C, 2 h, and then reaction conditions as Table 1, entry 1. SA = specific activity.

Encouraged by these results, we wondered if this protocol could be extended to alkyl and alkenyl boronic ester derivatives. After additional optimization, a modified procedure was developed in which alkenes or alkynes underwent hydroboration to afford alkyl or alkenyl 9-BBN derivatives that could be coupled to our standard radiolabeling conditions using the Pd-carboxylate labeling reagent. As shown, substrates containing furans (**17**), enolizable sites (**19**), phthalimides (**24**), or drug derivatives of the hormone estrone (**21**) and pharmaceutical gemfibrozil (**22**) were able to be isolated in high yields. Comparing this protocol to Cu-catalyzed carboxylation reactions[34] or Pd-catalyzed alkoxycarbonylation protocols of aryl boronic esters,[33] the corresponding reactions were performed under modified conditions limiting the isotopically labeled CO or CO_2 equivalence released to 1.5 equivalents from $BaCO_3$ or SilaCOgen, respectively. Under the Cu-catalyzed conditions, we observed significantly reduced yields (1−19%) for electronically varied substrates (**1**, **2**, and

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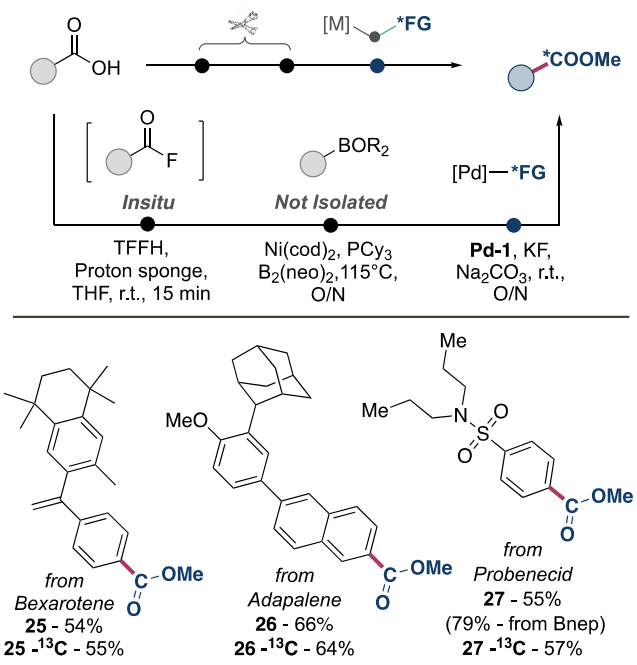
13) while the Pd-catalyzed conditions accessed these substrates in moderate yields (24−54% yield), supporting the notion that our approach offers complementary reactivity to existing protocols in the context of radiolabeling (see SI).

Lastly, we aimed to apply the developed reaction conditions for the carbon isotope labeling of carboxylic acids and pharmaceutically relevant compounds (Scheme 4). Building

Scheme 4. Applications to Carbon Isotope Replacement[a]



[a]aryl carboxylic acid (0.1 mmol), TFFH (0.1 mmol), proton sponge (0.1 mmol), THF (0.2 mL), 15 min, r.t., then PCy_3 (10 mol %), $Ni(COD)_2$ (5 mol %), B_2nep_2 (2.0 equiv), 115 °C, 24 h, and then reaction conditions as Table 1, entry 1.

on a report by the Sanford group, aryl carboxylic acids can be transformed into boronic acids in a single step.[35] We speculated this report could be coupled with **Pd-1** as a radiolabeling reagent for a carbon isotope replacement strategy. Gratifyingly, reacting pharmaceuticals bearing carboxylic acid moieties (Bexarotene, Adapalene, Probenecid) with the borylation conditions developed by Sanford, followed by our conditions with **Pd-1** after only filtration and no intermediate purification steps smoothly transformed these APIs into the labeled methyl carboxylic esters **25**−**27** (Scheme 4). Isolation of the neopentyl boronic ester intermediate of **27** resulted in an elevated yield of 79% for the single step reaction.

In summary, we have developed a simple synthesis of an organometallic capping reagent that can be accessed from commercial reagents and is effectively adapted to its radiolabeled analogues. This reagent is used in a mild and selective protocol to access valuable radiolabeled methyl esters from readily accessible alkyl, alkenyl and aryl boronic esters/acids in high radiochemical yields. The reaction is further characterized by its operational simplicity, broad substrate scope, and applicability to pharmaceutically relevant scaffolds. The potential of this capping reagent is also showcased in a carbon isotope replacement strategy from drugs containing carboxylic acids.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacsau.2c00708.

Experimental procedures and spectral and crystallographic data (PDF)

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Author Contributions

†S.J.T. and A.K.R. contributed equally to this work. CRediT: **Stephanie J. Ton** conceptualization, data curation, formal analysis, investigation, methodology, writing-original draft, writing-review & editing; **Anne Ravn** data curation, formal analysis, investigation, methodology; **Daniel Hoffmann** data curation, formal analysis; **Craig S. Day** data curation, formal analysis, investigation, methodology; **Lee Kingston** data curation, formal analysis; **Charles S. Elmore** formal analysis, project administration, supervision, writing-review & editing; **Troels Skrydstrup** conceptualization, formal analysis, funding acquisition, project administration, supervision, writing-review & editing.

Notes

The authors declare the following competing financial interest(s): T.S. is co-owner of SyTracks A/S, which commercializes the two-chamber system (COware) and SilaCOgen.

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