Core-Labeling Synthesis of Phenols

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Abstract: The synthesis of isotopically labeled compounds with site-specificity is critical to the pharmaceutical and agrochemical fields. For reasons of synthetic accessibility, isotopic labeling methods have traditionally been restricted to the molecular periphery, even among potentially skeletal elements (C, N, O, etc.), limiting the classes and isotopomers of compounds one can prepare in labeled form. Here, we report a method that enables fast incorporation of carbon isotopes into a core atom of an aromatic compound, specifically the *ipso* carbon of phenols. Our approach relies on the synthesis of a 1,5-dibromo-1,4-pentadiene precursor, which upon lithium-halogen exchange followed by treatment with carbonate esters results in a formal [5+1] cyclization to form the phenol product. Using this strategy, we have prepared twelve different *1*-^{13}C labeled phenols with a variety of alkyl and aryl substitutions via dibenzyl carbonate as a carbon-13 synthon. Additionally, we show proof of concept for labeling of phenols with other carbon radioisotopes — we demonstrate dibenzyl carbonate synthesis from common carbon-14 sources, as well as phenol synthesis directly from carbon dioxide, providing a potential entry into carbon-11 radiolabeling.

Site-specific carbon-isotope labeling of small molecules has wide ranging applications across fundamental biology, drug and agrochemical development, and medical imaging, with each isotope suited for different applications (**Figure 1a**).[1] Radioligands labeled with the short-lived carbon-11 isotope can be tracked using positron emission tomography (PET), a powerful and quantitative imaging modality for probing molecular interactions *in vivo*.[2] The carbon-13 isotope has found far-reaching utility in labeling of mass spectrometry internal standards and NMR spectroscopy probes in many fields including metabolomics,[3] proteomics,[4] and pharmacology.[5] Additionally, carbon-13 labeled molecules are gaining utility in the emerging molecular imaging technique of hyperpolarized magnetic resonance imaging.[6] Meanwhile, radioactive carbon-14 labeled compounds have long been considered the gold standard for adsorption-distribution-metabolism-excretion (ADME) studies, a vital development stage for determining the safety and efficacy of drug and agrochemical candidates.[7] Though incorporation of each isotope presents very different logistic challenges, (*e.g.* carbon-13 is stable whereas carbon-11 has a half-life of 20 minutes) they share a similar need for synthetic approaches that incorporate readily available single carbon synthons into molecular scaffolds.

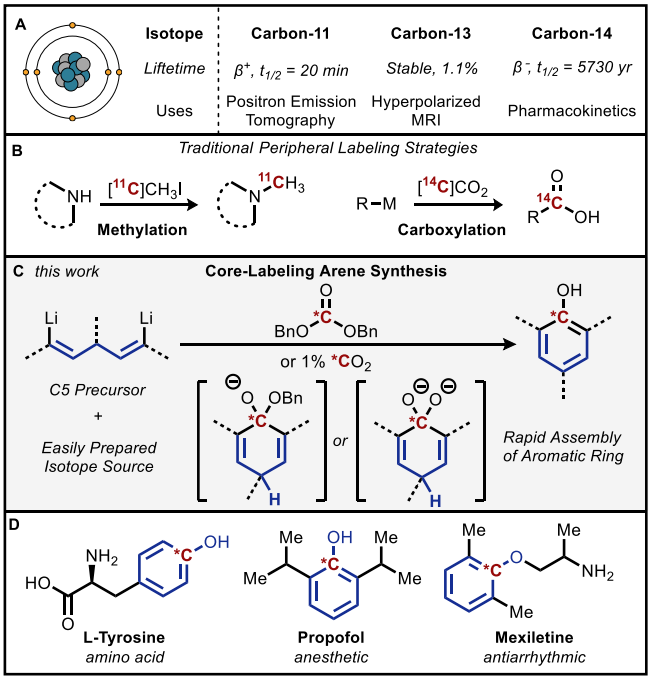


Figure 1. Introduction. (A) Properties and uses for carbon isotopes; (B) Common strategies for peripheral carbon isotope labeling; (C) This work, core labeling of phenols; (D) Phenols in biology and medicine.

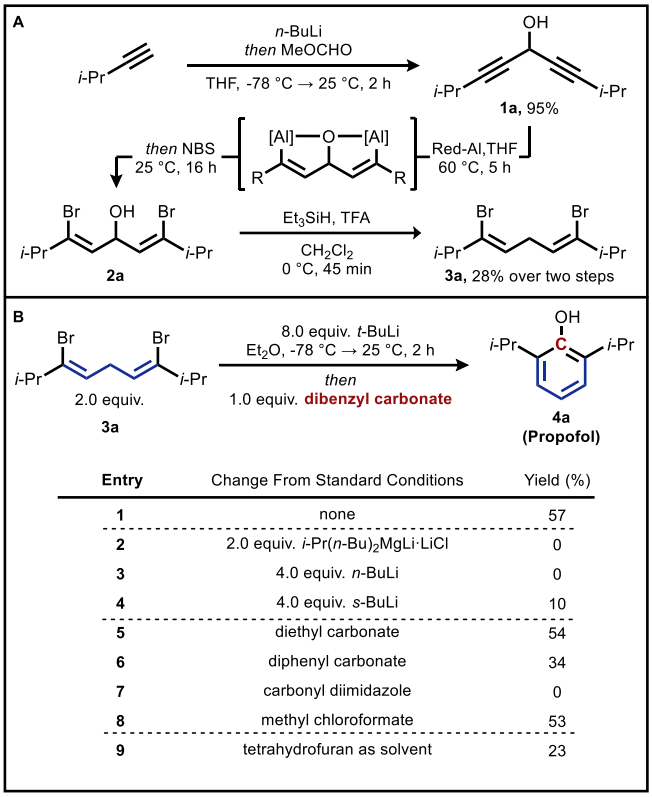
While there are many reported methods for the efficient incorporation of carbon isotopes into small molecules, most of these methods install the desired isotope on the molecule's periphery (**Figure 1b**). For example, the state of the art for carbon-11 radiolabeling is methylation of pendant alcohols or amines with [^{11}C]methyl iodide or [^{11}C]methyl triflate.[8] Similarly, carbon-14 is commonly incorporated into molecules via carboxylation, traditionally from direct fixation of organometallic precursors with [^{14}C]carbon dioxide,[9] though recent advances in isotopic exchange of carboxylic acids have also been reported.[10–16] These strategies in turn make the isotopic label more prone to metabolic cleavage, which can hinder the timing of imaging studies with radiotracers or limit the metabolites visible in pharmacokinetic assays.[17] Particularly for carbon-14 ADME studies, placement of the radioactive label dictates which radioactive metabolites are detected, with peripheral incorporation limiting the observable downstream metabolites.[18] Moreover, not all molecules of interest possess such peripheral functional handles, limiting the number of molecules that can be prepared via late-stage isotopic labeling. Even those which are amenable to peripheral incorporation would stand to benefit from the accessibility of additional isotopomers. Thus, novel methods are needed for the rapid incorporation of carbon isotopes into the core position of molecules, which would enable greater metabolic stability of the isotope and provide new potential targets for carbon-isotope labeling.

We report here a method that begins to address this challenge by allowing for a core-labeling synthesis of aromatic compounds. The protocol detailed below enables the incorporation of carbon isotopes into the aromatic *ipso* carbon of phenols (**Figure 1c**). Phenols are an interesting

scaffold target for core isotopic labeling, as they appear in many endogenous metabolites such as the amino acid tyrosine, hormone estradiol, or neurotransmitter dopamine. Additionally, they frequently appear in pharmaceuticals, such as the FDA approved drugs mexiletine (antiarrythmetic)[19] and propofol (anesthetic) (**Figure 1d**).[20] While methods for carbon-13 and carbon-14 labeling of phenols have been previously reported, they introduce the isotope early in the synthesis, with multiple subsequent steps required to assemble and functionalize the core phenol structure.[21,22] Late-stage incorporation of carbon isotopes into pre-functionalized precursors would limit depletion of the valuable isotope over iterative yield losses and enable translation to the short-lived carbon-11 radioisotope for which subsequent manipulations are typically not feasible.[23,24]

Accordingly, we aimed to develop a method of assembling phenols from readily available one-carbon building blocks that would be appropriate for carbon isotopic labeling. We were inspired by a recent report by Sparr and co-workers, who found that a 1,5-dimagnesiopentadiene reagent could undergo double addition to esters, with 1,4-elimination on acidic workup affording a new aromatic ring.[25] We envisioned a similar 1,5-diorganometallic reagent could react with simple 1-carbon electrophiles at the formal +4 oxidation state to form a new isotopically labeled phenol. Sparr's precursor synthesis, however, was only amenable to the unsubstituted parent reagent, which in this instance would yield an unsubstituted phenol, necessitating the development of an alternative protocol. A representative synthesis of the necessary 1,5-dibromo precursor is shown in **Figure 2a**. We began from the 1,4-dialkyne alcohol (**1a**) which was prepared in one step from the over-addition of a lithium acetylide onto a formate ester (or acid anhydride for *para*-substituted phenols). Next, double *trans*-hydroalumination using sodium bis(2-methoxyethoxy)aluminum hydride (Red-Al®) followed by quenching with *N*-bromosuccinimide formed the dibromide alcohol **2a** with the requisite *anti*-stereoselectivity. Such hydroaluminations are well studied for propargylic alcohols, sometimes referred to as a Chan reduction, but to our knowledge the simultaneous reduction of two alkynes in bis-propargylic alcohols is unprecedented.[26,27] Finally, a hydrosilane reduction activated by trifluoroacetic acid resulted in the final vinylic 1,5-dibromo precursor **3a**. Full details regarding syntheses for the remaining dibromo precursors employed below can be found in the Supporting Information.

With precursor in hand, we then screened different conditions for metal-halogen exchange[28] and subsequent cyclization with limiting one-carbon electrophiles to form our model substrate 2,6-diisopropylphenol (propofol, **4a**, **Figure 2b**). Our optimized conditions use 8 equivalents of *tert*-butyllithium (four relative to the dibromide precursor, or two per bromide, as is typical for *t*-BuLi halogen exchange) to produce a dilithiate intermediate followed by treatment with dibenzyl carbonate to form the desired phenol. An unusual finding here was that the yield of phenol was significantly higher when the metalation was allowed to proceed for 2 hours, despite lithium halogen exchange being complete on much shorter timescales, as judged by quenching studies. Such "aging effects" have been



Entry	Change From Standard Conditions	Yield (%)
1	none	57
2	2.0 equiv. *i*-Pr(*n*-Bu)$_2$MgLi·LiCl	0
3	4.0 equiv. *n*-BuLi	0
4	4.0 equiv. *s*-BuLi	10
5	diethyl carbonate	54
6	diphenyl carbonate	34
7	carbonyl diimidazole	0
8	methyl chloroformate	53
9	tetrahydrofuran as solvent	23

Figure 2. (a) Representative synthesis of 1,5-dibromide precursor and (b) Optimization of phenol cyclization. Reactions were performed under nitrogen on 0.04 mmol scale and yields determined by ^{1}H NMR using mesitylene internal standard.

observed as a consequence of organolithium aggregation state in prior studies.[31] Commonly used bromine-magnesium exchange reagents (e.g., *i*-PrMgCl•LiCl, *i*-Pr(*n*-Bu)$_2$MgLi)[29,30] did not result in effective metalation and afforded no phenol product. While *n*-butyllithium could perform the bromine-lithium exchange once, only a negligible amount of the doubly lithiated species was formed and no product was observed. The stronger *sec*-butyllithium could form the necessary intermediate; however, *tert*-butyllithium was found to be far superior. Of the electrophiles tested, alkyl carbonate esters and chloroformates proved to be the most effective, with an aryl carbonate and carbonyl diimidazole giving much lower yields. Interestingly, the reaction proceeds with the highest yields in diethyl ether, and solvents that coordinate more strongly with lithiates (*e.g.* tetrahydrofuran) give lower yields of phenol.[32–35]

Ultimately, the stability of carbonate esters compared to chloroformates led us to choose dibenzyl carbonate (**5**) as our optimized carbon isotope source, and we used carbon-13 to test our isotopic labeling method on a preparative scale. First, we prepared **5-*carbonyl*-^{13}C** from benzyl chloride and potassium carbonate, an economic source of carbon-13, on 5 millimole scale in 72% yield.[36] Our optimized synthesis relies on the combination of two phase transfer catalysts (18-crown-6 and Aliquat-336) to afford the product rapidly and reproducibly.

Delightfully, we found that the yield of our model substrate, propofol (**4a-*1*-^{13}C**), improved to 79% on larger scale, and in total we have prepared 12 different carbon-13

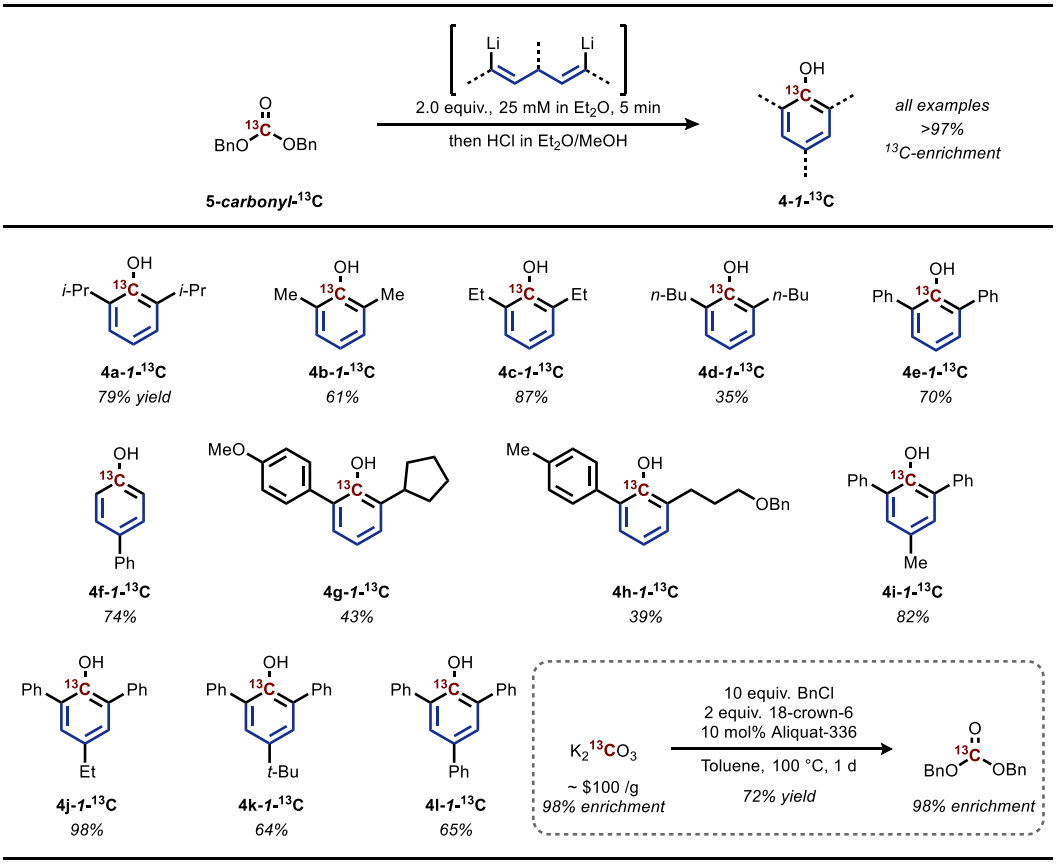


Figure 3. Synthesis of dibenzyl carbonate-*carbonyl*-^{13}C and scope of *1*-^{13}C phenols. Isolated yields on 0.20 mmol scale.

labeled phenol products (**Figure 3**). Other 2,6-alkyl substituted phenols were produced in good yields, with the exception of 2,6-dibutyl phenol (**4d-*1*-^{13}C**), which suffered from diminished yields that we tentatively attribute to disruption of the aforementioned aging effect. 2,6-diphenyl phenol (**4e-*1*-^{13}C**) was produced in high yield and two unsymmetric phenols featuring aromatic and alkyl ethers (**4g-*1*-^{13}C** and **4h-*1*-^{13}C**) were also isolated. Additionally, an *ortho*-unsubstituted example (4-phenyl phenol, **4f-*1*-^{13}C**) was well tolerated by the reaction conditions and produced in 74% yield. A series of alkyl and aryl *para*-substituted 2,6-diphenylphenols (**4i-*1*-^{13}C** – **4l-*1*-^{13}C**) were also prepared in good yields ranging from 64% to 98%. In all cases, ^{13}C-enrichment (as measured by quantitative ^{13}C-NMR) was greater than 97%.

This series of labeled phenols could be particularly useful as hyperpolarized MRI probes. An effective HP-MRI probe should have a carbon-13 enriched site with a long longitudinal relaxation time (T_1) to preserve the MR signal and provide more accurate quantification. The *1*-^{13}C label of these phenols is ideal as the carbon-13 isotope lacks directly attached hydrogen atoms that could shorten its T_1 time.[6,37] The T_1 of **4a-*1*-^{13}C** was measured to be 29.4 seconds at 11.7 Tesla, which is similar to other studied HP-MRI probes.

The success of our results with carbon-13 led us to pursue labeling of phenols from readily available sources of carbon-14 (**Figure 4a**). Since carbon-14 decays very slowly, we first sought to synthesize dibenzyl carbonate from commercially available sources of carbon-14. Sodium carbonate can also be used to produce dibenzyl carbonate in a similar manner described for potassium carbonate; however, use of *N,N*-dimethylformamide as a solvent and addition of cesium chloride was found to perform much better than our parent conditions due to the differing solubility properties of the sodium salt. While sodium [^{14}C]carbonate is commercially available, it is significantly more expensive than buying bulk barium [^{14}C]carbonate.[38] Indeed, barium [^{14}C]carbonate is the universal starting material for carbon-14 labeled compounds, from which [^{14}C]carbon dioxide can be released upon hydrolysis with concentrated sulfuric acid.[9,39] Thus, we additionally demonstrated the synthesis of dibenzyl carbonate from hydrolyzed barium carbonate in a COware two-chamber setup[40] modifying conditions from Hye-Young Jang and co-workers.[41]

Contrary to the other isotopes, carbon-11 has an exceptionally short half-life of approximately 20 minutes, precluding multi-step syntheses on the basis of lost radiochemical yield. While iodomethane is the most common [^{11}C] precursor, it is prepared directly before its use in radiosynthesis from cyclotron-produced [^{11}C]carbon dioxide. Indeed, fixation of carbon-11 with organometallic precursors has been well precedented,[42–44] and methods for direct incorporation of [^{11}C]carbon dioxide have seen a recent renewed interest.[45–52] Thus, we were interested in producing phenols directly from carbon dioxide as the source of the *ipso* carbon. Initial experiments treating the reactive propofol dilithiate precursor directly with an atmosphere of carbon dioxide gas resulted in simple double carboxylation to produce undesired acid **6**.

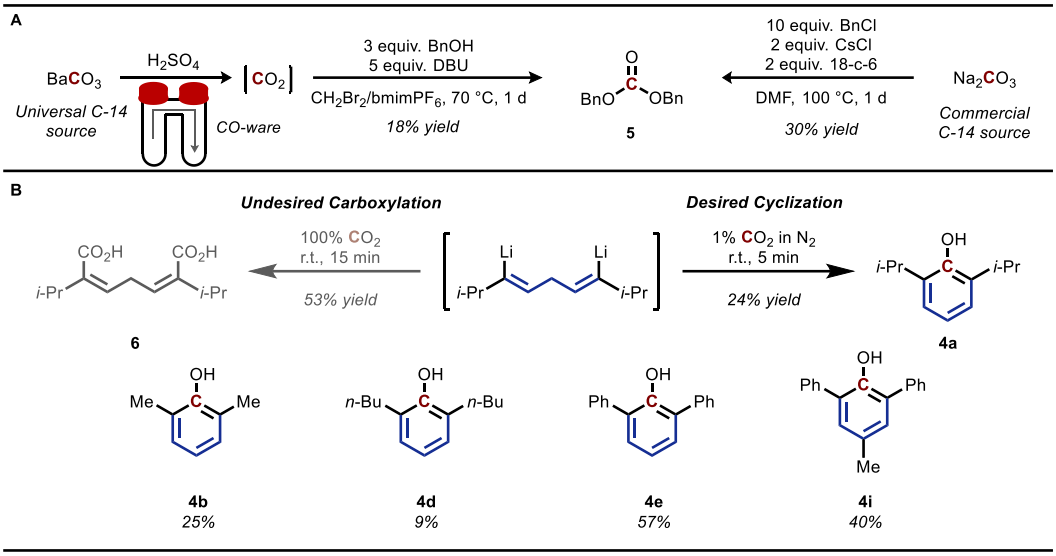


Figure 4. Proof-of-concept for carbon radioisotopes. (A) Synthesis of dibenzyl carbonate from $BaCO_3$ and Na_2CO_3, common carbon-14 sources. (B) Synthesis of phenols directly from dilute CO_2, a model system for carbon-11.

However, decreasing the concentration in the gaseous stream to 1% carbon dioxide resulted in the desired cyclization and propofol product in a modest yield of 24%, with the reaction completed in 5 minutes (**Figure 4b**). These conditions were repeated with a small group of precursors, with results following similar trends in yield seen for the carbonate protocol. Both alkyl and aromatic substituents are tolerated, with 2,6-phenyl substituted phenol products (**4e**, **4i**) giving the highest yields. Since this phenol synthesis occurs in <10 minutes and works well with low concentrations of carbon dioxide, it is particularly well suited to the low nanomole quantities of cyclotron-produced [^{11}C]carbon dioxide.[53]

In conclusion, we report a method that enables selective isotopic labeling of an aromatic carbon. This facile synthesis of phenols from a variety of 1-carbon synthons is enabled by lithium-halogen exchange of a newly designed 1,5-dibromide precursor. This work has direct applications to the synthesis of *1*-^{13}C labeled phenols, and we have prepared twelve labeled phenols from carbon-13 labeled dibenzyl carbonate. We additionally demonstrated the preparation of dibenzyl carbonate from common carbon-14 starting materials as well as the synthesis of phenols directly from carbon dioxide, which points the way towards radiosyntheses of carbon-14 and carbon-11 labeled phenols. More broadly, the demonstration of core-labeling synthesis of aromatic compounds should inform the preparation of a wide range of labeled compounds that have traditionally been considered inaccessible.

Supporting Information

Experimental procedures, supporting characterization data and spectra.

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Notes

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