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Development of Decarboxylative Cyanation Reactions for C-13/C-14 Carboxylic Acid Labeling Using an Electrophilic Cyanating Reagent

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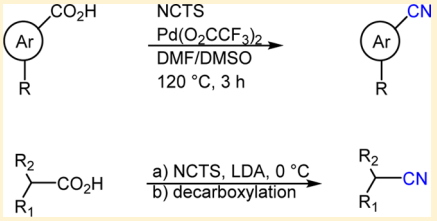
Supporting Information

ABSTRACT: Degradation-reconstruction approaches for isotope labeling synthesis have been known for their remarkable efficiency, but applications are scarce due to some fundamental limitations of the chemistries developed to date. The decarboxylative cyanation reaction, as a degradation-reconstruction approach, is especially useful in rapid carboxylic acid carbon isotope labeling, however development toward its application as a widespread technique has stalled at the early stages due to numerous limitations which include somewhat narrow applicability. Employing the electrophilic cyanating reagent *N*-cyano-*N*-phenyl-*p*-toluenesulfonamide (NCTS) as the cyano source, efficient decarboxylative cyanation chemistry has been developed for aryl and alkyl carboxylic acids respectively with two rationally designed reaction pathways. The reactions provided good yields of nitrile products from carboxylic acids, with complete retention of isotopic purity from the [^{13}CN]-NCTS used. The reaction conditions are relatively mild requiring no oxidant and no excess toxic heavy metal and the reagent [$^{13/14}$CN]-NCTS is a stable, easy-to-handle crystalline solid that can be prepared quickly and effectively from the readily available [$^{13/14}$C]-KCN. The following work describes this novel and efficient method for alkyl and aryl carboxylic acid isotopic labeling using a single reagent.



INTRODUCTION

Compounds labeled with carbon-14 or tritium are frequently used as tracers during the development of potential new drug candidates to aid in the understanding of their absorption, distribution, metabolism, and excretion properties. While compounds labeled with tritium are used during basic research studies, compounds labeled with carbon-14 are preferred for definitive drug metabolism and pharmacokinetics studies because their positions are inherently more resistant to cleavage from metabolic biotransformation. However, they are much more expensive to make, requiring many more synthetic steps that result in the increased expenditure of time and effort. If the economics of time and cost were to be significantly lowered (in line with tritium synthesis), earlier use of carbon-14 tracers would prevail by virtue of the higher quality information they afford leading to better candidate selection/deselection at much earlier stages of development, before greater investments are made.

One strategy to reduce time, effort, and cost of carbon-14 labeled compound preparation is to apply a degradation-reconstruction synthesis approach using the readily available parent compound as the starting material.[1] To this purpose, decarboxylative halogenations under Hunsdiecker or Barton conditions followed by cyanation of the resultant halides have been explored as a degradation-reconstruction approach for rapid C-13/C-14 labeling[2−5] (Scheme 1), taking advantage of the carboxylic acid functional group, common in drug candidates or advanced synthetic intermediates. While not a new concept, examples of its application are scarce due to the drawbacks associated with the two key steps involved, decarboxylative halogenation and subsequent cyanide substitution. Hunsdiecker's reaction along with its modifications, which includes the recent catalytic variant, suffers from either the requirement for oxidant, use of highly toxic reagents, or a limited scope of substrates.[6] Barton's decarboxylative halogenation does however work well with a somewhat broader range of substrates, but requires preparation of the Barton ester. Furthermore, the subsequent cyanide nucleophilic substitution is complicated by the competing elimination reaction for tertiary and secondary halides giving the nitrile product in low to moderate yields.[7] Therefore, a desirable one-step process namely decarboxylative cyanation has been developed which converts carboxylic acid directly into nitrile without going through the halide intermediate (Scheme 1).

In 1991 Barton reported the first practical decarboxylative cyanation using sulfonyl cyanides as the cyano source under photolysis conditions with the aim of introducing C-13/C-14 into carboxylic acid natural products bearing sensitive functional groups.[8,9] Despite being effective and versatile under mild reaction conditions, Barton's decarboxylative cyanation has to our knowledge never been applied to labeling synthesis. The reaction requires both preparation of the Barton ester (as an additional step) as well as a large excesses of the sulfonyl cyanide reagent (as the cyano source) in order to achieve good yields. This is especially the case where *p*-toluenesulfonyl cyanide is used, making this economically prohibitive for labeling synthesis. Considering the potential utility of this

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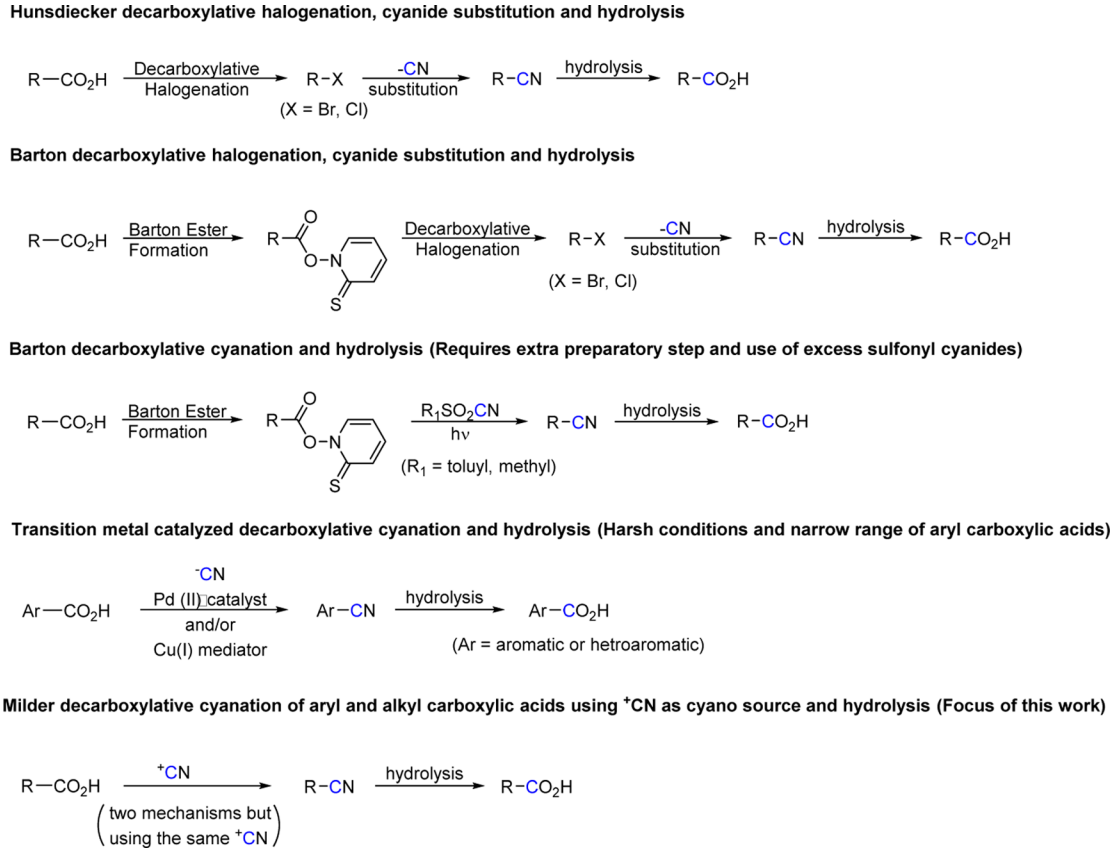
Scheme 1. Degradation-Reconstruction Approach for Carboxylic Acid C-13/C-14 Labeling



approach for C-13/C-14 labeling, it is perhaps surprising that this area remained untouched for more than two decades and only recently did pioneering research on transition-metal-catalyzed decarboxylative cyanation of aryl carboxylic acids appear.[10−12] The efficiency of the catalyzed reactions was demonstrated by a successful carbon-isotope exchange of an aryl carboxylic acid in only two steps with 54% overall yield,[11] however in general the reaction appeared to be limited to a very narrow range of aryl carboxylic acids while alkyl carboxylic acids do not work under these conditions. This combined with somewhat harsh reaction conditions, which require the presence of oxidants (excess Ag^+ or O_2) at high reaction temperature, prompted us to develop a milder decarboxylative cyanation that would be applicable to a wider range of carboxylic acids.

Thus far, decarboxylative cyanation has employed nucleophilic cyanides and radical acceptor sulfonyl cyanides as the cyano source.[13] Recently, nonmetallic cyano sources, including electrophilic cyanating reagents, have been developed.[14] With an electrophilic cyanating reagent, we conceived two unique decarboxylative cyanation reaction pathways for aryl and alkyl carboxylic acids, respectively. The following work describes our design rationale and development effort on the two reactions. Our goal is to provide alternative and efficient tools leading to much more rapid and cost-effective access to C-14 tracers for pharmaceutical research and development, with the view of changing when and how C-14 tracers are utilized in drug discovery and development.

RESULTS AND DISCUSSION

Palladium Catalyzed Decarboxylative Cyanation of Aryl Carboxylic Acid Using Electrophilic Cyanating Reagent NCTS. The decarboxylative cyanations of aryl carboxylic acids reported thus far utilize nucleophilic cyanides as the cyano source.[10−12] They are oxidative processes in which an oxidant (excess Ag^+ or O_2) is indispensable by the nature of the reaction of coupling between two nucleophiles. Additionally, the high affinity of cyanide toward the transition metal catalyst usually causes deactivation of the catalyst and so results in a hampered reaction. Inspired by the nonoxidative decarboxylative coupling reaction pioneered by Gooßen[15] and encouraged by the rhodium-catalyzed cyanation of aryl boronic acids using electrophilic cyanating reagent *N*-cyano-*N*-phenyl-*p*-toluenesulfonamide (NCTS),[16,17] we envisioned that replacement of the nucleophilic cyanating reagent, in the reported decarboxylative cyanation reactions, with an electrophilic cyanating reagent would render the reaction a nonoxidative process. Consequently, oxidant can be removed from the reaction system. Herein we report the first nonoxidative decarboxylative cyanation of aryl carboxylic acids.

Heating a mixture of 2,4-dimethoxybenzoic acid (**1a**) and NCTS in the presence of catalyst $Pd(O_2CCF_3)_2$ in DMF/DMSO gave the desired product 2,4-dimethoxybenzonitrile (**2a**) in 74% yield (Table 1, entry 1). To confirm the mechanism is independent of oxidant, the reaction was repeated in the absence of O_2 resulting in the same reaction outcome and yield. To trace the origin of the cyano group in the benzonitrile product **2a**, *N*-[^{13}C]-cyano-*N*-phenyl-*p*-toluenesulfonamide ([^{13}CN]-NCTS)[18] was reacted with 2,4-dimethoxybenzoic acid (**1a**) under the same conditions and

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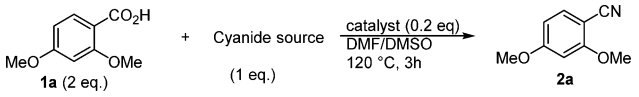
Table 1. Decarboxylative Cyanation of Aryl Carboxylic Acid



entry	cyanide source	catalyst	yield (%)
1	NCTS[a]	$Pd(O_2CCF_3)_2$	74%
2	[^{13}C]-NCTS	$Pd(O_2CCF_3)_2$	75%([^{13}C]-**2a**)
3	NCTS	No catalyst	N.D.[b]
4	NCTS	$Cu(O_2CCF_3)_2$	N.D[b]
5	KCN	$Pd(O_2CCF_3)_2$	trace (<5% by LCMS)
6	BtCN[c]	$Pd(O_2CCF_3)_2$	N.D[b]

[a]NCTS = *N*-cyano-*N*-phenyl-*p*-toluenesulfonamide. [b]N.D. = not detected by LCMS. [c]Bt-CN = 1*H*-benzotriazole-1-carbonitrile.

the product 2,4-dimethoxybenzo-[^{13}C]-nitrile ([^{13}C]-**2a**) was indeed isolated in 75% yield (Table 1, entry 2). LCMS confirmed the isotopic purity of the reagent [^{13}CN]-NCTS was retained in the nitrile product [^{13}C]-**2a**, which is critical for labeling synthesis. The Pd catalyst is essential to the reaction, as removal of Pd catalyst from the reaction system or replacing Pd with Cu prevents formation of the nitrile product (Table 1, entries 3 and 4). When nucleophilic KCN was used in place of NCTS, the reaction resulted in only a trace amount of **2a**. This is likely the result of initial reaction with cyanide before Pd(II) is exhausted (Table 1, entry 5). An alternative electrophilic cyanating reagent 1-*H*-benzotriazole-1-carbonitrile (BtCN)[19−21] was also explored, however, test reactions revealed that no product was formed (Table 1, entry 6). It should be noted that the advantage of NCTS is that it is a benchtop stable, easy-to-handle crystalline solid which makes it convenient for storage and use by radiochemists as a labeling reagent.

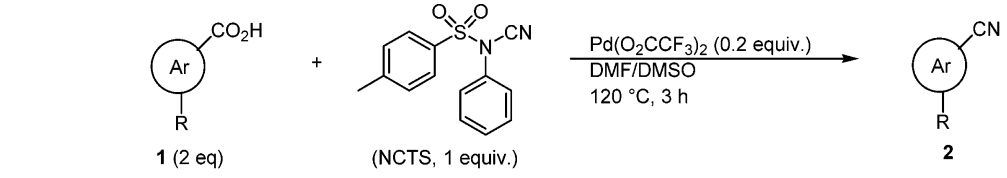
To probe the scope and limitations of this reaction, we carried out a series of nonoxidative decarboxylative cyanation reactions. Our preliminary results are shown in Scheme 2. Similarly to the narrow substrate scope observed for the oxidative decarboxylative cyanation,[10] the nonoxidative decarboxylative cyanation proceeded well only with electron-rich aryl carboxylic acids bearing at least one *ortho* substituent and certain heteroaryl carboxylic acids. On the other hand, it is interesting to note that this nonoxidative condition gave the product **2d** in much higher yield (75%) than the reported oxidative process did (29% yield).[10] Furthermore, the free phenol functional group is well tolerated under these reaction conditions and good yields were obtained for products **2g** and **2h**, while the corresponding oxidative process in the presence of Ag_2CO_3 gave much lower yield presumably due to harsher reaction conditions.

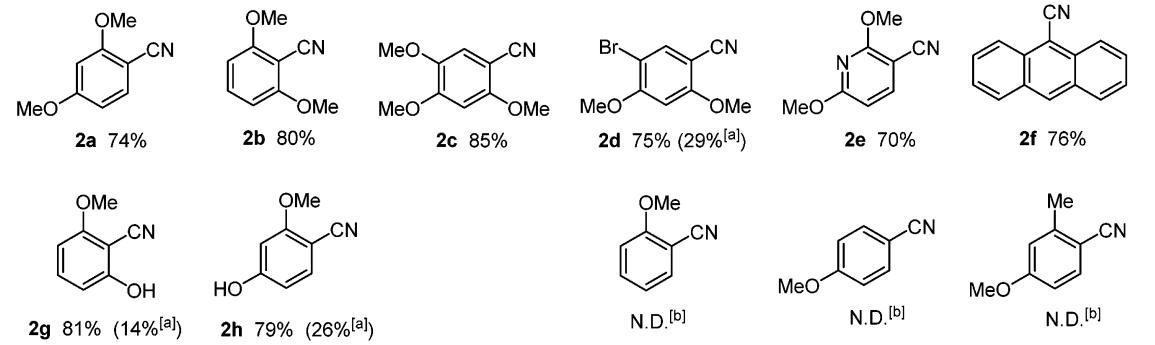
The reaction mechanism was postulated by analogy to the rhodium-catalyzed cyanation of aryl boronic acids.[16] In view of the reactivity of *ortho*-substituted aryl−palladium complex toward cyanamide giving product of the insertion of C≡N into aryl-Pd bond,[22] a reasonable explanation for the formation of benzonitrile in this nonoxidative decarboxylative cyanation can be represented in the catalytic cycle in Scheme 3. First decarboxylative palladation of aryl carboxylic acid generates arylpalladium trifluoroacetate **I**.[23] After coordination of NCTS to Pd, complex **II** is formed which allows insertion of C≡N into aryl-Pd bond to afford intermediate **III**. Rearrangement of **III** produces the benzonitrile product along with the species **IV**. Finally, aryl carboxylate displacement followed by decarboxylation affords the arylpalladium trifluoroacetate **I** to complete the catalytic cycle.

In summary, employing electrophilic NCTS, the palladium catalyzed nonoxidative decarboxylative cyanation converts aryl carboxylic acids directly to aryl nitrile products in good yield under mild conditions with no oxidant. Expansion of the narrow substrate scope is under further investigation.

Decarboxylative Cyanation of Alkyl Carboxylic Acid Using Electrophilic Cyanating Reagents. In 1979, Parnes reported the one-step synthesis of 6,11-dihyro[*b*,*e*]thiepin-11-

Scheme 2. Synthesis of Aryl Nitriles 2 (Isolated Yields) through Nonoxidative Decarboxylative Cyanation for Aryl Carboxylic Acids 1





[a]Yield under oxidative deacrboxylative cyanation in the presence of Ag_2CO_3. [b]N.D. = not detected by LCMS.

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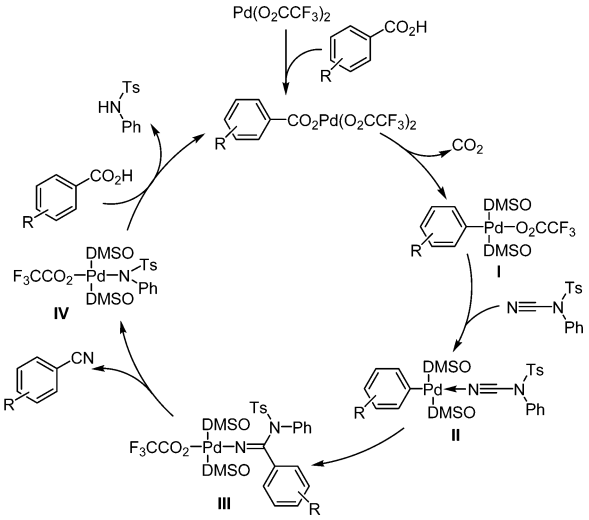
Scheme 3. Proposed Mechanism for Pd(II) Catalyzed Nonoxidative Decarboxylative Cyanation of Aryl Carboxylic Acids



one-3-yl acetic [^{14}C]-acid by trapping the dianion of the unlabeled acid with $^{14}CO_2$ followed by spontaneous decarboxylation of the resulting malonic acid.[24] The synthesis was exceptionally short, but it only produced the labeled acid in low specific activity because the decarboxylation of the malonic acid intermediate was not selective between C12 and C14 carboxylate and half of the $^{14}CO_2$ radioactivity ended up as waste. Nonetheless, encouraged by Parnes' initial work, our search for alternative pathways to fulfill decarboxylative cyanation of alkyl carboxylic acids led us to investigate the decomposable α-cyanocarboxylic acid as a key intermediate for the reaction. This gives the desired nitrile product via decarboxylation (Scheme 4). Retrosynthetically, the α-cyanocarboxylic acid intermediate could be accessed through α-cyanation of the alkyl carboxylic acid with an electrophilic cyanating reagent $^{+}$CN source. Through the sequential process, the alkyl carboxylic acid is degraded to CO_2 and replaced by cyanide, thus providing a pathway to decarboxylative cyanation of alkyl carboxylic acids.

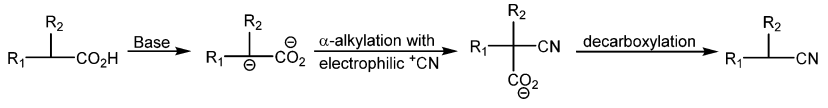
Consequently, 1-*H*-benzotriazole-1-carbonitrile (BtCN) was selected as the electrophilic cyanating reagent because it has been used for α-cyanation of alkyl nitrile and alkyl carboxylate esters providing malononitrile and cyanoacetate in good yields.[19,20,25−27] Treatment of the dianion of 3,4-dichlorophenylacetic acid (**1i**, 2eq) with Bt^{13}CN[28] (1 equiv) at 0 °C to room temperature followed by acidic workup gave 3,4-dichlorophenylaceto-[^{13}C]-nitrile ([^{13}C]-**2i**) in 71% yield (Scheme 5). Of particular interest is that the [^{13}C]-nitrile of Bt^{13}CN was transferred to the product without loss of the C-13 isotopic purity; essential for labeling synthesis. During our preparation of Bt^{13}CN, it was found that Bt^{13}CN decomposed gradually on silica gel, complicating its purification by flash chromatography on silica gel and reducing the yield. In contrast NCTS, used successfully for aryl carboxylic acid decarboxylative cyanation, is a benchtop stable and easy-to-handle crystalline solid. We hereto decided to explore NCTS as a reasonable substitute for BtCN.

Under identical reaction conditions to those used with BtCN, NCTS indeed gave the desired nitrile product **2i** in much higher yield (84%). To test this reagent on a pharmaceutical drug with a substituent at α-position of the carboxylic acid, we examined Ibuprofen (**1j**). After 18 h, the nonsteroidal anti-inflammatory drug was converted to the nitrile **2j** in 28% yield in one step. We reasoned the low yield of **2j** might be due to the incomplete decarboxylation of the intermediate α-cyanocarboxylic acid and thus a CuO catalyzed decarboxylation[29] of the crude mixture after cyanation reaction indeed improved the yield of the nitrile product to 71%. Cyanation of 2,4-dimethoxyphenyl acetic acid (**1k**) followed by CuO catalyzed decarboxylation gave high yield (90%) of 2,4-dimethoxyphenyl acetonitrile (**2k**). Compound 3-(3-methoxyphenyl)propanoic acid (**1l**), a "real" alkyl carboxylic acid with a nonbenzylic reaction site, was subjected to the same cyanation and subsequent thermal decarboxylation and the reaction provided 3-(3-methoxyphenyl)propanenitrile (**2l**) in 64% yield. Lastly, Naproxen (**1m**) was converted to the [^{13}C]-nitrile compound **2m** in 71% yield by the decarboxylative cyanation sequence. LCMS confirmed the isotopic purity of the reagent [^{13}CN]-NCTS was retained in the [^{13}C]-nitrile product **2m**.

It should be noted that this method is limited to primary and secondary carboxylic acids since sequential decarboxylative cyanation requires abstraction of an α-proton and some strong-base sensitive functional groups, such as −OH, −NH$_2$, −NHR, may also require protection prior to use of LDA to generate the dianion. These results have shown that the sequential decarboxylative cyanation of alkyl carboxylic acid to alkyl nitrile can be achieved in good yield under mild conditions in the absence of oxidant or excess toxic heavy metal and provides an alternative to Hunsdiecker or Barton reactions for rapid alkyl carboxylic acid C-13/C-14 labeling synthesis.

Synthesis of *N*-[$^{13/14}$C]-Cyano-*N*-phenyl-*p*-toluenesulfonamide ([$^{13/14}$CN]-NCTS). In order for the above decarboxylative cyanation chemistry to be practical to radiochemists and therefore reduced to practice, generation of the labeling reagent [$^{13/14}$CN]-NCTS should be simple and cost-effective from readily available $^{13/14}$C-feed stocks. We therefore developed an efficient two-step synthesis of [$^{13/14}$CN]-NCTS from readily available [$^{13/14}$C]-KCN (Scheme 6). Treatment of the readily available [^{13}C]-KCN with Br_2 at 0 °C rapidly afforded the intermediate [^{13}C]-BrCN, which was reacted directly with *N*-phenyl-*p*-toluenesulfonamide at 0 °C to give [^{13}CN]-NCTS in 83% yield after isolation. Following the same procedure starting from low specific activity [^{14}C]-KCN (2.9 mCi/mmol or 107.3 MBq/mmol), [^{14}CN]-NCTS was prepared conveniently in 68% radiochemical yield. The radiochemical purity of the prepared reagent [^{14}CN]-NCTS was found to be stable on storage as solid at room temperature for three months.

Scheme 4. Strategy for Decarboxylative Cyanation of Alkyl Carboxylic Acids



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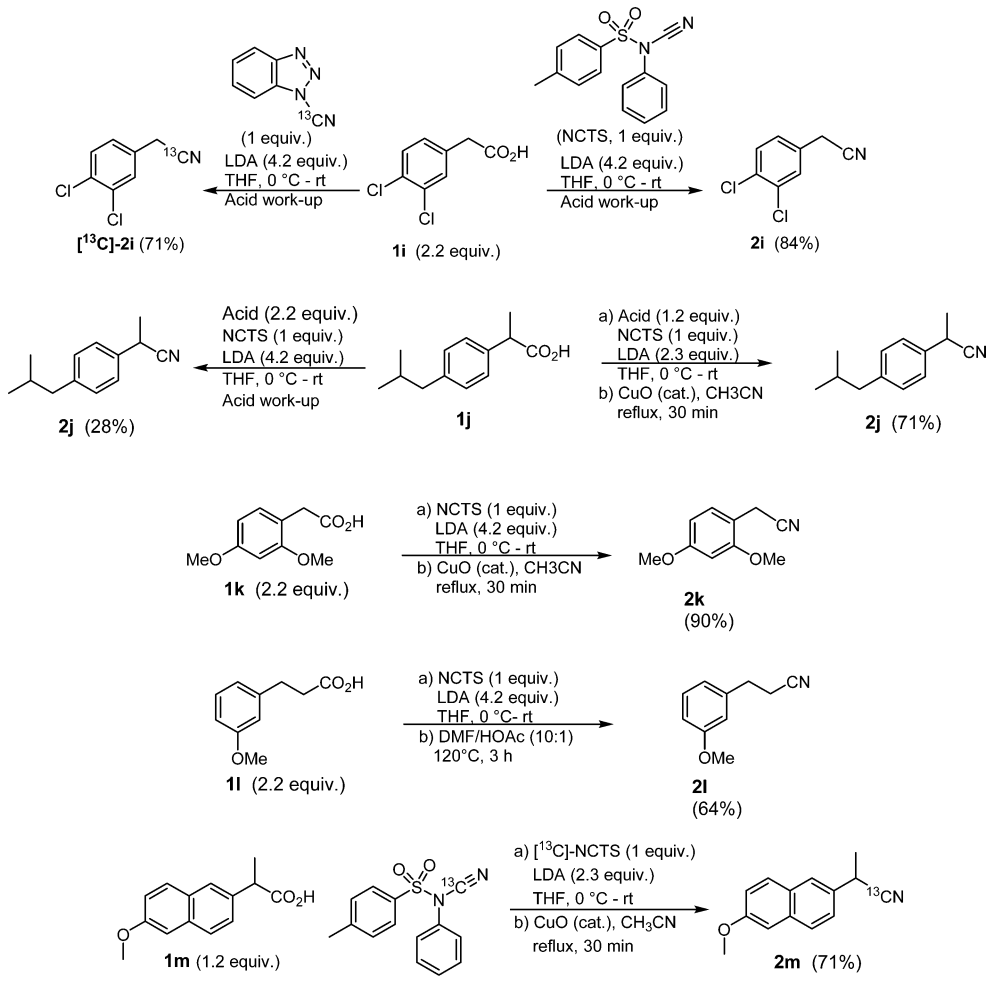
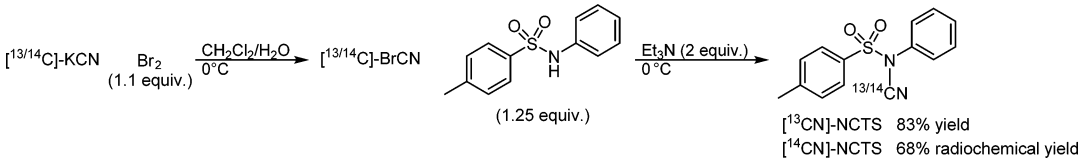
Scheme 5. Decarboxylative Cyanation of Alkyl Carboxylic Acids



Scheme 6. Synthesis of [$^{13/14}$CN]-NCTS



CONCLUSIONS

The aforementioned results demonstrate both the utility of this method and the application of the isotopically labeled electrophilic cyanating reagent [$^{13/14}$CN]-NCTS in providing efficient access to labeled nitrile products in good yield from both aryl and alkyl carboxylic acids under mild, nonoxidative conditions in the absence of excess toxic metals. The reagent itself is a benchtop stable and easy-to-handle crystalline solid that can be prepared quickly and effectively from the readily available [$^{13/14}$C]-KCN.

EXPERIMENTAL SECTION

All reagents were purchased from commercial sources and used without further purification unless otherwise noted. *N*-Cyano-*N*-phenyl-*p*-toluenesulfonamide (NCTS) was purchased from Combi-Blocks Inc. and purified by chromatography on silica gel (heptane to 50% EtOAc in heptane). K^{14}CN with specific activity 56 mCi/mmol or 2072 MBq/mmol was purchased from ViTrax Co., 660 S. Jefferson St., Placentia, CA 92870. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AC-400 (400 MHz) spectrometer using tetramethylsilane as an internal standard. Electrospray mass spectra (MS-ES) were recorded on a Hewlett-Packard 59987A spectrometer. HRMS was performed on TOF LC-MS in ESI mode.

2,4-Dimethoxybenzonitrile (2a).[30] *General Procedure A.* A solution of *N*-cyano-*N*-phenyl-*p*-toluenesulfonamide (NCTS) (87.1 mg, 0.32 mmol), 2,4-dimethoxybenzoic acid (116.6 mg, 0.64 mmol), and palladium(II) trifluoroacetate (21.3 mg, 0.06 mmol) in DMF/DMSO (19/1 v/v, 3 mL) was heated at 120 °C with stirring for 3 h. After it was cooled to room temperature, the reaction mixture was filtered and the solid was washed with EtOAc (2 mL X 3). The filtrate solution was concentrated and the residue was purified by chromatography on silica gel (heptane to 15% EtOAc in heptane) to give product **2a** (39.6 mg, 76%) as white solid: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.48 (d, J = 8.6 Hz, 1H), 6.52 (dd, J = 2.5, 8.6 Hz, 1H), 6.46 (d, J = 2.0 Hz, 1H), 3.90 (s, 3H), 3.86 (s, 3H); MS (ES, m/z) 164 ($M+H^+$).

2,4-Dimethoxybenzo-[^{13}C]-nitrile ([^{13}C]-2a).[11] The general procedure A was followed with [^{13}CN]-NCTS (136.7 mg, 0.50 mmol), 2,6-dimethoxybenzoic acid (182.2 mg, 1.00 mmol), Pd-$(O_2CCF_3)_2$ (33.2 mg, 0.10 mmol), and DMF/DMSO (19/1 v/v, 5

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mL). After the reaction was over, purification by chromatography on silica gel (heptane to 20% EtOAc in heptane) gave product [^{13}C]-**2a** (61.7 mg, 75%) as white solid: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.48 (dd, J = 5.9, 8.6 Hz, 1H), 6.52 (dd, J = 2.0, 8.6 Hz, 1H), 6.46 (t, J = 2.0 Hz, 1H), 3.90 (s, 3H), 3.86 (s, 3H); MS (ES, m/z) 165 ($M+H^+$); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 164.7, 162.9, 134.9, 116.9, 105.8 (d, J = 5.1 Hz), 98.6 (d, J = 3.6 Hz), 94.1 (d, J = 86.3 Hz), 56.0, 55.7; HRMS (ESI-TOF) m/z: $[M+H]^+$calcd for $C_8{}^{13}CH_{10}NO_2$ 165.0740, found 165.0745.

2,6-Dimethoxybenzonitrile (2b).[31] The general procedure A was followed with NCTS (87.1 mg, 0.32 mmol), 2,6-dimethoxybenzoic acid (116.6 mg, 0.64 mmol), $Pd(O_2CCF_3)_2$ (21.3 mg, 0.06 mmol), and DMF/DMSO (19/1 v/v, 3 mL). After the reaction was over, purification by chromatography on silica gel (heptane to 15% EtOAc in heptane) gave product **2b** (42.0 mg, 80%) as white solid: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.44 (t, J = 8.3 Hz, 1H), 6.55 (d, J = 8.6 Hz, 2H), 3.91 (s, 6H); MS (ES, m/z) 164 ($M+H^+$).

2,4,5-Trimethoxybenzonitrile (2c).[32] The general procedure A was followed with NCTS (109.0 mg, 0.40 mmol), 2,4,5-trimethoxybenzoic acid (169.9 mg, 0.80 mmol), $Pd(O_2CCF_3)_2$ (26.6 mg, 0.08 mmol), and DMF/DMSO (19/1 v/v, 3 mL). After the reaction was over, purification by chromatography on silica gel (heptane to 15% EtOAc in heptane) gave product **2c** (66.0 mg, 85%) as white solid: ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 6.97 (s, 1H), 6.50 (s, 1H), 3.95 (s, 3H), 3.92 (s, 3H), 3.84 (s, 3H); MS (ES, m/z) 194 ($M+H^+$).

5-Bromo-2,4-dimethoxybenzonitrile (2d).[10] The general procedure A was followed with NCTS (87.1 mg, 0.32 mmol), 5-bromo-2,4-dimethoxybenzoic acid (167.1 mg, 0.64 mmol), $Pd(O_2CCF_3)_2$ (21.3 mg, 0.06 mmol), and DMF/DMSO (19/1 v/v, 3 mL). After the reaction was over, purification by chromatography on silica gel (heptane to 25% EtOAc in heptane) gave product **2d** (58.2 mg, 75%) as white solid: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.67 (s, 1H), 6.46 (s, 1H), 3.97 (s, 3H), 3.95 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 162.6, 160.6, 136.9, 115.5, 102.3, 95.9, 94.9, 56.5, 56.4; MS (ES, m/z) 242 ($M+H^+$), 244 ($M+H^+$); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 162.6, 160.6, 136.9, 115.5, 102.3, 95.9, 94.9, 56.5, 56.4.

2,6-Dimethoxynicotinonitrile (2e).[33] The general procedure A was followed with NCTS (109.0 mg, 0.40 mmol), 2,6-dimethoxynicotinic acid (146.6 mg, 0.80 mmol), $Pd(O_2CCF_3)_2$ (42.0 mg, 0.13 mmol), and DMF/DMSO (19/1 v/v, 3 mL). After the reaction was over, purification by chromatography on silica gel (heptane to 15% EtOAc in heptane) gave product **2e** (46.0 mg, 70%) as white solid: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.70 (d, J = 8.6 Hz, 1H), 6.36 (d, J = 8.1 Hz, 1H), 4.04 (s, 3H), 3.98 (s, 3H): MS (ES, m/z) 165 ($M+H^+$).

Anthracene-9-carbonitrile (2f).[34] The general procedure A was followed with NCTS (109.0 mg, 0.40 mmol), anthracene-9-carboxylic acid (177.9 mg, 0.80 mmol), $Pd(O_2CCF_3)_2$ (42.0 mg, 0.13 mmol), and DMF/DMSO (19/1 v/v, 3 mL). After the reaction was over, purification by chromatography on silica gel (heptane to 15% EtOAc in heptane) gave product **2f** (62.0 mg, 76%) as white solid: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.70 (s, 1H), 8.41−8.47 (m, 2H), 8.09 (d, J = 8.1 Hz, 2H), 7.69−7.76 (m, 2H), 7.56−7.63 (m, 2H): MS (ES, m/z) 204 ($M+H^+$).

2-Hydroxy-6-methoxybenzonitrile (2g).[35] The general procedure A was followed with NCTS (68.1 mg, 0.25 mmol), 2-hydroxy-6-methoxybenzoic acid (84.1 mg, 0.50 mmol), $Pd(O_2CCF_3)_2$ (16.6 mg, 0.05 mmol), and DMF/DMSO (19/1 v/v, 2.5 mL). After the reaction was over, purification by chromatography on silica gel (heptane to 50% EtOAc in heptane) gave the product **2g** (30.1 mg, 81%) as white solid: ^{1}H NMR (CD_3OD, 400 MHz) δ 7.36 (dd, J = 8.0, 8.0 Hz, 1H), 6.55 (d, J = 8.0 Hz, 1H), 6.51 (d, J = 8.0 Hz, 1H), 3.88 (s, 3H): MS (ES, m/z) 150 ($M+H^+$); ^{13}C NMR (CD_3OD, 100 MHz) δ 164.0, 163.1, 136.1, 115.4, 109.0, 102.9, 90.6, 56.7; HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd for $C_8H_8NO_2^+$ 150.0550, found 150.0554.

4-Hydroxy-2-methoxybenzonitrile (2h). The general procedure A was followed with NCTS (43.6 mg, 0.16 mmol), 4-hydroxy-2-methoxybenzoic acid (53.8 mg, 0.32 mmol), $Pd(O_2CCF_3)_2$ (10.6 mg, 0.03 mmol), and DMF/DMSO (19/1 v/v, 1.5 mL). After the reaction was over, purification by chromatography on silica gel (heptane to 50% EtOAc in heptane) gave the product **2h** (18.9 mg, 79%) as white solid: ^{1}H NMR (CD_3OD, 400 MHz) δ 7.39 (d, J = 8.0 Hz, 1H), 6.51 (d, J = 4.0 Hz, 1H), 6.45 (dd, J = 4.0, 8.0 Hz, 1H), 3.87 (s, 3H): MS (ES, m/z) 150 ($M+H^+$); ^{13}C NMR (CD_3OD, 100 MHz) δ 165.2, 164.8, 136.0, 118.2, 109.5, 100.2, 92.6, 56.5.

2-(3,4-Dichlorophenyl)acetonitrile-1-^{13}C ([^{13}C]-2i). To a solution of diisopropylamine (0.84 mL, d= 0.722 g/mL, 6.06 mmol) in THF (2.8 mL) at −78 °C was added *n*-BuLi (2.40 mL, 2.5 M in hexanes, 6.0 mmol) dropwise. It was stirred at −78 °C for 30 min to give LDA at ∼1.0 M concentration.

To a solution of 2-(3,4-dichlorophenyl)acetic acid (451.1 mg, 2.20 mmol) in THF (4 mL) at 0 °C under N_2 was added the above LDA solution (4.20 mL, ∼ 1.0 M, 4.2 mmol) dropwise. The mixture became a yellow suspension. After the mixture was stirred at 0 °C for 15 min, a solution of 1*H*-benzo[*d*][1,2,3]triazole-1-carbonitrile-^{13}*C* (145.1 mg, 1.00 mmol) in THF (2 mL) was added. The resulted dark red solution was stirred for 18 h while the temperature slowly rose to room temperature. Water (2 mL) was added to the dark red solution and it was stirred at room temperature for 1 h. HCl aqueous solution (1N, 10 mL) was added to acidify the mixture. EtOAc (10 mL) was added to the acidified mixture and the mixture was stirred at room temperature for 10 min. Yellow precipitate was observed in the organic phase. The mixture was filtered. The organic phase was separated. The aqueous phase was extracted with EtOAc (10 mL × 3). The combined organic phase was dried over Na_2SO_4. Filtration and concentration of the filtrate gave the crude product as brown oil. Chromatography on silica-gel (heptane to 20% EtOAc in heptane) gave the product [^{13}C]-**2i** (133.8 mg, 71% yield) as colorless oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.47 (d, J = 8.0 Hz, 1H), 7.45 (d, J = 4.0 Hz, 1H), 7.19 (dd, J = 4.0, 8.0 Hz, 1H), 3.73 (d, J = 12.0 Hz, 3H); MS (ES, m/z) 187 ($M+H^+$), 189 ($M+H^+$); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 133.3, 132.5, 131.1, 129.9 (d, J = 3.6 Hz), 127.3 (d, J = 3.1 Hz), 116.9, 22.9 (d, J = 58.6 Hz); HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd for $C_7{}^{13}CH_6Cl_2N$ 186.9905, found 186.9906.

2-(3,4-Dichlorophenyl)acetonitrile (2i). *General Procedure B.* To a solution of 2-(3,4-dichlorophenyl)acetic acid (451.1 mg, 2.20 mmol) in THF (3 mL) at 0 °C under N_2 was added the prepared LDA solution (4.20 mL, ∼ 1.0 M, 4.2 mmol) dropwise. The mixture became a yellow solution. After the mixture was stirred at 0 °C for 15 min, a solution of NCTS (272.3 mg, 1.00 mmol) in THF (3 mL) was added. The reaction mixture turned into a yellow suspension after addition of NCTS solution. The reaction mixture was stirred for 18 h while the temperature slowly rose to room temperature. Water (2 mL) was added to the creamy suspension and the suspension turned into a clear biphase mixture. HCl aqueous solution (1N, 10 mL) was added to acidify the mixture. EtOAc (10 mL) was added to the acidified mixture and the mixture was stirred at room temperature for 10 min. The organic phase was separated and the aqueous phase was extracted with EtOAc (10 mL X 3). The combined organic phase was dried over Na_2SO_4. Filtration and concentration of the filtrate gave the crude product as yellowish oil. Chromatography on silica-gel (heptane to 20% EtOAc in heptane) gave the product **2i** (155.6 mg, 84% yield) as colorless oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.47 (d, J = 8.0 Hz, 1H), 7.45 (d, J = 4.0 Hz, 1H), 7.19 (dd, J = 4.0, 8.0 Hz, 1H), 3.73 (s, 3H); MS (ES, m/z) 186 ($M+H^+$), 188 ($M+H^+$); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 133.3, 132.5, 131.1, 129.9, 127.3, 116.9, 22.9.

2-(4-Isobutylphenyl)propanenitrile (2j).[36] The general procedure B was followed with Ibuprofen (247.5 mg, 1.20 mmol) in THF (3 mL), LDA solution (1.15 mL, 2.0 M in THF, 2.3 mmol), and NCTS (272.3 mg, 1.00 mmol) in THF (3 mL). After the α-cyanation reaction and workup, the yellowish oil crude product was dissolved in CH_3CN (5 mL) and treated CuO (36.0 mg, 0.45 mmol). The mixture was stirred at 85 °C for 30 min. Filtration and concentration of the filtrate gave the crude product. Chromatography on silica-gel (heptane to 30% EtOAc in heptane) gave the product **2j** (133.0 mg, 71% yield) as white solid: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.25 (d, J = 8.0 Hz, 2H), 7.15 (d, J = 8.0 Hz, 2H), 3.87 (q, J = 7.6 Hz, 1H), 2.47 (d, J = 7.1 Hz, 2H), 1.77−1.92 (m, 1H), 1.63 (d, J = 7.6 Hz, 3H), 0.90 (d, J = 8.0 Hz, 6H); MS (ES, m/z) 188 ($M+H^+$); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 141.6, 134.3, 129.8, 126.4, 121.9, 44.9, 30.9, 30.2, 22.3, 21.5; HRMS

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(ESI-TOF) m/z: $[M+H]^+$ calcd for $C_{13}H_{18}N$ 188.1434, found 188.1437.

2-(2,4-Dimethoxyphenyl)acetonitrile (2k). The general procedure B was followed with 2,4-dimethoxyphenylacetic acid (431.6 mg, 2.20 mmol) in THF (3 mL), LDA solution (4.20 mL, ~ 1.0 M, 4.2 mmol), and NCTS (272.3 mg, 1.00 mml) in THF (3 mL). After the α-cyanation reaction and workup, the yellowish oil crude product was dissolved in CH_3CN (5 mL) and treated CuO (36.0 mg, 0.45 mmol). The mixture was stirred at 85 °C refluxed for 30 min, and over weekend at room temperature. Filtration and concentration of the filtrate gave brown-yellowish oil. Chromatography on silica-gel (heptane to 30% EtOAc) gave the **2k** (159.0 mg, 90% yield) as white solid: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.24 (d, J = 8.1 Hz, 1H), 6.45−6.50 (m, 2H), 3.84 (s, 3H), 3.81 (s, 3H), 3.61 (s, 2H); MS (ES, m/z) 178.1 ($M+H^+$); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 161.0, 157.8, 129.7, 118.4, 111.0, 104.0, 98.7, 55.51, 55.47, 18.3; HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd for $C_{10}H_{12}NO_2$ 178.0863, found 178.0840.

3-(3-Methoxyphenyl)propanenitrile (2l). The general procedure B was followed with 3-(3-methoxyphenyl)propanoic acid (396.4 mg, 2.20 mmol) in THF (3 mL), LDA solution (4.20 mL, ~ 1.0 M, 4.2 mmol), and NCTS (272.3 mg, 1.00 mml) in THF (3 mL). After the α-cyanation reaction and workup, the crude product was dissolved in DMF (2 mL)/HOAc (0.2 mL) and the solution was heated at 120 °C for 3 h. Saturated $NaHCO_3$ aqueous solution was added to basify the cooled reaction mixture and it was extracted with Et_2O (10 mL × 3). The combined extracts were washed with brine, dried over Na_2SO_4. Filtration and concentration of the filtrate gave the crude product. Chromatography on silica gel (heptane to 30% EtOAc in heptane) gave the product **2l** (102.8 mg, 64% yield) as slightly yellowish oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.26 (t, J = 8.0 Hz, 1H), 6.76−6.84 (m, 3H), 2.94 (t, J = 8.0 Hz, 2H), 2.62 (t, J = 8.0 Hz, 2H); MS (ES, m/z) 162.1 ($M+H^+$); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 159.9, 139.6, 129.9, 120.5, 119.2, 114.1, 112.5, 55.2, 31.6, 19.3; HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd for $C_{10}H_{12}NO$ 162.0913, found 162.0902.

2-(6-Methoxynaphthalen-2-yl)propanenitrile-1-^{13}C (2m). The general procedure B was followed with 2-(6-methoxynaphthalen-2-yl)propanoic acid (138.2 mg, 0.60 mmol) in THF (1 mL), LDA solution (0.58 mL, 2 M in THF, 1.16 mmol), and NCTS (136.7 mg, 0.50 mmol) in THF (2 mL). After the α-cyanation reaction and workup, the yellowish oil crude product was dissolved in CH_3CN (3 mL) and treated CuO (40.0 mg, 0.49 mmol). The mixture was stirred at 85 °C for 1 h. Filtration and concentration of the filtrate gave the crude product as brown-yellowish oil. Chromatography on silica gel (heptane to 30% EtOAc in heptane) gave the product **2m** (75.1 mg, 71% yield) as white solid: ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.72−7.79 (m, 3H), 7.39 (dd, J = 4.0, 8.0 Hz, 1H), 7.12−7.21 (m, 2H), 3.98−4.08 (m, 1H), 3.93 (s, 3H), 1.72 (dd, J = 6.0, 7.0 Hz, 3H); MS (ES, m/z) 213.1 ($M+H^+$); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 158.1, 134.1, 132.0 (d, J = 3.0 Hz), 129.3, 128.8, 127.9, 125.4 (d, J = 2.9 Hz), 124.9 (d, J = 3.6 Hz), 121.7, 119.6, 105.7, 55.4, 31.3 (d, J = 56.4 Hz), 21.5 (d, J = 2.2 Hz); HRMS (ESI-TOF) m/z: $[M+H]^+$calcd for $C_{13}{}^{13}CH_{14}NO$ 213.1103, found 213.1109.

***N*-[^{13}C]-Cyano-*N*-phenyl-*p*-toluenesulfonamide ([^{13}CN]-NCTS).** To a vigorously stirred solution of Br_2 (186.0 mg, 1.17 mmol) in CH_2Cl_2 (3 mL) at 0 °C was added $K^{13}CN$ (70.0 mg, 1.06 mmol) in H_2O (1.2 mL) dropwise. The reaction mixture was allowed to stir for additional 5 min at 0 °C.

p-Toluenesulfonaniline (327.0 mg, 1.25 mmol) and Et_3N (0.30 mL, 2.16 mol) in CH_2Cl_2 (1.5 mL) were cooled in an ice−water bath. To it was added the above crude $Br^{13}CN$ solution (the aqueous layer was separated out and only the organic layer was added). After stirring for 10 min, the mixture was concentrated to dryness. Chromatography on silica gel (heptane to 20% EtOAc in heptane) gave [^{13}CN]-NCTS (242.0 mg, 83%) as white solid: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.64 (d, J = 8.1 Hz, 2H), 7.36−7.44 (m, 3H), 7.34 (d, J = 8.1 Hz, 2H), 7.20 (d, J = 1.0 Hz, 2H), 2.47 (s, 3H); MS (ES, m/z) 274 ($M+H^+$); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 146.7, 134.6, 132.3, 130.2, 130.0, 129.9, 128.4, 126.5 (d, J = 1.5 Hz), 108.7, 21.8; HRMS (ESI-TOF) m/z: $[M+H]^+$ calcd for $C_{13}{}^{13}CH_{13}N_2O_2S$ 274.0726, found 274.0734.

***N*-[^{14}C]-Cyano-*N*-phenyl-*p*-toluenesulfonamide ([^{14}CN]-NCTS).** To a vigorously stirred solution of Br_2 (186.0 mg, 1.17 mmol) in 3 mL CH_2Cl_2 at 0 °C was added the mixture of KCN (66.0 mg, 1.01 mmol) and $K^{14}CN$ (3.8 mg, 3.17 mCi or 117.29 MBq, specific activity 56 mCi/mmol or 2072 MBq/mmol) in H_2O (1.2 mL) dropwise. The reaction mixture was allowed to stir for additional 10 min at 0 °C.

p-Toluenesulfonaniline (382.0 mg, 1.55 mmol) and Et_3N (0.30 mL, 2.16 mmol) in CH_2Cl_2 (1.5 mL) were cooled in an ice−water bath. To it was added the above crude $Br^{14}CN$ solution (only the organic layer was added). After stirring for 10 min, the mixture was concentrated to dryness. Chromatography on silica gel (heptane to 20% EtOAc in heptane) gave [^{14}CN]-NCTS (198.0 mg, 2.15 mCi or 79.55 MBq, 68% radiochemical yield).

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.7b00033.

Characterization (^{1}H and ^{13}C NMR spectra) of the products and the reagent [^{13}CN]-NCTS (PDF)

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Notes

The authors declare no competing financial interest.

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