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Aerobic Copper-Catalyzed O-Methylation with Methylboronic Acid

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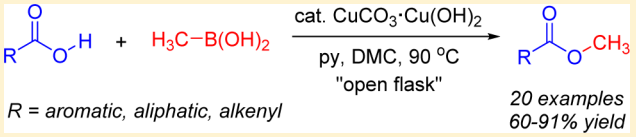
Supporting Information

ABSTRACT: The oxidative coupling of alkylboronic acids with oxygen nucleophiles offers a strategy for replacing toxic, electrophilic alkylating reagents. Although the Chan–Lam reaction has been widely applied in the arylation of heteroatom nucleophiles, O-alkylation with boronic acids is rare. We report a Cu-catalyzed nondecarboxylative methylation of carboxylic acids with methylboronic acid that proceeds in air with no additional oxidant. An isotope-labeling study supports an oxidative cross-coupling mechanism, in analogy to that proposed for Chan–Lam arylation.



The methylation of oxygen nucleophiles is ubiquitous in contemporary academic and industrial organic synthesis.[1] Typical methods use electrophilic reagents such as methyl iodide, dimethyl sulfate, and diazomethane.[2] While effective, these reagents are generally unstable and/or hazardous,[3] which has motivated chemists to seek safer alternatives, as in the use of (trimethylsilyl)diazomethane rather than diazomethane.[4] Unfortunately, (trimethylsilyl)diazomethane exposure is implicated in two recent laboratory-related deaths,[5] demonstrating the unmet need for safe, effective methylating reagents.

Therefore, we are pursuing alternate strategies and reagents for O-alkylation.[6] The use of a nucleophilic methyl source to replace typical reagents would avoid the intrinsic toxicity associated with electrophiles, offering a practical advantage.[7] Additionally, the selective oxidative cross-coupling of an alkylmetal(loid) reagent and an oxygen nucleophile might enable reaction selectivity and functional group compatibility that complement traditional methods.[8]

The Cu-catalyzed oxidative coupling of heteroatom nucleophiles with arylboronic acids, known as the Chan–Lam reaction, has been widely applied for N- and O-arylation.[9] In some cases, oxygen present under "open flask" conditions enables catalyst turnover, offering practical and green oxidative conditions.[10] Despite the success of Chan–Lam arylation, the first couplings of alkylboronic acids with heteroatom nucleophiles have emerged only recently.[11] Although stoichiometric Cu is often required,[11b–d,g] the alkylation of phenols, anilines, and amides proceeds with catalytic Cu using an organic peroxide as the terminal oxidant.[11e,f] To the best of our knowledge, Tsuritani's N-cyclopropylation of indoles is the sole Chan–Lam alkylation that proceeds with catalytic Cu and air as the only added oxidant.[11a]

Methylboronic acid (**1**) and related compounds, especially trimethylboroxine and methyltrifluoroborate salts, have been previously employed as methylating reagents.[12] Methyl transfer from **1** to canonical nucleophiles is rare; Cruces used stoichiometric Cu to mediate the N-methylation of anilines,[11c] but this has not yet been extended to any oxygen nucleophile.

Although an array of oxygen nucleophiles participate in Chan–Lam coupling, most examples use phenols or aliphatic alcohols and carboxylic acids are rarely employed. The use of carboxylic acids is complicated by the potential for decarboxylation, which occurs under an array of conditions.[13] Non-decarboxylative arylations and alkenylations of carboxylic acids with boronic acids have been reported, but the analogous alkylation has not been demonstrated.[14] We therefore chose to investigate the synthesis of methyl esters by cross-coupling of **1** and carboxylic acids.[15]

We report herein an aerobic, Cu-catalyzed methylation of carboxylic acids with **1**. The basic reaction conditions complement those of Fischer esterification, and the reaction proceeds open to air without any additional oxidant. Mechanistic studies support a Chan–Lam-type mechanism where the methyl group is transferred from the boronic acid to the substrate.

The reaction of 4-fluorobenzoic acid (**2a**) was chosen for preliminary study so that conversion to **3a** could be quantitatively determined by ^{19}F NMR. Initial screening conditions were adopted from close literature precedent, with the added constraint that only 0.2 equiv of the Cu catalyst was used. The reaction of **2a** and **1** under Cheng's conditions for the arylation of carboxylic acids[14c] yielded no product (Table 1, entry 1). In contrast, **3a** was formed in 54% yield using modified conditions from Cruces' methylation of anilines (entry 2).[11c] Surprisingly, this initial result demonstrated catalyst turnover under "open flask" conditions.

Other solvents were screened and found to be effective, including chlorobenzene and diethyl carbonate (DEC) (Table 1, entries 3 and 4). Dialkyl carbonates have emerged as nontoxic, green solvents, and therefore DEC was chosen for further optimization studies.[16]

Since carboxylic acids are substrates in this chemistry, we sought a catalyst precursor without carboxylate ligands. Although $CuBr_2$ was ineffective, Cu complexes with oxyanionic

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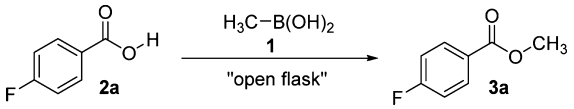
Table 1. Optimization of Cu-Catalyzed Esterification



entry[a]	[Cu]	additive	solvent	yield (%)[b]
1[c]	$Cu(OTf)_2$	urea	EtOAc	<1
2	$Cu(OAc)_2$	py	dioxane	54
3	$Cu(OAc)_2$	py	$Cl\text{-}C_6H_5$	64
4	$Cu(OAc)_2$	py	DEC	71
5	$CuBr_2$	py	DEC	<1
6	$Cu(OTf)_2$	py	DEC	47
7	$Cu(acac)_2$	py	DEC	46
8	$CuCO_3{\cdot}Cu(OH)_2$[d]	py	DEC	73
9	$CuCO_3{\cdot}Cu(OH)_2$[d]	Cs_2CO_3	DEC	<1
10	$CuCO_3{\cdot}Cu(OH)_2$[d]	Et_3N	DEC	10
11	$CuCO_3{\cdot}Cu(OH)_2$[d]	urea	DEC	13
12	$CuCO_3{\cdot}Cu(OH)_2$[d]	py	DMC	71 (76)[e]

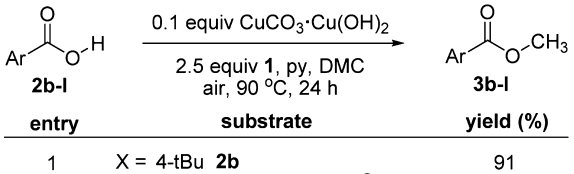
[a]Reaction conditions unless specified otherwise: [**2a**] = 0.2 M in solvent, 2.5 equiv of **1**, 0.2 equiv of [Cu], 3.5 equiv of additive, 90 °C, 24 h. [b]Determined by ^{19}F NMR against an internal standard. [c]Temperature 60 °C. [d]0.1 equiv. [e]Isolated yield.

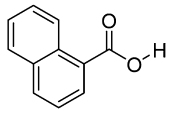
ligands of varying basicities, including $Cu(OTf)_2$ and $Cu(acac)_2$, catalyzed the formation of **3a** (Table 1, entries 4−8). Ultimately, cupric carbonate [$CuCO_3{\cdot}Cu(OH)_2$] emerged as the optimal Cu source (entry 8).[17]

Pyridine is essential for the reaction. When Cs_2CO_3 replaced pyridine, no **3a** was observed (entry 9). Low yields also resulted with triethylamine or urea (Table 1, entries 10 and 11). In the final, optimized conditions, dimethyl carbonate (DMC) replaced higher-boiling DEC to ease solvent removal, and **3a** was isolated in 76% yield (entry 12).

An array of aromatic carboxylic acids undergo Cu-catalyzed oxidative methylation. Alkyl-substituted **2b** provided ester **3b** in 91% yield (Table 2, entry 1). Despite the potential for Cu-mediated reactions of aryl halides,[18] brominated and chlorinated benzoic acid derivatives were smoothly transformed (Table 2, entries 2 and 3). However, no methyl ester was observed in the reaction with 4-iodobenzoic acid.

Table 2. Methylation of Aromatic Carboxylic Acids



entry	substrate	yield (%)
1	X = 4-tBu **2b**	91
2	4-Br **2c**	85
3	3-Cl **2d**	88
4	4-Ac **2e**	66
5	4-CN **2f**	79
6	3,4-(-OCH_2O-) **2g**	74
7	2-CH_3 **2h**	68
8	2-OMe **2i**	78
9	 **2j**	73
10	Y = H **2k**	0
11	CH_3 **2l**	67

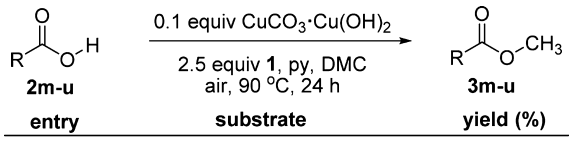
Electron-deficient substrates with ketone and nitrile substituents formed the corresponding methyl esters **3e,f** in 66% and 79% yields, respectively (Table 2, entries 4 and 5). Electron-donating substituents are similarly tolerated (entries 1 and 6−8). For example, piperonylic acid (**2g**) was methylated in 74% yield (entry 6).

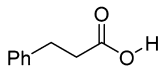
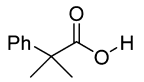
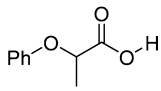
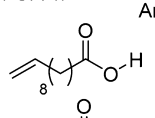
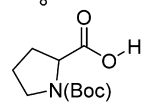
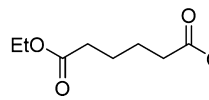
The methylation of 2-substituted benzoic acid derivatives proceeded despite the increased steric demands of the substrates (Table 2, entries 7−9). Notably, Pd-catalyzed carboxylate-directed C−H methylation of **2h** and similar compounds with **1** has been reported.[12b] This demonstrates that the chemoselectivity of the methylation event may be controlled by the choice of catalyst and reaction conditions.

Given the importance of aromatic heterocycles, the reaction of indole-2-carboxylic acid (**2k**) was investigated. Although no product was observed with the N−H indole (Table 2, entry 10), the *N*-methyl derivative **2l** was transformed into **3l** in 67% yield (entry 11).

The oxidative methylation was applied to aliphatic carboxylic acids to further probe the reaction scope. Hydrocinnamic acid (**2m**) was methylated in 80% yield (Table 3, entry 1).

Table 3. Esterification of Aliphatic and Alkenyl Substrates



entry	substrate	yield (%)
1	 **2m**	80
2	 **2n**	65
3	 **2o**	78
4	Ar = Ph **2p**	66
5	4-OMe-Ph **2q**	67
6	4-Cl-Ph **2r**	67
7	 **2s**	60
8	 **2t**	73
9	 **2u**	78

Neopentylic ester **3n** was also formed, albeit in reduced yield (entry 2). α-Oxygenated **2o**, which might be susceptible to elimination under the basic reaction conditions, provided **3o** in 78% yield (entry 3). Substrates with alkene functionalities are methylated in moderate yields, including cinnamic acid derivatives (entries 4−6) and the primary olefin **2s** (entry 7).

As demonstrated by the transformation of acid-sensitive N-Boc-proline (**2t**), this O-methylation is complementary to Fischer esterification (Table 3, entry 8). Ester **2u** was methylated to see if the ethyl ester would endure (entry 9). Mixed diester **3u** was exclusively observed, demonstrating that

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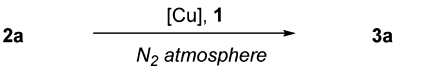
transesterification does not occur under the basic reaction conditions.

The coupling of **1** with a carboxylic acid requires an oxidation event, and we next investigated the terminal oxidant. Since the catalytic reaction proceeds under "open flask" conditions, we propose that molecular oxygen from the air serves as the ultimate electron acceptor. To test this, oxygen was excluded from the reaction, which resulted in only trace formation of **3a** (Table 4, entry 1). To exclude the possibility

Table 4. Terminal Oxidant Screen



entry[a]	additive (2 equiv)	NMR yield (%)
1	none	<1
2	H_2O	8
3	$PhI(OAc)_2$	<1
4	aqueous HOOtBu	12
5	tBuOOtBu	73

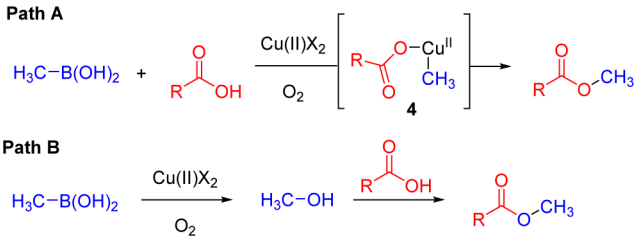
[a]Conditions: 0.1 equiv of $CuCO_3{\cdot}Cu(OH)_2$, 3.5 equiv of py, 2.5 equiv of **1**, DEC, 90 °C, 24 h.

that the combination of atmospheric water and methylboronic acid is the oxidant,[19] water was added to the reaction. Low product yield was observed, suggesting that oxygen is necessary (entry 2).

Other oxidants were also screened. While the use of HOOtBu and $PhI(OAc)_2$ resulted in low yields, tBuOOtBu provided **3a** in a yield comparable to that of the "open-flask" reaction (Table 4, entries 3–5). A control experiment in which **1** was omitted resulted in no product formation, suggesting that the peroxide is not the methyl source under these conditions (see the Supporting Information, eq S1).[20] While in a practical sense the use of air is advantageous, it is noteworthy that the successful reaction observed with tBuOOtBu parallels previous nonaerobic Cu-catalyzed Chan–Lam alkylations.[11e,f]

We next considered possible reaction mechanisms. The O-methylation may proceed similarly to Chan–Lam O-arylation, which has recently been studied (Scheme 1, path A).[21] In

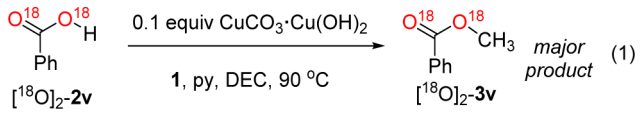
Scheme 1. Possible Mechanistic Pathways



accord with Stahl's studies, intermediate **4** may be formed by ligand exchange with the carboxylic acid and transmetalation with **1**. Reductive elimination, likely from a Cu(III) species, and oxidation with O_2 would yield the product and regenerate the Cu(II) catalyst.

Given the single prior report of aerobic Cu-catalyzed Chan–Lam alkylation,[11a] alternate mechanistic pathways were considered. Oxidation of aryl- or alkylboronic acids to the corresponding phenols and alcohols occurs under a variety of conditions,[22] and methanol formed in situ might react with the carboxylic acid to form the product (Scheme 1, path B).[23]

An isotope-labeling experiment was used to differentiate between the mechanistic proposals. The reaction of ^{18}O-labeled benzoic acid ($[^{18}O]_2$-**2v**) resulted in the formation of ester $[^{18}O]_2$-**3v** with both labeled atoms retained (eq 1). This is



inconsistent with a carbonyl substitution mechanism (path B). Additionally, no product was observed upon substitution of methanol for **1** (see the Supporting Information, eq S2). Taken together, these experiments suggest that Cu-catalyzed O-methylation proceeds via a cross-coupling mechanism analogous to that proposed for Chan–Lam arylation (path A).[21]

In conclusion, a Cu-catalyzed Chan–Lam methylation of carboxylic acids has been developed. The esterification of aryl, aliphatic, and alkenyl carboxylic acids with **1** proceeds in air without any additional oxidant. The basic reaction conditions complement those of Fischer esterification, and mechanistic studies support a methyl transfer mechanism from **1** to the substrate. This reaction expands the scope of Chan–Lam coupling to include nondecarboxylative alkylation of carboxylic acids and demonstrates a strategy to replace toxic electophilic reagents in O-alkylation.

EXPERIMENTAL SECTION

General Information. Unless otherwise noted, all reagents were obtained commercially and used without further purification. Basic cupric carbonate ($CuCO_3{\cdot}Cu(OH)_2$, CAS Registry 12069-69-1) was obtained from Fisher Scientific. TLC analysis of reaction mixtures was performed on silica gel 60 F254 TLC plates using $KMnO_4$ stain and UV light to visualize the reaction components. Column chromatography was carried out on 60 Å, 40–63 μm silica gel using mixtures of ethyl acetate and hexanes as eluent. ^1H NMR spectra were referenced to chloroform and obtained at a frequency of 300 or 500 MHz, as noted. ^1H-decoupled ^{19}F NMR spectra were referenced to 4-methoxy-3-nitrobenzotrifluoride and obtained at 470 MHz. GCMS analysis was performed using a J&W DB5 ms GC capillary column (0.25 mm × 30 m, 0.25 μM film thickness).

General Procedure for Optimizing the Methylation of 2a. In a 2 dram screw-top vial equipped with a magnetic stir bar were placed **2a** (31 mg, 0.22 mmol), 4-methoxy-3-nitrobenzotrifluoride (internal standard, 16 mg, 0.07 mmol), and the appropriate solvent (1.1 mL). The appropriate amine was added (3.5 equiv, 0.77 mmol). An aliquot (100 uL) was removed and used as the $T = 0$ sample for quantifying reaction progress. To the remaining solution was added the copper complex (0.2 equiv, 0.04 mmol) and methylboronic acid (**1**; 30 mg, 0.5 mmol). (For the reactions with $CuCO_3{\cdot}Cu(OH)_2$, 0.1 equiv of the copper complex was used.) A rubber septum with a vent needle was placed over the top of the screw-top vial, and the reaction mixture was heated to 90 °C. After it was stirred for 24 h, the reaction mixture was cooled and a second aliquot was removed. The $T = 0$ and $T = 24$ h aliquots were each diluted in $CDCl_3$ and analyzed by ^1H-decoupled ^{19}F NMR.

General Procedure for the Methylation of Carboxylic Acids (2a–u) with 1. In a 10 mL round-bottom flask equipped with magnetic stir bar and reflux condenser were placed the appropriate carboxylic acid (**2a–u**; 0.6 mmol), DMC (3 mL, 0.2 M substrate concentration), and pyridine (0.17 mL, 2.1 mmol). Cupric carbonate ($CuCO_3{\cdot}Cu(OH)_2$, 13.3 mg, 0.06 mmol) was added, followed by methylboronic acid (**1**; 90 mg, 1.5 mmol). The heterogeneous reaction mixture was left open to ambient air and heated to 90 °C. After 24 h, the reaction mixture was cooled to room temperature, filtered through Celite, and concentrated in vacuo. Pure methyl ester was obtained from the crude residue by flash column chromatography.

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*Methyl 4-Fluorobenzoate (**3a**, CAS Registry 403-33-8).* Carboxylic acid **2a** (84 mg, 0.60 mmol) was reacted according to the general procedure. After column chromatography (50/1 hexanes/ethyl acetate eluent), methyl ester **3a** was isolated as a clear oil (70.0 mg, 76% yield). The spectral data were consistent with reported values.[24] ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.06 (dd, 2 H, J = 9.0, 5.4 Hz), 7.11 (dd, 2 H, J = 8.7, 8.7 Hz), 3.91 (s, 3 H).

*Methyl 4-tert-Butylbenzoate (**3b**, CAS Registry 26537-19-9).* Carboxylic acid **2b** (107 mg, 0.60 mmol) was reacted according to the general procedure. After column chromatography (50/1 hexanes/ethyl acetate eluent), methyl ester **3b** was isolated as a clear oil (104.9 mg, 91% yield). The spectral data were consistent with reported values.[25] ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.00 (d, 2 H, J = 8.4 Hz), 7.47 (d, 2 H, J = 8.4 Hz), 3.92 (s, 3 H), 1.36 (s, 9 H).

*Methyl 4-Bromobenzoate (**3c**, CAS Registry 619-42-1).* Carboxylic acid **2c** (121 mg, 0.60 mmol) was reacted according to the general procedure. After column chromatography (50/1 hexanes/ethyl acetate eluent), methyl ester **3c** was isolated as a white solid (109.7 mg, 85% yield). The spectral data were consistent with reported values.[26] ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.88 (d, 2 H, J = 8.7 Hz), 7.56 (d, 2 H, J = 8.7 Hz), 3.90 (s, 3 H).

*Methyl 3-Chlorobenzoate (**3d**, CAS Registry 2905-65-9).* Carboxylic acid **2d** (94 mg, 0.60 mmol) was reacted according to the general procedure. After column chromatography (50/1 hexanes/ethyl acetate eluent), methyl ester **3d** was isolated as a clear oil (89.8 mg, 88% yield). The spectral data were consistent with reported values.[27] ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.02 (dd, 1 H, J = 1.8, 1.8 Hz), 7.92 (ddd, 1 H, J = 7.8, 1.5, 1.5 Hz), 7.53 (ddd, 1 H, J = 8.1, 2.1, 1.2 Hz), 7.38 (dd, 1 H, J = 7.8, 7.8 Hz), 3.93 (s, 3 H).

*Methyl 4-Acetylbenzoate (**3e**, CAS Registry 3609-53-8).* Carboxylic acid **2e** (98 mg, 0.60 mmol) was reacted according to the general procedure. After column chromatography (50/1 hexanes/ethyl acetate eluent), methyl ester **3c** was isolated as a white solid (70.0 mg, 66% yield). The spectral data were consistent with reported values.[28] ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.10 (d, 2 H, J = 8.4 Hz), 7.99 (d, 2 H, J = 8.4 Hz), 3.94 (s, 3 H), 2.63 (s, 3 H).

*Methyl 4-Cyanobenzoate (**3f**, CAS Registry 1129-35-7).* Carboxylic acid **2f** (88 mg, 0.60 mmol) was reacted according to the general procedure. After column chromatography (19:1 hexanes/ethyl acetate eluent), methyl ester **3f** was isolated as a white solid (76.3 mg, 79% yield). The spectral data were consistent with reported values.[29] ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.13 (d, 2 H, J = 8.7 Hz), 7.74 (d, 2 H, J = 8.7 Hz), 3.95 (s, 3 H).

*Methyl Piperonylate (**3g**, CAS Registry 326-56-7).* Carboxylic acid **2g** (100 mg, 0.60 mmol) was reacted according to the general procedure. After column chromatography (19/1 hexanes/ethyl acetate eluent), methyl ester **3g** was isolated as a white solid (80.4 mg, 74% yield). The spectral data were consistent with reported values.[30] ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.65 (dd, 1 H, J = 8.1, 1.5 Hz), 7.47 (d, 1 H, J = 1.8 Hz), 6.83 (d, 1 H, J = 8.1 Hz), 6.04 (s, 2 H), 3.88 (s, 3 H).

*Methyl 2-Methylbenzoate (**3h**, CAS Registry 89-71-4).* Carboxylic acid **2h** (82 mg, 0.60 mmol) was reacted according to the general procedure. After column chromatography (50/1 hexanes/ethyl acetate eluent), methyl ester **3h** was isolated as a clear oil (61.6 mg, 68% yield). The spectral data were consistent with reported values.[28] ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.93 (dd, 1 H, J = 8.1, 1.2 Hz), 7.41 (ddd, 1 H, J = 7.5, 7.5, 1.5 Hz), 7.27 (m, 2 H), 3.91 (s, 3 H), 2.63 (s, 3 H).

*Methyl 2-Methoxybenzoate (**3i**, CAS Registry 606-45-1).* Carboxylic acid **2i** (91 mg, 0.60 mmol) was reacted according to the general procedure. After column chromatography (19/1 hexanes/ethyl acetate eluent), methyl ester **3i** was isolated as a white solid (77 mg, 78% yield). The spectral data were consistent with reported values.[31] ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.81 (d, 1 H, J = 7.9, 1.9 Hz), 7.50 (m, 1H), 7.00 (m, 2 H), 3.90 (s, 3 H), 3.89 (s, 3 H).

*Methyl 1-Naphthoate (**3j**, CAS Registry 2459-24-7).* Carboxylic acid **2j** (103 mg, 0.60 mmol) was reacted according to the general procedure.[32] After column chromatography (50/1 hexanes/ethyl acetate eluent), methyl ester **3j** was isolated as a clear oil (81.4 mg, 73% yield). The spectral data were consistent with reported values.[33] ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.98 (d, 1 H, J = 8.7 Hz), 8.22 (dd, 1 H, J = 7.2, 1.2 Hz), 8.04 (d, 1 H, J = 8.1 Hz), 7.91 (d, 1 H, J = 8.1 Hz), 7.69−7.49 (m, 3 H), 4.04 (s, 3 H). Peaks corresponding to methyl 2-naphthoate (CAS Registry 2459-25-8)[28] were also observed:[32] δ 8.66 (s, 1 H), 8.11 (m, 1 H), 7.98 (m, 1 H), 7.90 (m, 2 H), 7.69−7.49 (m, 2 H), 4.02 (s, 3 H).

*Methyl 1-Methylindole-2-carboxylate (**3l**, CAS Registry 37493-34-8).* Carboxylic acid **2l** (105 mg, 0.60 mmol) was reacted according to the general procedure. After column chromatography (50/1 hexanes/ethyl acetate eluent), methyl ester **3l** was isolated as a white solid (76.5 mg, 67% yield). The spectral data were consistent with reported values.[34] ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.72 (d, 1 H, J = 7.8 Hz), 7.40 (m, 3 H), 7.20 (m, 1 H), 4.11 (s, 3 H), 3.96 (s, 3 H).

*Methyl 3-Phenylpropanoate (**3m**, CAS Registry 103-25-3).* Carboxylic acid **2m** (90 mg, 0.60 mmol) was reacted according to the general procedure. After column chromatography (50/1 hexanes/ethyl acetate eluent), methyl ester **3m** was isolated as a clear oil (78.7 mg, 80% yield). The spectral data were consistent with reported values.[35] ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.39−7.18 (m, 5 H), 3.71 (s, 3 H), 3.00 (t, 2 H, J = 8.1 Hz), 2.68 (t, 2 H, J = 8.1 Hz).

*2-Methyl-2-phenylpropionate Methyl Ester (**3n**, CAS Registry 57625-74-8).* Carboxylic acid **2n** (99 mg, 0.60 mmol) was reacted according to the general procedure. After column chromatography (100/1 hexanes/ethyl acetate eluent), methyl ester **3n** was isolated as a clear oil (69.4 mg, 65% yield). The spectral data were consistent with reported values.[36] ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.43−7.25 (m, 5 H), 3.69 (s, 3 H), 1.64 (s, 6 H).

*Methyl 2-Phenoxypropanoate (**3o**, CAS Registry 2065-24-9).* Carboxylic acid **2o** (100 mg, 0.60 mmol) was reacted according to the general procedure. After column chromatography (50/1 hexanes/ethyl acetate eluent), methyl ester **3o** was isolated as a clear oil (84.6 mg, 78% yield). The spectral data were consistent with reported values.[37] ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.30 (m, 2 H), 7.00 (t, 1 H, J = 7.5 Hz), 6.91 (m, 2 H), 4.80 (q, 1 H, J = 6.9 Hz), 3.77 (s, 3 H), 1.65 (d, 3 H, J = 6.9 Hz).

*Methyl Cinnamate (**3p**, CAS Registry 103-26-4).* Carboxylic acid **2p** (89 mg, 0.60 mmol) was reacted according to the general procedure. After column chromatography (50/1 hexanes/ethyl acetate eluent), methyl ester **3p** was isolated as a white solid (64.1 mg, 66% yield). The spectral data were consistent with reported values.[28] ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.72 (d, 1 H, J = 15.9 Hz), 7.54 (m, 2 H), 7.40 (m, 3 H), 6.47 (d, 1 H, J = 16.2 Hz), 3.83 (s, 3 H).

*Methyl 4-Methoxycinnamate (**3q**, CAS Registry 943-89-5).* Carboxylic acid **3q** (107 mg, 0.60 mmol) was reacted according to the general procedure. After column chromatography (50/1 hexanes/ethyl acetate eluent), methyl ester **3q** was isolated as a white solid (76.8 mg, 67% yield). The spectral data were consistent with reported values.[38] ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.65 (d, 1 H, J = 15.9 Hz), 7.47 (d, 2 H, J = 8.6 Hz), 6.90 (d, 2 H, J = 8.8 Hz), 6.32 (d, 1 H, J = 15.9 Hz), 3.83 (s, 3H), 3.80 (s, 3 H).

*Methyl 4-Chlorocinnamate (**3r**, CAS Registry 7560-44-3).* Carboxylic acid **2r** (110 mg, 0.60 mmol) was reacted according to the general procedure. After column chromatography (50/1 hexanes/ethyl acetate eluent), methyl ester **3r** was isolated as a white solid (79.6 mg, 67% yield). The spectral data were consistent with reported values.[39] ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.64 (d, 1 H, J = 16.2 Hz), 7.44 (d, 2 H, J = 8.4 Hz), 7.35 (d, 2 H, J = 8.7 Hz), 6.40 (d, 1 H, J = 15.9 Hz), 3.81 (s, 3 H).

*Methyl 10-Undecenoate (**3s**, CAS Registry 111-81-9).* Carboxylic acid **2s** (110 mg, 0.60 mmol) was reacted according to the general procedure. After column chromatography (50/1 hexanes/ethyl acetate eluent), methyl ester **3s** was isolated as a clear oil (70.5 mg, 60% yield). The spectral data were consistent with reported values.[40] ^{1}H NMR ($CDCl_3$, 300 MHz): δ 5.80 (m, 1 H), 4.95 (m, 2 H), 3.66 (s, 3 H), 2.30 (t, 2 H, J = 7.5 Hz), 2.03 (m, 2 H), 1.62 (m, 2 H), 1.29 (m, 10 H).

*Boc-Pro-OMe (**3t**, CAS Registry: 145681-01-2).* Carboxylic acid **2t** (129 mg, 0.60 mmol) was reacted according to the general procedure. After column chromatography (10/1 hexanes/ethyl acetate eluent), methyl ester **3t** was isolated as a clear oil (100.1 mg, 73% yield). The spectral data were consistent with reported values and indicated the

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presence of conformational isomers.[41] ^{1}H NMR ($CDCl_3$, 300 MHz): δ 4.27−4.15 (m, 1 H), 3.68 (s, 3 H), 3.54−3.30 (m, 2 H), 2.28−1.71 (m, 4 H), 1.43−1.36 (m, 9 H).

*Ethyl Methyl Adipate (**3u**, CAS Registry 18891-13-9).* Carboxylic acid **2u** (105 mg, 0.60 mmol) was reacted according to the general procedure. After column chromatography (19/1 hexanes/ethyl acetate eluent), methyl ester **3u** was isolated as a clear oil (88.8 mg, 78% yield). The spectral data were consistent with reported values.[42] ^{1}H NMR ($CDCl_3$, 500 MHz): δ 4.08 (2 H, q, J = 7.0 Hz), 3.62 (s, 3 H), 2.28 (m, 4 H), 1.62 (m, 4 H), 1.21 (t, 3 H, J = 7.0 Hz).

Procedure and GCMS Data for the Isotope-Labeling Experiment (Eq 1). $[^{18}O]_2$-**2v** was prepared from benzotrichloride (Acros) and $[^{18}O]$-water (97%, Cambridge Isotope) as previously reported.[43] The ^{1}H NMR spectral data were consistent with the values observed for **2v**. GCMS m/z (% relative intensity, ion): 126.2 (81%, M), 107.2 (100%, M − (^{18}OH)), 77.1 (94%, M − (C[^{18}O]$_2$H)). The molecular ion peak corresponding to $[^{18}O]$-**2v** was also identified: 124.1 (3.6%, M). The molecular ion peak corresponding to unlabeled **2v** was also identified: 122.1 (1.3%, M). The percentage of ^{18}O in synthetic $[^{18}O]_2$-**2v** was therefore calculated to be 96.5%.

$[^{18}O]_2$-**2v** was reacted with **1** according to the general methylation procedure. An aliquot was taken from the reaction mixture at T = 24 h and analyzed by GCMS. $[^{18}O]_2$-**3v** was identified. GCMS m/z (% relative intensity, ion): 140.2 (28.8%, M), 107.2 (100%, M − ($^{18}OCH_3$)). The molecular ion peak corresponding to $[^{18}O]$-**3v** was also identified: 138.2 (10.2%, M). The molecular ion peak corresponding to unlabeled **3v** was also identified: 136.2 (1.2%, M). The calculated percentages of product formed are 72% $[^{18}O]_2$-**3v**, 25% $[^{18}O]$-**3v**, and 3% **3v**. A peak for the benzoic acid ($[^{18}O]_2$**2v**) was also observed. m/z (% relative intensity, ion): 126.2 (71.8%, M), 107.2 (100%, M − ($^{18}OCH_3$)). The molecular ion peak corresponding to $[^{18}O]$-**2v** was also identified: 124.2 (28.5%, M). The molecular ion peak corresponding to unlabeled **2v** was also identified: 122.2 (12.6%, M). The calculated percentages of **2v** epitopes are 64% $[^{18}O]_2$-**2v**, 25% $[^{18}O]$-**2v**, and 11% **2v**.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Text and figures giving control experiments with tBuOOtBu (eq S1) and MeOH (eq S2) and ^{1}H NMR spectra for **3a**−**u**. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.5b01077.

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Notes

The authors declare no competing financial interest.

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