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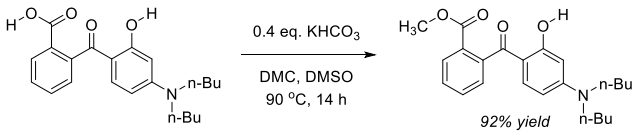
Abstract:



Although methylation reactions are commonplace, currently used reagents are hazardous, toxic, and/or unstable. Dimethylcarbonate has been put forth as an inexpensive, non-toxic, and "green" potential methylating reagent. Herein we report a general, base-catalyzed methyl transfer from dimethylcarbonate to carboxylic acids. High selectivity for esterification is observed even in the presence of unprotected phenols and the mild reaction conditions enable conservation of stereochemistry at epimerizable stereocenters. Isotope-labeling studies suggest a mechanism proceeding by direct methyl transfer from dimethylcarbonate to the substrate.

Methylation reactions of carboxylic acids are ubiquitously used in chemical research, including in natural product synthesis,[1] reaction development,[2] medicinal chemistry,[3] and polymer synthesis.[4] Although often effective, Fisher esterification is incompatible with acid-sensitive substrates.[5] This led to the development of electrophilic methylating reagents that react under mild conditions, such as diazomethane, dimethyl sulfate, and "magic methyl."[6]

Perhaps the most high-profile drawback of common methylating reagents is their extraordinary acute toxicity.[7-10] For example, trimethylsilyl diazomethane, sometimes considered a safer alternative to diazomethane due to its decreased volatility and increased stability,[11] has caused the deaths of two chemists since 2008.[7] Use of common methylating agents, including diazomethane, trimethylsilyldiazomethane, dimethyl sulfate, and iodomethane, is also complicated by their general instability to light, heat, and/or moisture, along with concerns about chronic health risks.[7-11] Despite their drawbacks, hazardous methylating reagents are regularly used in both academic and industrial laboratories.[1-4]

We have therefore initiated a program to develop new methylation methods that rely upon safe, stable reagents. While others have sought to mitigate the hazards of current reagents,[12-13] the development of non-explosive carbene precursors[14] and safer alternatives to hydrogen cyanide[15] inspired us to pursue altogether different methylating agents.[16] Increased safety and convenience will reduce the cost and risk of an immensely useful functional group manipulation.

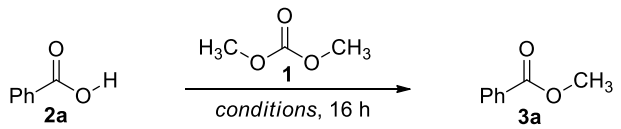
Dimethylcarbonate (DMC, **1**) is an inexpensive, non-toxic, and "green" potential methylating reagent.[17-19] Although DMC has been explored in methylations of a variety of nucleophiles, esterifications have generally been limited to electron-rich carboxylic acids and require stoichiometric activating agents, high (>150 °C) temperature, and/or special reactors such as autoclaves.[20-28] Perhaps due to the limited demonstrated substrate scope and harsh reaction conditions, methylation with DMC has not found routine application in synthetic organic chemistry.

Herein we report a general catalytic methyl transfer from DMC to carboxylic acid nucleophiles under basic conditions.[29] Both electron-rich and electron-poor substrates are readily esterified and the mild reaction

conditions enable conservation of stereochemistry at epimerizable α-carbonyl stereocenters. Mechanistic studies suggest that a direct methyl transfer from DMC, rather than a carbonyl substitution mechanism, is operative. The improved substrate scope and chemoselectivity demonstrated in this work suggest that DMC should be considered as an alternative to routinely-used hazardous methylating agents.

Our starting point for reaction development was Shieh's seminal report on methylation of carboxylic acids using stoichiometric DBU to activate DMC.[20,30-31] We hypothesized that co-solvents or less basic catalysts might ameliorate the need for stoichiometric quantities of catalyst.[32] Conversion of benzoic acid (**2a**) to methyl benzoate (**3a**) was quantified by GCMS. Under solvent-free conditions, catalytic quantities of DBU mediated the formation of **3a** in only 5% yield (Table 1, entry 1). Dramatic solvent effects were observed (entries 2-4). While increased **3a** was formed in DMF, higher yield and apparent catalyst turnover resulted from the reaction in DMSO.[33]

Table 1. Optimization of Base-Catalyzed Esterification.



entry[a]	catalyst[b]	solvent[c]	T (°C)	yield 3a[d]
1	DBU	-	90	5%
2	DBU	CH_3CN	75	trace
3	DBU	DMF	90	20%
4	DBU	DMSO	90	58%
5	DABCO	DMSO	90	94%
6	KOH	DMSO	90	88%
7	K_2CO_3	DMSO	90	98%
8	K_2CO_3	DMSO	75	20%
9	$KHCO_3$	DMSO	90	85%
10	KH_2PO_4	DMSO	90	trace
11	Na_2CO_3	DMSO	90	87%
12	Cs_2CO_3	DMSO	90	99%

a) Ratio of **1**:**2a** = 20:1. *b*) 0.2 equiv. *c*) [**2a**] = 0.2 M.
d) Determined by GCMS against an internal standard.

Other catalysts were investigated in DMSO. DABCO catalyzed formation of **3a** in high yield (Table 1, entry 5).[32] Surprisingly, inorganic bases such as K_2CO_3 and KOH catalyzed formation of **3a** with similar efficiencies at 90 °C (entries 6-7).[34] Although the K_2CO_3-catalyzed reaction still proceeded at lower

temperature, the rate was greatly slowed; only 20% conversion to **3a** was observed at 75 °C (entry 8). Although $KHCO_3$ effectively catalyzed formation of **3a**, KH_2PO_4 did not (entries 9-10). This suggests that sufficient basicity to deprotonate the nucleophile is necessary. The methylation proceeded regardless of the countercation used (entries 11-12).

Potassium carbonate was chosen for further investigation owing to its mild basicity, low cost, and high yield of product formed. The conditions discovered through GCMS screening were readily adaptable to synthetically useful scale. Methyl benzoate was synthesized on a 1 g scale in 93% isolated yield (Table 2, entry 1), although increased catalyst loading (0.4 equiv.) was necessary to maintain reasonable reaction time. Unlike in methylation with diazo reagents, no acidic quench was required;[3] pure **3a** was obtained after simple aqueous workup without need for further purification (see Experimental Section).

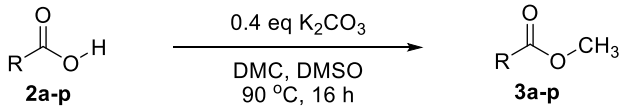
The substrate scope and functional group compatibility of the K_2CO_3-catalyzed methylation were investigated. Electron-rich benzoic acid derivatives were readily esterified (Table 2, entries 2-4). The reaction of 2-anisic acid (**2c**) proceeded in excellent yield even with decreased catalyst loading (entry 3).

In contrast to previous esterification reactions that employ DMC, electron-withdrawing groups were also well-tolerated (Table 2, entries 5-9).[20-27] Given the reported difficulties with electron-poor substrates, the successful esterification of 2-nitrobenzoic acid (**2h**, pKa = 2.2), which is far more acidic than even 4-nitrobenzoic acid (**2g,** pKa = 3.4),[35] is particularly noteworthy (entry 8).

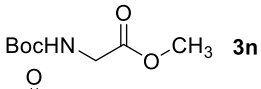
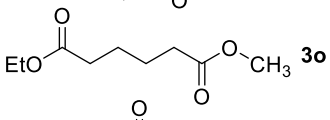
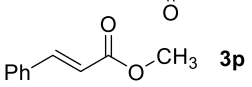
The methylation readily proceeded even with sterically hindered substrates. Ortho-disubstituted ester **3k** was synthesized in high yield (Table 2, entry 11). Furthermore, neopentylic ester **3m** was formed as efficiently as unhindered ester **3l** (entries 12-13).

An array of functional groups were compatible with the reaction conditions, including thioethers, aldehydes, and aryl halides (Table 2, entries 4, 6,10). The successful methylation of acid-sensitive substrate with acetal and Boc-carbamate moieties illustrates the complementarity of this method to acid-mediated Fisher esterification (entries 2, 14).

Table 2. Scope of the Methylation



2a-p **3a-p**

Entry	Product	Isolated Yield
1	X = H **3a**	93%[a]
2	3,4-(-OCH_2O-) **3b**	98%
3	2-OMe **3c**	96%[b]
4	4-SMe **3d**	97%
5	4-CN **3e**	93%
6	4-CHO **3f**	89%
7	4-NO_2 **3g**	86%
8	2-NO_2 **3h**	81%
9	2-CF_3 **3i**	82%
10	2-I **3j**	88%
11	2,3,5,6-$(CH_3)_4$ **3k**	90%
12	Y = H **3l**	89%
13	CH_3 **3m**	91%
14	 **3n**	76%
15	 **3o**	98%
16	 **3p**	96%[c]

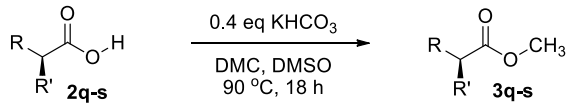
a) 1 g scale. *b*) 0.2 equiv. K_2CO_3 used as catalyst.
c) 0.4 equiv. $KHCO_3$ used as catalyst.

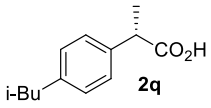
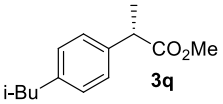
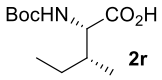
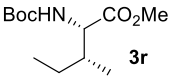
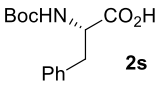
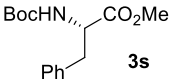
The mild reaction conditions are highlighted by formation of **3o** in 98% yield; no transesterification of the ethyl ester with MeOH was observed (entry 15). To determine whether even less basic conditions promote the reaction on useful synthetic scale, methylation of **2p** was investigated with $KHCO_3$ (entry 16). α,β-Unsaturated ester **3p** was isolated in 96% yield, confirming that bicarbonate can effectively catalyze the esterification.

Although significant racemization has previously been observed in DBU-mediated methylation reactions using DMC,[21] we hypothesized that epimerizable stereocenters might be compatible with our mild, bicarbonate-catalyzed method. R-Ibuprofen (**2q**), which might epimerize via an enolate intermediate, was methylated in 87% yield with high retention of stereochemistry (Table 3, entry 1).

Given the importance of reactions to modify amino acids and peptides without loss of stereochemistry, amino acid substrates were also investigated.[36] Methylated N-Boc-Ile (**3r**) was obtained as a single observable diastereomer, while N-Boc-Phe (**2s**) was methylated with a 7% decrease in enantiomeric ratio (Table 3, entries 2-3). Taken together, the syntheses of enantioenriched **3q**-**3s** suggest that bicarbonate-catalyzed methylation is suitable even for epimerizable substrates.

Table 3. Methylation with Conservation of Stereochemistry.



Entry	Substrate	Product	Yield
1[a]	 **2q** *91 : 9 e.r.*	 **3q** *88 : 12 e.r.*	87%
2[b]	 **2r** *>25 : 1 d.r.*	 **3r** *>25 : 1 d.r.*	83%
3[a]	 **2s** *86 : 14 e.r.*	 **3s** *79 : 21 e.r.*	68%

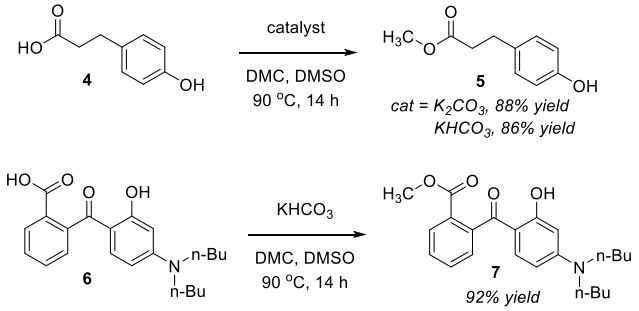
a) Enantiomeric ratio determined by polarimetry.
b) Diastereomeric ratio determined by ^{1}H NMR.

In previous methylations with DMC, chemoselectivity for esterification has been difficult to achieve in substrates bearing both carboxylic acid and phenol functional groups. Although zeolite catalysts displayed promising selectivity,[26] product mixtures are often observed.[24,37-38] Bifunctional substrate **4** was therefore investigated in reactions catalyzed by both potassium carbonate and potassium bicarbonate (Scheme 1). Regardless of the catalyst used, esterification product **5** was obtained in synthetically useful yield. Only trace (< 5%) etherification of the phenol was evident by ^{1}H NMR analysis of the crude reaction mixture, demonstrating high chemoselectivity for esterification.

The promising chemoselectivity observed with **4** suggested that the reaction should be applicable to densely functionalized substrates, such as **6** (Scheme 1). Under the standard reaction conditions with $KHCO_3$, only the carboxylic acid in **6** was methylated; no reaction of the other potentially nucleophilic

moieties was observed. Methyl ester **7**, which has potential application as a component in sunscreens,[39] was isolated in 92% yield, further demonstrating the compatibility of this method with relatively complex, useful small molecules.

Scheme 1. Chemoselective Esterification.



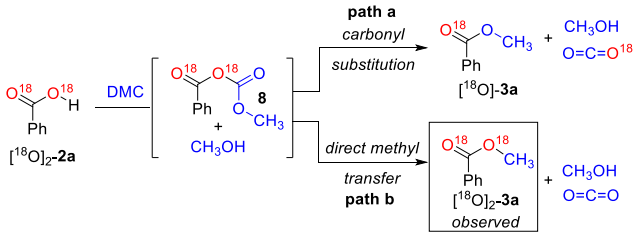
The mechanism of esterification with DMC in the absence of nucleophilic amine catalysts such as DBU and DABCO is unclear.[22-27] Practical similarities between our carbonate-catalyzed reaction and Shieh's DBU-mediated methylation suggest possible mechanistic parallels.[20] Both proceed at 90 °C with comparable reaction times. The DBU reaction is proposed to proceed via a N-carbomethoxy ammonium intermediate formed from DMC and DBU.[20,30] A similarly cationic activated intermediate is unlikely to form under the carbonate conditions.

Based on the proposed mechanism for DBU-mediated methylation,[30] we hypothesize that DMC is activated prior to the methylation step. Since activated covalent adducts of catalysts such as KOH and K_2CO_3 with DMC are unlikely, we propose the formation of carbonic carboxylic anhydride **8** by reaction of the substrate (**2a**) with DMC (Scheme 2).[40] Direct methylation of carboxylic acids with unactivated DMC is also possible, but is less consistent with studies of the DBU-mediated methylation.[30]

There are two likely general mechanisms for ester formation from **8**: carbonyl substitution by MeOH liberated from DMC (Scheme 2, path a) or direct transfer of a methyl group from DMC to the carboxylate oxygen (Scheme 2, path b). Notably, path b encompasses several possibilities, including intramolecular excision of CO_2 from **8** and intermolecular S_N2-type methyl transfer from **8** to a second molecule of **2a**.[40] Given the observed reactivity of **4** and **6**, we initially favored path a, but undertook further investigation.

To differentiate between paths a and b, an isotope-labeling experiment was performed with doubly ^{18}O-labeled benzoic acid ($[^{18}O]_2$-**2a,** Scheme 2)**.** The product mass corresponding to doubly-labeled $[^{18}O]_2$-**3a** was observed by GCMS, indicating that both oxygen atoms originally present in $[^{18}O]_2$-**2a** are retained in the product (see Experimental Section).

Scheme 2. Isotope-Labeling Suggests Methyl Transfer



This result supports path b, a direct methyl transfer from DMC to the substrate, and is inconsistent with path a. An S_N2-type methyl transfer from unactivated DMC (rather than **8**) to deprotonated **2a** is also consistent with formation of $[^{18}O]_2$-**2a**. To the best of our knowledge, this is the first conclusive evidence for direct methyl transfer in esterification with DMC absent a nucleophilic amine catalyst such as DBU. Overall, the labeling study suggests that DMC is behaving like diazomethane and other electrophilic methyl transfer reagents, rather than as a source of MeOH for a Fisher-type esterification.

In conclusion, a general base-catalyzed methylation of carboxylic acids, including those with electron-withdrawing groups, unprotected phenols, and epimerizable stereocenters, has been developed. The mild reaction conditions, formation of only MeOH and CO_2 as reaction byproducts, and use of inexpensive carbonate salts as catalysts suggest that methyl transfer from DMC should be considered as a viable alternative to common methods for the synthesis of methyl esters.

Experimental Section.

General Information. Unless otherwise noted, all reagents were obtained commercially and used without further purification. 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.

GC-MS quantitation of reaction progress was accomplished by end-point analysis using dimethyl pimelate as an internal standard. A J&W DB5-ms GC capillary column (0.25 mm x 30 m, 0.25 μM film thickness) was used. ^{1}H and ^{13}C NMR spectra were referenced to chloroform and recorded at room temperature unless otherwise noted. Optical rotation was determined at 589 nm. Enantiomeric ratios of both carboxylic acid starting materials and methyl ester products were determined by comparing observed optical rotations with previous literature reports (see Supporting Information, Table S-1).

Methyl benzoate (**2a**, *CAS Registry: 93-58-3*). To a 250 mL round-bottom flask equipped with magnetic stir bar, reflux condenser, and nitrogen inlet was added benzoic acid (**2a**) (1.00 g, 8.19 mmol, 1.0 equiv), DMSO (40 mL), and dimethylcarbonate (**1**) (13.8 mL, 160 mmol, 20.0 equiv). To the resulting solution was added potassium carbonate (0.453 g, 3.28 mmol, 0.4 equiv). The reaction mixture was stirred at 90 °C for 16 hours and then cooled to room temperature. Ethyl acetate (50 mL) was added and the mixture was washed with water (2 x 50 mL) and brine (1 x 50 mL). The organic layer was dried with magnesium sulfate, filtered, and concentrated to yield methyl benzoate (**3a**) as a clear liquid (1.043 g, 93% yield). The spectral data were consistent with reported values.[41] ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.06 (m, 2 H), 7.57 (m, 1 H), 7.45 (m, 2 H), 3.94 (s, 3 H).

General procedure for the methylation of carboxylic acids (2b-2s) with DMC. To a 25 mL round bottom flask equipped with magnetic stir bar, reflux condenser, and nitrogen inlet was added the appropriate carboxylic acid (~100 mg, 1 equiv.), DMSO (0.2 M substrate concentration) and DMC (20 equiv.). To the resulting solution was added potassium carbonate (0.4 equiv.) in one portion. The reaction mixture was magnetically stirred and heated to 90 °C for 16 hours. After cooling to room temperature, the reaction was diluted with ethyl acetate (15 mL), washed with water (2 x 10 mL) and brine (1 x 10 mL), and dried with magnesium sulfate. Unless otherwise noted, pure methyl ester was obtained upon removal of solvent.

Methyl piperonylate (**3b,** *CAS Registry: 326-56-7*). Carboxylic acid **2b** (100 mg, 0.60 mmol) was reacted according to the general procedure except that sodium sulfate replaced magnesium sulfate as the drying agent. Methyl ester **3b** was isolated as a white solid (106 mg, 98% yield). The spectral data were consistent with reported values.[42] ^{1}H NMR ($CDCl_3$, 300 MHz) 7.64 (dd, 1 H, *J* = 8.2, 1.7 Hz), 7.47 (d, 1 H, *J* = 1.7 Hz), 6.85 (d, 1 H, *J* = 8.2 Hz), 6.03 (s, 2 H), 3.88 (s, 3 H).

Methyl 2-methoxybenzoate (**3c**, *CAS Registry: 606-45-1*). Carboxylic acid **2c** (100 mg, 0.66 mmol) was reacted according to a modified general procedure. A decreased catalyst loading of potassium carbonate (18 mg, 0.13 mmol, 0.2 equiv) was used. After workup, the crude reaction mixture was further purified by column chromatography (9:1 hexanes:ethyl acetate eluent). Ester **3c** was isolated as a yellow oil (105 mg, 96% yield). The spectral data were consistent with reported values.[43] ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.79 (dd, 1 H, *J* = 1.7, 7.9 Hz), 7.46 (m, 1 H), 6.97 (m, 2 H), 3.89 (s, 3 H), 3.88 (s, 3 H).

Methyl 4-(methylthio)benzoate (**3d**, *CAS Registry: 3795-79-7*). Carboxylic acid **2d** (150 mg, 0.89 mmol) was reacted according to the general procedure. Methyl ester **3d** was isolated as an off-white solid (157 mg, 97% yield). The spectral data were consistent with reported values.[44] ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.95 (d, 2 H, *J* = 8.7 Hz), 7.26 (d, 2 H, *J* = 8.7 Hz), 3.92 (s, 3 H), 2.53 (s, 3 H).

Methyl 4-cyanobenzoate (**3e**, *CAS Registry: 1129-35-7*). Carboxylic acid **2e** (100 mg, 0.68 mmol) was reacted according to the general procedure except that sodium sulfate replaced magnesium sulfate as the drying agent. Methyl ester **3e** was isolated as a white solid (102 mg, 93% yield). The spectral data were consistent with reported values.[43] ^{1}H NMR ($CDCl_3$, 300 MHz) 8.14 (d, 2 H, *J* = 8.2 Hz), 7.77 (d, 2 H, *J* = 8.2 Hz), 3.97 (s, 3 H).

Methyl 4-formylbenzoate (**3f**, *CAS Registry: 1571-08-0*). Carboxylic acid **2f** (101 mg, 0.67 mmol) was reacted according to the general procedure. Methyl ester **3f** was isolated as an off-white solid (98 mg, 89% yield). The spectral data were consistent with reported values.[44] ^{1}H NMR ($CDCl_3$, 500 MHz) δ 10.10 (s, 1 H), 8.19 (d, 2 H, *J* = 8.3 Hz), 7.95 (d, 2 H, *J* = 8.4 Hz), 3.96 (s, 3 H).

Methyl 4-nitrobenzoate (**3g**, *CAS Registry: 619-50-1*). Carboxylic acid **2g** (100 mg, 0.60 mmol) was reacted according to the general procedure. Methyl ester **3g** was isolated as a pale yellow solid (93 mg, 86% yield). The spectral data were consistent with report values.[45] ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.3 (d, 2 H, *J* = 8.9 Hz), 8.2 (d, 2 H, *J* = 9.0 Hz), 4.0 (s, 3 H).

Methyl 2-nitrobenzoate (**3h**, *CAS Registry: 606-27-9*). Carboxylic acid **2h** (134 mg, 0.80 mmol) was reacted according to the general procedure. Methyl ester **3h** was isolated as a white solid (118 mg, 81% yield). The spectral data were consistent with reported values.[43] ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.81 (m, 1 H), 7.8-7.6 (m, 3 H), 3.92 (s, 3 H).

Methyl 2-(trifluoromethyl)benzoate (**3i**, *CAS Registry: 344-96-7*)**.** Carboxylic acid **2i** (100 mg, 0.53 mmol) was reacted according to the general procedure except that sodium sulfate replaced magnesium sulfate as the drying agent. Methyl ester **3i** was isolated as a white solid (88 mg, 82% yield). The spectral data were consistent with reported values.[41] ^{1}H NMR ($CDCl_3$, 300 MHz) 7.81 (m, 2 H), 7.62 (m, 2 H), 3.95 (s, 3 H)

Methyl 2-iodobenzoate (**3j**, *CAS Registry: 610-97-9*)**.** Carboxylic acid **2j** (103 mg, 0.415 mmol) was reacted according to the general procedure. Methyl ester **3j** was isolated as a clear oil (96 mg, 88% yield). The spectral data were consistent with reported values.[43] ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.01 (dd, 1 H, *J* = 8.0, 1.0 Hz), 7.82 (dd, 1 H, *J* = 7.8, 1.7 Hz), 7.41 (dt, 1 H, *J* = 7.7, 1.2), 7.16 (dt, 1 H, *J* = 7.7, 1.7 Hz), 3.94 (s, 3 H).

2,3,5,6-tetramethyl-benzoic acid methyl ester (**3k**, *CAS Registry: 22524-51-2*)**.** Carboxylic acid **2k** (100 mg, 0.56 mmol) was reacted according to the general procedure. After workup, the crude reaction mixture was further purified by column chromatography (50:1 hexanes:ethyl acetate eluent). Methyl ester **3k** was isolated as a white solid (97 mg, 90% yield). The spectral data were consistent with reported values.[46] ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.02 (s, 1 H), 3.96 (s, 3 H), 2.25 (s, 6 H), 2.18 (s, 6 H).

Methyl phenylacetate (**3l**, *CAS Registry: 101-41-7*)**.** Carboxylic acid **2l** (112 mg, 0.82 mmol) was reacted according to the general procedure. Methyl ester **3l** was isolated as a white solid (110 mg, 89% yield). The spectral data were consistent with reported values.[47] ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.5-7.2 (m, 5 H), 3.73 (s, 3 H), 3.67 (s, 2 H).

2-Methyl-2-phenylpropionate methyl ester (**3m**, *CAS Registry: 57625-74-8*)**.** Carboxylic acid **2m** (100 mg, 0.61 mmol) was reacted according to the general procedure. Methyl ester **3m** was isolated as a white solid (99 mg, 91% yield). The spectral data were consistent with reported values.[48] ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.5-7.2 (m, 5 H), 3.69 (s, 3 H), 1.64 (s, 6 H).

N-(tert-Butoxycarbonyl)glycine methyl ester (**3n**, *CAS Registry: 31954-27-5*)**.** Carboxylic acid **2n** (100 mg, 0.57 mmol) was reacted according to the general procedure. Methyl ester **3n** was isolated as a clear, colorless oil (82 mg, 76% yield). The spectral data were consistent with reported values.[45] ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.3 (bs, 1 H), 3.9 (d, 2 H, *J* = 5.6 Hz), 3.74 (s, 3 H), 1.45 (s, 9 H).

Ethyl methyl adipate (**3o**, *CAS Registry: 18891-13-9*)**.** Carboxylic acid **2o** (98 mg, 0.56 mmol) was reacted according to the general procedure. After workup, the crude reaction mixture was further purified by column chromatography (19:1 hexanes:ethyl acetate eluent). Methyl ester **3o** was isolated as a clear oil (103 mg, 98% yield). The spectral data were consistent with reported values.[49] ^{1}H NMR ($CDCl_3$, 300 MHz) δ 4.08 (2 H, q, *J* = 7.2 Hz), 3.62 (s, 3 H), 2.28 (m, 4 H), 1.62 (m, 4 H), 1.21 (t, 3 H, *J* = 7.2 Hz).

Methyl cinnamate (**3p**, *CAS Registry: 103-26-4*)**.** Carboxylic acid **2p** (100 mg, 0.68 mmol) was reacted according to a modified general procedure. Potassium bicarbonate (27 mg, 0.27 mmol, 0.4 equiv.) replaced potassium carbonate as the catalyst. Methyl ester **3p** was isolated as a white solid (105 mg, 96% yield). The spectral data were consistent with reported values.[45] ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.7 (d, 1 H, *J* = 16.0 Hz), 7.5 (m, 2 H), 7.4 (m, 3 H), 6.5 (d, 1 H, *J* = 16.0 Hz), 3.8 (s, 3 H).

(S)-ibuprofen methyl ester (**3q**, *CAS Registry: 81576-55-8*)**.** Carboxylic acid **2q** (100 mg, 0.49 mmol, 91:9 e.r.) was reacted according to a modified general procedure. Potassium bicarbonate (19 mg, 0.19 mmol, 0.4 equiv.) replaced potassium carbonate as the catalyst. After workup, the crude reaction mixture was further purified by column chromatography (50:1 hexanes: ethyl acetate eluent). Methyl ester **3q** was isolated as a white solid (93 mg, 87% yield, 88:12 e.r.). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.2 (d, 2 H, *J* = 8.0 Hz), 7.1 (d, 2 H, *J* = 8.0 Hz), 3.8 (q, 1 H, *J* = 7.2 Hz), 3.7 (s, 3 H), 2.5 (d, 2 H, *J* = 7.3 Hz), 1.9 (nonet, 1 H, *J* = 6.8 Hz), 1.5 (d, 3 H, *J* = 7.2 Hz), 0.9 (d, 6 H, *J* = 6.6 Hz). Optical rotation (see Table S-1): $[\alpha]^{D}_{25}$ = +49.4 (*c* 1.00, $CHCl_3$).

N-(tert-butyloxycarbonyl)-L-isoleucine methyl ester (**3r**, *CAS Registry: 17901-01-8*)**.** Carboxylic acid **2r** (125 mg, 0.54 mmol, >25 : 1 d.r.) was reacted according to a modified general procedure. Potassium bicarbonate (22 mg, 0.22 mmol, 0.4 equiv.) replaced potassium carbonate as the catalyst. Methyl ester **3r** was isolated as a clear, colorless oil (110 mg, 83% yield, >25 : 1 d.r.). The spectral data indicated the presence of a single diastereomer and were consistent with reported values.[50] NMR data was acquired at elevated temperature so that peaks arising from hindered rotation around the amide bond coalesced. ^{1}H

NMR ($CDCl_3$, 300 MHz, 47 °C) δ 5.0 (bs, 1 H), 4.2 (bs, 1 H), 3.7 (s, 3 H), 1.8 (bs, 1 H), 1.5-1.3 (m, 10 H), 1.2-1.0 (m, 1 H), 0.9-0.8 (m, 6 H).

N-(tert-butyloxycarbonyl)-L-phenylalanine methyl ester (**3s**, *CAS Registry: 51987-73-6*)**.** Carboxylic acid **2s** (100 mg, 0.377 mmol, 86:14 e.r) was reacted according to a modified general procedure. Potassium bicarbonate (15 mg, 0.15 mmol, 0.4 equiv.) replaced potassium carbonate as the catalyst. After workup, the crude reaction mixture was further purified by column chromatography (19:1 hexanes: ethyl acetate eluent). Methyl ester **3s** was isolated as a white solid (72 mg, 68% yield, 79:21 e.r.). NMR data was acquired at elevated temperature so that peaks arising from hindered rotation around the amide bond coalesced. ^{1}H NMR ($CDCl_3$, 300 MHz, 52 °C) δ 7.2-7.3 (m, 3 H), 7.1 (m, 2 H), 5.0 (bs, 1 H), 4.6 (bs, 1 H), 3.7 (s, 3 H), 3.1 (m, 2 H), 1.4 (s, 9 H). Optical rotation (see Table S-1): $[\alpha]^{D}_{25}$ = +35.0 (*c* 1.00, $CHCl_3$).

Methyl 3-(4-hydroxyphenyl)propionate (**5**, *CAS Registry:5597-50-2).* Carboxylic acid **4** (100 mg, 0.6 mmol) was reacted according to the general procedure using either potassium carbonate (33 mg, 0.24 mmol, 0.4 equiv.) or potassium bicarbonate (24 mg, 0.15 mmol, 0.4 equiv.) as the catalyst. After 14 hours, the reactions were subjected to the standard workup. The crude reaction mixtures were further purified by column chromatography (9:1 hexanes:ethyl acetate eluent). In the potassium carbonate-catalyzed case, **5** was isolated as a clear oil (95 mg, 88% yield). In the potassium bicarbonate-catalyzed case, **5** was isolated as a clear oil (94 mg, 86% yield). Spectral data were consistent with reported values.[51] ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.05 (d, 2 H, *J* = 8.4 Hz), 6.79 (d, 2 H, *J* = 8.4 Hz), 6.68 (bs, 1 H), 3.70 (s, 3 H), 2.90 (t, 2 H, *J* = 7.5 Hz), 2.64 (t, 2 H, *J* = 7.5 Hz).

Methyl 2-(4-dibutylamino-2-hydroxybenzoyl)benzoate (**7**, *CAS Registry: 302776-69-8*)**.** Carboxylic acid **6** (100 mg, 0.27 mmol) was reacted according to a modified general procedure. Potassium bicarbonate (11 mg, 0.11 mmol, 0.4 equiv.) replaced potassium carbonate as the catalyst. After workup, the crude reaction mixture was further purified by column chromatography (19:1 hexanes:ethyl acetate eluent). Methyl ester **7** was isolated as a yellow oil (95 mg, 92% yield). Spectral data has not previously been reported for **7**. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 12.63 (s, 1 H), 8.05 (dd, 1 H, *J* = 7.2, 1.2 Hz), 7.60 (td, 1 H, *J* = 7.2, 1.2 Hz), 7.52 (td, 1 H, *J* = 7.5, 1.5 Hz), 7.37 (dd, 1 H, *J* = 7.2, 1.2 Hz), 6.89 (d, 1 H, *J* = 9.0 Hz), 6.14 (d, 1 H, *J* = 2.4 Hz), 6.04 (dd, 1 H, *J* = 9.0, 2.4 Hz), 3.75 (s, 3 H,), 3.30 (t, 4 H, *J* = 7.5 Hz), 1.59

(m, 4 H), 1.34 (m, 4 H), 0.96 (t, 6 H, *J* = 7.5 Hz). ^{13}C NMR (75 MHz) δ 198.5, 166.5, 165.3, 154.3, 140.8, 134.4, 132.1, 130.2, 129.1, 128.8, 127.9, 109.9, 103.9, 97.3, 52.3, 50.9, 29.4, 20.2, 13.9. HRMS (EI) m/z calcd for $C_{23}H_{29}NO_4$ 383.2097, found 383.2088.

Procedure and GCMS data for the Isotope-Labeling Experiment. $[^{18}O]_2$-**2a** was prepared from benzotrichloride and ^{18}O-water (97%, Cambridge Isotope) according to published procedure.[52] The ^{1}H NMR spectral data were consistent with the values observed for **2a**. GC-MS *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]-**2a** was also identified: 124.1 (3.6%, M). The molecular ion peak corresponding to unlabeled **2a** was also identified: 122.1 (1.3%, M). The percentage of ^{18}O in synthetic $[^{18}O]_2$-**2a** was therefore calculated to be 96.5%.

$[^{18}O]_2$-**2a** was reacted with DMC according to the general methylation procedure. Aliquots were taken from the reaction at T = 6 h and 24 h and analyzed by GCMS.

T = 6 h aliquot. $[^{18}O]_2$-**3a** identified by GC-MS *m/z* (% relative intensity, ion): 140.2 (32%, M), 107.2 (100%, M - (^{18}OCH$_3$)), 77.1 (78%, M - (C[^{18}O]$_2$CH$_3$)). The molecular ion peak corresponding to [^{18}O]-**3a** was also identified: 138.2 (1.3%, M). The molecular ion peak corresponding to unlabeled **3a** was also identified: 136.2 (0.1%, M). The calculated percentages of product formed are 95.8% $[^{18}O]_2$-**3a**, 3.9% [^{18}O]-**3a**, and 0.3% **3a**.

T = 24 h aliquot. $[^{18}O]_2$-**3a** identified by GC-MS *m/z* (% relative intensity, ion): 140.2 (31%, M), 107.2 (100%, M - (^{18}OCH$_3$)), 77.1 (77%, M - (C[^{18}O]$_2$CH$_3$)). The molecular ion peak corresponding to [^{18}O]-**3a** was also identified: 138.2 (3.1%, M). The molecular ion peak corresponding to unlabeled **3a** was also identified: 136.2 (0.2%, M). The calculated percentages of product formed are 90.4% $[^{18}O]_2$-**3a**, 9.0% [^{18}O]-**3a**, and 0.6% **3a**.

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Supporting Information Available Optical rotation data and comparison with literature data for **2q**, **2s**, **3q,** and **3s**. Copies of ^{1}H NMR spectra for **2a**-**2s** and **5**. Copies of ^{1}H and ^{13}C NMR spectra for **7**. This material is available free of charge via the Internet at http://pubs.acs.org.

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