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Copper-Catalyzed O-Methylation of Carboxylic Acids Using DMSO as a Methyl Source

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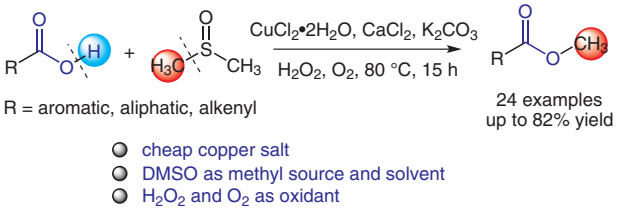

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Abstract A copper-catalyzed O-methylation of carboxylic acids using dimethyl sulfoxide (DMSO) as the methyl source is disclosed. This transformation exhibits a broad substrate scope and excellent functional group tolerance. Mechanistic studies indicate that a methyl radical is generated from dimethyl sulfoxide in the reaction process.

Key words carboxylic acids, O-methylation, dimethyl sulfoxide, hydrogen peroxide, methyl radical, esterification, esters

O-Methylation of carboxylic acids is a very common step in natural products synthesis.[1] Classical methods often involve electrophilic reagents such as diazomethane, (trimethylsilyl)diazomethane, dimethyl sulfate, and methyl iodide,[2] which are generally hazardous and/or unstable. Recently, the groups of Mao[3] and Chen[4] independently reported copper-catalyzed O-methylation reactions with organic peroxides as the methyl source. The groups of Selva, Aricò, and Gorin have reported that methyl could transfer from dimethyl carbonate to carboxylic acids.[5] Other O-methylation reactions with (diacetoxyiodo)benzene or methylboronic acid have been reported.[6] Despite the great progress being made in this field, safe and effective methyl sources are still highly desirable.

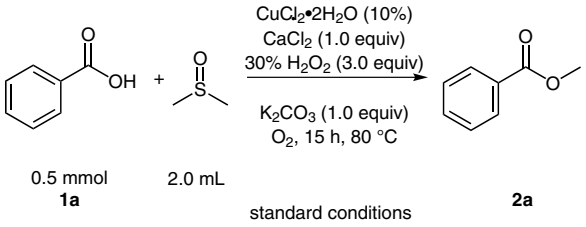
Dimethyl sulfoxide is widely used as a solvent in organic synthesis due to its low toxicity, low cost, great dissolving capacity, and relative stability. Moreover, it is also a versatile reactant and it has shown its importance in contemporary organic chemistry. For example, dimethyl sulfoxide is used as oxidant in the well-known Swern oxidation and Kornblum reaction. Recently, the Jiao group reported an efficient α-hydroxylation of ketones and the transformation of alkyl bromides or alkenes to bromohydrins using dimethyl sulfoxide as an oxidant and oxygen source.[7] Cheng and co-workers developed a method for the palladium-catalyzed cyanation of indole with dimethyl sulfoxide and ammonium hydrogencarbonate.[8] Many groups, such as the Suzuki,[9] Cheng,[10] Cao,[11] and Zhang groups,[12] have successfully introduced the formyl group into various substrates using dimethyl sulfoxide as a formyl source. In recent years, dimethyl sulfoxide has attracted increasing attention as a methylthiolation[13] and methyl sulfone source.[14] Although the use of dimethyl sulfoxide as a carbon source has been well studied, to the best of our knowledge the use of dimethyl sulfoxide as a methyl source has been less fruitful. There are only a few reports on the use of dimethyl sulfoxide as a methyl source, for example Bansal et al.[15] developed an efficient methylation reaction of 1,4-quinones, Li and co-workers[16] reported a palladium-catalyzed alkylation of isoquinoline *N*-oxides, and Xiao and co-workers[17] disclosed a method for the N-methylation of amines and nitro compounds with dimethyl sulfoxide. Herein, we report a copper-catalyzed O-methylation of carboxylic acids using dimethyl sulfoxide as the methyl source.

We envisioned that dimethyl sulfoxide could act as methyl donor with the help of a copper salt and hydrogen peroxide, and the O-methylation reaction of carboxylic acids could be realized under basic conditions. Initially, benzoic acid and dimethyl sulfoxide were chosen as the model substrates to optimize the reaction conditions. After extensively screening the reaction parameters (Table 1), benzoic acid (**1a**) gave the O-methylation product methyl benzoate (**2a**) in good yield using: benzoic acid (0.5 mmol, 1.0 equiv), $CuCl_2{\cdot}2\,H_2O$ (10%), $CaCl_2$ (1.0 equiv), 30% H_2O_2 (3.0 equiv), K_2CO_3 (1.0 equiv), DMSO (2.0 mL), 80 °C, 15 h under an O_2 atmosphere in a sealed tube (entry 1); these conditions are referred to as the 'standard conditions'. Other reaction factors were investigated and the results are listed in entries 2–23. Using the standard conditions but replacing the oxidant hydrogen peroxide with di-*tert*-butyl

peroxide (DTBP) or 3-chloroperoxybenzoic acid gave a trace amount of product **2a** only (entries 2 and 3). Performing the reaction under standard conditions but without the use of hydrogen peroxide did not give **2a** (entry 4), suggesting that hydrogen peroxide is vital in this transformation. Using the standard conditions but replacing calcium chloride by 10% 1,10-phenanthroline or 2,2′-bipyridine gave **2a** in very low yield (entries 5 and 6), and a similar result was obtained without the use of calcium chloride (entry 7). Using the standard conditions but varying the catalyst showed that iron(II) chloride tetrahydrate was not as effective as copper(II) chloride dihydrate in this system (entry 8) and using manganese(II) chloride tetrahydrate, nickel(II) chloride tetrahydrate, or cobalt(II) chloride hexahydrate as the catalyst gave almost no product **2a** (by GC, entries 9–11). In addition, no product was obtained in the absence of copper(II) chloride dihydrate (entry 12). Raising or lowering the temperature under the standard conditions gave lower yields of **2a** (entries 13 and 14). Using the standard conditions but varying the base suggested that it plays a very important role in this transformation as a very low yield or only trace amounts of **2a** were obtained using different bases or no base (entries 15–18). An oxygen atmosphere was not vital to this reaction, and changing from the use of an oxygen atmosphere to the use of an oxygen balloon or leaving the flask open to air had little influence on the reaction efficiency, but using a low oxygen concentration under nitrogen resulted in a low yield of **2a** (entry 1 vs. entries 19 and 20). The solvent in the standard conditions could not be changed and the use of acetonitrile–dimethyl sulfoxide gave only trace amounts of **2a** (entry 21). Under the standard conditions, replacing potassium carbonate/calcium chloride with potassium chloride/calcium carbonate gave **2a** in only 32% yield (entry 22). Finally, under the standard conditions, increasing the time from 15 hours to 24 hours did not improve the yield (entry 23).

With the optimized conditions in hand, we explored the scope of this copper-catalyzed O-methylation reaction of carboxylic acids with dimethyl sulfoxide. The results are summarized in Scheme 1. A variety of carboxylic acids were tolerated well in this system and this transformation afforded the corresponding products **2a**–**x** with moderate to good yields (14–82%). Benzoic acid substrates with electron-donating groups were well tolerated under the standard conditions and gave products **2b**–**e** in 76–82% yields, while those bearing electron-withdrawing groups gave **2f**,**g** in lower 64–67% yields. Unfortunately, when terephthalic acid was used as the substrate, dimethyl terephthalate (**2h**) was isolated in only 14% yield. Steric hindrance did not affect the reaction efficiency, 2,4,6-trimethylbenzoic acid (**1i**) reacted smoothly to afford **2i** in 65% yield. It is noteworthy that halo-substituted benzoic acids gave halo-substituted products **2j**–**l** in 61–72% yields, which could be used for further transformations. Interestingly, when 4-hydroxybenzoic acid (**1m**) was used as the substrate, only trace amounts of **2b** were observed by GC-MS, and methyl 4-hydroxybenzoate (**2m**) was obtained in 63% yield together with recovered **1m** (32%). Benzoic acids bearing CN and CHO groups were also tolerated in this transformation, generating **2n** and **2o** in 70% and 69% yields, respectively. The reaction of 2-aminobenzoic acid (**1p**) under the standard conditions gave methyl 2-aminobenzoate (**2p**) (43%) together with methyl 2-(methylamino)benzoate (**2p′**) (14%) and trace amounts of methyl 2-(dimethylamino)benzoate (by GC-MS). Increasing the reaction time had no influence on the ratio of **2p′**/**2p**, while increasing or decreasing the amount

Table 1 Screening the Reaction Conditions[a]



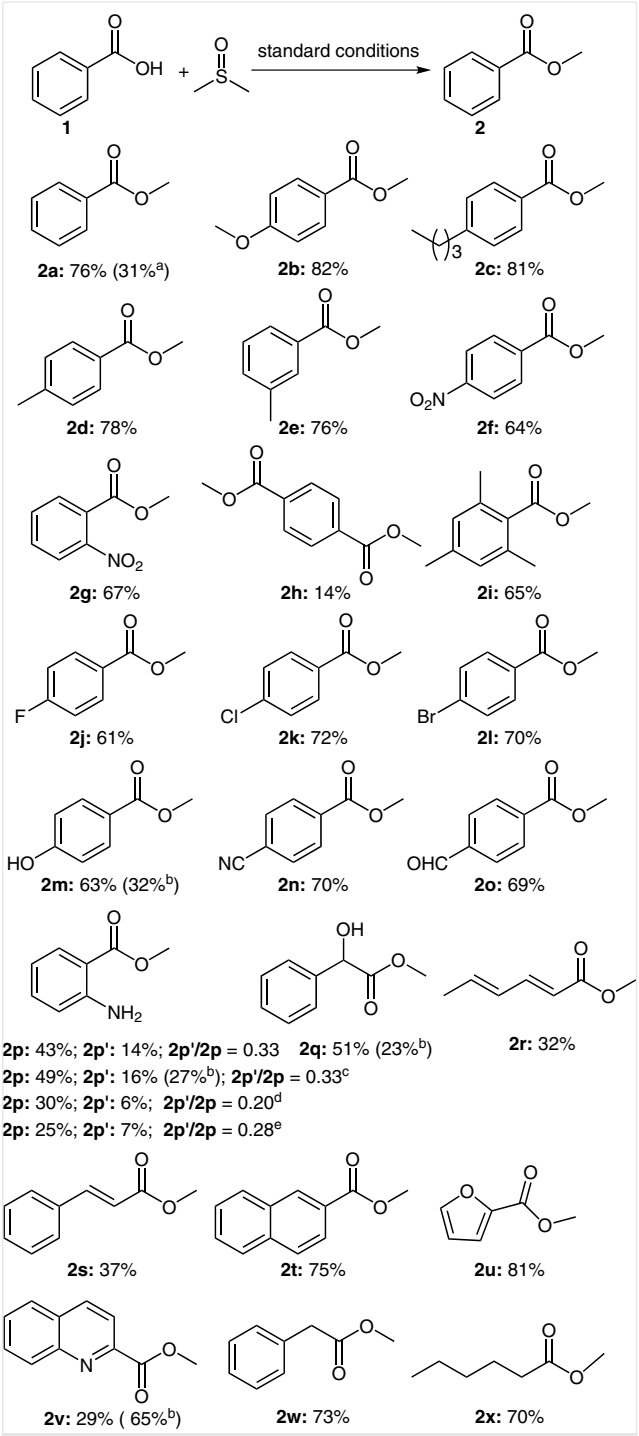
Entry	Variation from the standard conditions[a]	Yield[b] (%)
1	none (or with an O_2 balloon)	83 (80)
2	replace 30% H_2O_2 with DTBP	trace
3	replace 30% H_2O_2 with MCPBA	trace
4	without 30% H_2O_2	0
5	replace $CaCl_2$ with 10% 1,10-phenanthroline	8
6	replace $CaCl_2$ with 10% 2,2′-bipyridine	14
7	without $CaCl_2$	6
8	replace $CuCl_2{\cdot}2H_2O$ with $FeCl_2{\cdot}4H_2O$	35
9	replace $CuCl_2{\cdot}2H_2O$ with $MnCl_2{\cdot}4H_2O$	0
10	replace $CuCl_2{\cdot}2H_2O$ with $NiCl_2{\cdot}4H_2O$	0
11	replace $CuCl_2{\cdot}2H_2O$ with $CoCl_2{\cdot}6H_2O$	trace
12	without $CuCl_2{\cdot}2H_2O$	0
13	change 80 °C to 70 °C	71
14	change 80 °C to 90 °C	79
15	replace K_2CO_2 with Na_2CO_3	27
16	replace K_2CO_2 with $KHCO_3$	12
17	replace K_2CO_2 with KOH	trace
18	without base	trace
19	replace O_2 with air (or open to air)	71 (70)
20	replace O_2 with N_2	39
21	replace DMSO with MeCN (2.0 mL)–DMSO (4.0 equiv)	trace
22	replace $CaCl_2$–K_2CO_3 with KCl (2.0 equiv), $CaCO_3$ (1.0 equiv)	32
23	24 h instead of 15 h	82

[a] All reactions took place under the standard conditions with the variation of catalyst, reagent, solvent, temperature, and time noted.
[b] Determined by GC using 1,4-dichlorobenzene as internal standard.

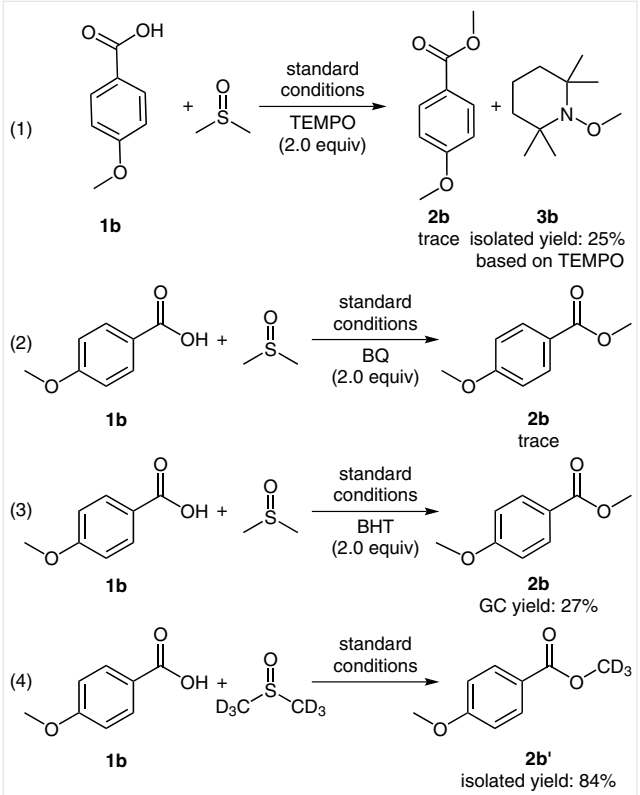
of hydrogen peroxide affected the yields and the ratio of **2p′**/**2p**. In addition, when 2-hydroxy-2-phenylacetic acid (**1q**) was reacted under the standard conditions, the sole methylation product was methyl 2-hydroxy-2-phenylacetate (**2q**) together with some other byproducts, such as **2a** (GC yield: 8%), methyl 2-oxo-2-phenylacetate (GC yield: <5%), and benzaldehyde (GC yield: 13%).

Furthermore, vinyl carboxylic acids also gave the desired products **2r**,**s** in low 32–37% yields. Other aromatic carboxylic acids also readily underwent the reaction to generate the expected products **2t**–**u**. Although quinoline-2-carboxylic acid (**1v**) did not work well in this transformation, no other methylation products other than **2v** were observed. Aliphatic acids such as 2-phenylacetic acid (**1w**) and hexanoic acid (**1x**) were also ideal substrates giving **2w**,**x** in 70% and 73% yield, respectively. Changing dimethyl sulfoxide to tetrahydrothiophene 1-oxide, dibutyl sulfoxide, or diphenyl sulfoxide disappointingly gave almost no desired product under the standard conditions, and only trace amounts of **2a** were detected by GC-MS when methyl phenyl sulfoxide and **1a** were utilized.

To get a good understanding of the reaction mechanism, control experiments were conducted and the results are displayed in Scheme 2. When the radical inhibitor 2,2,6,6-tetramethylpiperidin-1-oxy (TEMPO) was added under the standard conditions, the reaction was completely inhibited [Scheme 2 (1)]. Using GC-MS to analyze the reaction mixture, showed that the major product was 1-methoxy-2,2,6,6-tetramethylpiperidine (**3b**), and it was isolated in



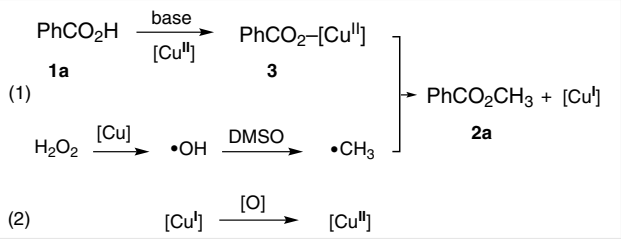
Scheme 1 Scope of the carboxylic acid substrate in O-methylation with dimethyl sulfoxide; the yields are isolated yields. [a] Using benzaldehyde instead of benzoic acid, GC yield. [b] Unreacted substrate. [c] Reaction time 24 h. [d] Using H_2O_2 (2.0 equiv). [e] Using H_2O_2 (4.0 equiv).



Scheme 2 Control experiments

25% yield based on TEMPO. Other radical inhibitors, such as benzoquinone (BQ) and 2,6-di-*tert*-butyl-4-methylphenol (BHT), had a similar effect on the reaction [Scheme 2 (2) and (3)]. In addition, an isotope-labeling experiment was conducted and the result confirmed that the methyl was from dimethyl sulfoxide [Scheme 2 (4)]. These results indicate that the reaction may take place by a radical pathway with dimethyl sulfoxide as the methyl donor.

Although the precise mechanism of the methyl transfer remains unknown. On the basis of these results and literature reports, a plausible mechanism for the copper-catalyzed O-methylation of carboxylic acids is proposed in Scheme 3. Firstly, the benzoic acid forms intermediate **3** by reacting with base and the copper salt, and the dimethyl sulfoxide is decomposed to form a methyl radical by the hydroxyl radical,[18] which is generated from hydrogen peroxide in the presence of a copper ion.[19] Then the methyl radical reacts with the intermediate **3** to obtain the desired product **2a**.[3,4,20]



Scheme 3 Proposed mechanism

In conclusion, we have demonstrated a novel, simple, and environmentally friendly copper-catalyzed O-methylation of carboxylic acids with dimethyl sulfoxide. This practical method offers a strategy for replacing toxic, electrophilic alkylation reagents. In this protocol, dimethyl sulfoxide not only serves as the solvent, but it is also a convenient methyl donor, and hydrogen peroxide is used as the oxidant which produces no toxic byproduct only water. In addition, a wide range of substrates, including some substrates bearing oxidant-sensitive groups, are well tolerated. Furthermore, this transformation is not sensitive to moisture and oxygen.

All reagents were commercially available and used without further purification. ^{1}H NMR spectra were recorded at 400 MHz and ^{13}C NMR at 100 MHz in $CDCl_3$ using TMS as the internal standard. The yield of methyl benzoate was measured by GC using 1,4-dichlorobenzene as internal standard when optimizing the reaction conditions. MS were recorded using EI. Column chromatography was performed on silica gel (200–300 mesh). Petroleum ether = PE.

Methyl Esters; General Procedure

Carboxylic acid (0.5 mmol, 1.0 equiv), K_2CO_3 (0.5 mmol, 1.0 equiv), and $CaCl_2$ powder (0.5 mmol, 1.0 equiv) were added to a 25-mL tube. 10% $CuCl_2$·2 H_2O in DMSO (2.0 mL) was added, followed by the dropwise addition of 30% aq H_2O_2 (1.5 mmol, 3.0 equiv). The tube was sealed with a Teflon-lined cap and the mixture was stirred at 80 °C under O_2 for 15 h. The mixture cooled and water (10 mL) was added; the mixture was extracted with EtOAc (3 × 10 mL). After evaporation of the solvent, the residue was purified by column chromatography (silica gel) to obtain the product.

Methyl Benzoate (2a)[21]

[CAS Reg. No. 93-58-3]

Purified by flash chromatography (PE–EtOAc, 10:1); colorless oil; yield: 51.7 mg (76%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.04 (d, *J* = 7.9 Hz, 2 H), 7.53 (t, *J* = 7.4 Hz, 1 H), 7.42 (t, *J* = 7.6 Hz, 2 H), 3.90 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.1, 132.9, 130.1, 129.6, 128.3, 52.1.

LRMS (EI, 70 eV): *m*/*z* (%) = 137 (M^+ + 1, 3), 136 (M^+, 33), 105 (100), 77 (71).

Methyl 4-Methoxybenzoate (2b)[21]

[CAS Reg. No. 121-98-2]

Purified by flash chromatography (PE–EtOAc, 10:1); colorless solid; yield: 68.1 mg (82%); mp 48–50 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.99 (d, *J* = 8.9 Hz, 2 H), 6.91 (d, *J* = 8.8 Hz, 2 H), 3.88 (s, 3 H), 3.84 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 166.8, 163.3, 131.6, 122.6, 113.6, 55.4, 51.8.

LRMS (EI, 70 eV): *m*/*z* (%) = 167 (M^+ + 1, 2), 166 (M^+, 25), 135 (100), 107 (15).

Methyl-d_3 4-Methoxybenzoate (2b′)[22]

[CAS Reg. No. 79825-71-1]

Purified by flash chromatography (PE–EtOAc, 10:1); colorless solid; yield: 71 mg (84%); mp 49–52 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.91 (d, *J* = 8.8 Hz, 2 H), 6.83 (d, *J* = 8.8 Hz, 2 H), 3.77 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.8, 162.3, 130.5, 121.5, 112.5, 54.4, 50.8 (m, CD_3).

LRMS (EI, 70 eV): *m*/*z* (%) = 170 (M^+ + 1, 3), 169 (M^+, 29), 135 (100), 107 (14).

Methyl 4-Butylbenzoate (2c)[21]

[CAS Reg. No. 20651-69-8]

Purified by flash chromatography (PE–EtOAc, 10:1); colorless oil; yield: 77.8 mg (81%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.94 (d, *J* = 8.1 Hz, 2 H), 7.23 (d, *J* = 8.0 Hz, 2 H), 3.89 (s, 3 H), 2.65 (t, *J* = 7.7 Hz, 2 H), 1.65–1.56 (m, 2 H), 1.40–1.30 (m, 2 H), 0.92 (t, *J* = 7.3 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.2, 148.5, 129.6, 128.4, 127.7, 51.9, 35.7, 33.3, 22.3, 13.9.

LRMS (EI, 70 eV): *m*/*z* (%) = 193 (M^+ + 1, 6), 192 (M^+, 45), 161 (58), 91 (100).

Methyl 4-Methylbenzoate (2d)[21]

[CAS Reg. No. 99-75-2]

Purified by flash chromatography (PE–EtOAc, 10:1); colorless oil; yield: 58.5 mg (78%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.93 (d, *J* = 8.1 Hz, 2 H), 7.23 (d, *J* = 8.0 Hz, 2 H), 3.89 (s, 3 H), 2.40 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.2, 143.5, 129.6, 129.1, 127.4, 51.9, 21.6.

LRMS (EI, 70 eV): *m*/*z* (%) = 151 (M^+ + 1, 3), 150 (M^+, 28), 119 (100), 91 (53).

Methyl 3-Methylbenzoate (2e)[21]

[CAS Reg. No. 99-36-5]

Purified by flash chromatography (PE–EtOAc, 10:1); colorless oil; yield: 57.0 mg (76%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.92–7.78 (m, 2 H), 7.37–7.29 (m, 2 H), 3.90 (s, 3 H), 2.39 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.3, 138.1, 133.7, 130.1, 130.1, 128.2, 126.7, 52.0, 21.2.

LRMS (EI, 70 eV): *m*/*z* (%) = 151 (M^+ + 1, 3), 150 (M^+, 28), 119 (100), 91 (69).

Methyl 4-Nitrobenzoate (2f)[3]

[CAS Reg. No. 619-50-1]

Purified by flash chromatography (PE–EtOAc, 10:1); colorless solid; 57.9 mg (64%); mp 94–96 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.30 (d, *J* = 8.9 Hz, 2 H), 8.22 (d, *J* = 8.9 Hz, 2 H), 3.99 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.2, 150.5, 135.5, 130.7, 123.6, 52.9.

LRMS (EI, 70 eV): *m*/*z* (%) = 182 (M^+ + 1, 2), 181 (M^+, 23), 164 (23), 150 (100).

Methyl 2-Nitrobenzoate (2g)[3]

[CAS Reg. No. 606-27-9]

Purified by flash chromatography (PE–EtOAc, 4:1); colorless oil; yield: 60.6 mg (67%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.91 (d, *J* = 7.9 Hz, 1 H), 7.74 (d, *J* = 7.4 Hz, 1 H), 7.72–7.60 (m, 2 H), 3.92 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.8, 148.2, 132.9, 131.8, 129.8, 127.5, 123.9, 53.2.

LRMS (EI, 70 eV) m/z (%):182 (M^+ + 1, 2), 181 (M^+, 12), 150 (100), 92 (18), 77 (27).

Dimethyl Terephthalate (2h)[21]

[CAS Reg. No. 120-61-6]

Purified by flash chromatography (PE–EtOAc, 10:1); colorless solid; yield: 13.6 mg (14%); mp 138–140 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.10 (s, 4 H), 3.95 (s, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 166.3, 133.9, 129.5, 52.4.

LRMS (EI, 70 eV): *m*/*z* (%) = 195 (M^+ + 1, 3), 194 (M^+, 23), 163 (100), 135 (31).

Methyl 2,4,6-Trimethylbenzoate (2i)[23]

[CAS Reg. No. 2282-84-0]

Purified by flash chromatography (PE–EtOAc, 10:1); colorless oil; yield: 57.9 mg (65%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.85 (s, 2 H), 3.89 (s, 3 H), 2.28–2.27 (d, 9 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.6, 139.3, 135.2, 130.9, 128.4, 51.8, 21.1, 19.8.

LRMS (EI, 70 eV): *m*/*z* (%) = 179 (M^+ + 1, 7), 178 (M^+, 53), 147 (100), 119 (64).

Methyl 4-Fluorobenzoate (2j)[21]

[CAS Reg. No. 403-33-8]

Purified by flash chromatography (PE–EtOAc, 10:1); colorless oil; yield: 47.0 mg (61%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.11–8.00 (m, 2 H), 7.11 (t, *J* = 8.6 Hz, 2 H), 3.91 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.0 (d, J_{C-F} = 252.1 Hz), 166.1, 132.1 (d, J_{C-F} = 9.2 Hz), 126.4 (d, J_{C-F} = 2.9 Hz), 115.6 (d, J_{C-F} = 21.8 Hz), 52.17.

^{19}F NMR (376 MHz, $CDCl_3$): δ = –105.8.

LRMS (EI, 70 eV): *m*/*z* (%) = 155 (M^+ + 1, 3), 154 (M^+, 25), 123 (100), 95 (44).

Methyl 4-Chlorobenzoate (2k)[21]

[CAS Reg. No. 1126-46-1]

Purified by flash chromatography (PE–EtOAc, 10:1); colorless oil; yield: 61.2 mg (72%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.98 (d, *J* = 8.3 Hz, 2 H), 7.42 (d, *J* = 8.3 Hz, 2 H), 3.92 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 166.2, 139.4, 131.0, 128.7, 128.6, 52.3.

LRMS (EI, 70 eV): *m*/*z* (%) = 172 (M^+ + 2, 7), 170 (M^+, 23), 139 (100), 111 (44).

Methyl 4-Bromobenzoate (2l)[21]

[CAS Reg. No. 619-42-1]

Purified by flash chromatography (PE–EtOAc, 10:1); colorless solid; yield: 74.9 mg (70%); mp 78–80 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.89 (d, *J* = 8.5 Hz, 2 H), 7.57 (d, *J* = 8.5 Hz, 2 H), 3.91 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 166.3, 131.7, 131.1, 129.0, 128.0, 52.3.

LRMS (EI, 70 eV): *m*/*z* (%) = 216 (M^+ + 2, 41), 214 (M^+, 42), 185 (96), 183 (100).

Methyl 4-Hydroxybenzoate (2m)[24]

[CAS Reg. No. 99-76-3]

Purified by flash chromatography (PE–EtOAc, 4:1); colorless solid; yield: 47.9 mg (63%); mp 127–130 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.95 (d, *J* = 8.7 Hz, 2 H), 6.90 (d, *J* = 8.7 Hz, 2 H), 6.74 (s, 1 H), 3.90 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.6, 160.4, 132.0, 122.1, 115.3, 52.2.

LRMS (EI, 70 eV): *m*/*z* (%) = 153 (M^+ + 1, 3), 152 (M^+, 30), 121 (100), 93 (25).

Methyl 4-Cyanobenzoate (2n)[6b]

[CAS Reg. No. 1129-35-7]

Purified by flash chromatography (PE–EtOAc, 10:1); colorless solid; yield: 56.4 mg (70%); mp 63–65 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.15 (d, *J* = 8.3 Hz, 2 H), 7.76 (d, *J* = 8.3 Hz, 2 H), 3.97 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.4, 133.9, 132.2, 130.1, 118.0, 116.4, 52.8.

LRMS (EI, 70 eV): *m*/*z* (%) = 162 (M^+ + 1, 2), 161 (M^+, 19), 130 (100), 102 (54).

Methyl 4-Formylbenzoate (2o)[5c]

[CAS Reg. No. 1571-08-0]

Purified by flash chromatography (PE–EtOAc, 10:1); colorless solid; yield: 56.6 mg (69%); mp 60–62 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 10.11 (s, 1 H), 8.20 (d, *J* = 8.0 Hz, 2 H), 7.96 (d, *J* = 8.1 Hz, 2 H), 3.97 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 191.7, 166.1, 139.1, 135.1, 130.2, 129.5, 52.6.

LRMS (EI, 70 eV): *m*/*z* (%) = 165 (M^+ + 1, 4), 164 (M^+, 41), 133 (100), 105 (38).

Methyl 2-Aminobenzoate (2p)[25]

[CAS Reg. No. 134-20-3]

Purified by flash chromatography (PE–EtOAc, 4:1); colorless oil; yield: 32.5 mg (43%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.85 (d, *J* = 8.0 Hz, 1 H), 7.34–7.22 (m, 1 H), 6.72–6.59 (m, 2 H), 5.69 (s, 2 H), 3.87 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.6, 150.4, 134.1, 131.2, 116.7, 116.3, 110.8, 51.52.

LRMS (EI, 70 eV): *m*/*z* (%) = 152 (M^+ + 1, 5), 151 (M^+, 50), 119 (100), 92 (61).

Methyl 2-(Methylamino)benzoate (2p′)[26]

[CAS Reg. No. 85-91-6]

Purified by flash chromatography (PE–EtOAc, 4:1); colorless oil; yield: 10.7 mg (14%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.89 (dd, *J* = 8.0, 1.6 Hz, 1 H), 7.63 (s, 1 H), 7.38 (m, 1 H), 6.66 (d, *J* = 8.5 Hz, 1 H), 6.58 (t, *J* = 7.5 Hz, 1 H), 3.85 (s, 3 H), 2.91 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.1, 152.0, 134.6, 131.6, 114.3, 110.7, 109.9, 51.4, 29.6.

LRMS (EI, 70 eV): *m*/*z* (%) = 166 (M^+ + 1, 7), 165 (M^+, 67), 132 (52), 105 (100), 77 (65).

Methyl 2-Hydroxy-2-phenylacetate (2q)[27]

[CAS Reg. No. 4358-87-6]

Purified by flash chromatography (PE–EtOAc, 4:1); colorless oil; yield: 42.3 mg (51%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.44–7.30 (m, 5 H), 5.17 (s, 1 H), 3.75 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 174.1, 138.3, 128.6, 128.5, 126.6, 72.9, 53.0.

LRMS (EI, 70 eV): *m*/*z* (%) = 166 (M^+, 6), 107 (100), 79 (91), 51 (20).

Methyl (2*E*,4*E*)-Hexa-2,4-dienoate (2r)[28]

[CAS Reg. No. 689-89-4]

Purified by flash chromatography (PE–EtOAc, 10:1); colorless oil; yield: 20.2 mg (32%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.30–7.22 (m, 1 H), 6.24–6.10 (m, 2 H), 5.78 (d, *J* = 15.4 Hz, 1 H), 3.74 (s, 3 H), 1.85 (d, *J* = 5.7 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.7, 145.2, 139.4, 129.8, 118.5, 51.4, 18.6.

LRMS (EI, 70 eV): *m*/*z* (%) = 127 (M^+ + 1, 5), 126 (M^+, 57), 111 (92), 95 (62), 67 (100).

Methyl Cinnamate (2s)[6b]

[CAS Reg. No. 103-26-4]

Purified by flash chromatography (PE–EtOAc, 10:1); colorless solid; yield: 30.0 mg (37%); mp 35–37 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.70 (d, *J* = 16.0 Hz, 1 H), 7.52 (dd, *J* = 6.7, 3.0 Hz, 2 H), 7.42–7.34 (m, 3 H), 6.44 (d, *J* = 16.0 Hz, 1 H), 3.81 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.4, 144.9, 134.4, 130.3, 128.9, 128.1, 117.8, 51.7.

LRMS (EI, 70 eV): *m*/*z* (%) = 163 (M^+ + 1, 4), 162 (M^+, 39), 131 (100), 103 (71).

Methyl 2-Naphthoate (2t)[3]

[CAS Reg. No. 2459-25-8]

Purified by flash chromatography (PE–EtOAc, 10:1); colorless solid; yield: 69.8 mg (75%); mp 76–78 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.60 (s, 1 H), 8.05 (d, *J* = 8.6 Hz, 1 H), 7.93 (d, *J* = 8.0 Hz, 1 H), 7.86 (d, *J* = 8.8 Hz, 2 H), 7.59–7.50 (m, 2 H), 3.97 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.3, 135.5, 132.5, 131.1, 129.4, 128.3, 128.2, 127.8, 127.4, 126.7, 125.2, 52.3.

LRMS (EI, 70 eV): *m*/*z* (%) = 187 (M^+ + 1, 7), 186 (M^+, 52), 155 (87), 127 (100).

Methyl Furan-2-carboxylate (2u)[3]

[CAS Reg. No. 611-13-2]

Purified by flash chromatography (PE–EtOAc, 10:1); colorless oil; yield: 51.0 mg (81%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.64–7.50 (m, 1 H), 7.19 (d, *J* = 3.5 Hz, 1 H), 6.52 (dd, *J* = 3.6, 1.7 Hz, 1 H), 3.90 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.1, 146.3, 144.6, 117.9, 111.9, 51.9.

LRMS (EI, 70 eV): *m*/*z* (%) = 127 (M^+ + 1, 2), 126 (M^+, 29), 95 (100), 39 (18).

Methyl Quinoline-2-carboxylate (2v)[29]

[CAS Reg. No. 19575-07-6]

Purified by flash chromatography (PE–EtOAc, 3:1); colorless solid; yield: 27.1 mg (29%); mp 174–177 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.31 (d, *J* = 8.6 Hz, 2 H), 8.20 (d, *J* = 8.5 Hz, 1 H), 7.88 (d, *J* = 8.2 Hz, 1 H), 7.80 (t, *J* = 7.6 Hz, 1 H), 7.66 (t, *J* = 7.5 Hz, 1 H), 4.09 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 166.0, 147.9, 147.5, 137.3, 130.7, 130.3, 129.4, 128.7, 127.6, 121.0, 53.2.

LRMS (EI, 70 eV): *m*/*z* (%) = 187 (M^+, 5), 157 (14), 129 (100), 101 (18).

Methyl 2-Phenylacetate (2w)[5c]

[CAS Reg. No. 101-41-7]

Purified by flash chromatography (PE–EtOAc, 10:1); colorless oil; yield: 54.8 mg (73%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.36–7.24 (m, 5 H), 3.69 (s, 3 H), 3.63 (s, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.1, 134.0, 129.3, 128.6, 127.1, 52.1, 41.2.

LRMS (EI, 70 eV): *m*/*z* (%) = 150 (M^+, 17), 91 (100), 65 (15), 43 (20).

Methyl Hexanoate (2x)[30]

[CAS Reg. No. 106-70-7]

Purified by flash chromatography (CH_2Cl_2); colorless oil; yield: 45.5 mg (70%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.67 (s, 3 H), 2.31 (t, *J* = 7.6 Hz, 2 H), 1.67–1.59 (m, 2 H), 1.34–1.28 (m, 4 H), 0.90 (t, *J* = 6.8 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 174.4, 51.5, 34.1, 31.3, 24.7, 22.3, 13.9.

LRMS (EI, 70 eV): *m*/*z* (%) = 101 (9), 99 (20), 87 (31), 74 (100).

1-Methoxy-2,2,6,6-tetramethylpiperidine (3b)[31]

[CAS Reg. No. 34672-84-9]

Purified by flash chromatography (PE–EtOAc, 10:1); colorless oil; yield: 43 mg (25%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.61 (s, 3 H), 1.45 (m, 6 H), 1.17 (s, 6 H), 1.08 (s, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 65.3, 59.7, 39.6, 33.0, 20.0, 17.0.

LRMS (EI, 70 eV): *m*/*z* (%) = 171 (M^+, 5), 156 (100), 125 (7), 109 (23).

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Supporting Information

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