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Palladium-Catalyzed *Ortho*- C−H Methylation of Benzoic Acids

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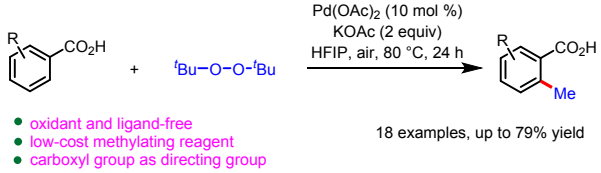


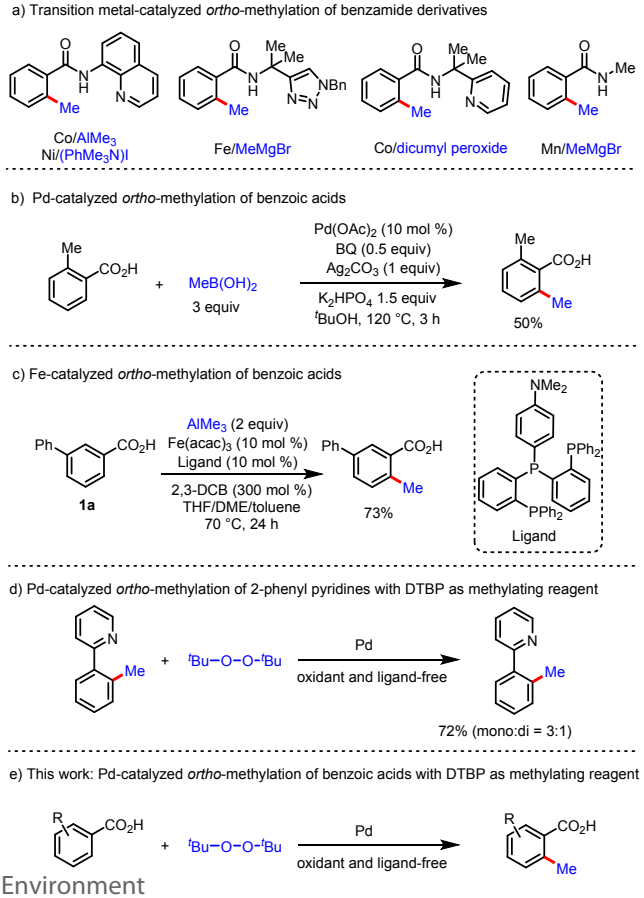
ABSTRACT: A palladium-catalyzed methylation of C–H bonds of benzoic acids with di-*tert*-butyl peroxide as the methylating reagent under external oxidant and ligand-free conditions has been achieved. The reaction is found to be directed by a weakly coordinating carboxyl group, offering a facile route for the synthesis of highly functionalized *ortho*-methyl benzoic acids.

The methyl group as the smallest alkyl group plays a very important role in biologically active molecules.[1] The introduction of a methyl group increases the hydrophobic character of organic compounds, thus can modulate the biological activity and physical property of a pharmacologically active molecule, which is the so-called "magic methyl" effect. For example, the replacement of C−H by C−Me can significantly improve the IC_{50} value of a drug candidate.[2]

The transition metal-catalyzed C−H methylation reactions are the most straightforward methods to installation of a methyl group.[3] Recently, a variety of monodentate and bidentatethe directing groups were developed to achieve *ortho*-methylation of benzamide derivatives using Mn,[4] Fe,[5] Co,[6] Ni,[7] and Pd[8] as catalysts (Scheme 1a). However, the requirement of installation and removal of an external directing group has hampered the use of simple benzoic acids, thus reducing their synthetic utility.[9] The examples of methylation of benzoic acids are extremely limited to only two reports until date. The Pd-catalyzed methylation of simple benzoic acids pioneered by Yu use $MeB(OH)_2$ and Ag_2CO_3 as the methylating reagent and oxidant, respectively (Scheme 1b).[10] In 2016, Nakamura described a tridentate phosphine ligand 4-(*bis*(2-(diphenylphosphanyl)phenyl)phosphanyl)-*N*,*N*-dimethylaniline enabled Fe-catalyzed methylation of simple benzoic acids under oxidative conditions (Scheme 1c).[11] Despite the significant progress offered by the aforementioned methods, there are still certain limitations, including the requirement of external oxidant and sophisticated ligand. In 2008, li and coworkers reported the first example of palladium-catalyzed *ortho*-C−H methylation of 2-phenyl pyridines with dicumyl peroxide as methylating reagent (Scheme 1d).[12a] Inspired by Li's work, herein, we reported a Pd-catalyzed *ortho*-methylation of benzoic acids using commercial available and low-cost di-*tert*-butyl peroxide (DTBP) as both the methylating reagent and hydrogen acceptor under external oxidant and ligand-free conditions (Scheme 1e).[13]

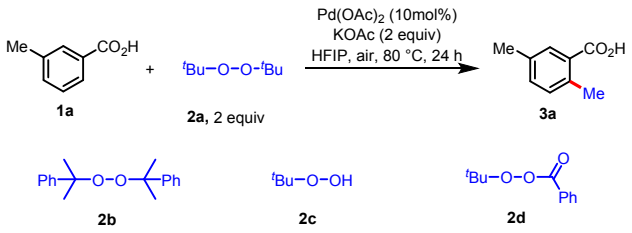
Initially, we began the studies with 3-methylbenzoic acid **1a** and DTBP **2a** to explore the reaction conditions. After systematic screening of the reaction conditions, the optimal conditions were achieved to be: $Pd(OAc)_2$ (10 mol %), KOAc (2 equiv) in HFIP under air at 80 °C to yield the desired

Scheme 1. Palladium-Catalyzed *Ortho*- C−H Methylation of Benzoic Acid Derivatives.



methylation product **3a** in 79% yield (Table 1, entry 1, see SI for details). Under other conditions, no desired product or only low yields were observed. No desired product **3a** was formed in the absence of either the base or Pd catalyst (entries 2, 3). Replacing KOAc with NaOAc decreased the yield to 15% (entry 4). The use of Ac-Gly-OH as ligand afforded a lower yield (entry 5). Interestingly, other solvents, such as ^{t}AmylOH and toluene, inhibited the reaction completely (entries 6, 7). Dicumyl peroxide **2b** also gave the methylation product in 23% yield. (entry 8). However, no reaction was observed when *tert*-butyl hydroperoxide **2c** instead of **2a** was used (entry 9). Only trace of **3a** was detected when *tert*-butyl peroxybenzoate **2d** was used (entry 10).

Table 1. Role of Select Parameters[a]



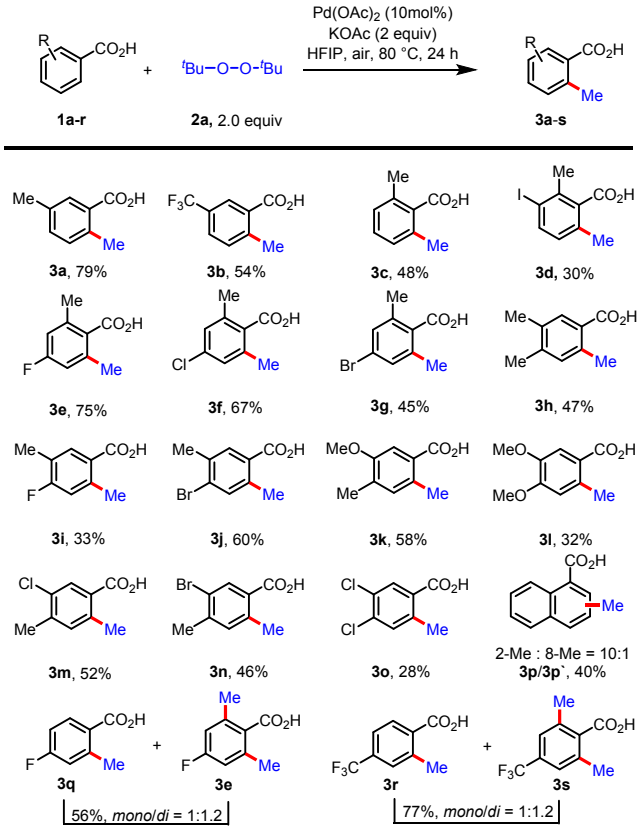
entry	deviation from standard conditions	yield (%)[b]
1	none	79
2	no KOAc	0
3	no $Pd(OAc)_2$	0
4	NaOAc instead of KOAc	15
5	Ac-Gly-OH (10 mol %) as ligand	63
6	^{t}AmylOH instead of HFIP	0
7	toluene instead of HFIP	0
8	**2b** instead of **2a**	23
9	**2c** instead of **2a**	0
10	**2d** instead of **2a**	trace

[a]Reaction conditions: **1a** (0.3 mmol), **2a** (0.6 mmol), $Pd(OAc)_2$ (10 mol%), KOAc (0.6 mmol) in HFIP (0.8 mL) at 80 °C under air atmosphere for 24 h. [b]Isolated yields. HFIP = 1,1,1,3,3,3-hexafluoro-2-propanol.

Next, the generality of this Pd-catalyzed methylation reaction was examined under the optimized reaction conditions (Scheme 2). In all tested cases, the desired methylation reaction proceeded smoothly. In general, the reaction process can be extended to various *meta*-, *ortho*-, *para*-, as well as disubstituted benzoic acids, thus giving the corresponding methyl substituted benzoic acids (**3a**–**s**) in 28–79% yields. Various valuable functional groups were tolerated, including trifluoromethyl, fluoro, chloro, bromo, iodo, and methoxyl. For *meta*-substituted benzoic acids, the C–H methylation occurred regioselectively at the sterically less hindered position (**3a**, **3b**, **3h**–**o**). Importantly, 1-naphthoic acid was found to be an applicable substrate, providing the desired 2-methyl (**3p**) and 8-methyl (**3p`**) products in 40% combined yield. The reactions of *para*-substituted benzoic acids resulted in 1:1.2 mixtures of mono- and dimethylated products (**3q**/**3e**; **3r**/**3s**).

To demonstrate the utility of this chemistry, the C–H methylation reactions were conducted on a gram-scale. The reaction of **1a** and **2a** was complete within 24 h, generating the desired

Scheme 2. Scope of Benzoic acids[a]



[a]Reaction conditions: 1a (0.3 mmol), 2a (0.6 mmol), $Pd(OAc)_2$ (10 mol%), KOAc (0.6 mmol) in HFIP (0.8 mL) at 80 °C under air atmosphere for 24 h.

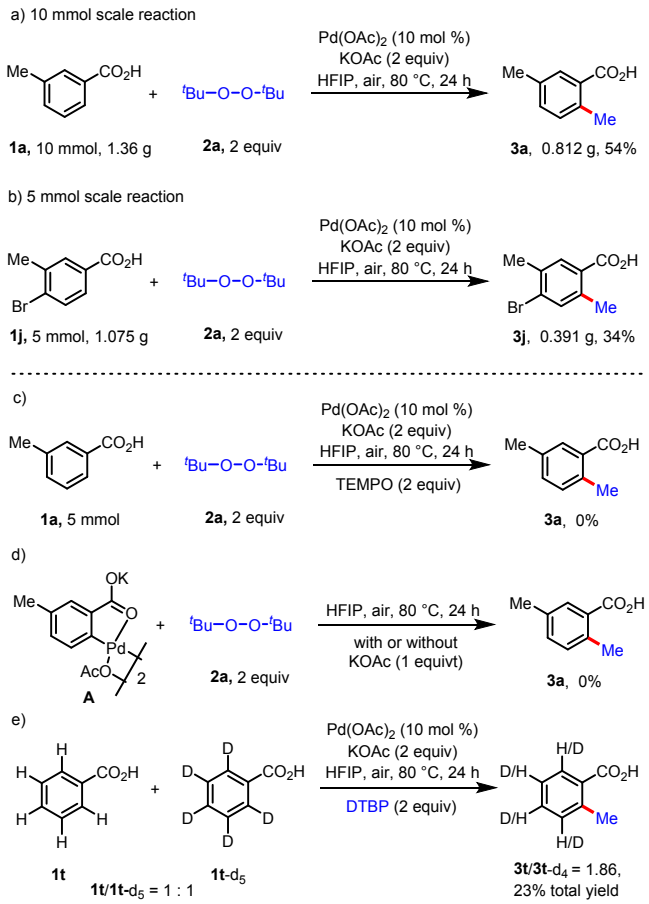
products (**3a**) in 54% yield (Scheme 3a). The reaction of **1j** and **2a** was carried out under standard conditions for 24 h, giving the desired products (**3a**) in 34% yield, and **1j** could be recovered in 60% yield (Scheme 3b).

To gain insight into the mechanism of this reaction, a radical trapping experiment was implemented. It was observed that the addition of 2 equiv of 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO) inhibited the reaction completely. This result suggested that a radical process might be involved in this transformation (Scheme 3c). The putative palladacycle **A** was independently prepared[9c] and resubmitted to the reaction conditions with or without 1 equiv KOAc. The desired product **3a** was not detected, which indicated that it is unlikely for palladacycle **A** to serve as an intermediate in this methylation reaction (Scheme 3d). We also performed kinetic isotope effects study. The competition reaction between benzoic acid **1t** and deuterated benzoic acid **1t**-d5 was managed in one-pot. After reacting 24 h, a mixture of **3t** and **3t**-d_4 was obtained in 23% total yield and 1.86:1 ratio. The observation of KIE effect demonstrated that the C–H cleavage step is not obvious participated in the rate-determining step (Scheme 3e).

On the basis of these results and the literature reports,[12] we proposed a catalytic cycle in Scheme 4. Initially, Pd^{II} complex **B** is formed through coordination of benzoic acid **1a** with $Pd(OAc)_2$. Then **B** is oxidized by *tert*-butoxy radical,

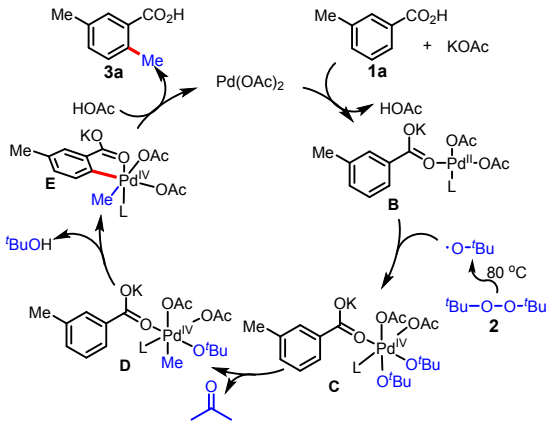
generated from the peroxide **2a**, through a single-electron transfer (SET) process giving the Pd^{IV} species **C**. Next, β-methyl

Scheme 3. Gram-Scale Reaction and Control Experiments



elimination of **C** gives Pd^{IV} species **D**, followed by *ortho*-C−H activation to deliver intermediate **E**. Finally, reductive elimination of **E** giving the methylation product **3a** and regenerating $Pd(OAc)_2$. However, the pd^0/Pd^{II} catalytic cycle could not be ruled out.[12a]

Scheme 4. Proposed Catalytic Cycle



CONCLUSION

In conclusion, we have developed a palladium-catalyzed C−H *ortho*-methylation reaction of benzoic acids with DTBP as the methylating reagent. This methodology provides a utility approach for the synthesis of methyl substituted benzoic acids with efficient. This approach is compatible with a wide spectrum of readily available functionalized benzoic acids.

EXPERIMENTAL SECTION

General Information. All the solvents were used without further purification. The other commercial chemicals were used without further purification. All reactions were performed under an inert atmosphere of nitrogen in flame-dried glassware, unless otherwise stated. Analytical thin layer chromatography was performed on 0.25 mm silica gel 60-F254. Visualization was carried out with UV light and Vogel's permanganate. Preparative TLC was performed on 1.0 mm silica gel. ^1H NMR spectra were recorded on Bruker DRX-500 instrument (500 MHz). ^{13}C NMR spectra were recorded on Bruker DRX-500 instrument (126 MHz) were fully decoupled by broad band proton decoupling. High-resolution mass spectra (HRMS) were recorded on an Agilent 1290 Mass spectrometer using ESI-TOF (electrospray ionization-time of flight). NMR spectra were recorded in $CDCl_3$. ^1H NMR spectra were referenced to residual $CHCl_3$ at 7.26 ppm, and ^{13}C NMR spectra were referenced to the central peak of $CDCl_3$ at 77.0 ppm. Chemical shifts (δ) are reported in ppm, and coupling constants (*J*) are in Hertz (Hz). Multiplicities are reported using the following abbreviations: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet.

Procedure for Preparation of 3.

A dried 10 mL Schlenk tube was charged with **1** (40.8 mg, 0.3 mmol), **2a** (87.6 mg, 0.6 mmol), $Pd(OAc)_2$ (6.8 mg, 10 mol %), KOAc (58.8 mg, 0.6 mmol) in HFIP (0.8 mL) under air. This mixture was heated to 80 °C in a heating plate for 24 h. Upon completion, the reaction mixture was cooled to room temperature, diluted with ethyl acetate, and filtered through a pad of celite. The filtrate was concentrated under vacuum, and the resulting residue was purified by preparative thin layer chromatography (PTLC) with ethyl acetate: hexane:AcOH (1:4:0.03) to give the corresponding products **3**.

2,5-dimethylbenzoic acid (3a)[14] (35.5 mg, 79%) as white solid. ^1H NMR (500 MHz, $CDCl_3$) δ 7.93 (s, 1H), 7.32 – 7.27 (m, 1H), 7.19 (d, *J* = 7.7 Hz, 1H), 2.65 (s, 3H), 2.40 (s, 3H); $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 173.7, 138.2, 135.4, 133.7, 132.0, 131.8, 128.1, 21.6, 20.7.

2-methyl-5-(trifluoromethyl)benzoic acid (3b) (33 mg, 54%) as white solid. ^1H NMR (500 MHz, $CDCl_3$) δ 8.34 (s, 1H), 7.70 (dd, *J* = 8.1, 1.9 Hz, 1H), 7.42 (d, *J* = 8.0 Hz, 1H), 2.73 (s, 3H); $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 171.8, 145.4, 132.6, 129.3 (q, *J* = 3.5 Hz), 128.9 (q, *J* = 28.1 Hz), 128.7 (q, *J* = 5.1 Hz), 128.6 (q, *J* = 4.2 Hz), 123.7 (q, *J* = 272.0 Hz), 22.1; HRMS (ESI-TOF) m/z: calcd for $C_9H_6F_3O_2^-$: 203.0325 $(M-H)^-$, found: 203.0320.

2,6-dimethylbenzoic acid (3c)[10] (21.6 mg, 48%) as white solid. ^1H NMR (500 MHz, $CDCl_3$) δ 7.28 – 7.23 (m, 1H), 7.10 (d, *J* = 7.6 Hz, 2H), 2.48 (s, 6H); $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 175.7, 135.6, 132.4, 129.9, 127.9, 20.1.

3-iodo-2,6-dimethylbenzoic acid (3d)[15] (24.8 mg, 30%) as white solid. ^1H NMR (500 MHz, $CDCl_3$) δ 7.77 (dd, J = 8.1, 1.4 Hz, 1H), 6.78 (d, J = 8.1 Hz, 1H), 2.49 (s, 3H), 2.34 (s, 3H); $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 174.3, 140.2, 137.1, 134.9, 134.0, 129.4, 98.6, 26.0, 19.5.

4-fluoro-2,6-dimethylbenzoic acid (3e) (37.8 mg, 75%) as white solid. ^1H NMR (500 MHz, $CDCl_3$) δ 6.78 (d, *J* = 9.3 Hz,

2H), 2.44 (s, 6H); $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 174.7, 163.0 (d, *J* = 249.6 Hz), 139.2 (d, *J* = 8.9 Hz), 128.2 (d, *J* = 2.9 Hz), 114.8 (d, *J* = 21.5 Hz), 20.5 (d, *J* = 1.5 Hz) ; HRMS (ESI-TOF) m/z: calcd for $C_9H_8FO_2^-$: 167.0514 (M - H)$^-$, found: 167.0510.

4-chloro-2,6-dimethylbenzoic acid (**3f**) (37 mg, 67%) as white solid. ^1H NMR (500 MHz, $CDCl_3$) δ 7.08 (s, 2H), 2.42 (s, 6H); $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 174.1, 137.9, 135.6, 127.9, 127.8, 20.2; HRMS (ESI-TOF) m/z: calcd for $C_9H_8ClO_2^-$: 183.0218 (M - H)$^-$, found: 183.0218.

4-bromo-2,6-dimethylbenzoic acid (**3g**)[16] (30.8 mg, 45%) as white solid. ^1H NMR (500 MHz, $CDCl_3$) δ 7.25 (s, 2H), 2.41 (s, 6H); $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 173.9, 138.0, 131.1, 130.8, 124.1, 20.1.

2,4,5-trimethylbenzoic acid (**3h**)[17] (23.1 mg, 47%) as white solid. ^1H NMR (500 MHz, $CDCl_3$) δ 7.86 (s, 1H), 7.04 (s, 1H), 2.59 (s, 3H), 2.28 (s, 3H), 2.27 (s, 3H); $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 173.3, 142.4, 138.8, 134.0, 133.3, 132.7, 125.5, 21.6, 19.8, 19.1.

4-fluoro-2,5-dimethylbenzoic acid (**3i**) (16.6 mg, 33%) as white solid. ^1H NMR (500 MHz, $CDCl_3$) δ 7.95 (d, *J* = 8.1 Hz, 1H), 6.91 (d, *J* = 10.4 Hz, 1H), 2.61 (s, 3H), 2.28 (d, *J* = 1.7 Hz, 3H); $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 172.2, 163.8 (d, *J* = 253.4 Hz), 142.1 (d, *J* = 9.1 Hz), 135.5 (d, *J* = 7.1 Hz), 123.9 (d, *J* = 2.9 Hz), 122.4 (d, *J* = 17.6 Hz), 118.3 (d, *J* = 22.5 Hz), 21.9, 14.0 (d, *J* = 3.0 Hz); HRMS (ESI-TOF) m/z: calcd for $C_9H_8FO_2^-$: 167.0514 (M - H)$^-$, found: 167.0515.

4-bromo-2,5-dimethylbenzoic acid (**3j**) (41 mg, 60%) as white solid. ^1H NMR (500 MHz, $CDCl_3$) δ 8.22 (s, 1H), 7.14 (s, 1H), 2.57 (s, 3H), 2.41 (s, 3H); $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 171.8, 143.4, 140.5, 135.3, 134.3, 127.2, 121.7, 22.9, 21.6; HRMS (ESI-TOF) m/z: calcd for $C_9H_8BrO_2^-$: 226.9713 (M - H)$^-$, found: 226.9717.

5-methoxy-2,4-dimethylbenzoic acid (**3k**) (31.3 mg, 58%) as white solid. ^1H NMR (500 MHz, $CDCl_3$) δ 7.52 (s, 1H), 7.03 (s, 1H), 3.86 (s, 3H), 2.56 (s, 3H), 2.24 (s, 3H); $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 173.2, 155.5, 134.3, 133.7, 132.7, 126.0, 112.3, 55.5, 21.2, 16.2; HRMS (ESI-TOF) m/z: calcd for $C_9H_{12}O_3^+$: 180.0786 (M)$^+$, found: 180.0784.

4,5-dimethoxy-2-methylbenzoic acid (**3l**)[14] (18.8 mg, 32%) as white solid. ^1H NMR (500 MHz, $CDCl_3$) δ 7.61 (s, 1H), 6.72 (s, 1H), 3.94 (s, 3H), 3.91 (s, 3H), 2.63 (s, 3H); $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 172.7, 152.6, 146.5, 136.4, 119.7, 114.2, 114.0, 56.0, 55.9, 22.1.

5-chloro-2,4-dimethylbenzoic acid (**3m**)[18] (28.7 mg, 52%) as white solid. ^1H NMR (500 MHz, $CDCl_3$) δ 8.00 (s, 1H), 7.11 (s, 1H), 2.56 (s, 3H), 2.37 (s, 3H); $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 172.1, 141.2, 139.5, 134.3, 131.8, 131.6, 127.6, 21.4, 20.1.

5-bromo-2,4-dimethylbenzoic acid (3n) (31.5 mg, 46%) as white solid. ^1H NMR (500 MHz, $CDCl_3$) δ 8.22 (s, 1H), 7.14 (s, 1H), 2.57 (s, 3H), 2.41 (s, 3H); $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 171.8, 143.4, 140.5, 135.3, 134.3, 127.2, 121.7, 22.9, 21.6; HRMS (ESI-TOF) m/z: calcd for $C_9H_{12}O_3^+$: 180.0786 (M)$^+$, found: 180.0784.

4,5-dichloro-2-methylbenzoic acid (3o) (17.1 mg, 28%) as white solid. ^1H NMR (500 MHz, $CDCl_3$) δ 8.10 (s, 1H), 7.36 (s, 1H), 2.58 (s, 3H); $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 171.3, 141.0, 137.1, 133.5, 133.1, 130.0, 128.1, 21.4; HRMS (ESI-TOF) m/z: calcd for $C_9H_8BrO_2^-$: 227.9713 (M - H)$^-$, found: 227.9714.

2-methyl-1-naphthoic acid (**3p**)[14] **and 8-methyl-1-naphthoic acid** (**3p`**)[19] (24.8 mg, 40%) as white solid. ^1H NMR (500 MHz, $CDCl_3$) δ 8.14 (d, *J* = 8.4 Hz, 1H), 7.85 (dd, *J* = 8.4, 2.0 Hz, 2H), 7.55 (t, *J* = 7.3 Hz, 1H), 7.51 – 7.47 (m, 1H), 7.37 (d, *J* = 8.4 Hz, 1H), 2.67 (s, 3H); $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 175.6, 173.4, 134.5, 134.4, 133.8, 132.4, 131.7, 130.3, 130.3, 130.0, 128.9, 128.7, 128.5, 128.1, 127.8, 127.7, 127.2, 127.2, 126.3, 125.5, 124.7, 123.9, 22.2, 20.6.

4-fluoro-2-methylbenzoic acid (**3q**)[20] (12.8 mg, 25%) as white solid. ^1H NMR (500 MHz, $CDCl_3$) δ 8.15 – 8.08 (m, 1H), 7.02 – 6.93 (m, 2H), 2.67 (s, 3H); $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 171.9, 165.2 (d, *J* = 254.4 Hz), 145.1 (d, *J* = 9.2 Hz), 134.4 (d, *J* = 9.6 Hz), 124.3 (d, *J* = 2.9 Hz), 118.7 (d, *J* = 21.4 Hz), 113.0 (d, *J* = 21.4 Hz), 22.4.

4-fluoro-2,6-dimethylbenzoic acid (**3e**) (17.4 mg, 31%) as white solid.

2-methyl-4-(trifluoromethyl)benzoic acid (**3r**)[21] (23.8 mg, 35%) as white solid. ^1H NMR (500 MHz, $CDCl_3$) δ 8.17 (d, *J* = 8.5 Hz, 1H), 7.60 – 7.51 (m, 2H), 2.72 (s, 3H); $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 172.3, 142.1, 134.3 (q, *J* = 32.5 Hz), 132.0, 131.5, 128.7 (q, *J* = 3.8 Hz), 123.5 (q, *J* = 272.8 Hz), 122.73 (q, *J* = 3.7 Hz), 22.04.

2,6-dimethyl-4-(trifluoromethyl)benzoic acid (**3s**)[22] (29.9 mg, 42%) as white solid. ^1H NMR (500 MHz, $CDCl_3$) δ 7.31 (s, 2H), 2.43 (s, 6H); $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$) δ 173.9, 153.6, 136.4 (q, *J* = 3.7 Hz), 136.0, 131.5 (q, *J* = 32.0 Hz), 125.8 (q, *J* = 272.7 Hz), 124.5 (q, *J* = 3.8 Hz), 19.9.

Procedure for Preparation of A.

3-Methylbenzoic acid **1a** (68 mg, 0.5 mmol) was treated with KOH (16 mg, 0.4 mmol) in water (0.5 mL) at room temperature for 1 h. Then solvent was removed in a rotary evaporator, and the white solid was washed with CH_2Cl_2 (1.0 mL × 3) and dried under vacuum at 100 °C to get potassium *m*-toluate (50 mg, 57% yield). Palladium acetate (56 mg, 0.25 mmol) was added to a suspension of potassium *m*-toluate (43.5 mg, 0.25 mmol) in 1,4-dioxane (3.0 mL), then the mixture was heated at reflux temperature in a heating plate for 2 h. The reaction mixture was filtered, and the residue was washed with CH_2Cl_2 (3 mL × 3) and dried under vacuum to get the palladacycle **A** (43.2 mg, 51% yield). ^1H NMR (500 MHz, DMSO – d6) δ 7.46 (d, *J* = 7.9 Hz, 1H), 6.93 (s, 1H), 6.88 (d, *J* = 7.9 Hz, 1H), 2.21 (s, 3H), 1.76 (s, 3H); $^{13}C\{^1H\}$ NMR (126 MHz, DMSO – d6) δ 178.2, 175.9, 143.1, 143.0, 133.5, 131.5, 131.0, 129.5, 25.2, 20.9.

Gram-Scale reaction experiment

A dried 50 mL Schlenk tube was charged with **1j** (1.075g, 5 mmol), **2a** (1.46 mg, 10 mmol), $Pd(OAc)_2$ (113 mg, 10 mol %), KOAc (0.98 g, 10 mmol) in HFIP (15 mL) under air. This mixture was heated to 80 °C in an oil bath for 24 h. Upon completion, the reaction mixture was cooled to room temperature, diluted with ethyl acetate, and filtered through a pad of celite. The filtrate was concentrated under vacuum, and the resulting residue was purified by flash chromatography on silica gel with ethyl acetate: hexane:AcOH (1:8:0.03) to give the corresponding products **3j** (0.387g, 34%) and **1j** (0.644g, 60%).

One-pot competition experiment

A dried 10 mL Schlenk tube was charged with Benzoic acid **1t** (12.2 mg, 0.1 mmol), deuterated benzoic acid **1t**-d5 (12.7 mg, 0.1 mmol), **2a** (58.4 mg, 0.4 mmol), $Pd(OAc)_2$ (4.5 mg, 10 mol %), KOAc (39.3 mg, 0.4 mmol) in HFIP (0.5 mL)

under air. This mixture was heated to 80 °C in a heating plate for 24 h. Upon completion, the reaction mixture was cooled to room temperature, diluted with ethyl acetate, and filtered through a pad of celite. The filtrate was concentrated under vacuum, and the resulting residue was purified by preparative thin layer chromatography (PTLC) with ethyl acetate: hexane:AcOH (1:4:0.03) to give a mixture of **3t** and **3t**-d_4 in 23% combined yield. The ratio of **3t**/**3t**-d_4 was determined to be 1.86 by the ^{1}H NMR spectrum of the mixture.

ASSOCIATED CONTENT

Supporting Information.
The Supporting Information is available free of charge on the ACS Publications website.
^{1}H and ^{13}C NMR spectra of new compounds.

AUTHOR INFORMATION

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Notes

The authors declare no competing financial interest.

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