JOC The Journal of Organic Chemistry

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Aldehydes and Ketones Formation: Copper-Catalyzed Aerobic Oxidative Decarboxylation of Phenylacetic Acids and α-Hydroxyphenylacetic Acids

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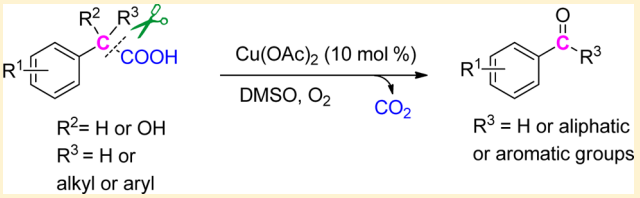
Supporting Information

ABSTRACT: Aromatic aldehydes or ketones from copper catalyzed aerobic oxidative decarboxylation of phenylacetic acids and α-hydroxyphenylacetic acids have been synthesized. This reaction combined decarboxylation, dioxygen activation, and C−H bond oxidation steps in a one-pot protocol with molecular oxygen as the sole terminal oxidant. This reaction represents a novel decarboxylation of an sp^3-hybridized carbon and the use of a benzylic carboxylic acid as a source of carbonyl compounds.



The transition-metal-catalyzed C−C bond cleavage has attracted much attention in recent years and has emerged as one of the major themes in organic synthetic chemistry.[1] This protocol leads to direct transformation of some inert starting materials and makes the reactions much simpler, easier, and cleaner. However, due to the inert nature of carbon−carbon σ-bonds, the selective cleavage of the C−C bond is a tremendous challenge for synthetic chemists and biologists as well. As one C−C cleavage strategy, transition-metal-catalyzed decarboxylation has attracted significant attention since the pioneering work of Myers,[2] Goossen,[3] and Forgione[4] due to the "neutral" conditions, the readily available starting materials, and the nontoxic byproduct (CO_2). Among all types of decarboxylation[5] reactions, decarboxylation at an sp^3-hybridized carbon for functional group introduction is relative rare[6] and remains a significant challenge. Liu and his co-workers developed several elegant palladium-catalyzed decarboxylations using a variety of aliphatic carboxylate salts[6b,c,7] in the past few years, yet the direct transition-metal-catalyzed decarboxylation of sp^3-hybridized carboxylic acids with formation of a new C═O bond in the adjacent carbon with O_2 as the oxidant is rare.[8] Aldehydes and ketones are important organic compounds and have been widely used in synthetic organic chemistry. Very recently Bi et al. reported a novel aldehyde formation by chemoselective oxidative C(CO)−C(methyl) bond cleavage catalyzed by CuI and O_2.[9] In continuation of our interest in C−C cleavage via transition-metal-catalyzed organic reactions, we herein report a novel Cu(II)-catalyzed aerobic oxidative decarboxylation of phenylacetic acids and α-hydroxyphenylacetic acids to aldehydes, without overoxidation into carboxylic acids. This reaction proceeds smoothly via decarboxylation, dioxygen activation, and oxidation of phenylacetic acid (and α-hydroxyphenylacetic acids) to afford aldehydes (or ketones). This transformation represents a novel protocol for the application of phenylacetic acids (and α-hydroxyphenylacetic acids).

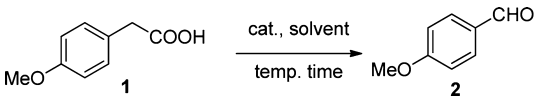
We began our evaluation with 4-methoxyphenylacetic acid (**1**) under $Cu(OAc)_2/O_2$ as a model reaction (Table 1). DMF was investigated first, and to our delight, the desired product was formed in 83% yield (Table 1, entry 1) with 10 mol % $Cu(OAc)_2$ at 120 °C under 1 atm of O_2. When the solvent was switched to DMSO, 4-methoxybenzaldehyde was obtained in 92% yield (Table 1, entry 2). However, when the temperature was reduced to 60 °C, no product was formed at all, and at 100 °C only a 12% yield of product was obtained (Table 1, entries 3 and 4). Interestingly, upon increasing the catalyst loading from 10 to 20 mol % at 120 °C, the yield dropped from 92% to 65% (Table 1, entry 5). Yet continuously reducing the catalyst loading to 5 mol % gave only 38% of the desired product. Several other copper catalysts were investigated at 120 °C; all showed inferior efficiencies for this transformation (Table 1, entries 7−10). When O_2 was replaced by air or N_2, only 42% and 10%, respectively, of the desired product was formed (Table 1, entries 11−12); these results suggested that O_2 is essential for the success of this transformation and that $Cu(OAc)_2$ and DMSO also play crucial roles in this transformation. After screening, the optimal reaction conditions eventually emerged as 4-methoxyphenylacetic acid (**1**) (0.5 mmol) and $Cu(OAc)_2$ (10 mol %) at 120 °C in DMSO (0.75 mL) under an O_2 atmosphere.

After establishing the optimized reaction conditions, we explored the substrate scope of phenylacetic acids (Table 2). Phenylacetic acids bearing electron-donating groups on the aromatic rings gave the desired products in good to excellent yields (**2**−**4**, **16**−**17** and **20** in Table 2). Phenylacetic acids

Received: December 18, 2013

dx.doi.org/10.1021/jo402778p | J. Org. Chem. XXXX, XXX, XXX−XXX

Table 1. Condition Screening[a]



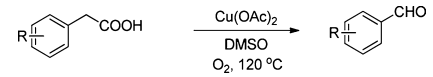
entry	catalyst	oxidant	solvent	temp (°C)	time (h)	yield (%)
1	$Cu(OAc)_2$ (10mol %)	O_2	DMF	120	18	83
2	$Cu(OAc)_2$ (10 mol %)	O_2	DMSO	120	18	92
3	$Cu(OAc)_2$ (10 mol %)	O_2	DMSO	60	18	0
4	$Cu(OAc)_2$ (10 mol %)	O_2	DMSO	100	18	12
5	$Cu(OAc)_2$ (20 mol %)	O_2	DMSO	120	18	65[b]
6	$Cu(OAc)_2$ (5 mol %)	O_2	DMSO	120	18	38
7	$Cu(OTf)_2$ (10 mol %)	O_2	DMSO	120	18	89
8	$Cu(TFA)_2$ (10 mol %)	O_2	DMSO	120	18	45
9	$CuBr_2$ (10 mol %)	O_2	DMSO	120	18	trace
10	$CuSO_4$ (10 mol %)	O_2	DMSO	120	18	49
11	$Cu(OAc)_2$ (10 mol %)	air	DMSO	120	18	42
12	$Cu(OAc)_2$ (10 mol %)	N_2	DMSO	120	18	10

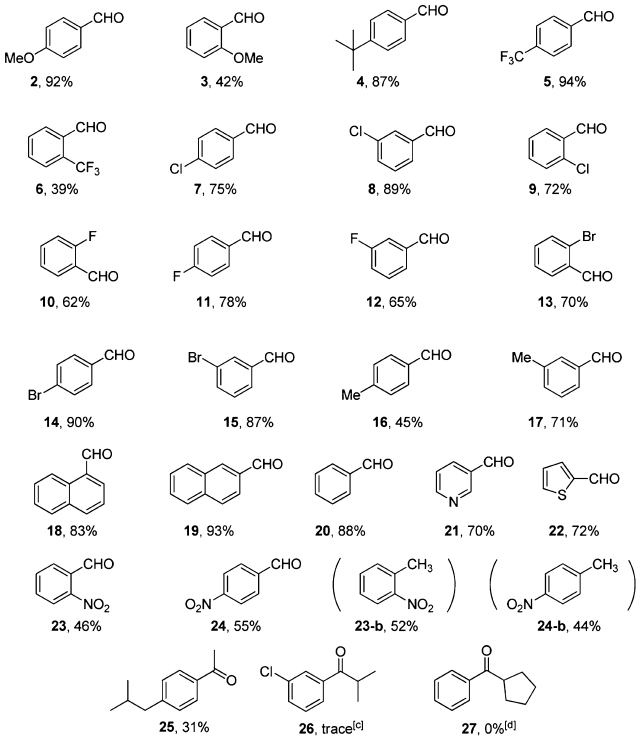
[a]Reaction conditions: phenyl acetic acid (0.5 mmol), catalyst in solvent (0.75 mL) in a sealed tube under corresponding atmosphere. [b]Possible that the excess catalyst decomposes some reactive intermediate.

possessing electron-withdrawing groups on the aromatic ring also reacted smoothly under standard conditions, and the desired aldehydes were obtained in good to excellent yields (Table 2, **5**−**15**, **23**−**24**). The position of the substituents on the aromatic rings had an effect on yields (Table 2, **2**−**3**, **5**−**6**, **7**−**9**, **10**−**12**, **13**−**15**, and **23**−**24**), with *o*-substitution usually giving lower yields of the aldehydes when compared to *m*- and *p*-substitution, probably as a result of steric hindrance. Both 1-naphthylacetic acid and 2-naphthylacetic acid reacted well and gave the corresponding aldehydes in 83% and 93% yields (Table 2, **18** and **19**). Heteroaromatic acetic acids also worked well under standard conditions; for instance, 3-pyridinecarboxaldehyde and 2-thiophenecarboxaldehyde were obtained from 3-pyridylacetic acid and 2-thienylacetic acid in 70% and 72% yields, respectively (Table 2, **21** and **22**).

Generally speaking, there is little difference in yields among most functional groups. However, a nitro group on the aromatic ring did give surprising results. When *o*-nitrophenylacetic acid and *p*-nitrophenylacetic acid in order to correspond to the following *o*-methylnitrobenzene and 4-methylnitrobenzene were used under standard conditions, *o*-methylnitrobenzene and 4-methylnitrobenzene were formed in 52% and 44% yields in addition to the desired aldehydes (only 46% and 55% yields, respectively) (Table 2, **23-b** and **24-b**). These results provided some hints with regard to the reaction mechanisms. It showed that the decarboxylation to generate an aliphatic radical is likely the first step, and this radical may be further oxidized into a carbonyl group or instead trapped at this stage. When substituents on methyl group were used as starting materials, corresponding ketones were obtained (Table 2, **25**, **26**, and **27**). As the bulkiness of the substituents increased

Table 2. Copper-Catalyzed Aerobic Oxidative Decarboxylation of Phenylacetic Acid to Aldehydes[a,b]





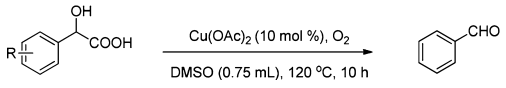
[a]Reaction conditions: **1** (0.5 mmol), $Cu(OAc)_2$ (10 mol %), DMSO (0.75 mL), O_2; the reaction was monitored by TLC plate. [b]Isolated yield. [c]Detected by GC and GCMS. [d]Detected by TLC plate and GC.

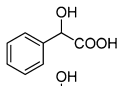
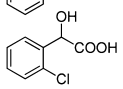
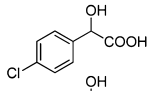
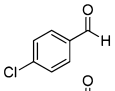
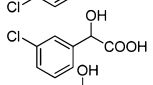
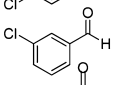
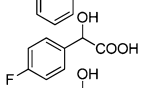
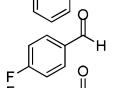
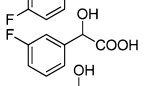
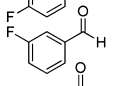
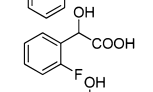
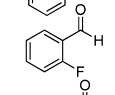
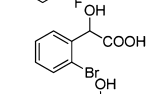
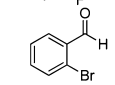
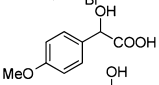
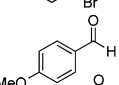
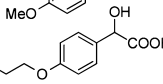
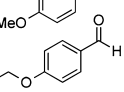
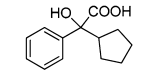
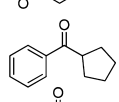
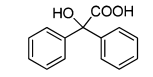
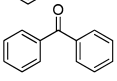
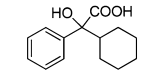
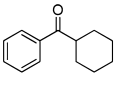
(from methyl to isopropyl to cyclopentyl), the yields of corresponding ketones decreased, and with cyclopentyl on the methylene group, no desired product was obtained. Fluoro, chloro, bromo, methoxy, methyl, *tert*-butyl, nitro, and trifluoromethyl groups were all well tolerated under the standard reaction conditions, and heteroaromatics were also well tolerated. This is the first example of a synthesis of aromatic aldehydes or ketones via decarboxylation of phenylacetic acid under a Cu-catalyzed oxidation reaction with O_2 as the terminal oxidant, and the process utilizes phenylacetic acid as an aromatic acyl surrogate.

Intrigued by the above results, we applied the same conditions to α-hydroxyphenylacetic acids. To our delight, 4-methoxybenzaldehyde (**2**) was obtained in 75% yield (Table 3, entry 9). Without further optimization, we found that α-hydroxyphenylacetic acids worked well under standard conditions to give corresponding aldehydes in moderate to good yields (Table 3). And both electron-donating and -withdrawing groups worked well and halo-substituted α-hydroxyphenylacetic acid survived well, leading to halo-substituted benzaldehyes, which could be used for further transformation. Notably, when 2-cyclopentyl-2-hydroxy-2-phenylacetic acid (Table 3, **38**) was subjected to the standard conditions, cyclopentyl phenyl ketone (**27**) was obtained in 93% yield (Table 3, entry 11). And two other aromatic ketones (**42** and **43**) were also obtained in excellent yields under the standard conditions (Table 3, entries 12−13).

dx.doi.org/10.1021/jo402778p | J. Org. Chem. XXXX, XXX, XXX−XXX

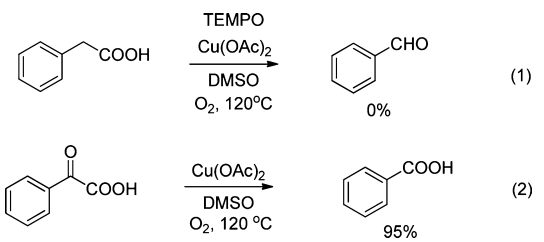
Table 3. Copper-Catalyzed Aerobic Oxidative Decarboxylation of α-Hydroxyphenylacetic Acid to Aldehydes and Ketones



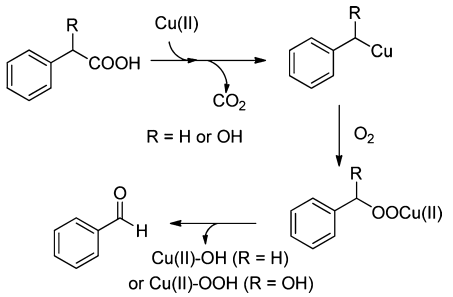
Entry	Substrate		Product		yield (%)
1		28		20	73
2		29		9	69
3		30		7	73
4		31		8	36
5		32		11	61
6		33		12	58
7		34		10	47
8		35		13	52
9		36		2	75
10		37		41	66
11		38		27	93
12		39		42	95
13		40		43	95

In order to elucidate the reaction mechanism, several control experiments were carried out. Since the reaction involves oxygen, radical trapping experiments were conducted by employing 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) with phenylacetic acid under standard conditions; the results showed that the reactions were inhibited by TEMPO (Scheme 1, eq 1). The reaction of 2-oxo-2-phenylacetic acid under standard conditions suggested that it could not be an intermediate of the reaction because the majority of it was converted into benzoic acids (Scheme 1, eq 2). Based on the above results, we give a plausible reaction mechanism (Scheme 2): phenylacetic acid is decarboxylated to give an active copper species, which was further oxidized into aldehydes.

Scheme 1. Control Experiments under Standard Conditions with Phenylacetic Acids



Scheme 2. Plausible Reaction Mechanism



In summary, Cu(II)/O_2 systems that catalyze the oxidative decarboxylation of phenylacetic acids and α-hydroxyphenylacetic acids have been developed. Aldehydes (or ketones) were obtained from phenylacetic acids and α-hydroxyphenylacetic acids in good to excellent yields. The excellent functional group tolerance observed recommends that these methods be applied for the synthesis of medically important compounds. These reactions will expand the utility of decarboxylation in organic synthesis.

EXPERIMENTAL SECTION

General Information. All experiments were conducted with a sealed pressure vessel. Flash column chromatography was performed over silica gel (200−300 mesh). ^{1}H NMR spectra were recorded on a 400 M spectrometers. Chemical shifts (in ppm) were referenced to $CDCl_3$ (δ = 7.26 ppm) as an internal standard. ^{13}C NMR spectra were obtained by using the same NMR spectrometers and were calibrated with $CDCl_3$ (δ = 77.0 ppm). Unless otherwise noted, all starting materials obtained from commercial suppliers were used without further purification.

Procedure and Characterization Data for Products. *4-Methoxybenzaldehyde (**2**, CAS: 123-11-5).*[10] A sealed pressure vessel was charged with 2-(4-methoxyphenyl) acetic acid (83.0 mg, 0.5 mmol), $Cu(OAc)_2$ (9 mg, 10 mol %, 0.05 mmol), and DMSO (0.75 mL). The resulting solution was purged by O_2 and then sealed, with subsequent stirring at 120 °C under O_2 (monitored by TLC and GC). Upon completion of the reaction, ethyl acetate (20 mL) was added, the organic layer was washed with H_2O (20 mL) solution twice and brine (20 mL) once, and the combined aqueous layers was extracted with ethyl acetate (20 mL) twice. The combine organic layers were dried over anhydrous Na_2SO_4. The solvents were removed via rotary evaporator, and the residue was purified with flash chromatography (silica gel, ethyl acetate/petroleum ether = 50:1) to give 4-methoxybenzaldehyde **2** in 92% yield (62.6 mg) as a faint yellow oil liquid. ^{1}H NMR: (400 MHz, $CDCl_3$, ppm) δ 9.81 (1H, s), 7.77−7.75 (2H, m), 6.94−6.92 (2H, m), 3.81 (3H, m). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, ppm) δ 190.6, 164.4, 131.7, 129.7, 114.1, 55.3.

The same procedure was used for 2-hydroxy-2-(4-methoxyphenyl)-acetic acid **36** and gave 51.0 mg of 4-methoxybenzaldehyde **2** in 75% yield.

*2-Methoxybenzaldehyde (**3**, CAS: 135-02-4).*[10] 42% yield (28.6 mg) as a colorless crystal. ^{1}H NMR: (400 MHz, $CDCl_3$, ppm) δ 10.39 (1H, s), 7.74 (1H, dd, J = 7.6, 0.8 Hz), 7.73−7.44 (1H, m), 6.92 (q, J = 7.0 Hz). 3.83 (3H, s). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, ppm) δ 189.6, 161.8, 135.9, 128.3, 124.7, 120.5, 111.7, 55.5. Mp 35−39 °C.

*4-(tert-Butyl)benzaldehyde (**4**, CAS: 939-97-9).*[11] 87% yield (70.5 mg) as a faint yellow oil liquid. ^{1}H NMR: (400 MHz, $CDCl_3$, ppm) δ 9.96 (1H, s), 7.80 (2H, d, J = 8.0 Hz), 7.54 (2H, d, J = 8.0 Hz), 1.34 (9H, s). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, ppm) δ 191.9, 158.3, 134.0, 129.6, 125.9, 35.2, 31.0.

dx.doi.org/10.1021/jo402778p | J. Org. Chem. XXXX, XXX, XXX−XXX

*4-(Trifluoromethyl)benzaldehyde (**5**, CAS: 455-19-6).*[12] 94% yield (81.8 mg) as a faint yellow oil liquid. ^{1}H NMR: (400 MHz, $CDCl_3$, ppm) δ 10.07 (1H, s), 7.98 (2H, d, J = 8.4 Hz), 7.77 (2H, d, J = 8.4 Hz). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, ppm) δ 191.0, 138.7, 135.5 (q, J = 65.0 Hz), 129.8, 126.0 (d, J = 3.7 Hz), 123.4 (q, J_{CF_3} = 271.3 Hz, CF).

*2-(Trifluoromethyl)benzaldehyde (**6**, CAS: 447-61-0).*[12] 39% yield (34 mg) as a faint yellow oil liquid. ^{1}H NMR: (400 MHz, $CDCl_3$, ppm) δ 10.34 (1H, q, J = 2.4 Hz), 8.07−8.05 (1H, m), 7.74−7.71 (1H, m), 7.69−7.63 (2H, m). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, ppm) δ 188.7 (d, J = 2.5 Hz), 133.6, 133.5, 132.2, 130.8 (q, J = 32.3 Hz), 129.0, 126.0 (q, J = 5.7 Hz), 123.7 (q, J_{CF_3} = 272.7 Hz, CF).

*4-Chlorobenzaldehyde (**7**, CAS: 104-88-1).*[13] 75% yield (52.5 mg) as a colorless flaky crystal. ^{1}H NMR: (400 MHz, $CDCl_3$, ppm) δ 9.97 (1H, s), 7.81 (2H, d, J = 8.0 Hz), 7.49 (2H, d, J = 8.4 Hz). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, ppm) δ 190.8, 140.9, 134.7, 130.8, 129.4. Mp 45−47 °C.

The same procedure was used as for 2-(4-chlorophenyl)-2-hydroxyacetic acid **30** and gave 51.1 mg of 4-chlorobenzaldehyde **7** in 73% yield.

*3-Chlorobenzaldehyde (**8**, CAS: 587-04-2).*[14] 89% yield (62.3 mg) as a faint yellow oil liquid. ^{1}H NMR: (400 MHz, $CDCl_3$, ppm) δ 9.93 (1H, s), 7.80 (1H, d, J = 1.2 Hz), 7.72 (1H, d, J = 7.2 Hz), 7.55 (1H, dd, 8.4, 1.2 Hz), 7.44 (1H, 8.0 Hz). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, ppm) δ 190.7, 137.7, 135.3, 134.2, 130.3, 129.1, 127.9.

The same procedure was used for 2-(3-chlorophenyl)-2-hydroxyacetic acid **31** and gave 25.2 mg of 3-chlorobenzaldehyde **8** in 36% yield.

*2-Chlorobenzaldehyde (**9**, CAS: 89-98-5).*[14] 72% yield (50.4 mg) as a colorless oil liquid. ^{1}H NMR: (400 MHz, $CDCl_3$, ppm) δ 10.4 (1H, s), 7.88 (1H, dd, J = 3.2, 7.6 Hz), 7.51−7.47 (1H, m), 7.42−7.40 (1H, m), 7.37−7.33 (1H, m). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, ppm) δ 189.6, 137.8, 135.0, 132.4, 130.5, 129.2, 127.2.

The same procedure was used for 2-(2-chlorophenyl)-2-hydroxyacetic acid **29** and gave 48.3 mg of 2-chlorobenzaldehyde **9** in 69% yield.

*2-Fluorobenzaldehyde (**10**, CAS: 446-52-6).*[14] 62% yield (38 mg) as a faint yellow oil liquid. ^{1}H NMR: (400 MHz, $CDCl_3$, ppm) δ 10.32 (1H, s), 7.84−7.80 (1H, m), 7.59−7.53 (1H, m), 7.26−7.20 (1H, m), 7.15−7.10 (1H, m). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, ppm) δ 187.0 (d, J = 6.6 Hz), 164.5 (d, J_{CF_3} = 257.1 Hz, CF_3), 136.2 (d, J = 9.1 Hz), 128.6 (2C), 124.5 (d, J = 3.6 Hz), 116.4 (d, J = 20.3 Hz).

The same procedure was used for 2-(2-fluorophenyl)-2-hydroxyacetic acid **34** and gave 28.8 mg of 2-fluorobenzaldehyde **10** in 47% yield.

*4-Fluorobenzaldehyde (**11**, CAS: 459-57-4).*[15] 78% yield (48.4 mg) as a colorless oil liquid. ^{1}H NMR: (400 MHz, $CDCl_3$, ppm) δ 9.91 (1H, s), 7.86 (2H, dd, J = 8.8, 5.6 Hz), 7.15 (2H, t, J = 8.4 Hz). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, ppm) δ 190.3, 166.4 (d, J_{CF_3} = 254.9 Hz, CF), 132.9 (d, J = 2.4 Hz), 116.2 (d, J = 22.1 Hz).

The same procedure was used for 2-(4-fluorophenyl)-2-hydroxyacetic acid **32** and gave 37.8 mg of 4-fluorobenzaldehyde **11** in 61% yield.

*3-Fluorobenzaldehyde (**12**, CAS: 456-48-4).*[14] 65% yield (40.3 mg) as a faint yellow oil liquid. ^{1}H NMR: (400 MHz, $CDCl_3$, ppm) δ 9.98 (1H, d, J = 2.0 Hz), 7.67−7.65 (1H, m), 7.56−7.49 (2H, m), 7.34−7.29 (1H, m). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, ppm) δ 190.8 (d, J = 1.9 Hz), 163.0 (d, J_{CF_3} = 247.8 Hz, CF), 138.4 (d, J = 6.1 Hz), 130.7 (d, J = 7.6 Hz), 126.0 (d, J = 2.8 Hz), 121.5 (d, J = 21.5 Hz), 115.2 (d, J = 21.7 Hz).

The same procedure was used for 2-(3-fluorophenyl)-2-hydroxyacetic acid **33** and gave 35.9 mg of 3-fluorobenzaldehyde **12** in 58% yield.

*2-Bromobenzaldehyde (**13**, CAS: 6630-33-7).*[16] 70% yield (64.7 mg) as a faint yellow liquid. ^{1}H NMR: (400 MHz, $CDCl_3$, ppm) δ 10.22 (1H, s), 7.78−7.76 (1H, m), 7.52−7.50 (1H, m), 7.33−7.30 (2H, m). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, ppm) δ 191.2, 135.0, 133.5, 133.1, 129.5, 127.6, 126.7.

The same procedure was used for 2-(2-bromophenyl)-2-hydroxyacetic acid **35** and gave 48.1 mg of 2-bromobenzaldehyde **13** in 52% yield.

*4-Bromobenzaldehyde (**14**, CAS: 1122-91-4).*[10] 90% yield (83.2 mg) as a faint yellow solid liquid. ^{1}H NMR: (400 MHz, $CDCl_3$, ppm) δ 9.92 (1H, s), 7.69 (2H, d, J = 8.4 Hz), 7.62 (2H, d, J = 8.4 Hz). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, ppm) δ 190.8, 134.9, 132.2, 130.8, 129.5.

*3-Bromobenzaldehyde (**15**, CAS: 3132-99-8).*[17] 87% yield (80.5 mg) as a colorless oil liquid. ^{1}H NMR: (400 MHz, $CDCl_3$, ppm) δ 9.86 (1H, s), 7.88 (1H, d, J = 3.2 Hz), 7.71 (1H, dd, J = 7.6, 1.2 Hz), 7.66 (1H, dd, J = 8.0, 0.8 Hz), 7.32 (1H, t, J = 8.0 Hz). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, ppm) δ 190.4, 137.7, 136.9, 131.9, 130.4, 128.1, 123.0.

*4-Methylbenzaldehyde (**16**, CAS: 104-87-0).*[12] 45% yield (27.1 mg) as a faint yellow oil liquid. ^{1}H NMR: (400 MHz, $CDCl_3$, ppm) δ 9.95 (1H, s), 7.76 (2H, d, J = 8.0 Hz), 7.31 (2H, d, J = 8.0 Hz), 2.42 (3H, s). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, ppm) δ 191.9, 145.5, 134.2, 129.8, 129.6, 21.8.

*3-Methylbenzaldehyde (**17**, CAS: 620-23-5).*[12] 71% yield (42.6 mg) as a faint yellow oil liquid. ^{1}H NMR: (400 MHz, $CDCl_3$, ppm) δ 9.97 (1H, s), 7.67 (2H, d, J = 6.8 Hz), 7.41 (2H, d, J = 7.2 Hz), 2.42 (3H, s). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, ppm) δ 192.5, 138.9, 136.4, 135.2, 129.9, 128.8, 127.1, 21.1.

*1-Naphthaldehyde (**18**, CAS: 66-77-3).*[10] 83% yield (64.7 mg) as a faint yellow crystal. ^{1}H NMR: (400 MHz, $CDCl_3$, ppm) δ 10.39 (1H, s), 9.26 (1H, d, J = 8.8 Hz), 8.08 (1H, d, J = 8.0 Hz), 7.96 (1H, d, J = 6.2 Hz), 7.91 (1H, d, J = 8.4 Hz). 7.71−7.68 (1H, m), 7.63−7.57 (1H, m). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, ppm) δ 193.4, 136.5, 135.2, 133.6, 131.4, 130.5, 129.0, 128.4, 126.9, 124.8 (2C).

*2-Naphthaldehyde (**19**, CAS: 66-99-9).*[14] 93% yield (72.5 mg) as a faint yellow crystal. ^{1}H NMR: (400 MHz, $CDCl_3$, ppm) δ 10.14 (1H, s), 8.31 (1H, s), 7.99−7.88 (4H, m), 7.65−7.55 (2H, m). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, ppm) δ 192.1, 136.4, 134.4, 134.4, 132.6, 129.4, 129.0 (2C), 128.0, 127.0, 122.7.

*Benzaldehyde (**20**, CAS: 100-52-7).*[10] 88% yield (46.6 mg) as a colorless liquid. ^{1}H NMR: (400 MHz, $CDCl_3$, ppm) δ 10.01 (1H, s), 7.88−7.86 (2H, m), 7.64−7.60 (1H, m), 7.54−7.50 (2H, m). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, ppm) δ 192.3, 136.4, 134.4, 129.7, 128.9.

The same procedure was used for 2-hydroxy-2-phenylacetic acid **28** and gave 38.7 mg of benzaldehyde **20** in 73% yield.

*Nicotinaldehyde (**21**, CAS: 500-22-1).*[18] 70% yield (37.5 mg) as a colorless liquid. ^{1}H NMR: (400 MHz, $CDCl_3$, ppm) δ 10.03 (1H, s), 9.99 (1H, d, J = 2.0 Hz), 8.76−8.74 (1H, m), 8.10−8.07 (1H, m), 7.42−7.39 (1H, m). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, ppm) δ 190.3, 154.0, 151.2, 135.2, 130.8, 123.4.

*Thiophene-2-carbaldehyde (**22**, CAS: 98-03-3).*[12] 72% yield (40.3 mg) as a pale yellow oil liquid. ^{1}H NMR: (400 MHz, $CDCl_3$, ppm) δ 9.88 (1H, d, J = 1.2 Hz), 7.74−7.71 (2H, m), 7.17−7.15 (1H, m). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, ppm) δ 182.7, 143.7, 136.2, 134.8, 128.1.

*2-Nitrobenzaldehyde (**23**, CAS: 552-89-6).*[19] 46% yield (34.7 mg) as a flaky crystal. ^{1}H NMR: (400 MHz, $CDCl_3$, ppm) δ 10.36 (1H, s), 8.07 (1H, d, J = 7.6 Hz), 7.90 (1H, d, J = 7.2 Hz), 7.80−7.73 (2H, m). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, ppm) δ 188.1, 149.4, 134.0, 133.6, 131.2, 129.5, 124.3.

*1-Methyl-2-nitrobenzene (**23-b**, CAS: 88-72-2).*[20] 52% yield (35.6 mg) as a yellow liquid. ^{1}H NMR: (400 MHz, $CDCl_3$, ppm) δ 7.96 (1H, d, J = 8.4 Hz), 7.49 (1H, t, J = 7.2 Hz), 7.35−7.32 (2H, m), 2.60 (3H, s). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, ppm) δ 133.5, 132.9, 132.7, 126.8, 124.6.

*4-Nitrobenzaldehyde (**24**, CAS: 555-16-8).*[19] 55% yield (41.5 mg) as a yellow crystal. ^{1}H NMR: (400 MHz, $CDCl_3$, ppm) δ 10.14 (1H, s), 8.35 (2H, d, J = 8.4 Hz), 8.06 (2H, d, J = 8.4 Hz). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, ppm) δ 190.3, 151.0, 140.0, 130.4, 124.2.

*1-Methyl-4-nitrobenzene (**24-b**, CAS: 99-99-0).*[20] 44% yield (30.1 mg) as a yellow crystal. ^{1}H NMR: (400 MHz, $CDCl_3$, ppm) δ 8.08 (2H, d, J = 8.8 Hz), 7.29 (2H, d, J = 8.4 Hz), 2.45 (3H, s). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, ppm) δ 145.9 (2C), 129.7, 123.4, 21.5. Mp 52−54 °C.

dx.doi.org/10.1021/jo402778p | J. Org. Chem. XXXX, XXX, XXX−XXX

*1-(4-Isobutylphenyl)ethanone (**25**, CAS: 38861-78-8).*[21] 31% yield (27.2 mg) as a colorless liquid. ^{1}H NMR: (400 MHz, $CDCl_3$, ppm) δ 7.83 (2H, d, J = 8.0 Hz), 7.18 (2H, d, J = 8.0 Hz), 2.51 (3H, d, J = 12.0 Hz), 2.47 (2H, s), 1.90−1.80 (1H, m), 0.87 (6H, d, J = 6.4 Hz). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, ppm) δ 197.4, 147.3, 134.8, 129.0, 128.1, 45.1, 29.9, 26.2, 22.1

*4-Propoxybenzaldehyde (**41**, CAS: 5736-85-6).*[22] 66% yield (54.1 mg) as a colorless liquid. ^{1}H NMR: (400 MHz, $CDCl_3$, ppm) δ 9.86 (1H, s), 7.81 (2H, ddd, J = 11.2, 9.2, 4.4, 2.4 Hz), 6.98 (2H, d, J = 8.8 Hz), 3.99 (2H, t, J = 6.8 Hz), 1.83 (2H, ddd, J = 28, 21.2, 18.0, 7.2 Hz), 1.04 (3H, t, J = 7.6 Hz). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, ppm) δ 190.7, 164.2, 131.9, 129.7, 114.7, 69.8, 22.3, 10.4.

*Cyclopentyl(phenyl)methanone (**27**, CAS: 5422-88-8).*[23] 93% yield (80.9 mg) as a colorless liquid. ^{1}H NMR: (400 MHz, $CDCl_3$, ppm) δ 7.98 (2H, dd, J = 6.4, 0.8 Hz), 7.55−7.51 (1H, m), 7.46−7.43 (2H, m), 3.73−3.70 (1H, m), 1.95−1.90 (4H, m), 1.75−1.64 (4H, m). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, ppm) δ 202.7, 137.0, 132.6, 128.5, 128.5, 46.3, 30.0, 26.3.

*Benzophenone (**42**, CAS: 119-61-9).*[24] 95% yield (86.5 mg) as a colorless oil liquid. ^{1}H NMR: (400 MHz, $CDCl_3$, ppm) δ 7.80 (4H, d, J = 7.2 Hz), 7.57 (2H, t, J = 7.6 Hz), 7.47 (4H, t, J = 7.6 Hz). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, ppm) δ 196.5, 137.5, 132.3, 129.9, 128.1.

*Cyclohexyl(phenyl)methanone (**43**, CAS: 712-50-5).*[25] 95% yield (89.3 mg) as a colorless oil liquid. ^{1}H NMR: (400 MHz, $CDCl_3$, ppm) δ 7.98 (2H, d, J = 8.0 Hz), 7.57 (1H, t, J = 6.8 Hz), 7.48 (2H, t, J = 7.6 Hz), 3.34−3.26 (1H, m), 1.95−1.85 (4H, m), 1.78−1.76 (1H, m), 1.59−1.25 (5H, m). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, ppm) δ 203.6, 136.2, 132.5, 128.4, 128.1, 45.4, 29.3, 25.8, 25.7.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

General experimental considerations and copies of NMR spectra for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

The authors are grateful for financial support from the National Science Foundation of China (21202049), the Recruitment Program of Global Experts (1000 Talents Plan), Fujian Hundred Talents Program, and Research Funds of Huaqiao University.

■ REFERENCES

(1) (a) Jun, C.-H. *Chem. Soc. Rev.* **2004**, *33*, 610−618. (b) Tobisu, M.; Chatani, N. *Chem. Soc. Rev.* **2008**, *37*, 300−307. (c) Crabtree, R. H. *Chem. Rev.* **1985**, *85*, 245−269. (d) Murakami, M.; Matsuda, T. *Chem. Commun.* **2011**, *47*, 1100−1105. (e) Masarwa, A.; Marek, I. *Chem.—Eur. J.* **2010**, *16*, 9712−9721.

(2) (a) Tanaka, D.; Romeril, S. P.; Myers, A. G. *J. Am. Chem. Soc.* **2005**, *127*, 10323−10333. (b) Myers, A. G.; Tanaka, D.; Mannion, M. R. *J. Am. Chem. Soc.* **2002**, *124*, 11250−11251.

(3) (a) Goossen, L. J.; Rodríguez, N.; Goossen, K. *Angew. Chem., Int. Ed.* **2008**, *47*, 3100−3120. (b) Goossen, L. J.; Rodríguez, N.; Melzer, B.; Linder, C.; Deng, G.; Levy, L. M. *J. Am. Chem. Soc.* **2007**, *129*, 4824−4833.

(4) (a) Forgione, P.; Brochu, M.-C.; St-Onge, M.; Thesen, K. H.; Bailey, M. D.; Bilodeau, F. *J. Am. Chem. Soc.* **2006**, *128*, 11350−11351. (b) Bilodeau, F.; Brochu, M.-C.; Guimond, N.; Thesen, K. H.; Forgione, P. *J. Org. Chem.* **2010**, *75*, 1550−1560.

(5) (a) Dzik, W. I.; Lange, P. P.; Goossen, L. J. *Chem. Sci.* **2012**, *3*, 2671−2678. (b) Shang, R.; Liu, L. *Sci. China Chem.* **2011**, *54*, 1670−1687. (c) Rodriguez, N.; Goossen, L. J. *Chem. Soc. Rev.* **2011**, *40*, 5030−5048.

(6) (a) Torregrosa, R. R. P.; Ariyarathna, Y.; Chattopadhyay, K.; Tunge, J. A. *J. Am. Chem. Soc.* **2010**, *132*, 9280−9282. (b) Shang, R.; Yang, Z.-W.; Wang, Y.; Zhang, S.-L.; Liu, L. *J. Am. Chem. Soc.* **2010**, *132*, 14391−14393. (c) Shang, R.; Ji, D.-S.; Chu, L.; Fu, Y.; Liu, L. *Angew. Chem., Int. Ed.* **2011**, *50*, 4470−4474. (d) Zhang, C.; Seidel, D. *J. Am. Chem. Soc.* **2010**, *132*, 1798−1799.

(7) (a) Shang, R.; Huang, Z.; Chu, L.; Fu, Y.; Liu, L. *Org. Lett.* **2011**, *13*, 4240−4243. (b) Shang, R.; Huang, Z.; Xiao, X.; Lu, X.; Fu, Y.; Liu, L. *Adv. Synth. Catal.* **2012**, *354*, 2465−2472.

(8) (a) Song, Q.; Feng, Q.; Zhou, M. *Org. Lett.* **2013**, *15*, 5990−5993. (b) Song, Q.; Feng, Q.; Yang, K. *Org. Lett.* **2014**, *16*, 624−627. (c) Feng, Q.; Song, Q. *Adv. Synth. Catal.* **2014**, *356*, DOI: 10.1002/adsc.201301001.

(9) Zhang, L.; Bi, X.; Guan, X.; Li, X.; Liu, Q.; Barry, B.-D.; Liao, P. *Angew. Chem., Int. Ed.* **2013**, *52*, 11303−11307.

(10) Zhu, Y.; Zhao, B.; Shi, Y. *Org. Lett.* **2013**, *15*, 992−995.

(11) Wang, T.; Jiao, N. *J. Am. Chem. Soc.* **2013**, *135*, 11692−11695.

(12) Tang, L.; Sun, H.; Li, Y.; Zha, Z.; Wang, Z. *Green Chem.* **2012**, *14*, 3423−3428.

(13) Kawahara, R.; Fujita, K.-i.; Yamaguchi, R. *Angew. Chem., Int. Ed.* **2012**, *51*, 12790−12794.

(14) Wu, X.-F. *Chem.—Eur. J.* **2012**, *18*, 8912−8915.

(15) Tang, L.; Guo, X.; Li, Y.; Zhang, S.; Zha, Z.; Wang, Z. *Chem. Commun.* **2013**, *49*, 5213−5215.

(16) Hajimohammadi, M.; Safari, N.; Mofakham, H.; Deyhimi, F. *Green Chem.* **2011**, *13*, 991−997.

(17) Karimi, B.; Badreh, E. *Org. Biomol. Chem.* **2011**, *9*, 4194−4198.

(18) Korsager, S.; Taaning, R. H.; Lindhardt, A. T.; Skrydstrup, T. *J. Org. Chem.* **2013**, *78*, 6112−6120.

(19) Sun, H.-y.; Hua, Q.; Guo, F.-f.; Wang, Z.-y.; Huang, W.-X. *Adv. Synth. Catal.* **2012**, *354*, 569−573.

(20) Yadav, R. R.; Vishwakarma, R. A.; Bharate, S. B. *Tetrahedron Lett.* **2012**, *53*, 5958−5960.

(21) Liu, R.; Yuan, G.; Joe, C. L.; Lightburn, T. E.; Tan, K. L.; Wang, D. *Angew. Chem., Int. Ed.* **2012**, *51*, 6709−6712.

(22) Liu, W.; Wang, Y.; Sun, M.; Zhang, D.; Zheng, M.; Yang, W. *Chem. Commun.* **2013**, *49*, 6042−6044.

(23) Li, M.; Wang, C.; Ge, H. *Org. Lett.* **2011**, *13*, 2062−2064.

(24) Basavaraju, K. C.; Sharma, S.; Maurya, R. A.; Kim, D.-P. *Angew. Chem., Int. Ed.* **2013**, *52*, 6735−6738.

(25) Sumino, S.; Ui, T.; Ryu, I. *Org. Lett.* **2013**, *15*, 3142−3145.