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Iodide-Catalyzed Reductions: Development of a Synthesis of Phenylacetic Acids

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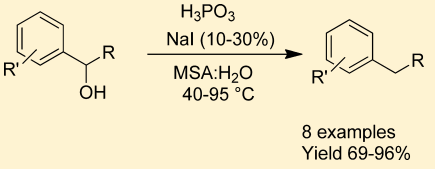
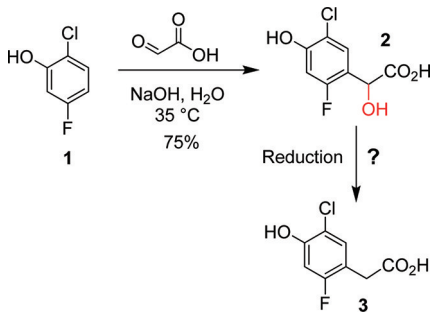
Supporting Information

ABSTRACT: A new convenient and scalable synthesis of phenylacetic acids has been developed via the iodide catalyzed reduction of mandelic acids. The procedure relies on in situ generation of hydroiodic acid from catalytic sodium iodide, employing phosphorus acid as the stoichiometric reductant.



Phenylacetic acids are an important class of compounds prevalent in both pharmaceutical and natural products. They exhibit a diverse range of biological properties including anti-inflammatory, antifungal, antityrosinase, and antimicrobial activity.[1] For example, Ibuprofen and Diclofenac are two nonsteroidal anti-inflammatory drugs that contain a phenylacetic acid moiety. During the development of a synthesis for a recent clinical drug candidate, we required a scalable method for the preparation of the key phenylacetic acid building block **3** (Scheme 1). Although there are an assortment of available

Scheme 1. Proposed Synthesis



methods[2] to prepare phenylacetic acids and esters, a number of these require expensive metal catalysts; for example, the Pd-catalyzed α-arylation of esters or the Pd- or Rh-catalyzed carbonylation of benzyl halides. During the process of route selection and optimization, we focus on the identification of robust, efficient, and cost-effective processes, while observing the principles of green chemistry.[3] In fact, throughout the chemical industry there has been a growing drive to reduce any unnecessary environmental burden created during processing. A convenient route to phenylacetic acids entails reduction of the α-hydroxyl group of the corresponding mandelic acids.[4] Mandelic acids are attractive precursors because a large number are commercially available or readily prepared,[5] as in the case of mandelic acid **2**, from which **3** would be derived via reduction. We recently reported a palladium-catalyzed deoxygenation of mandelate esters through activation as phosphate esters followed by palladium-catalyzed reduction with sodium borohydride.[4g] Although this method had a good substrate scope, it requires the synthesis of a mandelate ester from the corresponding acid. Furthermore, for the synthesis of **3**, it would require protection of the phenol to avoid the formation of the phosphate ester at this position. We therefore continued to explore alternative conditions for the reduction that would overcome these two limitations.

The mandelic acid **2** was prepared by treatment of commercially available 2-chloro-5-fluorophenol **1** with glyoxylic acid and aqueous NaOH at 35 °C (Scheme 1).[6] The target product **2** was obtained in high purity and good yield. Unfortunately, a screen of the currently known reduction methods either did not lead to the desired deoxygenation or did not meet our criteria for scale-up. For example, attempts at metal-catalyzed hydrogenolysis gave poor conversion to the desired phenylacetic acid product. In general, conditions that favored cleavage of the C−O bond led to hydrodechlorination as a competing side reaction. Silane-mediated hydrogenation[7] was also evaluated but required excess reagents and multiple charges of reductant to obtain full conversion.

A review of the literature revealed a century-old paper by von Kostanecki and co-workers[8−10] that described an interesting reduction process (Scheme 2). The reaction involved the treatment of mandelonitrile **4** with fuming hydroiodic acid at reflux, which simultaneously reduced the C−O bond of the benzyl alcohol, cleaved the methyl ether, and hydrolyzed the nitrile functional group to furnish the phenylacetic acid **5**.

To explore this reaction for the synthesis of our desired phenylacetic acid **3**, the starting mandelonitrile **8** was prepared from commercially available 2-fluoro-4-methoxybenzaldehyde **6**

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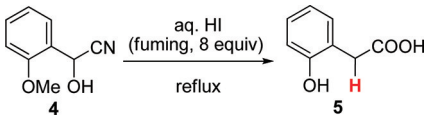
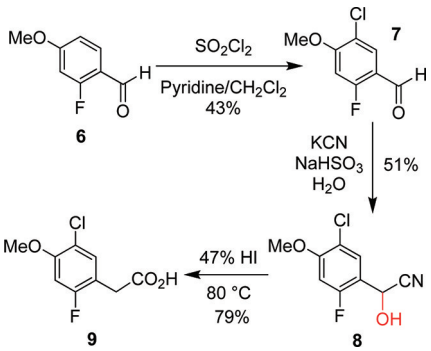
Scheme 2



using standard conditions. It was expected that the methyl ether would cleave during the reduction, ultimately affording the target compound **3**.

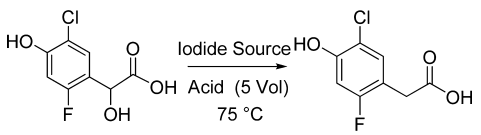
Following the original procedure,[8] subjection of mandelonitrile **8** to hydroiodic acid at 80 °C led to clean deoxygenation, along with nitrile hydrolysis, to provide **9** in good yield (79%) (Scheme 3). However, under these conditions the cleavage of

Scheme 3. Synthesis via Mandelonitrile 8



the methyl-ether was only detected as a minor side reaction (<10%). To our delight, treatment of the mandelic acid **2** to the same conditions led to a very clean formation of the desired product (Table 1, entry 1). It should be noted that no reductive dehalogenation was observed for either substrate.

Table 1. Reaction Optimization[a]



	iodide (equiv)	acid (wt %)	reducing agent (equiv)	yield (%)
1	none	HI (47)		100
2	NaI (1)	MSA (50)		41
3	NaI (1)	HCl (37)		45
4	NaI (1)	H_3PO_3 (50)		65
5	NaI (1)	MSA (50)	H_3PO_3 (3)	98
6	NaI (1)	HCl (37)	H_3PO_3 (3)	99
7	NaI (1)	MSA (50)	NaH_2PO_2 (3)	92
8	NaI (0.1)	MSA (50)	H_3PO_3 (1.5)	100
9	NaI (0.1)	HCl (37)	H_3PO_3 (1.5)	98
10	KI (0.1)	MSA (50)	H_3PO_3 (1.5)	97
11	NH_4I (0.1)	MSA (50)	H_3PO_3 (1.5)	99
12	LiI (0.1)	MSA (50)	H_3PO_3 (1.5)	99
13	NaBr (0.1)	MSA (50)	H_3PO_3 (1.5)	0

[a]Reactions performed at 0.5 g (2.27 mmol) scale, 18 h.

Our ultimate goal was to identify a method that would be suitable to prepare **3** on a commercial scale with the criteria that it be operationally convenient, inexpensive, robust, and conforming to the elements of green chemistry. With this in mind, the use of hydroiodic acid as both the solvent and stoichiometric reductant presented a number of concerns because it is relatively expensive, highly corrosive, and classified as a Federal DEA List I Chemical. As a result, an extensive screen was performed to identify milder conditions (Table 1). Initially, our objective was to avoid the direct handling of HI; therefore, its in situ formation was explored. Experiments demonstrated that when HI was replaced with iodide (1 equiv NaI) and an alternative acid, only modest conversion to the desired product was observed. Methanesulfonic acid, hydrochloric acid, and phosphorus acid were most effective, providing the phenylacetic acid in yields ranging from 41 to 65% (Table 1, entries 2–4). However, it should be noted that in these screens only 1 equiv of NaI was employed in comparison to the use of excess HI as a solvent. Interestingly, in the reactions where methanesulfonic acid (MSA) or hydrochloric acid were employed, the reactions turned dark and formation of solid iodine was observed.[11] Thus, the regeneration of HI by the reduction of the iodine was explored. From an extensive screen of reducing agents,[12] sodium hypophosphite (NaH_2PO_2) and phosphorus acid (H_3PO_3) were the most promising and were evaluated further. H_3PO_3 in combination with either HCl or MSA performed well and increased the yield to ≥98% (Table 1, entries 5–6). Having established proof-of-principle for regeneration of HI through a stoichiometric reductant, we sought to reduce the total amount of iodide required for the reaction. Gratifyingly, the reaction proceeded in excellent yield using only catalytic quantities of NaI (10 mol %), without compromising conversion or selectivity (Table 1, entries 8–9). Alternative halide sources were also evaluated, and although the reduction proceeded well with a variety of iodides (KI, NH_4I, LI, Table 1, entries 10–12), a bromide (NaBr) failed to promote the desired reaction (Table 1, entry 13). It is noteworthy that our optimized conditions are similar to the related work of Fry and coworkers, who previously reported a reduction of aryl ketones and benzhydrols with H_3PO_2 and I_2 in refluxing acetic acid.[9g,h]

Having established an optimal protocol, we next investigated the generality and the scope of the reaction. As illustrated in Table 2 (entries 1–4), a wide range of substrates with a variety of functional groups were well-tolerated in this transformation. Mandelic acids containing both electron-rich and -poor aromatic rings were reduced to the corresponding phenylacetic acid in good to excellent yields. In particular, aromatic bromides such as 4-bromomandelic acid (Table 2, entry 2) could be successfully reduced without concomitant C–Br cleavage, a limitation of the alternative reduction methods. The reaction also succeeded in the precence of α-substitution, providing α-substituted phenylacetic acids in high yield (Table 2, entries 5–7). It is noteworthy that when the reaction is performed employing enantiopure 2-hydroxy-2-phenylpropanoic acid, complete racemization is observed.

In addition to the reduction of mandelic acids, the method was also readily extended to the reduction of other functional groups (Scheme 4). For example, the ketone group of phenylglyoxylic acid **10** was efficiently reduced to afford the corresponding phenylacetic acid **11**. In addition, an aryl group could replace the carboxylic acid moiety, enabling access to the 1,1-diarylethane motif **13** from 1,1-diphenylethanols **12**.[9g] Furthermore, sulfoxides could be reduced to sulfides using this approach.

The chemistry to prepare **3** via this methodology has been successfully performed on a multi-kilogram scale. In practice, the mandelic acid **2** was crystallized directly from the reaction

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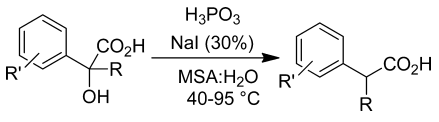
Table 2. Substrate Scope[a]



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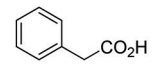
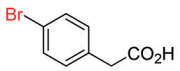
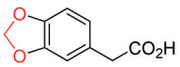
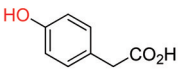
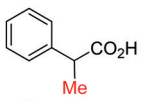
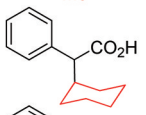
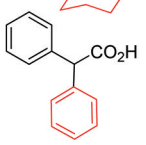
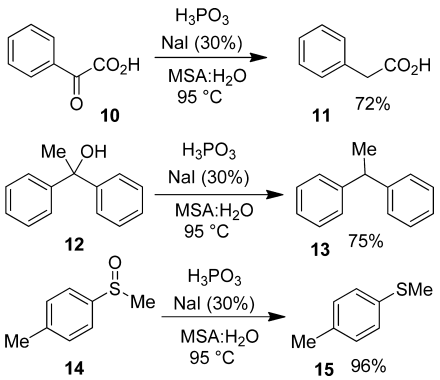
1		95	69%
2		95	87%
3		40	93%
4		40	69%
5		95	96%
6		95	92%
7		95	93%

[a]Reactions performed at 1 g scale.

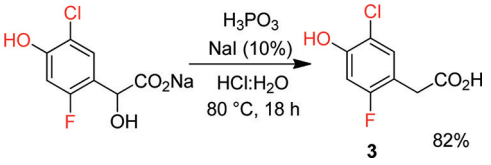
Scheme 4. Extension to the Reduction of Other Functional Groups



mixture as the monosodium salt and isolated by filtration. This volumetrically efficient chemistry allowed for the manufacture of 25 kg of monosodium salt in a single batch using a 100 L reactor (93% yield). Application of our iodide-catalyzed reduction afforded the desired phenylacetic acid **3** in 84% yield on similar scale. The phenylacetic acid was isolated from the reaction by simple cooling crystallization from the end-of-reaction solution. This route was a particularly attractive approach to **3** because it involved a limited number of processing operations and was highly volumetrically efficient. Both attributes are advantageous because they shorten cycle times and reduce manufacturing costs.

Additional research showed that 8 M HCl[13,14] could be used in place of MSA with no significant difference in reaction yield or purity profile. This afforded isolated product that was comparable to the product isolated from the previous conditions (Scheme 5).

Scheme 5



In summary, we have demonstrated an efficient and practical new procedure for the synthesis of functionally diverse phenylacetic acids from readily available mandelic acid precursors. Our procedure relies on the in situ formation of hydroiodic acid from catalytic sodium iodide, with phosphorus acid as the terminal reductant.

EXPERIMENTAL SECTION

General Experimental Methods. Flash chromatography was performed on silica gel 60 (230−400 mesh) in glass columns or prepacked cartridges using HPLC-grade solvents. Analytical thin layer chromatography was performed on 0.25 mm silica gel plates. Visualization was accomplished with UV light and anisaldehyde, ceric ammonium nitrate stain, potassium permanganate stain, or phosphomolybdic acid. Commercial reagents and solvents were used as received and were not purified unless otherwise stated. All air and moisture sensitive reactions were performed under a nitrogen atmosphere. ^{1}H NMR and ^{13}C NMR were recorded in $CDCl_3$ using a 400 mHz spectrometer unless otherwise stated. For NMR in $CDCl_3$, chemical shifts are reported in ppm relative to internal tetramethylsilane (δ 0.00 ppm) for ^{1}H and $CDCl_3$ for ^{13}C. Purity analyzed by HPLC (LCAP = liquid chromatography area percent, LCWP = liquid chromatography weight percent).

5-Chloro-2-fluoro-4-methoxybenzaldehyde (7). 2-Fluoro-4-methoxybenzaldehyde (28.8 g, 187 mmol) was dissolved in dichloromethane (35 mL). Pyridine (0.4 mL, 5 mmol) was added, followed by addition of sulfuryl chloride (18.2 mL, 224 mmol). The reaction mixture was stirred at rt overnight and then diluted with dichloromethane (250 mL) and quenched with saturated aq sodium bicarbonate (150 mL). The phases were separated, and the organic phase was washed with additional saturated aq sodium bicarbonate (150 mL), followed by 10 wt % aq sodium sulfite (100 mL). The organic phase was dried over sodium sulfate, filtered, and evaporated to dryness. The residue was recrystallized from refluxing methylcyclohexane (200 mL), affording the target compound as an off-white crystalline solid (15.0 g, 43% yield): mp 106 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ ppm 10.19 (s, 1H), 7.89 (d, $^{4}J_{H,F}$ = 7.2 Hz, 1H), 6.72 (d, $^{3}J_{H,F}$ = 11.7 Hz, 1H), 3.99 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ ppm 184.8, 164.6 ($^{1}J_{C,F}$ = 261.2 Hz), 161.0 ($^{3}J_{C,F}$ = 10.3 Hz), 129.3, 119.5, 117.7 ($^{3}J_{C,F}$ = 9.5 Hz), 100.3 ($^{2}J_{C,F}$ = 26.9 Hz), 56.9. HRMS: *m*/*z* Calcd. for $C_8H_7ClFO_2$ $(M + H)^+$: 189.0113. Found: 189.0108. IR: 1678, 1610, 1574, 1483, 1455, 1437, 1403, 1332, 1272, 1225, 1180, 1141, 1043, 981, 903, 836, 662 cm^{-1}.

2-(5-Chloro-2-fluoro-4-methoxyphenyl)-2-hydroxyacetonitrile (8). 5-Chloro-2-fluoro-4-methoxybenzaldehyde (9.43 g, 50 mmol) was suspended in water (200 mL) and sodium bisulfite (10.46 g, 100 mmol) was added in one portion. The reaction mixture was heated to 45 °C for 3.5 h and then cooled to rt. A solution of potassium cyanide (13.02 g, 200 mmol) in water (50 mL) was added while keeping an internal temperature of 0−10 °C. The mixture was warmed to rt and aged for 3 h. It was diluted with MTBE (100 mL) and the pH was adjusted to 7.2 using acetic acid. The layers were separated and the aq layer was extracted with MTBE (50 mL). The combined organic layers were washed with saturated aq sodium bicarbonate (50 mL) and brine (50 mL). The organic phase was dried

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over magnesium sulfate, filtered, and evaporated to dryness. The residue was purified by chromatography on silica gel (hexanes/ethyl acetate 4:1 → 2:1), affording the target compound as a yellow crystalline solid (5.46 g, 51% yield): mp 84 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ ppm 7.63 (d, $^4J_{H,F}$ = 7.6 Hz, 1H), 6.75 (d, $^3J_{H,F}$ = 11.5 Hz, 1H), 5.71 (d, J = 6.4 Hz, 1H), 3.93 (s, 3H), 2.81 (d, J = 6.1 Hz, 1H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ ppm 159.0 ($^1J_{C,F}$ = 250.6 Hz), 157.2 ($^3J_{C,F}$ = 10.4 Hz), 129.1, 118.4, 117.7, 115.2 ($^3J_{C,F}$ = 14.8 Hz), 100.6 ($^2J_{C,F}$ = 26.9 Hz), 57.1, 56.6. HRMS: m/z Calcd. for $C_8H_7ClFO_2$ (M − CN): 189.0113. Found: 189.0113. IR: 3428, 1622, 1585, 1496, 1467, 1443, 1397, 1306, 1242, 1197, 1138, 1074, 1050, 1029, 985, 935, 887, 832, 819, 732, 706 cm^{-1}.

2-(5-Chloro-2-fluoro-4-methoxyphenyl)acetic acid (9). 2-(5-Chloro-2-fluoro-4-methoxyphenyl)-2-hydroxyacetonitrile (500 mg, 2.32 mmol) was suspended in hydroiodic acid (2 mL) and heated to 80 °C for 15 h. The reaction mixture was cooled to rt and water was added (10 mL). The precipitated solids were isolated by vacuum filtration and rinsed with water (3 × 2 mL). The material was dried on the filter under a stream of nitrogen, affording the target compound as a brown crystalline solid (400 mg, 80% yield): mp 165 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ ppm 7.28 (d, $^4J_{H,F}$ = 7.6 Hz, 1H), 6.71 (d, $^3J_{H,F}$ = 10.9 Hz, 1H), 3.89 (s, 3H), 3.64 (s, 2H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ ppm 176.2, 160.0 ($^1J_{C,F}$ = 247.1 Hz), 155.4 ($^3J_{C,F}$ = 10.4 Hz), 131.9, 117.5, 112.9 ($^3J_{C,F}$ = 17.3 Hz), 100.4 ($^2J_{C,F}$ = 27.8 Hz), 56.4, 32.2. HRMS: m/z Calcd. for $C_9H_9ClFO_3$ (M + H)$^+$: 219.0219. Found: 219.0217. IR: 3431, 1699, 1624, 1502, 1451, 1409, 1305, 1240, 1203, 1189, 1138, 1052, 910, 886, 843, 828, 725 cm^{-1}.

Sodium 2-(5-Chloro-2-fluoro-4-hydroxyphenyl)-2-hydroxyacetate. A 100 L jacketed reactor was set at 5 °C and purged with nitrogen. 2-Chloro-5-fluorophenol (14.000 kg, 95.9 mol, 1.0 equiv), sodium chloride (4.764 kg, 81.5 mol, 0.85 equiv), glyoxylic acid (50 wt %, 17.041 kg, 115.1 mol, 1.2 equiv), and water (15.260 kg, 1.09 vol) were charged to the reactor. The reaction temperature was maintained below 40 °C, and 10 N sodium hydroxide (26.237 kg, 172.6 mol, 1.8 equiv) was added to the reactor (typically pH 9 ± 0.5 at end of the addition). The reaction was heated to 35 °C for ≥21 h until reaction completion (target is ≤3% 2-chloro-5-fluorophenol), then cooled to 20 °C. The pH was adjusted to 5.9 ± 0.1 by charging concd HCl at a rate to maintain the temperature below 40 °C. The reactor contents were cooled to 5 °C over a period of 4 h and aged for ≥2 h. The mixture was filtered, and the solid product was washed with aqueous sodium chloride solution cooled to 5 °C (sodium chloride (2.800 kg, 47.9 mol, 0.5 equiv) and water (25.200 kg)). The product was dried under a vacuum to yield 24.8 kg, 21.593 kg (corrected), 89.1 mol, 93%: mp 101 °C; ^{1}H NMR (DMSO-d_6, 400 MHz) δ ppm 7.14 (d, J = 7.63 Hz, 1H), 6.68 (d, J = 11.35 Hz, 1H), 4.62 (s, 1H), 3.41 (br s, 2H); ^{13}C NMR (DMSO-d_6, 101 MHz) δ ppm 174.1, 160.1, 157.7, 153.1, 153.0, 128.5, 122.4, 114.7, 103.5, 103.3, 66.9. HRMS: m/z calcd for $C_8H_6ClFNaO_4$ (M + H)$^+$: 242.9836. Found: 242.9832. IR: 3653, 3560, 3495, 3324, 2435, 1688, 1613, 1566, 1511, 1323, 1287, 1241, 1127 cm^{-1}.

2-(5-Chloro-2-fluoro-4-hydroxyphenyl)acetic Acid (3). A jacketed reactor was set at 15 ± 10 °C and purged with nitrogen prior to proceeding. The reactor was then charged with 3-chloro-6-fluoro-4-hydroxy-mandelic acid sodium salt (11.7 g (adjusted for 85% LCWP), 41.2 mmol, 1.0 equiv), sodium iodide (617.5 mg, 4.12 mmol, 0.10 equiv), phosphorous acid (3.38 g, 41.2 mmol, 1.0 equiv), water (25 mL, 2.5 vol), and concd HCl (25 mL, 2.5 vol). The stirred mixture was heated to an internal temperature of 80 ± 5 °C for 18 h until reaction completion (target is <0.5 LCAP mandelic acid). The reaction starts homogeneous then goes heterogeneous after around 5 h because of the low solubility of the product in HCl. The reaction was cooled to 0 ± 5 °C over a period of 4 h and held at 0 °C for 3 h. The mixture was filtered and the solid product washed with cold brine (12 mL) to provide solid (10.54 g). The crude product was loaded back into a flask and slurried with water (50 mL) for 17 h. The mixture was cooled to 0 °C and held at 0 °C for 3 h. The mixture was filtered and the solid product washed with cold water (6 mL) to provide solid (6.91 g, 82% yield): mp 140 °C; ^{1}H NMR (DMSO-d_6, 400 MHz) δ ppm 12.43 (br s, 1H), 10.54 (br s, 1H), 7.32 (d, J = 8.02 Hz, 1H), 6.75 (d, J = 10.95 Hz, 1H), 3.50 (s, 2H); ^{13}C NMR (DMSO-d_6, 101 MHz) δ ppm 171.7, 160.6, 158.2, 153.1, 152.9, 132.0, 114.7, 113.9, 113.7, 103.7, 103.4, 33.1. HRMS: m/z calcd for $C_8H_7ClFO_3$ (M + H)$^+$: 205.0068. Found: 205.0064. IR: 3399, 2961, 1694, 1622, 1587, 1501, 1444, 1423, 1405, 1242, 1203, 1127 cm^{-1}.

General Procedures for Reduction. *Procedure A.* A 20 mL Wheaton vial equipped with a stirbar was charged with 1.0 g of substrate, sodium iodide (0.3 equiv), and phosphorous acid (1.5 equiv). The vial was flushed with N_2 and charged with 1.7 mL of H_2O and 3.3 mL of methanesulfonic acid. The reaction was then heated to 95 °C and monitored by LC until no further conversion to product was observed. When complete, the reaction was cooled to rt and worked up accordingly.

Procedure B. A 20 mL Wheaton vial equipped with a stirbar was charged with 1.0 g of substrate, sodium iodide (0.3 equiv), and phosphorous acid (1.5 equiv). The vial was flushed with N_2 and charged with 3.0 mL of H_2O and 2.0 mL of methanesulfonic acid. The reaction was then heated to 40 °C and monitored by LC until no further conversion to product was observed. The reaction was cooled to rt and worked up accordingly.

Phenylacetic Acid[15] (Table 2, Entry 1). Procedure A was followed using mandelic acid (1.0 g, 6.6 mmol). The reaction was heated for 2 days until conversion was complete. Work-up was performed by extraction into isopropyl acetate (IPAC) (2 × 5 vol) followed by purification by column chromatography (SiO_2; IPAC). Product was isolated as a white solid (615 mg, 90.5% LCAP, 90.2% LCWP, 68.7% yield): ^{1}H NMR (DMSO-d_6, 400 MHz) δ ppm 12.30 (br s, 1H), 7.33−7.21 (comp, 5H), 3.56 (s, 2H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ ppm 172.7, 135.0, 129.4, 128.2, 126.6, 40.7. HRMS: m/z calculated for $C_8H_9O_2$ (M + H)$^+$: 137.0597. Found: 137.0596. IR: 3033, 2971, 2655, 1691, 1407, 1337, 1228, 1186, 892, 839, 752, 699, 677 cm^{-1}.

4-Bromophenylacetic Acid[16] (Table 2, Entry 2). Procedure A was followed using 4-bromomandelic acid (1.0 g, 4.3 mmol). The reaction was heated for 3 days until complete. The solution was cooled to 0 °C and the product was isolated by filtration, washed with cold water, and dried to constant mass under a vacuum at 40 °C. Product was isolated as an off-white crystalline solid (809 mg, 98.7% LCAP, 83.6% LCWP, 86.9% yield): ^{1}H NMR (DMSO-d_6, 400 MHz) δ ppm 12.40 (br s, 1H), 7.50 (d, J = 7.5 Hz, 2H), 7.23 (d, J = 7.5 Hz, 2H), 3.57 (s, 2H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ ppm 172.3, 134.5, 131.7, 131.0, 119.8, 39.9. HRMS: m/z calculated for $C_8H_8BrO_2$ (M + H)$^+$: 214.9708. Found: 214.9705. IR: 2917, 1694, 1488, 1405, 1337, 1245, 1170, 1071, 1014, 926, 854, 802, 728 cm^{-1}.

3,4-Methylenedioxyphenylacetic Acid[17] (Table 2, Entry 3). Procedure B was followed using 3,4-(methylenedioxy)mandelic acid (1.0 g, 5.1 mmol). The reaction was heated for 2 days until complete. The solution was cooled to 0 °C and filtered, and the solid was washed with cold water and dried under a vacuum to constant mass at rt. Product isolated as a white solid (851 mg, 98.4% LCAP, 99.6% LCWP, 92.6% yield): ^{1}H NMR (DMSO-d_6, 400 MHz) δ ppm 12.25 (br s, 1H), 6.84−6.82 (m, 2H), 6.71 (dd, J = 7.8, 1.8 Hz, 1H), 5.98 (s, 2H), 3.47 (s, 2H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ ppm 172.7, 147.1, 145.9, 128.6, 122.4, 109.8, 107.9, 100.8, 40.2. HRMS: m/z calculated for $C_9H_9O_4$ (M + H)$^+$: 181.0495. Found: 181.0494. IR: 2909, 1692, 1500, 1408, 1249, 1181, 1035, 922, 784, 690 cm^{-1}.

4-Hydroxyphenylacetic Acid[18] (Table 2, Entry 4). Procedure B was followed using 4-hydroxymandelic acid (1.0 g, 5.9 mmol). The reaction was heated for 2 days until complete. After cooling to rt, the solution was extracted with IPAC (2 × 5 vol) and concentrated to dryness. Product was purified by column chromatography (SiO_2; 3:1 heptanes/IPAC). Product isolated as a pale pink solid (523 mg, 62.2% LCAP, 61.3% LCWP, 52.8% yield): ^{1}H NMR (DMSO-d_6, 400 MHz) δ ppm 12.10 (br s, 1H), 9.24 (br s, 1H), 7.03 (d, J = 8.5 Hz, 2H), 6.68 (d, J = 8.5 Hz, 2H), 3.41 (s, 2H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ ppm 173.1, 156.0, 130.2, 125.1, 115.0, 39.9. HRMS: m/z calculated for $C_8H_9O_3$ (M + H)$^+$: 153.0546. Found: 153.0544. IR: 3249, 2982, 1704, 1601, 1517, 1446, 1409, 1211, 1190, 1170, 902, 822, 788 cm^{-1}.

2-Phenylpropionic Acid[19] (Table 2, Entry 5). Procedure A was followed using 2-hydroxy-2-phenylpropionic acid (740 mg, 4.5 mmol)

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and heated for 1 day until complete. The reaction was cooled to rt, extracted with Et_2O (2 × 5 vol), concentrated, and dried to constant mass under a vacuum at rt. Product was isolated as a light brown oil (747 mg, 96.2% LCAP, 85.4% LCWP, 95.7% yield): ^{1}H NMR (DMSO-d_6, 400 MHz) δ ppm 12.06 (br s, 1H), 7.34−7.22 (comp, 5H), 3.67 (q, J = 7.0 Hz, 1H), 1.36 (d, J = 7.0 Hz, 3H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ ppm 175.4, 141.3, 128.4, 127.4, 126.8, 44.7, 18.6. HRMS: m/z calculated for $C_9H_{11}O_2$ $(M + H)^+$: 151.0754. Found: 151.0753. IR: 2984, 2938, 1699, 1454, 1413, 1228, 932, 860, 726, 695 cm^{-1}.

Cyclohexylphenylacetic Acid[20] (Table 2, Entry 6). Procedure A was followed using cyclohexylmandelic acid (1.0 g, 4.3 mmol). The reaction was heated for 2 days until complete. After cooling to 0 °C, the reaction was filtered, washed with cold water (2 × 5 vol), and dried to constant mass under a vacuum at rt. Product was isolated as an off-white solid (859 mg, 93.0% LCAP, 92.3% LCWP, 92.2% yield): ^{1}H NMR (DMSO-d_6, 400 MHz) δ ppm 12.24 (br s, 1H), 7.33−7.29 (comp, 4 H), 7.27−7.22 (m, 1H), 3.17 (d, J = 10.6 Hz, 1H), 1.94−1.85 (m, 1H), 1.84−1.77 (m, 1H), 1.74−1.66 (m, 1H), 1.62−1.51 (comp, 2H), 1.31−1.14 (comp, 2H), 1.13−0.97 (comp, 3H), 0.77−0.67 (m, 1H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ ppm 174.5, 138.3, 128.3, 128.2, 126.9, 58.0, 31.4, 29.7, 25.8, 25.5, 25.4. HRMS: m/z calculated for $C_{14}H_{19}O_2$ $(M + H)^+$: 219.1380. Found: 219.1380. IR: 2981, 2930, 1697, 1383, 1296, 1235, 1155, 1069, 957, 703 cm^{-1}.

Diphenylacetic Acid[21] (Table 2, Entry 7). Procedure A was followed using benzilic acid (1.0 g, 4.4 mmol). The reaction was heated for 1 day until complete. The reaction was cooled to 0 °C, filtered, washed with cold water (2 × 5 vol), and dried to constant mass under a vacuum at rt. Product was isolated as a fluffy white solid (869 mg, 99.3% LCAP, 94.9% LCWP, 93.4% yield): ^{1}H NMR (DMSO-d_6, 400 MHz) δ ppm 12.71 (br s, 1H), 7.34−7.31 (comp, 8H), 7.27−7.22 (comp, 2H), 5.06 (s, 1H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ ppm 173.4, 139.5, 128.5, 128.4, 126.8, 56.3. HRMS: m/z calculated for $C_{14}H_{13}O_2$ $(M + H)^+$: 213.0910. Found: 213.0910. IR: 2904, 2604, 1694, 1497, 1449, 1411, 1315, 1222, 933, 732, 695 cm^{-1}.

Phenylacetic Acid (11). Procedure A was followed using phenylglyoxylic acid (1.0 g, 6.7 mmol) with 2.0 equiv H_3PO_3. The reaction was heated for 2 days until complete. Work-up was performed by extracting into IPAC (2 × 5 vol) and concentrating to dryness, followed by recrystallization from boiling heptanes. Product was isolated as a white solid (651 mg, 86.1% LCAP, 94.3% LCWP, 71.8% yield). Analytical data (^{1}H NMR, ^{13}C NMR, HRMS, and IR) were consistent with data reported above.

1,1-Diphenylethane[22] (13). Procedure A was followed with 1,1-diphenylethanol (1.0 g, 5.0 mmol). The reaction was heated for 1 day until complete. The solution was cooled to rt and the product was isolated as an oil that separated from the water. The aqueous layer was extracted with IPAC (2 × 5 vol) and concentrated, and the combined organics were dried to a constant mass under a vacuum at 40 °C. Product was isolated as a colorless oil (691 mg, 99.6% LCAP, 62.2% LCWP, 75.2% yield): ^{1}H NMR (DMSO-d_6, 400 MHz) δ ppm 7.30−7.25 (comp, 8H), 7.18−7.14 (comp, 2H), 4.15 (q, J = 7.2 Hz, 1H), 1.57 (d, J = 7.2 Hz, 3H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ ppm 146.2, 128.3, 127.3, 125.9, 44.0, 21.4. HRMS: m/z calculated for $C_{14}H_{14}$ M^+: 182.1096. Found: 182.1097. IR: 3026, 2969, 1599, 1493, 1448, 1026, 755, 696 cm^{-1}.

Methyl *p*-Tolyl Sulfide[23] (15). Procedure A was followed using methyl *p*-tolyl sulfoxide (1.0 g, 6.5 mmol). The reaction was heated for 1 day until complete. The reaction was cooled to rt, extracted with Et_2O (2 × 5 vol), concentrated, and dried to a constant mass under a low vacuum at rt. Product was isolated as a brown oil (948 mg, 98.6% LCAP, 90.7% LCWP, 96.0% yield): ^{1}H NMR (DMSO-d_6, 400 MHz) δ ppm 7.17−7.11 (comp, 4H), 2.43 (s, 3H), 2.26 (s, 3H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ ppm 134.4, 134.2, 129.5, 126.4, 20.4, 15.2. HRMS: m/z calculated for $C_8H_{11}S$ $(M + H)^+$: 139.0576. Found: 139.0575. IR: 3659, 2981, 2889, 1492, 1382, 1252, 1152, 1092, 956, 799 cm^{-1}.

■ ASSOCIATED CONTENT

Supporting Information

^{1}H and ^{13}C NMR spectra for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(11) Not observed in the phosphorus acid reaction.

(12) Sulfur-containing reductants such as sodium bisulfite $NaHSO_3$, sodium thiosulfate $Na_2S_2O_3$, sodium hydrosulfite $Na_2S_2O_4$, and sodium sulfite Na_2SO_3 were explored and provided poorer conversions with lower purity in comparison to either phosphorus acid (H_3PO_3) or sodium hypophosphite (NaH_2PO_2).

(13) There are a number of advantages to using MSA on a commercial scale that lead to a reduction in production costs: its ease of handling (liquid to −60 °C), when neutralized it is readily biodegradable, it is water soluble, and it can recycled. However, because of its flammability in some cases, HCl can provide an attractive alternative. In addition, the use of MSA can be a regulatory concern because of the potential for formation of genotoxic alkyl sulfonates from remaining MSA during subsequents steps of the synthesis.

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