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Synthesis of α-Hydroxyacetophenones

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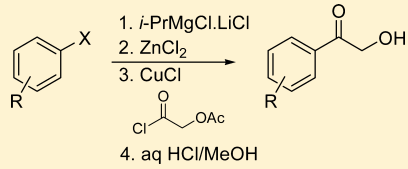
Supporting Information

ABSTRACT: A general method for the preparation of α-hydroxyacetophenones is presented. Functionalized arylmagnesium species are transmetalated to the corresponding arylzinc intermediates, which undergo Cu(I)-catalyzed reaction with acetoxyacetyl chloride. Acidic hydrolysis of the acetate group releases the target α-hydroxyacetophenones with minimal production of undesired polymeric degradates that are often observed under alternative conditions.



α-Hydroxyacetophenones are useful synthetic intermediates amenable to various asymmetric transformations capable of generating valuable chiral compounds.[1] A number of methods for the preparation of α-hydroxyacetophenones have been described in the literature. Acetophenones can be oxidized directly to 2-hydroxyacetophenones or indirectly via oxidation of the corresponding silyl enol ethers.[2] Alternatively, acetophenones can be halogenated at the α-position and then subjected to nucleophilic displacement and in situ solvolysis/hydrolysis to provide α-hydroxyacetophenones.[3] Another procedure utilizing α-bromoacetophenones involves nucleophilic displacement with acetate followed by enzymatic cleavage of the resulting α-acetoxyacetophenones.[4] Enzyme-mediated hydroxymethylation of benzaldehydes has also been reported.[5] Hydroxymethylation via chemocatalysis (*N*-heterocyclic carbenes) is also known.[6] Epoxides and 1,2-diols derived from styrenes can be further oxidized to yield α-hydroxyacetophenones.[7,8] α-diazoacetophenones can be hydrolyzed under acidic conditions to provide α-hydroxyacetophenones.[9] In this paper, we present a convenient method for the preparation of α-hydroxyacetophenones that allows flexibility and control with regard to the substituents on the aromatic ring.

At the outset of our studies, we envisaged a two-step sequence involving direct acylation[10] of arylzinc intermediates to form α-acetoxyacetophenones, followed by deprotection of the acetate group (Figure 1). An important feature of this

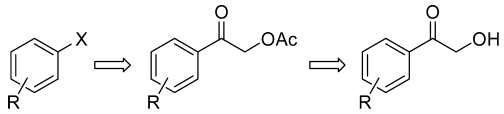
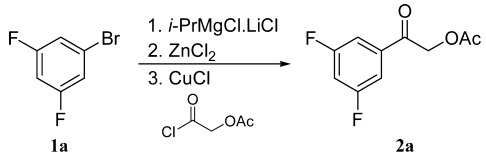


Figure 1. Proposed synthesis of α-hydroxyacetophenones.

approach is the ability to incorporate highly functionalized aromatic nucleophiles that are readily available via one of several elegant procedures developed by Knochel.[11−13] It is also worth noting that this strategy leads to well-defined and in some cases alternative regioselectivity to that expected from Friedel−Crafts reaction between acid chlorides and arenes. For reasons of practicality, we selected Mg−X exchange chemistry followed by transmetalation to the arylzinc reagent as our standard method.[14,15]

Optimization of the stoichiometry for the preparation of α-acetoxyacetophenones using **1a** is shown in Table 1. Initially,

Table 1. Optimization of α-Acetoxyacetophenone Synthesis



1a **2a**

entry	$ZnCl_2$ (equiv)	CuCl (equiv)	AY (%)
1	1	0.1	85
2	1	0.05	83
3	1	0.01	82
4	0.5	0.01	83

using 1 equiv of $ZnCl_2$ and 10 mol % of CuCl led to an assay yield of 85% for **2a**. Attempts to reduce the loading of CuCl required for this reaction established that 1 mol % of CuCl was adequate to achieve similar results.[16] Last, it was shown that using only 0.5 equiv of $ZnCl_2$ had no detrimental effect on yield, and these conditions were selected as standard for preparation of other substrates.[17]

As shown in Table 2, application of the general procedure to a series of diversely functionalized aryl iodides and bromides generally afforded moderate to good yields of the desired α-acetoxyacetophenones (**2a**−**k**). Of particular note are examples where Friedel−Crafts processes would afford alternative or limited regioselection. In most cases, the products were isolated as crystalline solids in high purity following standard aqueous workup and crystallization from an appropriate solvent mixture (typically heptane/MTBE). For certain products that would not crystallize, silica chromatography could be used to isolate analytically pure material.

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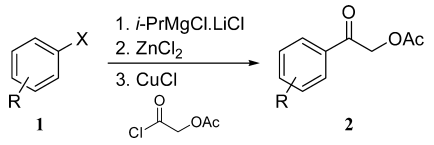
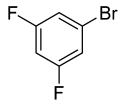
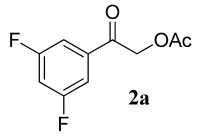
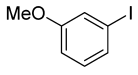
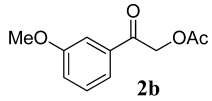
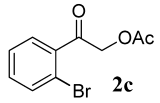
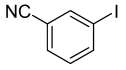
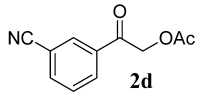
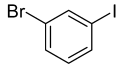
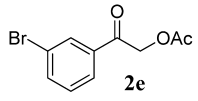
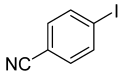
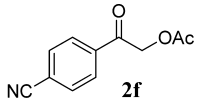
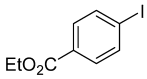
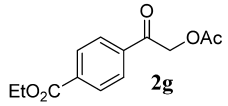
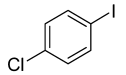
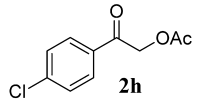
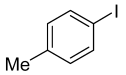
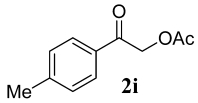
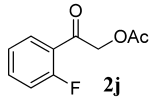
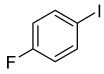
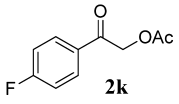
Table 2. Synthesis of α-Acetoxyacetophenones



entry	aryl halide	product	isolated yield
1		 **2a**	74
2		 **2b**	68
3		 **2c**	85
4		 **2d**	54
5		 **2e**	64
6		 **2f**	60
7		 **2g**	63
8		 **2h**	55
9		 **2i**	62
10		 **2j**	82
11		 **2k**	82

Having secured access to the intermediate α-acetoxyacetophenones, attention was turned to the development of conditions for unmasking the desired 2-hydroxacetophenones. Although this transformation appears trivial, certain reactivity features exhibited by this class of compound preclude the use of commonly applied conditions for acetate deprotection. Our initial attempt to cleave the acetate ester under relatively standard K_2CO_3/MeOH conditions resulted in the formation of multiple products, confirming our suspicion that these compounds are intolerant of basic conditions. Presumably, this is due to the acidity of the methylene group and subsequent uncontrolled reactivity of the resulting enolate species.[18] A literature method[3] for the synthesis of α-hydroxyacetophenones recommends conversion of separately prepared α-bromoacetophenones into the corresponding formate ester via nucleophilic displacement using sodium formate followed by in situ hydrolysis/solvolysis under nonbasic conditions. It is noted in this report that "nucleophiles other than formate such as acetate or hydroxide are not desirable for the synthesis of α-hydroxyacetophenones". Although these conditions are close to neutral pH, application to substrates of interest at Merck still led to significant polymerization/degradation and difficulties in isolating the products without recourse to chromatography. With these results in mind, we examined the use of acidic conditions for acetate deprotection in the hope that better results could be obtained.[19] Following some experimentation, it was found that α-acetoxyacetophenones can be deprotected at low pH without the extensive degradation observed under basic

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conditions. Treatment of the α-acetoxyacetophenones with 5 N aqueous HCl at 40 °C, using MeOH as a cosolvent to aid solubility, leads to cleavage of the acetate group within 3−6 h. It was observed that the hydroxyketone products are relatively sensitive to oxygen when in solution, presumably via facile oxidation of equilibrium concentrations of the enol tautomer. For this reason, best results are obtained when the hydrolysis is conducted under a nitrogen atmosphere. Notably, under these conditions the formation of polymeric degradates is minimized and assay yields of the α-hydroxyketones are generally good. In most cases the product can be isolated by direct crystallization after dilution of the reaction mixture with additional water. Table 3 presents yields for the preparation of a range of α-hydroxyacetophenones via acetate cleavage under the developed acidic conditions. Substrates bearing potentially sensitive functional groups such as nitrile or ethyl ester are tolerated, although for the latter case EtOH is used in place of MeOH to avoid transesterification.

The ability to avoid isolation of intermediates when conducting multikilogram-scale synthesis is often desirable since this operation can be time/resource consuming. Through-processing of the crude product from a reaction can be more efficient on large scale so the direct preparation of α-hydroxyacetophenones without isolating the intermediate α-acetoxyacetophenones was investigated. To our satisfaction, it was indeed possible to achieve this, and Figure 2 displays the results from implementation of this procedure on 100 g scale for the conversion of **1a** into **3a**.

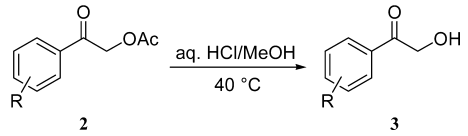
In summary, we have described a straightforward approach to the synthesis of α-hydroxyketones that employs simple procedures and commercially available reagents. By utilizing mild conditions to generate functionalized organometallic species (Mg-X exchange) it is possible to prepare α-acetoxyacetophenones substituted at various positions on the aromatic ring with interesting functional handles. Significantly, we have shown that the target α-hydroxyacetophenones can be unmasked under acidic hydrolysis conditions that do not cause extensive degradation and are tolerated by potentially sensitive functional groups. Although α-hydroxyacetophenones have featured many times in the chemical literature, the apparent absence of reports focused on general procedures for their preparation is perhaps indicative of underlying issues associated with these intermediates. In this regard, the method presented in this paper may be of use for the synthesis of this useful class of organic compounds.

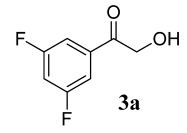
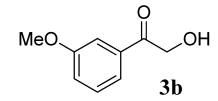
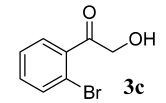
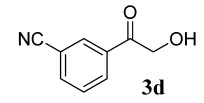
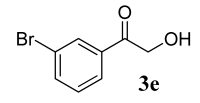
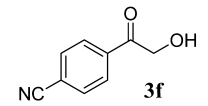
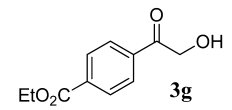
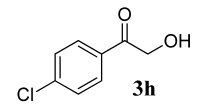
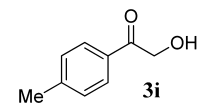
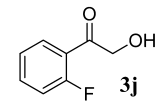
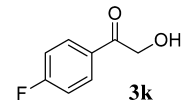
EXPERIMENTAL SECTION

Screening reactions were conducted under a nitrogen atmosphere in 8 mL vials equipped with magnetic stir-bars and septa. Larger scale preparative reactions were conducted in standard round-bottom flasks under a nitrogen atmosphere. HPLC-grade solvents were used with no additional purification/drying. All other reagents were standard grade and used without further purification. Reaction conversion and assay yields were monitored using reversed-phase HPLC with reference to purified standards for quantification purposes. NMR spectra were recorded using 400 and 500 MHz spectrometers; ^{1}H NMR recorded at 400 and 500 MHz and ^{13}C recorded at 100 or 125 MHz. High-resolution mass data were obtained using electrospray ionization (positive ion mode). Flash column chromatography was performed using a robotic instrument fitted with an appropriately sized silica cartridge.

General Procedure for Synthesis of α-Acetoxyacetophenones (2). *Representative Procedure for the Synthesis of α-Acetoxyacetophenones: Synthesis of 1-(3,5-Difluorophenyl)-α-acetoxyethanone.* A 40 mL vial equipped with a septum cap, stir bar, nitrogen inlet, and temperature probe was charged with *i*-PrMgCl·LiCl (14 wt % in THF, 9.9 mL, 10.0 mmol, 1 equiv). Neat 1-bromo-3,5-difluorobenzene **1a** (1.93 g, 10.0 mmol, 1 equiv) was added dropwise via syringe at 20−30 °C over 10 min, and the Mg−Br exchange was complete within 1 h as monitored via quenching a sample into MeOH

Table 3. Synthesis of α-Hydroxyacetophenones



entry	substrate	product	isolated yield
1	**2a**	 **3a**	86
2	**2b**	 **3b**	78
3	**2c**	 **3c**	77
4	**2d**	 **3d**	61
5	**2e**	 **3e**	82
6	**2f**	 **3f**	66
7	**2g**	 **3g**	85
8	**2h**	 **3h**	86
9	**2i**	 **3i**	77
10	**2j**	 **3j**	81
11	**2k**	 **3k**	79

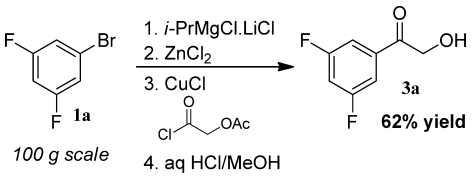


Figure 2. α-Hydroxyacetophenone through-process.

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for reversed-phase HPLC analysis. The resultant solution of ArMgX was cooled to 0 °C and subjected to transmetalation via treatment with $ZnCl_2$ (0.5 M in THF, 10.0 mL, 0.5 equiv), maintaining <20 °C. To the resultant solution was added CuCl (9.9 mg, 0.1 mmol, 1 mol %) followed by neat acetoxyacetyl chloride (1.18 mL, 11.0 mmol, 1.1 equiv) dropwise via syringe, maintaining <30 °C. The cooling bath was removed, and the resultant solution was aged until conversion of the ArMgX species was observed via reversed-phase HPLC analysis. The solution was poured into 2 M aqueous HCl (30 mL) and extracted with MTBE (75 mL). The organic phase was washed with brine (30 mL) and then dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The solvent was eventually switched to heptane, causing crystallization of the α-acetoxyacetophenone, which was collected by filtration. 1-(3,5-Difluorophenyl)-α-acetoxyethanone **2a** was obtained as a white solid.

General Procedure for Synthesis of α-Hydroxyacetophenones (3). Representative α-acetoxyacetophenone hydrolysis procedure: A mixture of 1-(3,5-difluorophenyl)-α-acetoxyethanone **2a** (1.19 g, 5.0 mmol, 1 equiv), MeOH (6 mL), and 5 M aqueous HCl (6 mL, 30.0 mol, 6 equiv) was heated at 40 °C under a nitrogen atmosphere for 4–6 h, after which time HPLC analysis indicated complete conversion of the acetate. The orange mixture was concentrated under reduced pressure to remove the MeOH, causing crystallization of the desired hydroxyketone. The final aqueous slurry was cooled to 0–5 °C for 1 h before the solid was collected by filtration and rinsed with water. 1-(3,5-Difluorophenyl)-α-hydroxyethanone **3a** was obtained as an orange solid.

*α-Acetoxy-3,5-difluoroacetophenone (**2a**).* Following the general procedure, **2a** was obtained as a white solid: 1.58 g (74%); mp 70–73 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.25 (s, 3H), 5.28 (s, 2H), 7.07–7.11 (m, 1H), 7.41–7.47 (m, 2H); ^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$) δ 20.4, 65.8, 109.2 (t, J_{CF} = 26 Hz) 110.9 (m), 136.9 (t, J_{CF} = 8 Hz), 163.2 (dd, J_{CF} = 252, 12 Hz), 170.2, 190.2; HRMS calcd for $C_{10}H_9F_2O_3$ (M + H) 215.0520, found 215.0519.

*α-Acetoxy-3-methoxyacetophenone (**2b**).* Following the general procedure, **2b** was obtained as a white solid: 1.41 g (68%); ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.27 (s, 3H), 3.88 (s, 3H), 5.35 (s, 2H), 7.16–7.19, (m, 1H), 7.39–7.43 (m, 1H), 7.46–7.51 (m, 2H); ^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$) δ 20.6, 55.5, 66.1, 112.1, 120.2, 120.4, 129.9, 160.0, 170.4, 192.0; HRMS calcd for $C_{11}H_{13}O_4$ (M + H) 209.0814, found 209.0813.

*α-Acetoxy-3-fluoroacetophenone (**2c**).* Following the general procedure, **2c** was obtained as a white solid: 1.14 g (85%); mp 91–93 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.20 (s, 3H), 5.18 (s, 2H), 7.34–7.40 (m, 1H), 7.42–7.47 (m, 1H), 7.52–7.56 (m, 1H), 7.64–7.67 (m, 1H); ^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$) δ 20.4, 67.7, 119.1, 127.6, 129.3, 132.5, 133.8, 138.2, 170.2, 196.4; HRMS calcd for (M + H) $C_{10}H_{10}BrO_3$ 256.9813, found 256.9806.

*α-Acetoxy-3-cyanoacetophenone (**2d**).* Following the general procedure, **2d** was obtained as a white solid: 1.10 g (54%); ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.26 (s, 3H), 5.33 (s, 2H), 7.67 (t, J = 8.2 Hz, 1H), 7.91 (d, J = 8.2 Hz, 1H), 8.15 (d, J = 8.2 Hz, 1H), 8.22 (s, 1H); ^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$) δ 20.5, 65.8, 113.6, 117.6, 130.0, 131.5, 131.7, 135.1, 136.7, 170.3, 190.6; HRMS calcd for $C_{11}H_{10}NO_3$ (M + H) 204.0661, found 204.0661.

*α-Acetoxy-3-bromoacetophenone (**2e**).* Following the general procedure, **2e** was obtained as a white solid: 1.64 g (64%); ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.26 (s, 3H), 5.31 (s, 2H), 7.39–7.42 (m, 1H), 7.76–7.78 (m, 1H), 7.84–7.87 (m, 1H), 8.06–8.08 (m, 1H); ^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$) δ 20.5, 65.9, 123.2, 126.3, 130.5, 130.9, 135.9, 136.7, 170.3, 191.0; HRMS calcd for $C_{10}H_{10}BrO_3$ (M + H) 256.9813, found 256.9815.

*α-Acetoxy-4-cyanoacetophenone (**2f**):* Following the general procedure, **2f** was obtained as a white solid: 1.22 g (60%); mp 102–104 °C: ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.23 (s, 3H), 5.32 (s, 2H), 7.81 (d, J = 8.0 Hz, 2H), 8.02 (d, J = 8.0 Hz, 2H); ^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$) δ 20.4, 65.9, 117.2, 117.6, 128.3, 132.7, 137.2, 170.3, 191.3; HRMS calcd for $C_{11}H_{10}NO_3$ (M + H) 204.0661, found 204.0663.

*4-(α-Acetoxyacetyl)benzoic Acid Ethyl Ester (**2g**).* Following the general procedure, **2g** was obtained as a white solid: 1.57 g (63%); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.45 (t, J = 7.2 Hz, 3H), 2.26 (s, 3H), 4.45 (q, J = 7.2 Hz, 2H), 5.37 (s, 2H), 7.99 (d, J = 8.3 Hz, 2H), 8.18 (d, J = 8.3 Hz, 2H); ^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$) δ 14.2, 20.5, 61.5, 66.1, 127.7, 130.0, 135.0, 137.3, 165.4, 170.3, 191.9; HRMS calcd for $C_{13}H_{15}O_5$ (M + H) 251.0919, found 251.0916.

*α-Acetoxy-4-chloroacetophenone (**2h**):* Following the general procedure, **2h** was obtained as a white solid: 1.17 g (55%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.23 (s, 3H), 5.29 (s, 2H), 7.46 (d, J = 8.5 Hz, 2H), 7.85 (d, J = 8.5 Hz, 2H); ^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) δ 20.5, 65.9, 129.2, 129.3, 132.6, 140.4, 170.4, 191.8; HRMS calcd for $C_{10}H_{10}ClO_3$ (M + H) 213.0318, found 213.0316.

*α-Acetoxy-4-methylacetophenone (**2i**).* Following the general procedure, **2i** was obtained as a white solid: 1.19 g (62%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.23 (s, 3H), 2.42 (s, 3H), 5.31 (s, 2H), 7.27 (d, J = 8.2 Hz, 2H), 7.81 (d, J = 8.2 Hz, 2H); ^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) δ 20.6, 21.7, 65.9, 127.9, 129.5, 131.8, 144.9, 170.4, 191.4; HRMS calcd for $C_{11}H_{13}O_3$ (M + H) 193.0865, found 193.0861.

*α-Acetoxy-2-fluoroacetophenone (**2j**).* Following the general procedure, **2j** was obtained as a white solid: 1.41 g (82%); ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.25 (s, 3H), 5.25 (s, 2H), 7.17–7.22 (m, 1H), 7.28–7.33 (m, 1H), 7.58–7.64 (m, 1H), 7.98–8.02 (m, 1H); ^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$) δ 20.5, 69.1 (d, J_{CF} = 15 Hz), 116.5 (d, J_{CF} = 24 Hz), 122.4 (d, J_{CF} = 14 Hz), 124.8 (d, J_{CF} = 4 Hz), 130.7 (d, J_{CF} = 4 Hz), 135.6 (d, J_{CF} = 9 Hz), 162.3 (d, J_{CF} = 254 Hz), 170.3, 190.4 (d, J_{CF} = 20 Hz); HRMS calcd for $C_{10}H_{10}FO_3$ 197.0614, found 197.0611.

*α-Acetoxy-4-fluoroacetophenone (**2k**).* Following the general procedure, **2k** was obtained as a white solid: 1.41 g (82%); ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.25 (s, 3H), 5.32 (s, 2H), 7.16–7.21 (m, 2H), 7.95–7.99 (m, 2H); ^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$) δ 20.5, 65.8, 116.1 (d, J_{CF} = 22 Hz), 130.5 (d, J_{CF} = 10 Hz), 130.7 (d, J_{CF} = 3 Hz), 166.1 (d, J_{CF} = 256 Hz), 170.4, 190.7; HRMS calcd for $C_{10}H_{10}FO_3$ (M + H) 197.0614, found 197.0610.

*α-Hydroxy-3,5-difluoroacetophenone (**3a**):* Following the general procedure, **3a** was obtained as a white solid: 0.74 g (86%); mp 95–97 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.42 (br, 1H), 4.85 (s, 2H), 7.07–7.13 (m, 1H), 7.41–7.47 (m, 2H); ^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$) δ 65.7, 109.5 (t, J_{CF} = 26 Hz) 110.7 (m), 136.1 (t, J_{CF} = 8 Hz), 163.2 (dd, J_{CF} = 252, 12 Hz), 196.4; HRMS calcd for $C_8H_7F_2O_2$ (M + H) 173.0414, found 173.0406.

*α-Hydroxy-3-methoxyacetophenone (**3b**).* Following the general procedure, **3b** was obtained as a white solid: 0.65 g (78%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.55 (br, 1H), 3.88 (s, 3H), 4.87 (s, 2H), 7.13–7.19, (m, 1H), 7.38–7.44 (m, 1H), 7.46–7.49 (m, 2H); ^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$) δ 55.5, 65.5, 112.1, 120.1, 120.6, 129.9, 134.7, 160.0, 198.3; HRMS calcd for $C_9H_{11}O_3$ (M + H) 167.0708, found 167.0712.

*α-Hydroxy-2-bromoacetophenone (**3c**):* Following the general procedure, **3c** was obtained as a white solid: 0.83 g (77%); ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.40 (br, 1H), 4.78 (s, 2H), 7.35–7.43 (m, 2H), 7.51–7.54 (m, 1H), 7.64–7.67 (m, 1H); ^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$) δ 68.0, 119.9, 127.6, 129.4, 133.0, 134.4, 136.8, 201.6; HRMS calcd for $C_8H_8BrO_2$ (M + H) 214.9708, found 214.9706.

*α-Hydroxy-3-cyanoacetophenone (**3d**):* Following the general procedure, **3d** was obtained as a white solid: 0.49 g (61%); ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.38 (br, 1H), 4.93 (s, 2H), 7.69 (t, J = 8.1 Hz, 1H), 7.93 (d, J = 8.1 Hz, 1H), 8.16 (d, J = 8.1 Hz, 1H), 8.23 (s, 1H); ^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$) δ 65.7, 113.7, 117.5, 130.1, 131.4, 131.6, 134.3, 137.0, 196.8; HRMS calcd for $C_9H_8NO_2$ (M + H) 162.0555, found 162.0551.

*α-Hydroxy-3-bromoacetophenone (**3e**):* Following the general procedure, **3e** was obtained as a white solid: 0.88 g (82%); ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.40 (br, 1H), 4.88 (s, 2H), 7.40–7.45 (m, 1H), 7.76–7.79 (m, 1H), 7.83–7.86 (m, 1H), 8.08 (s, 1H); ^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$) δ 65.6, 123.3, 126.2, 130.6, 130.8, 135.1, 137.1, 197.3; HRMS calcd for $C_8H_8BrO_2$ (M + H) 214.9708, found 214.9714.

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*α-Hydroxy-4-cyanoacetophenone (**3f**).* Following the general procedure, **3f** was obtained as a white solid: 0.53 g (66%); ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.37 (br, 1H), 4.93 (s, 2H), 7.84 (d, J = 8.0 Hz, 2H), 8.04 (d, J = 8.0 Hz, 2H); ^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$) δ 65.9, 117.6, 128.2, 132.8, 136.4, 197.4; HRMS calcd for $C_9H_8NO_2$ (M + H) 162.0555, found 162.0553.

*4-(α-Hydroxyacetyl)benzoic Acid Ethyl Ester (**3g**).* Following the general procedure, **3g** was obtained as a white solid: 0.89 g (85%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.45 (t, J = 7.2 Hz, 3H), 3.47 (br, 1H), 4.45 (q, J = 7.2 Hz, 2H), 4.93 (s, 2H), 7.99 (d, J = 8.3 Hz, 2H), 8.20 (d, J = 8.3 Hz, 2H); ^{13}C {^{1}H} NMR (125 MHz, DMSO) δ 14.6, 61.7, 66.2, 128.4, 129.8, 134.1, 135.5, 165.5, 199.5; HRMS calcd for $C_{11}H_{13}O_4$ (M + H) 209.0814, found 209.0806.

*α-Hydroxy-4-chloroacetophenone (**3h**).* Following the general procedure, **3h** was obtained as a white solid: 0.73 g (86%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.43 (br, 1H), 4.85 (s, 2H), 7.49 (d, J = 8.2 Hz, 2H), 7.87 (d, J = 8.2 Hz, 2H); ^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) δ 65.4, 129.1, 129.4, 131.7, 140.8, 197.3; HRMS calcd for $C_8H_8ClO_2$ (M + H) 171.0213, found 171.0211.

*α-Hydroxy-4-methylacetophenone (**3i**).* Following the general procedure, **3i** was obtained as a white solid: 0.58 g (77%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.43 (s, 3H), 3.54 (br, 1H), 4.84 (s, 2H), 7.30 (d, J = 8.0 Hz, 2H), 7.82 (d, J = 8.0 Hz, 2H); ^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) δ 21.8, 65.3, 127.8, 129.6, 130.9, 145.4, 197.9; HRMS calcd for $C_9H_{11}O_2$ 151.0759, found 151.0763.

*α-Hydroxy-2-fluoroacetophenone (**3j**).* Following the general procedure, **3j** was obtained as a white solid: 0.62 g (81%); ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.62 (br, 1H), 4.81 (s, 2H), 7.17−7.22 (m, 1H), 7.28−7.33 (m, 1H), 7.59−7.64 (m, 1H), 8.05−8.09 (m, 1H); ^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$) δ 69.3 (d, J_{CF} = 15 Hz), 116.8 (d, J_{CF} = 23 Hz), 121.6 (d, J_{CF} = 13 Hz), 124.8 (d, J_{CF} = 3 Hz), 130.6 (d, J_{CF} = 3 Hz), 135.9 (d, J_{CF} = 9 Hz), 162.8 (d, J_{CF} = 256 Hz), 196.9 (d, J_{CF} = 5 Hz); HRMS calcd for $C_8H_8FO_2$ (M + H) 155.0508, found 155.0507.

*α-Hydroxy-4-fluoroacetophenone (**3k**).* Following the general procedure, **3k** was obtained as a white solid: 0.61 g (79%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.50 (br, 1H), 4.87 (s, 2H), 7.19−7.23 (m, 2H), 7.97−8.01 (m, 2H); ^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$) δ 65.3, 116.2 (d, J_{CF} = 22 Hz), 129.9 (d, J_{CF} = 3 Hz), 130.4 (d, J_{CF} = 10 Hz), 166.4 (d, J_{CF} = 256 Hz), 196.8; HRMS calcd for $C_8H_8FO_2$ (M + H) 155.0508, found 155.0506.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

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.

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(14) Direct preparation of the requisite arylzinc intermediates would ultimately be more efficient, but the use of commercial *i*-PrMgCl·LiCl and $ZnCl_2$ solutions was deemed more user-friendly in the short term. Additionally, the use of *i*-PrMgCl·LiCl rather than *i*-PrMgCl led to more predictable and better results for Mg−X exchange for the substrates studied here.

(15) As a control, direct reaction between ArMgX and acetoxyacetyl chloride was studied, but this led to low yields of the desired ketone.

(16) No reaction was observed in the absence of a Cu additive.

(17) Cu-catalyzed acylation of the ArMgX without prior transmetalation using $ZnCl_2$ was also studied. This more direct approach is successful with certain substrates and significantly simplifies the experimental procedure, however the desired product is usually contaminated with 5−10% of the tertiary alcohol resulting from overaddition.

(18) This facility of enolization was also observed during attempts to hydrogenolize *O*-benzyl protected α-hydroxyacetophenones, where the primary product obtained was the 2-benzyloxy-1-phenyl-ethanol derivative, resulting from hydrogenation of the enol carbon-carbon double bond.

(19) In-house experience with the HCl promoted cleavage of *O*-THP protected α-hydroxyacetophenones indicated that the desired products were relatively stable under aqueous HCl conditions.