[Supporting Information for:]
Efficient and Selective Al-Catalyzed Alcohol Oxidation via Oppenauer Chemistry

Christopher R. Graves, Bi-Shun Zeng, and SonBinh T. Nguyen*

*Department of Chemistry and the Institute for Environmental Catalysis, Northwestern University, 2145 Sheridan Road,
Evanston, Illinois 60208-3113, USA*

General procedures, materials, and instrumentation. All reactions involving pure AlMe_3 were run in anhydrous toluene and carried out under nitrogen in a Vacuum Atmospheres Company drybox. Reactions involving a pre-made AlMe_3 solution in toluene (2 M) were carried out on the bench-top using anhydrous toluene, oven-dried glassware, and syringe techniques. Anhydrous toluene was obtained by passing commercial toluene (Fisher Scientific) over alumina and Q5 catalysts in a Dow-Grubbs solvent system¹ installed by Glass Contours (Laguna Beach, CA). Reactions involving $\text{Al}(\text{O}^i\text{Pr})_3$ were carried out on the bench-top using oven-dry glassware under air and with as-available commercial toluene. When not available commercially, alcohol substrates were prepared via the NaBH_4 reduction of the starting ketone or aldehyde. All other reagents were purchased from the Aldrich Chemical Company and used without further purification, unless otherwise noted. All starting materials and products are either commercially available or known compounds.

^1H and ^{13}C NMR spectra were recorded on a Varian INOVA 500 (499.47 MHz for ^1H , 125.6 MHz for ^{13}C) FT-NMR spectrometer. ^1H NMR data are reported as follows: chemical shift (multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, p = pentet, and m = multiplet), coupling constant, and integration). ^1H and ^{13}C chemical shifts are reported in ppm downfield from tetramethylsilane (TMS, δ scale) using the residual solvent resonances as internal standards.

GC analyses of reaction mixtures were carried out on a computer-interfaced Agilent Technologies 6890 Network instrument equipped with an FID detector. The column used was a 30-m HP-5 capillary column with a 0.32-mm inner diameter and a 0.25- μm film thickness. Flow rate = 1.8 mL/min. GC yields were determined through integration of the product peak against 1,2,4,5-tetramethylbenzene (internal standard in toluene, 11.3 mg/mL) using pre-established response factors. GC retention times of products were confirmed with commercially available samples.

Chiral HPLC analyses were carried out on a computer-interfaced automated Agilent 1100 series HPLC equipped with a diode-array detector, ChemStation software, and a 25-cm (*S*, *S*) Whelk-O 1 column (Regis Technologies, Inc.) with a 0.46-cm inner diameter. Retention times of enantiomerically enriched products were referenced to racemic samples.

General procedure for the aldehyde screens in the Oppenauer oxidation of α - i butylbenzyl alcohol to i butyl phenyl ketone. In the drybox, an 8-mL vial equipped with a magnetic stir bar was charged with α - i butylbenzyl alcohol (164 mg, 1.0 mmol) and internal standard-containing anhydrous toluene (4 mL). AlMe_3 (9.6 μL , 0.1 mmol) was added via syringe and the vial was capped with a Teflon-lined silicone septa. The mixture was stirred for 0.5 h after which the aldehyde oxidant (2.0-3.0 mmol) was added neat and the resulting homogeneous reaction was taken out of the drybox to stir. At the times indicated in Table 1, a 100- μL fraction was taken via gas-tight syringe, loaded onto a plug of alumina, and eluted with MeOH (15 mL) and directly analyzed by GC using temperature program 1: Initial temp = 50 $^\circ\text{C}$, initial time = 4 min; ramp rate = 10 $^\circ\text{C}/\text{min}$, final temp = 250 $^\circ\text{C}$, final time = 5 min (ketone retention time = 12.72 min; alcohol retention time = 13.32 min).

General procedure for the Oppenauer oxidation of 1 $^\circ$ and 2 $^\circ$ alcohols using AlMe_3 . In the drybox, an 8-mL vial equipped with a magnetic stirring bar was charged with the alcohol substrate (1.0 mmol) and internal standard-containing anhydrous toluene (4 mL). AlMe_3 (9.6 μL , 0.1 mmol) was added via syringe, the vial was capped with a Teflon-lined silicone septa, and the reaction was stirred for 0.5 h (albeit 10 minutes is often sufficient). 3-Nitrobenzaldehyde (0.45 g, 3.0 mmol) (or 2,4-dinitrobenzaldehyde for the more difficult substrates) was added as a solid and the resulting homogeneous mixture was allowed to stir. Over the course of the reaction, a light yellow solid (the nitroalcohol) precipitated out of the solution. After the indicated time, stirring was stopped and the reaction was diluted with CH_2Cl_2 (20 mL) and quenched with H_2O (20 mL). The organic layer was separated, washed with 1 M HCl (20 mL), saturated aqueous NaHCO_3 (20 mL), and H_2O (20 mL), followed by drying over anhydrous Na_2SO_4 . After filtration, solvents were reduced and the reaction was analyzed directly by GC using either temperature program 1 (*vide supra*), GC temperature program 2 (initial temp = 30 $^\circ\text{C}$, initial time = 4 min; ramp rate = 10 $^\circ\text{C}/\text{min}$, final temp = 250 $^\circ\text{C}$, final time = 5 min), or GC temperature program 3 (initial temp = 80 $^\circ\text{C}$, initial time = 4 min; ramp rate = 5 $^\circ\text{C}/\text{min}$, final temp = 200 $^\circ\text{C}$, final time = 2 min) (see Table S1).

Table S1. GC retention times for alcohol starting materials and carbonyl products from the catalytic O oxidation.

entry	alcohol	product	GC temp program	GC retention time for alcohol (min)	GC retention time for product (min)
	<i>Alkyl</i>	<i>Alkyl</i>			
1	Me	Me	3	6.75	6.91
2	<i>i</i> Pr	<i>i</i> Pr	1	12.38	12.15
3	<i>t</i> Bu	<i>t</i> Bu	1	12.72	13.32
4	CH ₂ Br	CH ₂ Br	3	10.01	9.51
5	Ph	Ph	1	18.21	17.89
6	1-naphthyl	1-naphthyl	1	18.02	17.36
7	2-naphthyl	2-naphthyl	1	17.74	17.84
8	2-furyl	2-furyl	1	10.93	10.16
9	2-thiophenyl	2-thiophenyl	1	9.86	10.43
10	3-thiophenyl	3-thiophenyl	1	10.15	10.30
11	3-pyridyl	3-pyridyl	1	10.52	10.72
12	4-pyridyl	4-pyridyl	1	10.37	10.54
13			1	2.70	2.56
14			1	13.91	13.57
	<i>Alkyl</i> ¹ <i>Alkyl</i> ²	<i>Alkyl</i> ¹ <i>Alkyl</i> ²			
15	hexyl Me	hexyl Me	1	9.50	8.657
16	<i>t</i> Bu Me	<i>t</i> Bu Me	2	4.36	5.64
17	Cy Me	Cy Me	1	9.62	9.35
18	borneol	camphor	1	12.01	11.34
19	isoborneol	camphor	1	11.63	11.34
20	benzyl alcohol	benzaldehyde	2	9.90	7.92
21	4-methoxybenzyl alcohol	4-methoxybenzaldehyde	2	15.39	16.46
22	4-chlorobenzyl alcohol	4-chlorobenzaldehyde	1	9.25	9.51
23			2	7.53	7.09
24			1	2.37	2.24
25			2	7.63	5.95
26	citronellol	citronellal	1	13.02	11.97

Procedure for testing the functional group compatibility of the O oxidation protocol.

To a 100-mL oven-dried Schlenk flask equipped with a magnetic stir bar was added α -methylbenzyl alcohol (0.73 g, 6.0 mmol), methyl benzoate (2.45 g, 18.0 mmol), benzonitrile (1.85 g, 18.0 mmol), *N,N*-dimethylbenzamide (2.69 g, 18.0 mmol), and triphenylmethanol (4.69 g, 18.0 mmol). The reaction flask was capped with a septa and purged with nitrogen. Anhydrous toluene (19 mL) containing 1,2,4,5-tetramethylbenzene as internal standard was added by cannula, followed by AlMe₃ (300 μ L of a 2 M solution in toluene, 0.6 mmol) via syringe. The reaction was stirred for 10 min after which 3-nitrobenzaldehyde (2.77 g, 18.0 mmol) in anhydrous toluene (5 mL) was added. After 2 h, a fraction of the reaction was taken, loaded onto a plug of alumina (activated, neutral, Brockmann activity 1, ~150 mesh), eluted with MeOH, and directly analyzed by GC using temperature program 3. It is important to note that after 1 h a small amount (~10%) of starting alcohol was still present, indicating that the addition of these functional compounds does slow down the reaction rate. However, after 2 h, complete conversion of the alcohol was obtained.

Note: Individual control experiments with each of the additives (1:1 molar ratio with the substrate) were also carried out with no adverse effects on the reaction yield after a 1-h period.

Table S2. Extra substrates not included in the main text.

entry	alcohol	conversion (%)	entry	alcohol	conversion (%)
1		>99	8		>99
2		>99	9		>99
3		>99	10		>99
4		>99	11		>99
5		>99	12		>99
6		>99	13		>99
7		>99	14		75

General procedure for the 6-mmol-scale Oppenauer oxidation of alcohols. To a 100-mL oven-dried Schlenk flask equipped with a magnetic stir bar was added the alcohol substrate (6.0 mmol). The reaction flask was capped with a septa and purged with nitrogen. Anhydrous toluene (19 mL) was added by cannula, followed by AlMe_3 (300 μL of a 2 M solution in toluene, 0.6 mmol) via syringe. The reaction was stirred for 10 min after which 3-nitrobenzaldehyde (2.77 g, 18.0 mmol) in anhydrous toluene (5 mL) was added and the resulting homogeneous mixture was allowed to stir. Over the course of the reaction, a light yellow solid (the nitroalcohol) precipitated out of the solution. After the 1 h, the reaction was diluted with CH_2Cl_2 (100 mL) and washed with 1 M aqueous HCl (50 mL), saturated aqueous NaHCO_3 (50 mL), and H_2O (50 mL). The organic layer was collected, dried over anhydrous Na_2SO_4 , and reduced to a minimum under vacuum. The crude reaction mixture was dissolved in a minimal amount of hexanes and passed through a plug of alumina (20 cm $\times$ 2 cm, activated, neutral, Brockmann activity 1, $\sim$ 150 mesh) with hexanes elutant. Solvent was removed from the filtrate to give pure carbonyl compound (characterization data matched those for commercial samples).

Note: In some instances the isolated yields of alcohol could be reduced during the purification process when elution of the product from the alumina plug is not complete. For these cases, increased elution volume increases the yield of reaction.

Procedure for removing 3-nitrobenzaldehyde and 3-nitrobenzyl alcohol from reaction mixture. The removal of both 3-nitrobenzaldehyde and 3-nitrobenzyl alcohol (as well as 2,4-dinitrobenzaldehyde and 2,4-dinitrobenzyl alcohol) from the O-oxidation products is quite facile. The crude reaction was dissolved in a minimal amount of hexanes, passed through a plug of alumina (20 cm $\times$ 2 cm, activated, neutral, Brockmann activity 1, $\sim$ 150 mesh) and flushed with hexanes. Elution was continued until product was fully removed from the column, as determined by TLC. Both the nitrobenzaldehyde and nitrobenzyl alcohol are not eluted by hexanes.

Procedure for the large-scale oxidation of α -methylbenzyl alcohol. On the bench-top, a 1000-mL round-bottom flask equipped with a magnetic stir bar was charged with α -methylbenzyl alcohol (10.0 g, 82 mmol) and toluene (330 mL). AlMe_3 (4.1 mL of a 2 M solution in toluene, 8.2 mmol) was next added via syringe under air and the reaction was stirred for 10 min. It should be noted that in the adding of AlMe_3 the syringe needle was submerged into the alcohol solution prior to addition to minimize exposure of the reagent to air. 3-Nitrobenzaldehyde (37 g, 346 mmol) was then added as a solid and the resulting homogeneous mixture was allowed to stir for 1 h. Over the course of the reaction, a light yellow solid (the nitroalcohol) precipitated out of the solution which was filtered over a Büchner funnel before the reaction was quenched with 1 M HCl (100 mL). The organic layer was collected in a separatory funnel, washed with a saturated aqueous NaHCO_3 solution (100 mL) and H_2O (100 mL), followed by drying over anhydrous Na_2SO_4 . The mixture was filtered over a Büchner funnel and solvents were removed from the filtrate under reduced pressure. The crude reaction product was loaded onto a plug of alumina (10 cm

× 20 cm, activated, neutral, Brockmann activity 1, ~ 150 mesh) and flushed with hexanes until product elution was no longer evidenced by TLC to give the desired methyl phenyl ketone (9.1 g, 92% yield).

Procedure for the O oxidation of α -methylbenzyl alcohol using $\text{Al}(\text{O}^i\text{Pr})_3$. On the bench-top, alcohol α -methylbenzyl alcohol (0.73 g, 6.0 mmol) was added to a 100-mL oven-dried round-bottom flask equipped with a magnetic stir bar. ACS-grade toluene (19 mL) containing internal standard was then added, followed by $\text{Al}(\text{O}^i\text{Pr})_3$ (123 mg, 0.6 mmol) as a solid. The reaction was stirred for 10 min after which 3-nitrobenzaldehyde (2.77 g, 18.0 mmol) in toluene (5 mL) was added. The reaction turns homogeneous after a brief period and then eventually becomes cloudy with a light yellow precipitate (the nitroalcohol). After 2 h, the reaction was diluted with CH_2Cl_2 (100 mL) and washed with 1 M aqueous HCl (50 mL), saturated aqueous NaHCO_3 (50 mL), and H_2O (50 mL). The organic layer was collected, dried over anhydrous Na_2SO_4 , reduced to a minimum under vacuum, and directly analyzed by GC using GC method 3.

General procedure for the kinetic comparison of the O oxidation catalyzed by AlMe_3 or $\text{Al}(\text{O}^i\text{Pr})_3$. In the drybox, an 8-mL vial equipped with a magnetic stirring bar was charged with the alcohol (1.0 mmol) and dissolved in anhydrous toluene (4 mL) containing internal standard. The specific aluminum reagent (either AlMe_3 (9.6 μL , 0.1 mmol) or $\text{Al}(\text{O}^i\text{Pr})_3$ (20.5 mg, 0.1 mmol)) was added, the vial was capped with a Teflon-lined silicone septa, and the reaction was stirred for 10 min. 3-Nitrobenzaldehyde (0.45 g, 3.0 mmol) was then added as a solid; the reaction was taken out of the drybox and stirred. At the time indicated for each data point, a 100- μL fraction was taken via gas-tight syringe, loaded onto a plug of alumina, and eluted with MeOH (15 mL) and directly analyzed by GC using the appropriate temperature program (Figure S1).

Figure S1. Plots of conversion versus time for the Oppenauer oxidation of α -methylbenzyl alcohol ($\text{R}^1 = \text{Me}$) catalyzed by AlMe_3 (A) and $\text{Al}(\text{O}^i\text{Pr})_3$ (C) and the Oppenauer oxidation of α - t -butylbenzyl alcohol ($\text{R}^1 = t\text{Bu}$) catalyzed by AlMe_3 (B) and $\text{Al}(\text{O}^i\text{Pr})_3$ (D).

Synthesis of (1R, 2S)-(-)-(N- t -butoxycarbonyl)ephedrine.²

To an oven-dried 100-mL round-bottom equipped with a magnetic stir bar was added (1R, 2S)-(-)-ephedrine (2.0 g, 12.0 mmol). This solid was dissolved in a 1:1 v/v mixture of MeOH and H_2O (50 mL total) and combined with solid K_2CO_3 (3.32 g, 24.0 mmol). Di- t -butyl dicarbonate (3.14 g, 14.4 mmol) was added and the resulting solution was stirred vigorously. After 16 h, MeOH was removed under reduced pressure and the resulting aqueous media was extracted with EtOAc (3×50 mL). The organic layers were combined and dried over anhydrous Na_2SO_4 . The drying agent was removed via filtration and the filtrate was concentrated *in vacuo*. The crude reaction product was purified by column chromatography on silica gel (15 cm ×

4 cm,) with acetone/CH₂Cl₂ eluants (30/70) to give (1*R*, 2*S*)-(-)-(N-*t*-butoxycarbonyl)ephedrine as a slightly yellow-tinted oil (2.70 g, 85% yield). ¹H NMR (499.6 MHz, CDCl₃): δ 1.19 (d, *J* = 7.0 Hz, 3 H), 1.34 (s, 9 H), 3.64 (s, 1H), 4.12 (p, *J* = 7 Hz, 1 H), 4.68 (d, *J* = 4.5 Hz, 1 H), 7.20-7.32 (m, 5 H). ¹³C{¹H} NMR (125.6 MHz, CDCl₃): δ 14.2, 21.1, 28.4, 60.5, 79.7, 126.4, 127.5, 128.1, 142.5, 171.3.

Oppenauer oxidation of (1*R*, 2*S*)-(-)-(N-*t*-butoxycarbonyl)ephedrine.²

A 100-mL oven-dried Schlenk flask equipped with a magnetic stir-bar was charged with (1*R*, 2*S*)-(-)-(N-*t*-butoxycarbonyl)ephedrine (0.79 g, 3.0 mmol) and the reaction vessel was flushed with nitrogen. Anhydrous toluene (8 mL) was added, followed by AlMe₃ (150 μL of a 2 M solution in toluene) via syringe. The reaction was stirred for 10 min after which 3-nitrobenzaldehyde (1.39 g, 9.0 mmol) in anhydrous toluene (4 mL) was added. After 20 min, stirring was stopped and the reaction was diluted with CH₂Cl₂ (50 mL) and washed with H₂O (3 × 50 mL). The organic layer was collected, dried over anhydrous Na₂SO₄, and solvents were removed from the resulting filtrate. Crude oxidation product was loaded onto a plug of alumina (20 cm × 2 cm, activated, neutral, Brockmann activity 1, ~ 150 mesh) and flushed with hexanes until product elution ceased. 2-(N-*t*-Butoxycarbonyl-*N*-methylamino)-1-phenyl-1-propanone was collected as a colorless oil (0.67 g, 86% yield). ¹H NMR (499.6 MHz, CDCl₃): 1.35, (d, *J* = 6.5 Hz, 3 H), 1.40 (s, 2 H), 1.44 (s, 7 H), 2.61 (s, 2 H), 2.75 (s, 1 H), 5.68 (q, *J* = 6.5 Hz, 1 H), 7.42-7.53 (m, 3 H), 7.90 (d, *J* = 7 Hz, 1 H), 7.98 (d, *J* = 7.5 Hz, 1 H). ¹³C{¹H} NMR (125.6 MHz, CDCl₃): δ 13.5, 28.5, 28.6, 29.9, 54.9, 128.4, 128.6, 128.8, 133.4, 155.7, 200.0. The ee of the product was determined via chiral HPLC (Conditions: 5% 2-propanol in hexanes, flow rate = 0.5 mL/min, detector set at 254 nm). Retention time of the *R* enantiomer = 13.20 min, Retention time of the *S* enantiomer = 15.50 min (Figure S2).

Note: reaction monitoring is crucial in the oxidation of this substrate. Once the oxidation is complete, the reaction should immediately be quenched with H₂O. Continued exposure of the oxidized product to the reaction conditions will eventually lead to racemization.

Figure S2. Chiral HPLC traces of 2-(N-*t*-butoxycarbonyl-*N*-methylamino)-1-phenyl-1-propanone: (a) racemic sample. (b) enantiomerically pure sample from the oxidation of (1*R*, 2*S*)-(-)-(N-*t*-butoxycarbonyl)ephedrine.

General procedure for the kinetic comparison of the O oxidation of 1° and 2° benzylic alcohols. In the drybox, an 8-mL vial equipped with a magnetic stirring bar was charged with the alcohol (1.0 mmol) and dissolved in anhydrous toluene (2 mL) containing internal standard. AlMe₃ (9.6 μL, 0.1 mmol) was added via gas tight syringe and the vial was capped with a Teflon-lined silicone septa. The reaction was removed from the drybox, and stirred for 10 min. 3-Nitrobenzaldehyde (151 mg, 1.0 mmol) was then added as a solution in toluene (2 mL) and the reaction was stirred. At the time indicated for each data point, a 100-μL fraction was taken via gas-tight syringe, loaded onto a plug of alumina, eluted with MeOH (15 mL) and directly analyzed by GC using the appropriate temperature program. The time-dependent yield profiles of the organic carbonyl products are plotted in Figure S3.

Figure S3. Plots of GC-yields versus time for the Oppenauer oxidation of α -methylbenzyl alcohol (R = Me, A) and benzyl alcohol (R = H, B) catalyzed by AlMe₃.

Cost comparison of our O-oxidation system against other commonly employed oxidation procedures. Our system fared quite well against other commonly employed oxidation procedures in a cost analysis (Table S3). Considering a 0.5-mol alcohol oxidation, the total cost of reagents for our Oppenauer oxidation is about 2.6 times less than that for a Swern oxidation, without the typical smell associated with SMe₂.³ The corresponding oxidation using Dess-Martin periodinane⁴ would cost 145 times as much as ours. Oxidations implementing the chromium reagents PCC⁵ and PDC⁶ would be approximately 1.5 and 5.6 times more expensive, respectively. Finally, use of MnO₂⁷ as the oxidant results in an oxidation procedure approximately 11.4 times more expensive than our Oppenauer oxidation procedure. These Cr- and Mn-mediated oxidation processes also have the drawback of generation of heavy metal waste. Although oxoammonium-based oxidation protocols are prevalent, included those catalyzed by TEMPO, they are not included in this cost analysis given their varying procedures and co-oxidants employed.⁸

Table S3. Cost comparison of our O oxidation system against other commonly employed oxidation methods.

entry	oxidant	equiv ^a	cost (US \$) ^b	ratio
1	AlMe ₃ ^c /3-nitrobenzaldehyde	0.1/3.0	42	---
2	Dess-Martin periodinane	1.1	6094	145
3	DMSO/oxalyl chloride/NEt ₃	2/1.1/5	111	2.6
4	PCC	1.5	64	1.5
5	PDC	7	236	5.6
6	MnO ₂	11	478	11.4

^a Equivalents of oxidant needed according to the appropriate procedure. ^b Cost based on the lowest cost-per-gram from the 2005-2006 Aldrich catalog, rounded to the whole dollar. ^c Purchased as a 2 M solution in toluene.

References:

- 1) Pangborn, A. B.; Giardello, M. A.; Grubbs, R. H.; Rosen, R. K.; Timmers, F. J. *Organometallics* **1996**, *15*, 1518-1520.
- 2) Fraser, D. S.; Park, S. B.; Chong, J. M. *Can. J. Chem.* **2004**, *82*, 87-101.
- 3) Omura, K.; Swern, D. *Tetrahedron* **1978**, *34*, 1651-1660.
- 4) Dess, D. B.; Martin, J. C. *J. Am. Chem. Soc.* **1991**, *113*, 7277-7287.
- 5) Corey, E. J.; Suggs, J. W. *Tetrahedron Lett.* **1975**, 2647-2650.
- 6) Corey, E. J.; Schmidt, G. *Tetrahedron Lett.* **1979**, 399-402.
- 7) Highet, R. J.; Wildman, W. C. *J. Am. Chem. Soc.* **1955**, *77*, 4399-4407.
- 8) *Modern Oxidation of Alcohols Using Environmentally Benign Oxidants*. Arends, I. W. C. E.; Sheldon, R. A. In *Modern Oxidation Methods*; Backvall, J.-E., Ed; Wiley-VCH: Weinheim, 2004; pp 83-86.