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# Efficient and Selective Al-Catalyzed Alcohol Oxidation via Oppenauer Chemistry

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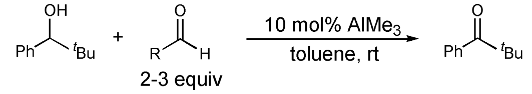
The selective oxidation of alcohols to their corresponding carbonyls is one of the most widely employed transformations in organic synthesis.[1] Although numerous such protocols are available, many employ stoichiometric heavy metal complexes[2] or suffer from selectivity issues when $H_2O_2$ or NaOCl are used as oxidants.[3] Organic oxidants, such as Swern and Dess−Martin reagents, are more selective but can be either difficult to handle[4] or hazardous.[5] While selective catalytic oxidation methodologies[6] have recently become available, they draw on expensive metal complexes and/or elevated temperatures, issues that can be circumvented with the Oppenauer (O) oxidation. Along with the benefits of being highly chemoselective, the O oxidation employs easily handled organic-based oxidants and aluminum, an inexpensive and innocuous metal, as key reactants.[7] Although discovered in the mid-1930s,[8] only recently have Al-based O oxidation catalysts been reported, albeit with specialized ligated aluminum complexes and a fairly limited substrate set.[9] Herein, we describe an Oppenauer oxidation protocol that utilizes simple organoaluminum complexes as precatalysts that is highly active and selective for the oxidation of a diverse array of alcohol substrates, even in the presence of nitriles, esters, amides, halides, and tertiary alcohols. Most importantly, our protocol is easily extendable to large-scale oxidations performed on the benchtop with facile purification.

Our recent success[10] in the application of organoaluminum compounds as precatalysts for the Meerwein−Schmidt−Ponndorf−Verley (MSPV) reduction of ketones suggested that under the right conditions a similarly efficient Al-based catalytic O oxidation could be developed. As the MSPV reduction and O oxidation are mirror processes,[7] selecting a highly reactive aldehyde as the oxidant for the O oxidation of alcohol should shift the equilibrium toward the desirable oxidation products. On the basis of relative reduction potentials,[11] a series of benzaldehyde derivatives (**A**−**D**) were screened as the hydrogen acceptor in the O oxidation of α-$^t$butylbenzyl alcohol, a difficult-to-oxidize substrate,[12] using *only* $AlMe_3$ as a precatalyst.[13] Although benzaldehyde (**A**) gave a low yield (Table 1, entry 1), changing oxidant to the more active 2,6-dichloro- (**B**) (Table 1, entry 2) and 2,4-dinitrobenzaldehydes (**C**) (Table 1, entry 3) afforded quantitative oxidation of α-$^t$butylbenzyl alcohol in short reaction time. The use of 3-nitrobenzaldehyde (**D**) (Table 1, entry 4) as the oxidant was most appealing, as it is both inexpensive and readily available.[14] An added bonus is the easy removal of excess **D** and the reduced nitrobenzyl alcohol from reaction products for various substrates by simple filtration over an alumina plug with hexanes eluent, even on a 10 g scale (see Supporting Information). Gratifyingly, in the presence of 3 equiv of 3-nitrobenzaldehyde, α-$^t$butylbenzyl alcohol was quantitatively oxidized to $^t$butyl phenyl ketone in less than 0.5 h (Table 1, entry 5).

***Table 1.*** Benzaldehydes as Hydrogen Acceptors for the Catalytic Oppenauer Oxidation of α-$^t$Butylbenzyl Alcohol



(1)

| entry | R | equiv | time (h) | GC yield (%) |
|---|---|---|---|---|
| 1 | Ph (**A**) | 2 | 2 | 25 |
| 2 | 2,6-$Cl_2$−Ph (**B**) | 2 | 4 | >99 |
| 3 | 2,4-$(NO_2)_2$−Ph (**C**) | 2 | 4 | >99 |
| 4 | 3-$NO_2$−Ph (**D**) | 2 | 4 | 90 |
| 5 | 3-$NO_2$−Ph (**D**) | 3 | <0.5 | >99 |

The O oxidation of various 2° alcohols was carried out using the established conditions of Table 1, entry 5. Excellent yields were obtained in the oxidation of various 2° benzylic alcohols (Table 2, entries 1−9). That a readily available commercial solution of $AlMe_3$ in toluene can be employed effectively as the catalyst precursor in a large-scale benchtop reaction (Table 2, entry 2) makes our protocol very appealing to the average researcher, who may not have access to either a Schlenk line or a drybox. Remarkably, our protocol even allows for the use of solid $Al(O^iPr)_3$ as a precatalyst, albeit with much slower kinetics (Table 2, entry 3; also see Supporting Information). Even in the presence of excess esters, amides, nitriles, and tertiary alcohols, the oxidation of **1** proceeds in excellent conversion (see Supporting Information).

Our oxidation protocol was also applicable for the quantitative oxidation of hetero-functionalized alcohols. Both furyl and thiophenyl substituents were tolerated (Table 2, entries 10−12), as was pyridyl, although oxidation of α-(2-pyridyl)ethanol, **11**, was not possible (Table 2, entries 13−15), potentially due to chelative inhibition of the catalyst. Importantly, the mechanistic pathway[11,15] of the O oxidation does not allow for *S*- or *N*-oxidation to occur, demonstrating its inherent chemoselectivity. Additionally, our system was applicable for the selective oxidation of the alcohol moiety in α,*β*-unsaturated alcohols (Table 2, entries 16 and 17), comprising a chemoselective advantage over transition metal catalysts that operate through metal hydride intermediates.[16] Quantitative oxidation of a variety of 2° aliphatic alcohols was possible (Table 2, entries 18−20), including the facile oxidation of both borneol and isoborneol to camphor (Table 2, entries 21 and 22, respectively). The appeal of our system is further demonstrated in the smooth oxidation of the alcohol moiety in (1*R*,2*S*)-(−)-(*N*-$^t$butoxycarbonyl)ephedrine with no racemization of the α-chiral amino center (see Supporting Information).

Preliminary kinetic data show that 2° alcohols are oxidized at a dramatically faster rate (at least 3600 times) than corresponding 1° alcohols (see Supporting Information). Nevertheless, the oxidation of primary alcohols to aldehydes can still be accomplished easily using our O oxidation protocol. While both benzylic (Table 3, entries 1−3) and allylic (Table 3, entry 4) 1° alcohols were readily converted to their corresponding aldehydes in short reaction times using 3-nitrobenzaldehyde, this oxidant was not an appropriate hydrogen acceptor for the oxidation of 1° aliphatic alcohols. However, switching the oxidant to the more active 2,4-dinitroben-

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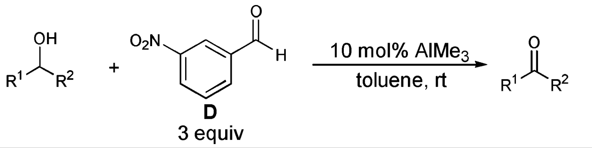
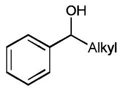
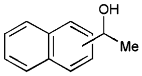
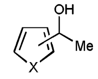
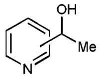
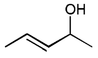
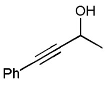
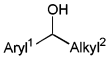
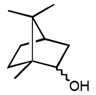
***Table 2.*** Scope of the Oppenauer Oxidation of 2° Alcohols

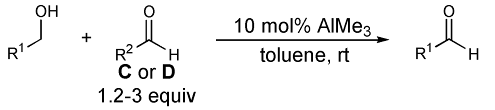


(2)

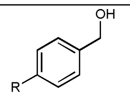
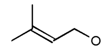
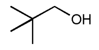
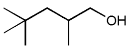
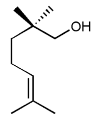
| entry | alcohol | | | time (h) | GC yield [isolated yield][a] |
|---|---|---|---|---|---|
| | | | *Alkyl* | | |
| 1 |  | **1** | Me | <<0.5 | >99% |
| 2 | | **1** | Me | 0.5[a] | >99% [93%] {92%}[b] |
| 3 | | **1** | Me | 2.0[c] | 73% |
| 4 | | **2** | $^i$Pr | 0.5 | >99% |
| 5 | | **3** | $^t$Bu | 0.5 | >99% [85%] |
| 6 | | **4** | CH$_2$Br | 0.5 | >99% |
| 7 | | **5** | Ph | 0.5 | >99% [88%] |
| 7 |  | **6** | 1-napthyl | 0.5 | >99% [89%] |
| 9 | | **7** | 2-napthyl | 0.5 | >99% |
| 10 |  | **8** | 2-furyl | 0.5 | >99 |
| 11 | | **9** | 2-thiophenyl | 0.5 | 98% |
| 12 | | **10** | 3-thiophenyl | 0.5 | >99% [84%] |
| 13 |  | **11** | 2-pyridyl | 0.5-18 | 0 |
| 14 | | **12** | 3-pyridyl | 1 | >99% [75%][d] |
| 15 | | **13** | 4-pyridyl | 1 | >99% |
| 16 |  | **14** | | 0.5 | >99% |
| 17 |  | **15** | | 0.5 | 97% [78%][d] |
| | | | *Alkyl*[1] *Alkyl*[2] | | |
| 18 |  | **16** | hexyl Me | 0.5 | >99 |
| 19 | | **17** | $^t$Bu Me | 0.5 | >99 |
| 20 | | **18** | Cy Me | 0.5 | >99 |
| 21 |  | **19** | borneol | 0.5 | >99% [94%] |
| 22 | | **20** | isoborneol | 0.5 | >99% [90%] |

[a] Isolated yield based on a 6-mmol oxidation performed on the benchtop using simple syringe techniques with a 2 M solution of AlMe$_3$ in toluene. [b] Isolated yield of a 10-g scale reaction. [c] On the benchtop, in ACS-grade toluene, with 10 mol % of solid Al(O$^i$Pr)$_3$ as the catalytic precursor. [d] Minor loss of yield during purification (see Supporting Information).

***Table 3.*** Scope the Oppenauer Oxidation of 1° Alcohols



(4)

| entry | alcohol | | | time (h) | oxidant (equiv) | GC yield [isolated yield][a] |
|---|---|---|---|---|---|---|
| | | | *R* | | | |
| 1 |  | **21** | H | 0.5 | **D** (3) | >99% [82%] |
| 2 | | **22** | OMe | 0.5 | **D** (3) | >99% [90%] |
| 3 | | **23** | Cl | 0.5 | **D** (3) | >99% |
| 4 |  | **24** | | 0.5 | **D** (3) | >99% |
| 5 |  | **25** | | 1 | **C** (1.2) | 94% [70%][b] |
| 6 |  | **26** | | 1 | **C** (1.2) | >99% |
| 7 |  | **27** | | 1 | **C** (1.2) | 88% |

[a] Isolated yield based on a 6-mmol oxidation performed using standard Schlenk-line techniques with a 2 M solution of AlMe$_3$ in toluene. [b] Minor loss of yield during purification (see Supporting Information).

zaldehyde readily allowed for the oxidation of this class of alcohols (Table 3, entries 5−7).

Excitingly, this is the first example of a simple Al-catalyzed O oxidation that is applicable for primary aliphatic alcohols, an unreactive substrate class for Maruoka's (*N*,*O*)-ligated aluminum catalyst.[9a,17] The versatility of our system is apparent through the facile and selective oxidation of $\beta$-citronellol (**27**, Table 3, entry 7), a sensitive primary alcohol that is known to suffer selectivity issues under other oxidation methods.[2b,c]

In conclusion, we have demonstrated a highly active Oppenauer oxidation system comprising catalytic amounts of simple AlMe$_3$ precursor and the inexpensive and readily available 3-nitrobenzaldehyde oxidant. This system is active for the selective oxidation of a variety of benzylic, allylic, and aliphatic secondary as well as primary alcohols. Direct comparison of this system with other oxidation manifolds shows superior reactivity, selectivity, and cost advantages (see Supporting Information) relative to other commonly utilized oxidation processes.

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**Supporting Information Available:** Experimental procedures and compound characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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(12) SooKim, S.; Rajagopal, G. *Synth. Commun.* **2004**, *34*, 2237−2243.
(13) Although AlMe$_3$ is used extensively throughout this study, the less expensive AlEt$_3$ can also be used effectively as a precatalyst without adverse effects.
(14) When purchased in bulk, 3-nitrobenzaldehyde can be bought for $0.10/g (U.S.) (Aldrich Chemical Co., 500 g scale).
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(17) $^t$Butyl aldehyde and not 3-nitrobenzaldehyde was used as the oxidant for this O oxidation protocol.

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