Air-stable iron catalyst for the Oppenauer-type oxidation of alcohols

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ABSTRACT

An alcohol oxidation process using an air-stable iron tricarbonyl compound structurally similar to Shvo's diruthenium bridging hydride was developed. Secondary benzylic and allylic alcohols are oxidized in high yields, and evidence for an Oppenauer-type mechanism is presented.

Alcohol oxidations are of fundamental importance in synthetic organic chemistry. Traditionally these transformations have been achieved using stoichiometric amounts of strong oxidants such as chromium oxides,[1] activated DMSO,[2] and hypervalent iodine species.[3] In an alternative approach, transition metal compounds can be used to catalytically oxidize alcohols, but a stoichiometric oxidant is still needed. Aerobic oxidations have been extensively explored because molecular oxygen is abundant, inexpensive, and appealing from an environmental perspective,[4] but safety concerns (such as organic peroxide formation) arise when an organic substrate or solvent is treated with O_2. In order to develop a simple, safe, environmentally benign alcohol oxidation, consideration must be given to nature of the oxidant, the catalyst, and the solvent. Oppenauer oxidations use acetone as both an oxidant and a solvent and produce isopropanol as a byproduct. Both acetone and isopropanol have been listed by Pfizer as preferred solvents based on their environmental solvent selection guidelines.[5] A number of main group and transition metal-based compounds catalyze Oppenauer-type oxidations including aluminum, magnesium, samarium, ruthenium, and iridium.[6] Using iron-based catalysts in Oppenauer-type oxidations is desirable due to iron's high natural abundance, low cost, and low toxicity.[7] While there are reports of iron compounds catalyzing the reductions of ketones to alcohols by transfer hydrogenation,[8] there are few reports of the reverse reaction.[9]

Casey and Guan have explored the application of the Shvo-type iron hydride **1** to the hydrogenation of aldehydes and ketones.[10] Compound **1** catalyzes the reductions using either H_2 or 2-propa-nol (in a transfer hydrogenation) as the hydrogen source. Experimental[10] and computational[11] studies support concerted hydrogen transfer outside of the coordination sphere of the metal, which results in a mechanism for the transfer hydrogenation process analogous to the proposed mechanism for the ruthenium-based Shvo catalyst **2** (Scheme 1).[12] Although the initial application of catalyst **1** was in reductive reactions, the reversibility of the process suggests that by using acetone as the solvent, alcohol oxidations should be possible.

When compound **1** (10 mol%) was treated with 1-phenylethanol in acetone at reflux acetophenone formed in 89% yield (Table 1, entry 1). The successful application of **1** to an Oppenauer-like oxidation was consistent with Guan's results which were published during our work.[9b] While compound **1** is an active catalyst, it is air sensitive and, in our hands, decomposed from a yellow to a brown solid within 2.5 h of exposure to air.[10b,13] Compound **2** is air and moisture stable, which has presumably aided in its popularity, and we sought out to discover an air-stable, iron-based oxidation catalyst that was user-friendly.

For Shvo's catalyst (**2**) to be active, the diruthenium bridging hydride must dissociate into an oxidative and a reductive component (Scheme 1, **4** and **5**, respectively).[6d,14] Both species are catalytically active: **4** can immediately oxidize an alcohol, and **5** must reduce acetone to 2-propanol before it can react with an alcohol. The iron compound **1** is analogous to the reductive ruthenium species **5**. While **1** is unstable in the air and therefore not an ideal place to enter the catalytic cycle, we thought we could generate the coordinatively unsaturated species **3** (which is analogous to **4**, the oxidative component of Shvo's catalyst) by ligand dissociation from an 18-electron iron compound. Therefore we synthesized known compounds **6**[15] and **7**[16] (Fig. 1), both of which are stable for many months in air, and

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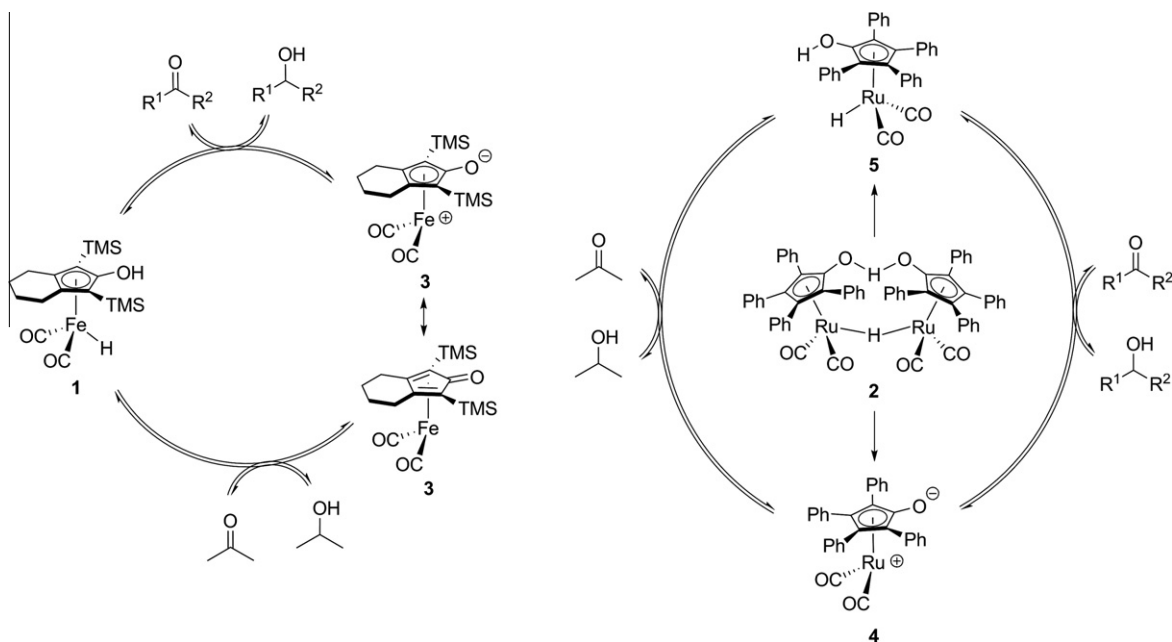
Scheme 1. Simplified mechanisms of transfer reductions/oxidations using **1** and **2**.

Table 1
Oxidation of 1-phenylethanol with iron compounds
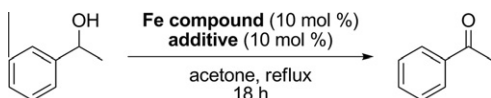
Entry	Fe compound	Additive	Conversion[a] (%)
1	**1**	None	89
2	**6**	None	6
3	**7**	None	<2
4	**6**	Me$_3$NO	97
5	**8**	Me$_3$NO	79
6	**9**	Me$_3$NO	36
7[b]	**6**	Me$_3$NO	~2

[a] Determined by ^{1}H NMR spectroscopy.
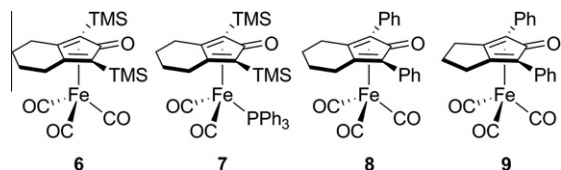[b] Reaction done in a sealed vessel.

Figure 1. Structures of iron compounds examined in alcohol oxidation reaction.

treated a solution of 1-phenylethanol in acetone with them (Table 1, entries 2 and 3).

Neither **6** nor **7** was active enough to even stoichiometrically oxidize 1-phenylethanol under these conditions. Presumably the Fe–CO and Fe–PPh$_3$ bonds are not labile enough for ligand dissociation to occur, and therefore a coordination site does not become available.[17] Interestingly, compound **7** is synthesized by treating **6** with trimethylamine N-oxide and triphenylphosphine in acetone at reflux.[16] Trimethylamine N-oxide oxidatively removes a CO ligand from **6** to generate the 16-electron species **3**, and triphenylphosphine coordinates to the empty site. Because generating **3** in

Table 2
Substrate scope of alcohol oxidations with **6** and Me$_3$NO[a]
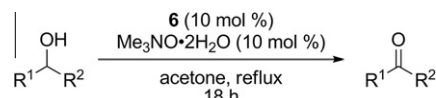
Entry	Alcohol	Ketone/aldehyde	Isolated yield[b] (%)
1			92
2			94
3			69
4			85
5			93
6			63
7			77
8			87

Table 2 (continued)

Entry	Alcohol	Ketone/aldehyde	Isolated yield[b] (%)
9			80
10		5.5 : 1	(91)
11			69
12			40
13			42
14			(29)
15			(4)
16[c]	1 : 1		46

[a] Reaction conditions:[23] alcohol (1 equiv), **6** (0.1 equiv), Me$_3$NO·2H$_2$O (0.1 equiv) in acetone (0.5 M in alcohol) at reflux under N$_2$ for 18 h.
[b] Values in parentheses are NMR conversions.
[c] No octanal was observed.

solution was our goal, we treated **6** with Me$_3$NO in the presence of 1-phenylethanol and obtained acetophenone in 97% conversion (Table 1, entry 4).[18] The success of this approach encouraged us to try known compounds **8** and **9** as catalysts,[16] but the conversions were lower than with compound **6** (Table 1, entries 5 and 6).[19]

The reaction conditions used to collect the data in Table 1 are the optimized conditions. Larger amounts of trimethylamine N-oxide afforded the alcohol in lower yields. This result was not surprising because trimethylamine N-oxide has been used to remove the cyclopentadienone ligand from complex **6**,[15,20] so the low yields are most likely due to decomposition of the catalyst. ^{1}H NMR spectra of the crude reaction mixtures showed free cyclopentadienone, supporting this hypothesis. We observed no difference in the conversions when trimethylamine N-oxide dihydrate

was used in place of anhydrous trimethylamine N-oxide. Alcohol concentrations of 0.5–1.0 M afforded the ketone in high yields, but concentrations lower than 0.25 M were detrimental to the conversions.

When the reaction was run in a sealed vessel, almost no alcohol oxidation occurred (Table 1, entry 7). The large impact of running the reaction in an open versus a closed system can be explained by the presence or absence of an amine by-product. When **6** is treated with trimethylamine N-oxide unsaturated iron species **3**, CO$_2$ and an amine are generated (Scheme 2). While trimethylamine N-oxide-mediated decarbonylations of iron carbonyls are known to release trimethylamine,[21] there are also a few examples of iron tricarbonyl compounds similar to **6** forming dimethylamine.[22] In a sealed vessel, the gaseous di- or trimethylamine is trapped and coordinates to **3** forming compound **10**. In a flask that is open to a mineral oil bubbler the amine can ultimately escape and the unsaturated species **3** can interact with alcohol. This proposal is consistent with the inactivity of compounds **6** and **7** in alcohol oxidations.

The substrate scope of the reaction was explored, and the results are depicted in Table 2.[23] Secondary benzylic and allylic alcohols were readily oxidized (Table 2, entries 1–9). Benzylic alcohols with electron-donating groups (Table 2, entry 2) were more reactive than those containing electron-withdrawing substituents (Table 2, entry 3), which supports a mechanism where the HOC**H**RR′ hydrogen is removed as a hydride. An allylic alcohol containing a terminal alkene afforded primarily the product from alkene isomerization and a small amount of the α,β-unsaturated ketone (Table 2, entry 10). Aliphatic secondary alcohols were oxidized less efficiently (Table 2, entries 11–13), and primary alcohols afforded aldehydes in low conversions (Table 2, entries 14–15). The difficulty in oxidizing primary alcohols in Oppenauer oxidations is common and can be explained by a disfavored equilibrium between 1° alcohol/acetone and aldehyde/isopropanol.[6,9b,24]

If primary alcohols react poorly exclusively because of an unfavorable equilibrium, acetophenone should be generated in high yield in a reaction containing both 1-phenylethanol and 1-octanol. When equimolar amounts of 1-phenylethanol and 1-octanol were treated with **6** under the optimized reaction conditions, acetophenone formed in only 46% conversion and no octanal was present (Table 2, entry 16); the primary alcohol acted as more than a simple spectator. A potential explanation for this inhibition of catalytic activity is that primary alcohols preferentially coordinate to **3** over secondary alcohols, and if the dehydrogenation of secondary alcohols is not rapid, alcohol exchange may occur before the oxidation process takes place.[25]

While mechanistic experiments with **1** support a reversible transfer of hydrogen from alcohols to ketones, the studies were focused on ketone and aldehyde hydrogenations.[10,11] Alcohol oxidations may occur through an Oppenauer-type mechanism or a direct
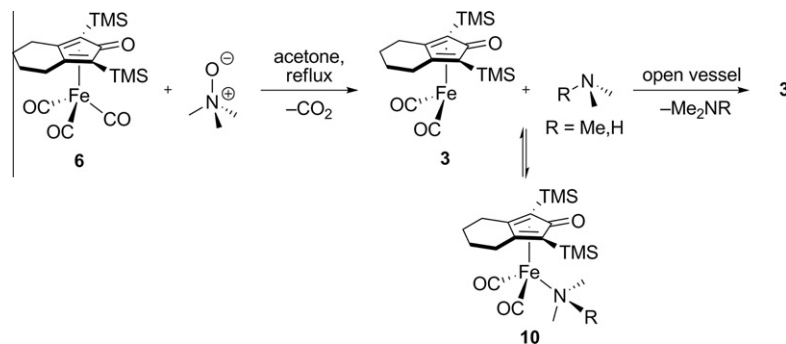
Scheme 2. Loss of amine in an open reaction vessel.

loss of H_2 from **1**, which is known to occur when **2** is used at elevated temperatures.[26] To distinguish between these two mechanisms, 1-phenylethanol was oxidized using the optimized reaction conditions in acetone-d_6 in an open system. A ^{1}H NMR spectrum of the crude reaction mixture showed acetophenone and isopropanol-d_6 in a one-to-one ratio. This result is consistent with an Oppenauer-type oxidation where 1 equiv of acetone is reduced for each equivalent of alcohol that is oxidized (Scheme 1). If it proceeded through a direct loss of H_2, no deuterated isopropanol would have been observed.
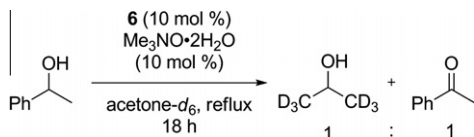
In summary, an air-stable, well-defined iron compound was discovered to be an active catalyst for Oppenauer-type alcohol oxidations. By removing one of the carbonyl ligands from an 18-electron iron species using trimethylamine N-oxide, a coordinatively unsaturated species that was catalytically active could be generated. Secondary benzylic and allylic alcohols are easily oxidized with this catalyst system. Primary alcohols are oxidized in low yields and appear to partially inhibit the catalytic activity of the iron species. We have provided evidence that the oxidation proceeds through a transfer dehydrogenation (Oppenauer-type oxidation) process, which is consistent with the detailed kinetic and spectroscopic studies of the reverse reaction.[10,11] Current and future work will be focused on applying this catalytic system to other transformations and developing new air-stable, user-friendly iron catalysts by modifying compound **6**.

Acknowledgment

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23. *Representative procedure for alcohol oxidation by* **6**: To a solution of **6** (34 mg, 0.082 mmol, 0.1 equiv) and trimethylamine N-oxide dihydrate (9.2 mg, 0.082 mmol, 0.1 equiv) in 1.6 mL degassed acetone in a round-bottomed flask with a condenser connected to a mineral oil bubbler was added 1-phenylethanol (100 mg, 0.82 mmol, 1 equiv, 0.5 M in acetone), and the solution was heated to reflux for 18 h. The solvent was removed under reduced pressure and the remaining residue was purified by flash chromatography on silica gel (3% ethyl acetate/97% hexanes) to afford 91 mg (92% yield) of acetophenone.
24. Equilibrium constants can be calculated from oxidation potentials of aldehydes and ketones using the Nernst equation. For the Oppenauer oxidation using acetone (oxidation potential = 129 mV) as the oxidant, the equation becomes $[10079.5(0.129 - E°)]/T = \log K_{eq}$, where $E°$ is the oxidation potential of the aldehyde or ketone formed in the reaction in volts and T is the temperature in K. This calculation does not take into consideration the large excess of acetone used in the reactions. Adkins, H.; Elofson, R. M.; Rossow, A. G.; Robinson, C. C. *J. Am. Chem. Soc.* **1949**, *71*, 3622.
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