Air-Stable, Nitrile-Ligated (Cyclopentadienone)iron Dicarbonyl Compounds as Transfer Reduction and Oxidation Catalysts

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Abstract: A series of air-stable, nitrile-ligated (cyclopentadienone)iron dicarbonyl compounds was synthesized and their activities as catalysts in the transfer reduction of acetophenone were explored. While all were active catalysts, the acetonitrile adduct was chosen for further study and was found to be active in the transfer reduction of aldehydes and ketones and in the Oppenauer-type oxidation of secondary alcohols. The acetonitrile catalyst exhibited activities similar to those of an analogous air-sensitive iron hydride, but unlike the iron hydride it was unreactive in carbonyl reductions using hydrogen gas.

Keywords: alcohols; aldehydes; homogeneous catalysis; iron; ketones; oxidation; reduction

Carbonyl reductions and alcohol oxidations are fundamental organic transformations, and a wide range of stoichiometric reductants and oxidants is known to mediate these processes. Efforts to minimize the amount of waste produced have led to the development of metal-catalyzed reactions, although stoichiometric reductants or oxidants are still necessary to induce catalyst turnover. Carbonyl transfer reduction reactions (Meerwein-Ponndorf-Verley-type reductions) and alcohol transfer oxidations (Oppenauertype oxidations) are desirable from a practical standpoint: the solvent also acts as a mild reductant or oxidant, respectively.^[1] Historically, complexes based on main group metals, such as aluminum and boron, or on lanthanides have catalyzed these reactions,^[1] but ruthenium^[2] and iridium^[3] catalysts are also known. Many of the main group and lanthanide catalysts are Lewis acidic and moisture sensitive and must be handled with care. The transition metal catalysts are

highly active and stable in the air but are based on precious metals. Replacing platinum group metal catalysts with iron-based catalysts is desirable because of iron's abundance and low cost.^[4]

A few examples of iron compounds catalyzing transfer reductions of ketones are known,^[5,6] and we became interested in iron hydride **1** because of its structural similarity to the versatile diruthenium bridging hydride **2** known as Shvo's catalyst (Figure 1).^[7] Compound **1** is an active catalyst for both transfer reductions^[6] and transfer oxidations,^[8] and detailed mechanistic work by Casey and Guan showed that its reduction mechanism is similar to that of **2**.^[6] Unfortunately its major practical limitation is its air sensitivity. While **1** is stable for a brief time in the air, it must be stored at -30 °C under an inert atmosphere.^[6b,9]

Because of its potential as a catalyst for reductive and oxidative transformations, attempts to access user-friendly, air-stable derivatives of **1** have been made by us and others. In all cases an air-stable (cyclopentadienone)iron tricarbonyl compound was used as a pre-catalyst and was treated with either water,^[10] trimethylamine *N*-oxide,^[11] or UV-Vis radiation^[12] to remove a CO ligand and generate an active species in solution (Scheme 1). Catalyst turnover numbers (TONs) were typically low in most cases (less than 10 TONs) with the highest being 18. The low TONs may be due to a combination of incomplete pre-cata-



Figure 1. Iron hydride 1 and the structurally similar Shvo's catalyst 2.



Scheme 1. Simplified reaction mechanism and access to catalytic cycle from (cyclopentadienone)iron tricarbonyls.

lyst activation and decomposition of the 16-electron active species (A) in solution.

In an attempt to avoid these issues and access more active air-stable catalysts, we decided to replace one of the carbon monoxide ligands of the (cyclopentadienone)iron tricarbonyl compounds with a labile ligand that could dissociate in solution. The air-stable, benzonitrile-ligated compound **4** is known^[6b] and was an appealing starting point because a series of iron complexes containing aliphatic nitriles or substituted benzonitriles bearing electron-donating or electronwithdrawing groups could be synthesized. Using the established procedure, a series of five nitrile-ligated iron compounds was synthesized from 3, which is airstable and accessible in two steps from commercial chemicals (Table 1).^[9,13] All of the iron nitriles in Table 1 could be purified by flash chromatography and all were air-stable, orange solids.

The activity of compounds 4-8 as catalysts in the transfer reduction of acetophenone in 2-propanol was explored (Table 2). Catalyst loadings of 10 mol% were common when (cyclopentadienone)iron tricarbonyl compounds were used,^[10-12] so our initial explorations used the same amount. At 80°C all five compounds were active catalysts with acetonitrile-derived 7 affording 1-phenylethanol in the highest yield (Table 2, entry 4). At lower temperatures the conversions were reduced, presumably because nitrile dissociation to form the active 16-electron species (A in Scheme 1) is favored at elevated temperatures.

Based on the results in Table 2, we explored the activity of acetonitrile-ligated 7 in more detail. We dis-

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[a] Reaction conditions: 3 (1 equiv.), nitrile (2 equiv.), and trimethylamine N-oxide (1.2 equiv.) in acetone (0.025 M with respect to 3) at reflux for 20 h.

^[b] Isolated yield.

Table 2. Transfer reduction of acetophenone with the iron nitriles.^[a]

	O catalyst (10 mol%) 2-PrOH, 80 °C 18 h	ОН
Entry	Catalyst	Conversion [%] ^[b]
1	4	91
2	5	91
3	6	85
4	7	96
5	8	87

[a] Reaction conditions: acetophenone (0.21 mmol, 1 equiv.) and catalyst (0.021 mmol, 0.1 equiv.) in 2-propanol (0.4 mL) at 80 °C for 18 h.

[b] Determined by ¹H NMR spectra of crude reaction mixtures.

covered that high yields in aldehyde transfer reductions occurred with 2 mol% of 7 (Table 3). Benzaldehydes substituted with aryl halides were tolerated (Table 3, entries 2 and 4) as well as those bearing ortho substituents (Table 3, entries 5 and 6). 4-Cyanobenzaldehyde was reduced in low yield (Table 3, entry 7), which we attributed to catalyst inhibition caused by nitrile coordination. No alkene reduction was observed in the reactions with α,β -unsaturated aldehydes (Table 3, entries 9, 10, and 12).^[14] Aliphatic aldehydes are also reduced cleanly (Table 3, entries 11 and 13). Imine reductions are also possible using these conditions (Table 3, entry 14), although some unreacted imine remains even after three days.

Table 3. Transfer reductions of aldehydes catalyzed by 7.^[a] O H H 2-PrOH. 80 °C H

18 h				
Entry	Substrate	Product	Yield [%] ^[b]	
1	0	ОН	85	
2	Br	Вг	96	
3	MeO	МеО	98	
4	F	F	76	
5	0	ОН	88	
6	o o	ОН	87	
7	NC	NCOH	(18)	
8	€ C C C C	OH	83	
9	0	ОН	98	
10	0	ОН	97	
11	Ph O	Ph	97	
12	~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~	ОН	85	
13	()O	()→OH	83	
14 ^[c]	N ^{-Ph}	N ^{Ph} H	(67)	

[a] Reaction conditions: aldehyde (1 mmol, 1 equiv.) and 7 (0.02 mmol, 2 mol%) in 2 mL 2-propanol at 80 °C for 18 h.

- ^[b] Isolated yield; values in parentheses are NMR conversions.
- ^[c] Three days reaction time.

Ketones were also reduced using **7** in 2-propanol (Table 4). A catalyst loading of 5 mol% was found to generally give secondary alcohols in high yields. Both aromatic and aliphatic ketones reacted under these conditions (Table 4, entries 1–4). The reduction of 2-acetylpyridine did not go to completion (Table 4, entry 5), which again may be due to catalyst inhibition by substrate coordination. Substituted cyclohexanones were reduced with low to modest diastereoselectivi-



7 (5 mol %) 2-PrOH, 80 °C R² 18 h Entry Substrate Yield [%]^[b] Product OH 1 92 OH 2 93 CI CI MeC Me 3 87 OH 4 98 ОН 5 63 81 (3.3:1 cis/ 6 trans)



[a] Reaction conditions: ketone (1 mmol, 1 equiv.) and 7 (0.05 mmol, 5 mol%) in 2 mL 2-propanol at 80°C for 18 h.

^[b] Isolated yield.

7

8

ties. For example, the cis isomer was the major product from the reduction of 2-methylcyclohexanone (Table 4, entry 6), indicating that the hydride was delivered to the carbonyl from the side opposite relative to the methyl group. The major isomer from the reduction of 4-tert-butylcyclohexanone is the trans compound (Table 4, entry 7). (R)-Carvone is reduced in low yield with a majority of the remaining mass being unreacted starting material (Table 4, entry 8). Unlike the reactions with α,β -unsaturated aldehydes, a mixture of products was obtained when 4-phenyl-3-buten-2-one (9) was reduced (Scheme 2). Some variation in product distribution was observed over multiple runs. The minor products could have formed from alkene reduction of 9 or from alkene isomerization of major product 10 followed by tautomerization. This process would yield 12, which could be reduced to 11.

While aldehydes and ketones were reduced under transfer reduction conditions with 7, esters, alkynes, and aliphatic epoxides did not react (Figure 2). Interestingly, styrene oxide underwent a selective, reductive ring-opening to afford 2-phenylethanol in the



Scheme 2. Transfer reduction of ketone 9 with 7.



Figure 2. Substrates not reduced by 7.

presence of **7** and 2-propanol (Scheme 3). An analysis of the ¹H NMR spectrum of the crude reaction mixture showed approximately 2% of the product from



Scheme 3. Reductive ring-opening of styrene oxide.

nucleophilic ring-opening by 2-propanol at the more sterically hindered epoxide carbon. This result is in contrast to the reaction of styrene oxide with **1** in the presence of dihydrogen. When iron hydride **1** was treated with styrene oxide and H_2 in toluene, no ring-opening was observed.^[6a]

In addition to being active in transfer reductions, nitrile-ligated compound 7 also catalyzed Oppenauertype oxidation reactions (Table 5). Conversions were low in acetone at reflux, so the reactions were carried out in sealed vessels at 90 °C. Secondary benzylic, allylic, and aliphatic alcohols were all oxidized to ketones (Table 5, entries 1-6). When an allylic alcohol bearing a terminal alkene was treated with 7 and acetone, the major product was due to alkene isomerization (Table 5, entry 7). Due to a disfavored equilibrium, primary alcohols are typically not oxidized in high yields in Oppenauer oxidations,^[1] and that trend can be seen here in the oxidation of benzyl alcohol (Table 5, entry 8). A diol underwent an oxidative cyclization to form a lactone (Table 5, entry 9). The vields of these reactions are equal to or higher than those using 10 mol% of iron tricarbonyl 3 and trimethylamine N-oxide.[11a]





[a] Reaction conditions: alcohol (1 mmol, 1 equiv.) and 7 (0.05 mmol, 5 mol%) in 2 mL acetone at 90 °C in a sealed vessel for 18 h.

^[b] Isolated yield; values in parentheses are NMR conversions.

The success of compound **7** as an active transfer reduction catalyst prompted us to test its activity in reductions with H_2 . Iron hydride **1** catalyzed carbonyl reductions using three atmospheres of hydrogen at room temperature.^[6] Because nitrile dissociation from **7** occurred at elevated temperatures, we used conditions identical to those with hydride **1** but at 80 °C (Scheme 4). No reduction of acetophenone was observed with **7**. Substrates bearing nitriles completely



Scheme 4. Inactivity of 7 in reductions with H₂.

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inhibited the reactivity of **1** at room temperature,^[6a] so nitrile dissociation may be disfavored under a hydrogen pressure.

In summary, a series of air-stable, nitrile-ligated (cvclopentadienone)iron dicarbonyl compounds was synthesized and their reactivities in transfer reductions was explored. While they were all active catalysts, the acetonitrile-ligated 7 was chosen for further examination. Compound 7 was found to catalyze transfer reductions of aldehydes and ketones and Oppenauertype oxidations of secondary alcohols, but it was unreactive in carbonyl reductions using H₂. It is accessible in three steps from commercially available compounds, is air-stable, and is easy to handle. Importantly, compound 7 is more active and catalyzes reactions with greater TONs than the reported (cyclopentadienone)iron tricarbonyl complexes that must be treated with additives. Future studies will focus on the continued development of air-stable, highly active (cyclopentadienone)iron-based catalysts and their applications to a variety of oxidative and reductive transformations.

Experimental Section

General Information

All reactions were done under an atmosphere of nitrogen. Reagent grade acetone and 2-propanol were degassed by bubbling nitrogen through them for at least 15 min prior to use, but no attempts were made to remove residual water. The synthetic procedures and spectroscopic data of all iron compounds along with the experimental details and spectroscopic data for all isolated compounds are provided in the Supporting Information.

General Procedure for Transfer Reductions

A solution of aldehyde or ketone (1 mmol) and 7 (0.02-0.05 mmol, 2-5 mol%) in 2 mL of 2-propanol was stirred at 80 °C for 18 h. The volatiles were removed by evaporation under reduced pressure, and the residue was purified by flash chromatography on silica gel.

General Procedure for Oppenauer-Type Oxidations

A solution of alcohol (1 mmol) and **7** (0.05 mmol, 5 mol%) in 2 mL of acetone in a sealed vessel was stirred at 90 °C for 18 h. The volatiles were removed by evaporation under reduced pressure, and the residue was purified by flash chromatography on silica gel.

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