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# Wacker-Type Oxidation Using an Iron Catalyst and Ambient Air and Its Application to Late-Stage Oxidation of Complex Molecules

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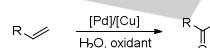
**Abstract:** We present a practical and general iron-catalyzed Wacker-type oxidation of olefins to ketones which uses ambient air as the sole oxidant. The mild oxidation conditions enable exceptional functional group tolerance, which has not been demonstrated for any other Wacker-type reaction to date. The inexpensive and nontoxic reagents [iron(II) chloride, PMHS (polymethylhydrosiloxane), and air] can, therefore, also be employed to oxidize complex natural-product derived and polyfunctionalized molecules.

The palladium(II)-catalyzed oxidation of olefins into carbonyl compounds, a reaction best known as Wacker-Tsuji oxidation,<sup>[1]</sup> possesses several highly advantageous features such as: (1) readily available, inexpensive, and thermally-, air- and water-stable substrates; (2) wide applicability to a broad range of substrates; (3) high yield and efficiency.<sup>[2]</sup> This transformation has become one of the most straightforward and convenient processes for the preparation of carbonyl compounds and found wide applications in the synthesis of natural products, pharmaceuticals, and commodity chemicals.<sup>[3]</sup> However, challenges in the field include achieving reactive and selective oxidation of internal alkenes,<sup>[2,4-6]</sup> electron-deficient internal alkenes in particular, because of the increased congestion and the decreased electron density of double bonds leading to the strong reluctance to form a key intermediate  $\eta^2$ -Pd-olefin complex.<sup>[7]</sup> Wacker-type oxidations of electron-deficient internal alkenes  $\beta$ -aryl substituted  $\alpha$ ,  $\beta$ -unsaturated carbonyl compounds have not yet been achieved. In addition, styrene derivatives are problematic substrates in classical Wacker oxidations owing to their facile polymerization and oxidative cleavage to benzaldehydes and/or benzoic acids.<sup>[6d-e,8]</sup> These aspects considerably limit the scope of the transformation.

Conventionally, the Wacker-Tsuji oxidation employs catalytic PdCl<sub>2</sub>, stoichiometric CuCl<sub>2</sub> and O<sub>2</sub> in a DMF–H<sub>2</sub>O solvent system.<sup>[1,2]</sup> This process, however, brings about several drawbacks, including degradation of the palladium catalyst, isomerization of the olefin, chlorinated byproducts, and copper waste.<sup>[2]</sup> Although diverse co-oxidants or oxidants, such as hypervalent iodine,<sup>[9]</sup> 1,4-benzoquinone,<sup>[5a-b,10]</sup> *tert*-butyl hydroperoxide,<sup>[6a-d,f]</sup> H<sub>2</sub>O<sub>2</sub>,<sup>[11]</sup> and others,<sup>[12-13]</sup> have been utilized to overcome these problems, they also cause high cost, chemical waste, and/or safety concerns. Molecular oxygen (O<sub>2</sub>) is an ideal oxidant and using it as oxidant has become one of

the ultimate goals of modern oxidation methods.<sup>[14]</sup> A number of the Wacker-Tsuji oxidation systems using O<sub>2</sub> as the sole oxidant have appeared, but most of them suffer from low efficiency, a limited substrate scope, and/or require the use of high oxygen pressures.<sup>[5c-d,6e,15]</sup> Compared to pure O<sub>2</sub>, ambient air is a more-abundant natural resource and ideally fulfill the requirement of “green chemistry”<sup>[16]</sup> as an oxidant. Nevertheless, the use of air as the sole oxidant with no co-oxidants still remains an important challenge in the field of oxidation.

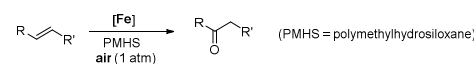
## Classic Wacker-Type Oxidation of Olefins



unmet challenges: - internal olefins are unreactive

- $\beta$ -aryl substituted  $\alpha$ ,  $\beta$ -unsaturated carbonyl compounds are problematic substrates
- active groups require protection in the late-stage oxidation
- general noble-metal-free process is absent

## This work: Iron-Catalyzed Wacker-Type Oxidation of Olefins Using Ambient Air as the Sole Oxidant



- general (internal olefins, styrenes)
- 1 atm of air as the sole oxidant
- iron catalysis
- exceptional functional group tolerance [B(OH)<sub>2</sub>, SiMe<sub>3</sub>, OH, ArOH, pyridyl, CHO, COOH, OAc, CO<sub>2</sub>R, CH<sub>3</sub>CO, NO<sub>2</sub>, PO(OEt)<sub>2</sub>, F, Cl, Br, I, OCH<sub>3</sub>, alkyl]

**Scheme 1.** Strategies for Wacker-type Oxidations of Olefins.

Hitherto, the significant progress of the Wacker-type oxidation is based on palladium catalysis. The high cost and low abundance of Pd (1 × 10<sup>-6</sup> wt% in the earth crust) have hastened the development of alternative catalysts based on earth-abundant transition metals. In this context, an effective system based on cobalt<sup>[17]</sup> has been reported to promote the Wacker-type oxidation, albeit restricted to styrenes. Iron is an ideal candidate for catalysis, since it is the second most earth-abundant metal and biocompatible,<sup>[18]</sup> but iron-catalyzed Wacker-type oxidation of olefins to ketones has not been developed thus far.<sup>[19]</sup> Herein we report the first iron-catalyzed Wacker-type oxidations of olefins to ketones using ambient air as the sole oxidant under mild conditions. This catalytic system is general, exceptionally functional group tolerant, and highly efficient even toward styrenes, internal olefins, electron-deficient internal aryl olefins as well as applicable for the late-stage oxidation of complex small molecules.

Cytochrome “P-450” plays a critical role in metabolizing numerous xenobiotics and biomolecules by generating a strong oxidant, iron-oxenoid through the reductive activation of molecular oxygen on its iron protoporphyrin IX (hemin).<sup>[20]</sup> The essential components of this system are iron as the active center, oxygen gas as the oxidant, and a reductant as the activator.<sup>[21]</sup> Recently, Baran and co-workers reported iron hydride could be generated from Fe(III) species and hydrosilane (often with PhSiH<sub>3</sub>) and subsequently reacted with alkene to form a carbon radical intermediate<sup>[22]</sup> that would be readily

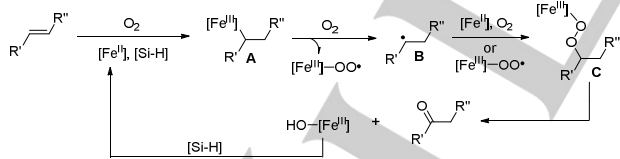
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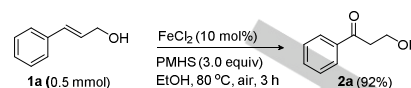
oxidized by molecular oxygen in the presence of iron catalyst.<sup>[23]</sup> Based on these advancements, we hypothesized that the iron-catalyzed Wacker-type oxidation of olefins to ketones using molecular oxygen as the sole oxidant in the presence of a reductive hydrosilane might be possible.

The presumed mechanism for this iron-catalyzed aerobic Wacker-type oxidations of olefins is shown in Scheme 2. Olefin would react with iron(III) hydride that derived from iron(II) and hydrosilane in the presence of oxygen, to generate adduct alkyl iron intermediate **A**.<sup>[23b-f]</sup> Subjecting 4-methoxystyrene to the normal reaction conditions using EtOD as the solvent led to the isolation of the desired ketone without bearing a deuterium atom. Furthermore, approximately 96% deuterium was incorporated into the  $\alpha$ -position of the ketone when (EtO)<sub>3</sub>SiD was employed as the silane (for details, see the ESI). These results indicate the H that adds across the olefin stems from hydrosilane. Subsequently, the reaction of organoiron **A** with oxygen would give the carbon-centered radical **B**, followed by generation of the iron peroxide complex **C**. The process involving radical **B** was supported by the interception of carbon-centered radical intermediate with radical scavenger galvinoxyl (for details, see the ESI). At this point, the peroxide complex **C** would undergo a concerted path with O-O and C-H bond breaking to deliver the product ketone, while providing the Fe(III)-OH species which can be reduced by the hydrosilane to regenerate the Fe(II) catalyst.<sup>[23b,25]</sup> A primary intermolecular isotope effect ( $k_H/k_D = 1.7$ ) was observed in the reaction of a 1 : 1 mixture of 4-methoxystyrene and deuterium-labeled 4-methoxystyrene (for details, see the ESI). Recently, Baran reported radical **B** could be generated through olefin abstracting a hydrogen radical from iron(III) hydride.<sup>[22c-d]</sup> However, under the Baran's conditions,<sup>[22d]</sup> Wacker-type oxidation of styrene didn't occur.<sup>[24]</sup> This result suggests that hydrogen radical transfer process might be not involved in the present reaction. Additionally, exposing 1-(4-chlorophenyl)ethanol and styrene oxide to normal conditions didn't afford the corresponding ketones,<sup>[24]</sup> implying that the mechanisms of the hydration-dehydrogenation<sup>[26]</sup> and the epoxidation-Meinwald rearrangement<sup>[27]</sup> of alkenes could be ruled out.



**Scheme 2.** Proposed Pathway of Iron-Catalyzed Aerobic Wacker-Type Oxidations of Olefins.

Our initial investigation of the proposed iron-catalyzed aerobic Wacker-type oxidation commenced with exposure of cinnamyl alcohol (**1a**) to iron species in the presence of PMHS (polymethylhydrosiloxane) as reductant and EtOH as solvent under aerobic conditions at 80 °C (Figure 1). We were delighted to observe that FeCl<sub>2</sub> showed excellent reactivity and selectivity (entry 5, 92% yield). Using other iron sources such as Fe(acac)<sub>2</sub> and Fe(acac)<sub>3</sub> gave poorer results than FeCl<sub>2</sub> (entries 1-2).



Entry	Deviation from above	Yield (%)	Entry	Deviation from above	Yield (%)
1	Fe(acac) <sub>2</sub>	39	5	Et <sub>3</sub> SiH or PhSiH <sub>3</sub>	trace
2	Fe(acac) <sub>3</sub>	30	6	(EtO) <sub>3</sub> SiH	58
3	no [Fe]	0	7	NaBH <sub>4</sub> instead of PMHS	0
4	no [Si-H]	0	8	FeCl <sub>2</sub>	94 <sup>[a]</sup>

Yields of the isolated products are given. [a] Ultrapure FeCl<sub>2</sub> (99.99% based on trace metals, Alfa Aesar).

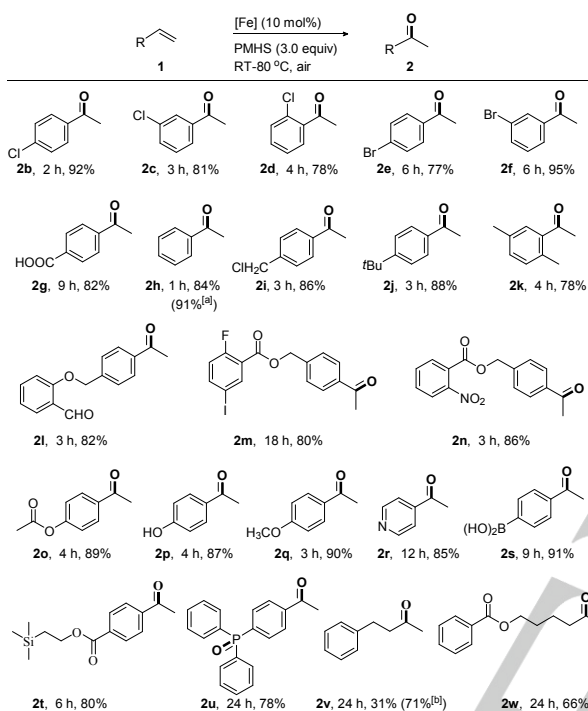
**Figure 1.** Optimization of Iron-Catalyzed Aerobic Wacker-type Oxidation.

Control experiments performed in the absence of iron catalyst, hydrosilane (entries 3-4), or molecular oxygen<sup>[24]</sup> resulted in no formation of the desired product, emphasizing the indispensable role of all these components in the catalytic cycle. We then investigated the influence of hydrosilane. Both Et<sub>3</sub>SiH and PhSiH<sub>3</sub> afforded trace amounts of the ketone **2a** (entry 5). When (EtO)<sub>3</sub>SiH was used in place of PMHS, the yield decreased from 92% to 58% (entry 6) and the corresponding silyl ether wasn't detected. Other type of reductant, NaBH<sub>4</sub> didn't work at all (entry 7). None of other solvents, *i*PrOH, *t*BuOH, MeOH, 1,4-dioxane, toluene, DMA, CH<sub>3</sub>CN, and CHCl<sub>3</sub>, could substitute the EtOH.<sup>[24]</sup> The use of ultrapure FeCl<sub>2</sub> (99.99% based on trace metals) resulted in a slightly better yield of **2a** and showed that trace quantities of other metals in the iron sources do not affect the efficiency of the olefin oxidation (entry 8). Additionally, inductively coupled plasma atomic emission spectroscopy (ICP-AES) analysis of the reaction system under optimized conditions confirmed that the concentrations of transition metals, such as Pd, Ru, and Cu were below the detection limit of the instrument. These results suggest that the catalytic reaction is based on iron.

The optimized conditions were then tested with a wide range of functionalized terminal olefins (Scheme 3). A variety of styrenes were oxidized in an efficient manner. Varying the substituents on the aromatic unit showed that electron-withdrawing (**2b-2g** and **2r-2t**), electron-neutral (**2h**), and electron-rich (**2i-2q**) styrenes were competent substrates. The position of the chloro substituent on the phenyl ring almost did not affect the reactivity (**2b-2d**). Particularly illustrative is the chemoselectivity profile of our protocol, as aryl halides (Cl, Br, I, and F) (**2b-2f** and **2m**), a benzyl chloride (**2i**), esters (**2m-2o**, **2t**, and **2w**), a nitro compound (**2n**) and even a carboxylic acid (**2g**) were tolerated. Notably, even readily oxidized aldehyde, phenolic hydroxyl, trimethylsilyl and boronic acid groups (**2l**, **2p**, and **2s-2t**), and a potentially coordinating pyridyl group (**2r**) did not reduce the efficacy of the oxidation event, which is an important challenge in Wacker-type oxidations. When diphenylphosphinostyrene was subjected to the conditions, the two-fold oxidized 1-(4-(diphenylphosphoryl)phenyl)ethan-1-one (**2u**) was obtained in 78% yield. Further submission of an aliphatic terminal olefin, 4-phenyl-1-butene (**1v**) led to 31% yield of **2v**, accompanied by 47% of 3-phenylpropanal resulted from oxidative cleavage of the carbon-carbon double bond and two unidentified side products. Gratifyingly, after a concise optimization, aliphatic terminal olefins were compatible with the conditions of Fe(acac)<sub>2</sub> (20 mol%) as the catalyst, and *t*BuOH as the solvent at room temperature, to afford the desired products

in good yields and complete Markonnikov selectivity (**2v** and **2w**). Indeed, the following study proved the new conditions were also successful in the wacker-type oxidations of other aliphatic olefins. In a couple of cases traces of aldehydes were observed, but the amount was well below 3% by  $^1\text{H}$  NMR analysis.

Furthermore, a range of unactivated internal olefins, a challenging class of substrates for Pd-catalyzed Wacker-type oxidation, were suitable partners under the iron-catalyzed aerobic oxidation conditions (Table 1). Considering cinnamyl



**Scheme 3.** Iron-Catalyzed Aerobic Wacker-Type Oxidations of Terminal Olefins. *Reaction conditions* (unless otherwise stated): **1** (0.5 mmol),  $\text{FeCl}_2$  (10 mol%), PMHS (1.5 mmol), EtOH (2.0 mL), 80 °C, and air. Yields of the isolated products are given. Completion of the reactions was indicated by TLC analysis. [a] Based on  $^1\text{H}$  NMR analysis on the crude reaction mixture with *n*-hexadecane as the internal standard. [b] **1** (0.5 mmol),  $\text{Fe}(\text{acac})_2$  (20 mol%), PMHS (1.5 mmol), *t*BuOH (2.0 mL), RT, and air.

moiety as an indispensable component of natural products, and drug candidates,<sup>[28]</sup> cinnamyl derivatives, cinnamyl alcohol (**1a**), cinnamyl chloride (**3a**), and diethyl cinnamylphosphonate (**3b**) were tested and underwent successful Wacker-type oxidations for the first time, providing full regioselectivity for the Markonnikov products **2a**, **4a** and **4b** in 92%, 90%, and 88% yields, respectively. When oxidation of the cinnamyl chloride (**3a**) was performed in EtOH with PMHS as the silane, 3-ethoxy-1-phenylpropan-1-one was obtained owing to the alcoholysis of **4a** during work-up. Cyclic olefins were also suitable substrates for the present oxidation (**4c** and **4d**). Especially noteworthy, catalytic oxidations of electron-deficient internal alkenes  $\beta$ -aryl substituted  $\alpha$ ,  $\beta$ -unsaturated carbonyl compounds to ketones, which have not been achieved by the reported Wacker-type oxidation systems, proceeded well under iron-based catalysis.<sup>[29]</sup> Specifically, *trans*-benzylideneacetone (**3e**), methyl cinnamate

(**3g**), and heterocyclic *trans*-4-(2-thienyl)but-3-en-2-one (**3f**) were reactive in the reaction, delivering the expected products in 77%, 85%, and 80% yields, respectively. However, 3-penten-2-one (**3h**) failed to undergo the Wacker-type oxidation. Aliphatic internal olefins were more unreactive than aliphatic terminal olefins and need relatively high temperature to complete their oxidations (**3i-3l**). The unsaturated alcohol (**3i**), an unsymmetrical *cis* alkene that failed to generate a ketone in Sigman's system,<sup>[5e]</sup> proved reactive by producing ketones in 71% yield, albeit in a nearly 1:1 mixture of regioisomers (**4i**). Analogously, submission of the other nonbiased *cis*-alkene *cis*-hex-3-en-1-yl benzoate (**3j**) resulted in a 1.2:1 mixture of 3-oxohexyl and 4-oxohexyl benzoates (**4j**). In addition, a trisubstituted olefin (**3k**) produced a hydroxylated product (**4k**) in moderate yield while (*E*)-2-methylbut-2-en-1-yl benzoate (**3l**) suffered oxidative C=C bond cleavage to an aldehyde (**4l**).<sup>[19c]</sup>

To further demonstrate the utility of this method, the present procedure was amenable to a gram-scale reaction. Thus, starting from 5.0 mmol of **1a**, 0.615 g of **2a** was obtained, which corresponds to a yield of 82%.

**Table 1.** Iron-Catalyzed Aerobic Wacker-Type Oxidations of Internal Olefins.<sup>[a]</sup>

Alkene ( <b>3</b> )	Product ( <b>4</b> )	Yield (%)
<b>1a</b>	<b>2a</b>	92%
<b>3a</b>	<b>4a</b>	90% <sup>[b]</sup>
<b>3b</b>	<b>4b</b>	88%
<b>3c</b>	<b>4c</b>	93%
<b>3d</b>	<b>4d</b>	85%
<b>3e</b>	<b>4e</b>	77%
<b>3f</b>	<b>4f</b>	80%
<b>3g</b>	<b>4g</b>	85%
<b>3h</b>	<b>4h</b>	-
<b>3i</b>	<b>4i</b>	71% (1.3:1) <sup>[c]</sup>
<b>3j</b>	<b>4j</b>	67% (1.2:1) <sup>[c]</sup>
<b>3k</b>	<b>4k</b>	50% <sup>[c]</sup>
<b>3l</b>	<b>4l</b>	52% <sup>[c]</sup>

[a] *Reaction conditions* (unless otherwise stated): **3** (0.5 mmol),  $\text{FeCl}_2$  (10 mol%), PMHS (1.5 mmol), EtOH (2.0 mL), 80 °C, and air. Yields of the isolated products are given. Product ratio was determined by  $^1\text{H}$  NMR. Completion of the reactions was indicated by TLC analysis. [b] **3** (0.5 mmol),  $\text{Fe}(\text{acac})_2$  (20 mol%),  $(\text{EtO})_3\text{SiH}$  (1.5 mmol), *t*BuOH (2.0 mL), RT and air. [c] **3** (0.5 mmol),  $\text{Fe}(\text{acac})_2$  (20 mol%), PMHS (1.5 mmol), *t*BuOH (2.0 mL), 50 °C and air.

We also anticipated that the present protocol might be applicable to the oxidation of natural products or synthetic compounds with high complexity due to its operational convenience and the mild oxidation conditions. To our delight, the iron-catalyzed aerobic Wacker-type oxidation is general beyond simple olefins (Table 2). For instance, a late stage oxidation of unprotected quinine monohydrochloride (**5a**), which is a commercial pharmaceutical for treatment of severe



**Table 2.** Iron-Catalyzed Aerobic Wacker-Type Oxidations of Complex Small Molecules.<sup>[a]</sup>

Entry	Olefin	Product
1		
2		
3		
4 <sup>[b]</sup>		
5		
6 <sup>[c]</sup>		
7 <sup>[c]</sup>		
8 <sup>[c]</sup>		

[a] Reaction conditions (unless otherwise stated): **5** (0.25 mmol), Fe(acac)<sub>2</sub> (20 mol%), PMHS (0.75 mmol), tBuOH (2.0 mL), 50 °C, and air. Yields of the isolated products are given. Completion of the reactions was indicated by TLC analysis. [b] PMHS (4.5 equiv). [c] **5** (0.25 mmol), FeCl<sub>2</sub> (10 mol%), PMHS (0.75 mmol), EtOH (2.0 mL), 80 °C, and air.

falciparum malaria, provided the expected product **6a** in a reasonable yield (50%) (entry 1). In addition, steroidal substrates **5b**, **5c**, and **5d** prepared from epiandrosterone, testosterone, and cholic acid, respectively, were also readily oxidized to give the corresponding products **6b**, **6c**, and **6d** in satisfactory yields (entries 2-4). Notably, three hydroxyl groups of **5d** remained intact. Similarly, molecule **5e** derived from an antibacterial drug pleuromutilin was also successfully oxidized (entry 5, 70% yield). Furthermore, complex aromatic olefins bearing estrone and thymidine moieties, were submitted to the reaction conditions, giving the **6f** and **6g** with excellent yields (entries 6-7, 90-92% yields). Also an unprotected carbohydrate fragment in **5h** was

compatible with the reaction conditions and allowed to furnish ketone **6h** (entry 8, 90% yield), which cannot be accomplished by palladium-catalyzed Wacker-type oxidation.<sup>[30]</sup> General high chemoselectivity of the iron-catalyzed oxidation is an additional advantage over the known palladium-based Wacker-type reactions.

In summary, we have developed a highly efficient and selective catalytic system consisting of iron catalyst, PMHS as the reductant, ambient air as the oxidant, and alcoholic solvents for the aerobic oxidation of styrenes, internal olefins, and electron-deficient aryl olefins to ketones. The functional group compatibility and substrate scope presented here are unprecedented by other Wacker-type oxidations to date. Importantly, compared to the classic palladium-catalyzed Wacker-type oxidations, advantages of our oxidative transformation are far milder reaction conditions, iron as catalyst and tolerance toward protic functional groups. These features render our protocol particularly useful for late-stage oxidation of complex small molecules, which offers an excellent option for establishing a new horizon for Wacker-type oxidations of olefins. Further studies into the use of the powerful iron-based catalytic system for other oxidation reactions, as well as further studies into the details of the underlying mechanism are in progress in our laboratory.

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**Keywords:** air • alkenes • iron • ketones • Wacker oxidation

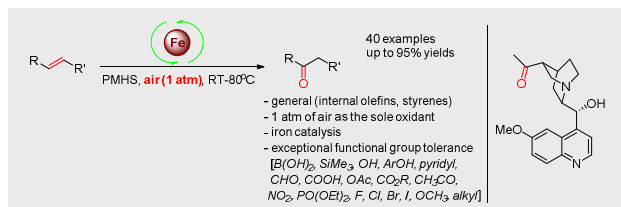
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## Entry for the Table of Contents (Please choose one layout)

Layout 2:

## COMMUNICATION



Author(s), Corresponding Author(s)\*

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**Wacker-Type Oxidation Using an Iron Catalyst and Ambient Air and Its Application to Late-Stage Oxidation of Complex Molecules**

**Air is enough!** A convenient and general iron-catalyzed oxidation of internal olefins, electron-deficient olefins, and styrenes to ketones by using 1 atm of air as the sole oxidant has been developed. This protocol efficiently incorporated atmospheric  $\text{O}_2$  into synthetically useful compounds under mild conditions, which render it environmentally benign, economical, and operationally simple. Applications to the oxidation of complex small molecules are demonstrated.