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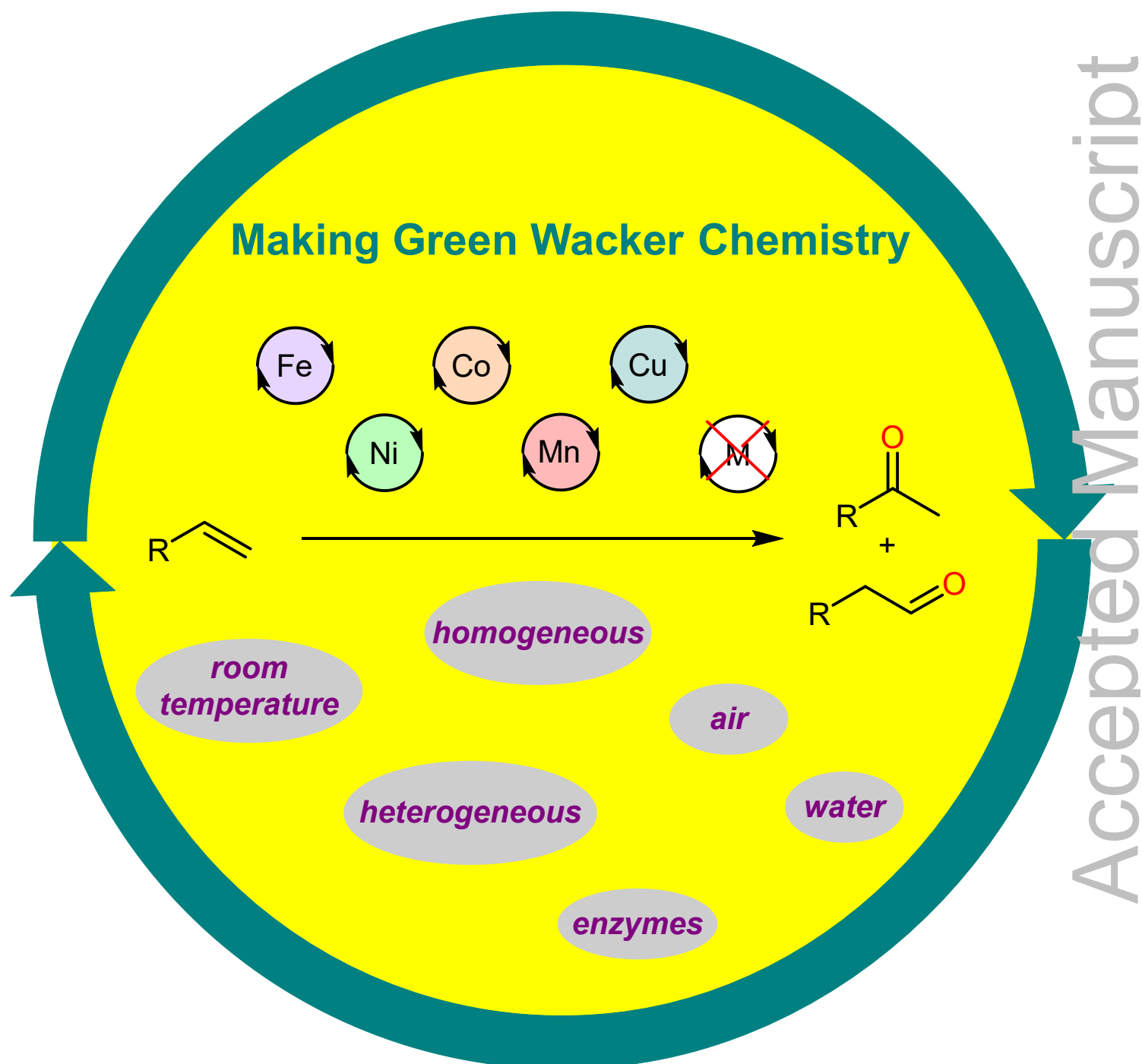
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MINIREVIEW

Sustainable Wacker-type Oxidations

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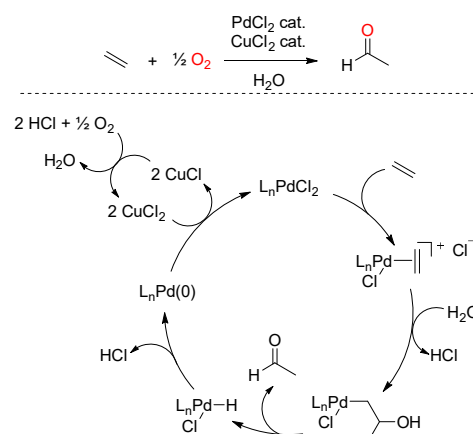
Abstract: The Wacker reaction is the oxidation of olefins to ketones and typically require expensive and scarce palladium catalysts in the presence of an additional copper co-catalyst under harsh conditions (acidic media, high pressure of air/dioxygen, elevated temperatures). Such transformation is relevant for industry as shown by the synthesis of acetaldehyde from ethylene as well as for fine chemicals due to the versatility of a carbonyl group placed at specific positions. In this regard, many contributions have focused on controlling the chemo- and regio-selectivity of the olefin oxidation by means of well-defined palladium catalysts under different set of reaction conditions. However, the development of Wacker-type processes avoiding the use of palladium catalysts has just emerged in the last years paving the way for generating more sustainable protocols including milder reaction conditions and green chemistry technologies. In this minireview, we discuss the development of new catalytic processes utilizing more benign catalysts and sustainable reaction conditions.

1. Introduction

The sustainable production of daily-life chemicals is a major challenge for the evolution of humankind.^[1] In this regard, oxidation methodologies starting from raw chemicals provide highly functionalized building blocks in an efficient manner.^[2] In particular, the access to carbonyl-containing compounds, either ketones or aldehydes, is crucial as they are straightforward transformed into complex materials and active pharmaceutical ingredients just to mention a few applications.^[3] For instance, carbonyl compounds are typically prepared in the bulk industry as well as for the preparation of fine chemicals for the fragrance industry by means of transition metal-catalyzed carbonylations of alkenes and alkynes.^[4] Alternatively, carbonyl-containing compounds can be obtained from oxidation processes without increasing the number of carbon atoms in the starting material, in contrast to the carbonylations. In this context, Wacker-type oxidations occupy a central place.^[5] Since its discovery in the late 1950's by Smidt and co-workers and the later implementation at industrial scale by the Wacker Chemie company,^[6] this transformation has found a wide range of applications ranging from natural product synthesis to the preparation of pharmaceuticals and commodity chemicals. This reaction is highly relevant since millions of tons of acetaldehyde, a key precursor in a myriad of chemical processes, are prepared by oxidation of ethylene following the Hoechst-Wacker process (Scheme 1, top).^[8]

In the broad sense, the Wacker oxidation reaction consists of the oxidation of olefins to ketones (or aldehydes) using a palladium(II) catalyst and a copper(II) co-catalyst under acidic conditions at high pressures of molecular oxygen (O_2) following the reaction mechanism depicted in Scheme 1 (bottom).^[7] In the case of larger olefins, two products can form depending on which carbon bond is oxidized. As such, the control of this regio-selectivity can lead to the Markovnikov product (ketone) or the anti-Markovnikov one (aldehyde, Figure 1). The regio-selectivity

is typically imposed by the steric and electronic nature of the substrate or tuned by the reaction conditions including the palladium-coordinated ligand employed that favors a specific reaction coordinate pathway.^[9]



Scheme 1. Hoechst-Wacker process (acetaldehyde formation from ethylene, top) and its simplified reaction mechanism (bottom).

Besides the breakthroughs achieved in the selectivity of Wacker-type reactions as well as the important progress being made to make such reactions more benign and respectful with the environment (decreasing reaction temperature, avoiding copper salts and chloride ions, using air instead of pure O_2),^[10] a major limitation still concerns the use of palladium complexes as catalysts (Figure 1). In fact, palladium is a precious noble metal that is scarce in Earth's crust, costly and not biological compatible, which is important considering that trace amounts can remain in the products obtained. Consequently, the last decades have witnessed a strong interest to replace palladium catalysts by those derived from the first row of the periodic table, with the aim to develop sustainable oxidations including metal-free processes.^[11] In addition, decreasing the catalytic loadings as well as providing milder reaction conditions, i.e. under non-acidic conditions and at atmospheric pressure, may turn the Wacker-type reaction compatible with sensitive functional groups found in the substrates. In this review, we summarize in a comprehensive manner the most important achievements accomplished in view to evolve the Wacker-type reaction greener and ready to face the challenges associated to the 21st century. Because the aim of this minireview is to focus on atom-economy as well as sustainable transformations relevant for the Wacker-type process, methodologies involving two-step sequences^[12] or the use of other noble metal-based catalysts instead of palladium are not discussed herein.^[13]

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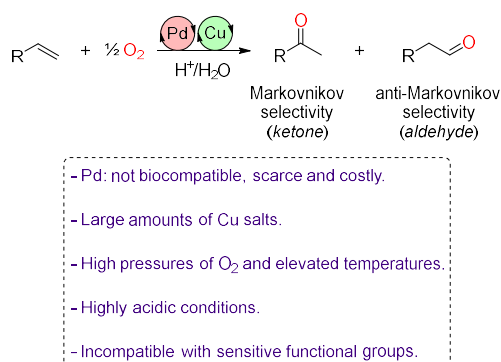


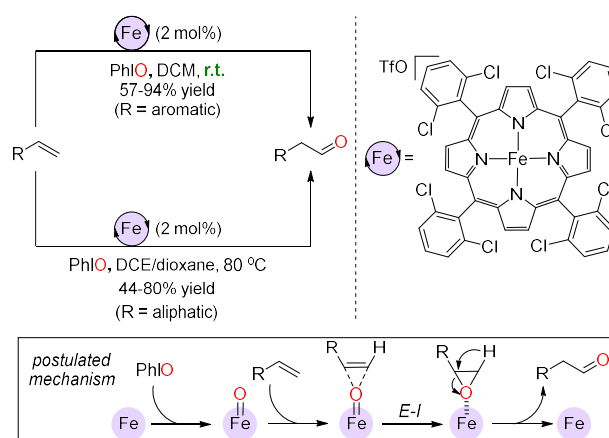
Figure 1. General palladium-catalyzed Wacker-type oxidation reaction of olefins and challenges associated for developing greener approaches (framed).

2. Iron-based Catalysts for Wacker-type Reactions

Much inspired from the oxidase activity encountered in the natural enzymes from the cytochromes family, immeasurable efforts have been devoted to develop iron catalysts enabling oxidation reactions.^[14] These natural enzymes and their genetically modified analogues as well as purely abiological iron complexes are powerful catalysts for hydroxylation of aliphatic C-H bonds and epoxidation of olefins with high levels of regio-, enantio- and stereo-control.^[15] Interestingly, a couple of contributions noted that traces of aldehydes (one of the products resulting from the Wacker-type reaction) formed during oxidation studies of olefins with different types of cytochromes P450 as catalysts under specific reaction conditions.^[16] Such promiscuous activity encountered in these enzymes indicated that iron complexes could be suitable for application as catalysts in the Wacker-type reaction. On the other hand, the fact that iron complexes catalyze reactions typical of noble metals (i.e. hydrogenation, hydrogen borrowing, olefin metathesis, polymerization, hydroformylation, C-H bond functionalizations, etc.) made their application in Wacker-type reactions conceivable.^[17]

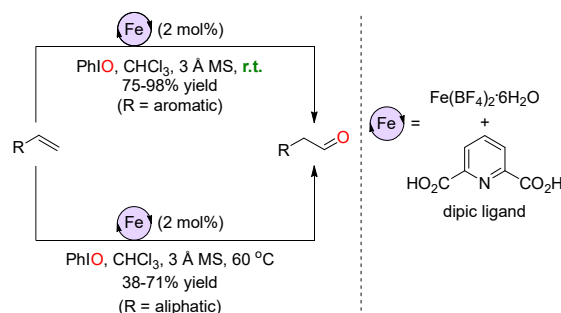
2.1. Iron-based Catalysts with anti-Markovnikov Selectivity

In 2011, Che and co-workers reported the first example of a Wacker-type oxidation of olefins into aldehydes by means of an iron(III) catalyst (Scheme 2).^[18] They employed an iron(III)-tetraphenylporphyrin featuring 2,6-dichloro-substitution patterns in the phenyl groups at *meso* position and one weakly coordinating ligand $CF_3SO_3^-$ (TfO^-), which renders the iron center a stronger Lewis acid. With 2 mol% of iron catalyst in the presence of over-stoichiometric amounts of $PhIO$ oxidant as the oxygen source, a large panel of aryl olefins were transformed at room temperature into the corresponding aldehydes without formation of ketones side-products. For the case of terminal aliphatic olefins, the reactions required 80 °C using a mixture of DCE (1,2-dichloroethane) and dioxane as the solvents. Such high anti-Markovnikov selectivity was rationalized by formation of a transient epoxyde that undergoes *in situ* isomerization similar to that known for ruthenium(IV)-porphyrin catalysts.^[13b,c]



Scheme 2. Wacker-type oxidation of terminal olefins to aldehydes catalyzed by an iron(III)-porphyrin with triflate as the anion and its reaction mechanism (framed, the porphyrin backbone around iron is not depicted for the sake of clarity). DCM = dichloromethane, DCE = 1,2-dichloroethane, *E-I* = epoxidation-isomerization.

Similar reaction conditions, but with chloroform instead of dichloromethane as solvent, were compatible for the formation of aldehydes from terminal olefins employing a non-porphyrin iron(III) catalyst (Scheme 3).^[19] As in the example above, terminal aliphatic olefins required higher temperature (60 °C) than the aromatic ones (r.t.). The interest of this transformation relies on the use of a trivial ligand, namely pyridine-2,6-dicarboxylic acid (dipic), and a readily available iron salt such as $[Fe(BF_4)_2 \cdot 6H_2O]$. Moreover, the authors noted that the reaction was sensitive to water and required molecular sieves.

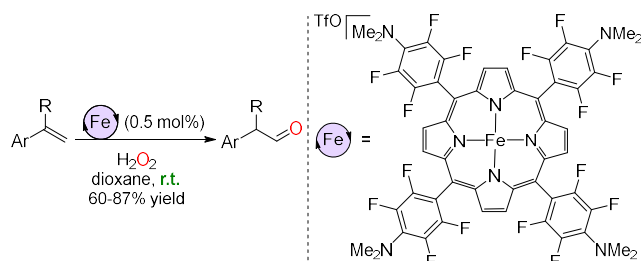


Scheme 3. Iron-catalyzed Wacker-type oxidation of terminal olefins to aldehydes using dipic as the iron-coordinating ligand.

These previous examples show the possibility to use iron catalysts for the Wacker-type production of aldehydes from olefins. However, they relied on the use of $PhIO$, a highly oxidizing species that needs to be handled with care and generates stoichiometric amounts of PhI or related derivatives as side-products, thus limiting the overall atom efficiency. In search for more convenient oxidizing sources for iron-catalyzed Wacker-type reactions, Che and co-workers reported the ability of a specific iron(III)-porphyrin to catalyze this transformation in the presence of H_2O_2 , which upgrades the level of atom-economy (Scheme 4).^[20] The catalyst was designed in a way that the corresponding catalytically productive $LFe^{IV}=O$ species would be more stable and less oxidizing than state-of-the-art systems considering the electron-donating character of the tetrafluoro-

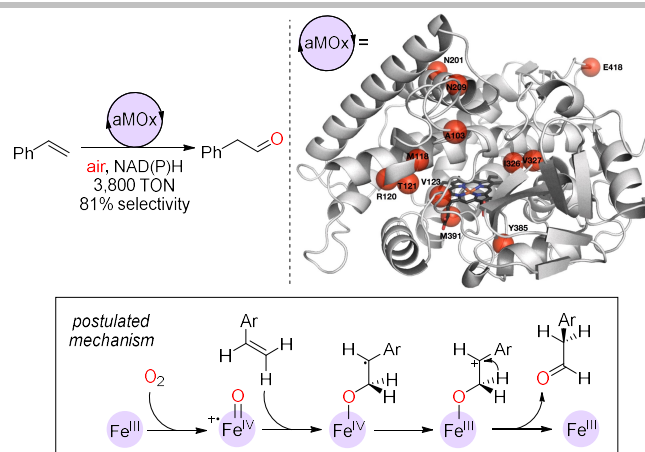
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para-dimethylanilino functionalities located at the *meso* position of the porphyrin. This catalyst significantly avoids over-oxidation side-reaction pathways at room temperature leading to full conversion of styrene derivatives and excellent isolated yields of the corresponding aldehydes. Although no examples were reported for aliphatic olefins, the catalyst loading was reduced to 0.5 mol% compared to the 2 mol% from previous examples.^[18-19]

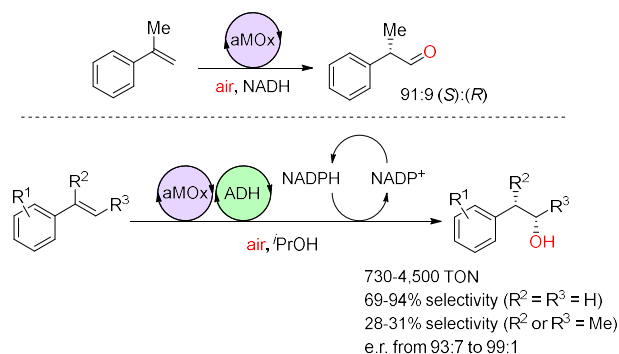


Scheme 4. Wacker-type oxidation of styrene derivatives to aldehydes catalyzed by an iron(III)-porphyrin using H_2O_2 as the chemical oxidant.

The above-described examples indicate that both iron(II) and iron(III) complexes are suitable catalysts for the selective anti-Markovnikov oxidation of olefins into aldehydes provided the active $\text{LFe}^{\text{IV}}=\text{O}$ species is formed under catalytic conditions.^[18-20] Typically, relatively high oxidizing agents (i.e. PhIO , H_2O_2) are required in over-stoichiometric amounts. Obviously, the O_2 directly from air could be an ideal oxidant for this type of oxidation reactions due to its availability and enhanced compatibility with sensitive functional groups. Such breakthrough was accomplished in 2017 by Arnold's group who engineered by directed evolution the enzyme aMOx (anti-Markovnikov oxygenase) which operates under ambient pressure of air (Scheme 5).^[21] This enzyme, which is derived from the cytochrome P450 family found in the rhodobacterium *Labrenzia aggregata*, contains an iron-heme active site that catalyzes the oxidation of styrene derivatives into aldehydes with impressive turnover numbers (TON) above 4,000. The standard reaction conditions required the use of NADH or NADPH as co-factors. It was demonstrated that the catalysis proceeded without the formation of epoxide intermediate and *via* an additional electron transfer leading to a high-energy carbocation intermediate that further undergoes 1,2-hydride migration, thus generating the anti-Markovnikov product in the final elementary step (Scheme 5, framed). Recent computational calculations support this mechanism.^[22] Moreover, it was possible to control the enantioselectivity of the oxidation by employing a pro-chiral olefin that yielded the corresponding aldehyde in an enantiomeric ratio up to 91:9 (Scheme 6).^[21] Additionally, the potential of such approach was exemplified by performing a one-pot two-step sequence involving two different enzymes, namely aMOx and an alcohol deshydrogenase (ADH), making possible to use NADP^+ in catalytic amounts in order to formally hydrate alkenes to α -substituted, enantiomerically pure secondary alcohols (Scheme 6).^[21] This study is the first example of a palladium-free asymmetric Wacker-type oxidation and it demonstrates the power of biocatalysis to tackle challenging asymmetric reactions.



Scheme 5. Aerobic anti-Markovnikov olefin oxidation with the engineered enzyme aMOx found by directed evolution and its postulated reaction mechanism (framed, the heme backbone around iron is not depicted for the sake of clarity). NADH = reduced form of NAD^+ (nicotinamide adenine dinucleotide), NADPH = reduced form of NADP^+ (NAD^+ phosphate), TON = turnover number. Scheme adapted from [reference 21]. Reprinted with permission from AAAS.



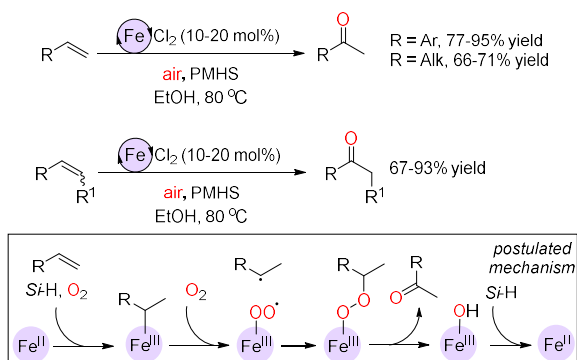
Scheme 6. Application of the enzyme aMOx in asymmetric catalysis (top) and in combination with an alcohol dehydrogenase (ADH) to biosynthetically afford anti-Markovnikov chiral alcohol products in a one-pot fashion (bottom). e.r. = enantiomeric ratio.

2.2. Iron-based Catalysts with Markovnikov Selectivity

Besides the use of iron catalysts enabling anti-Markovnikov selectivity for terminal olefins, important achievements have been accomplished for developing iron-catalyzed processes delivering Markovnikov products, namely ketones. The pioneering contribution in this respect is ascribed to Han's group.^[23] In 2017, they reported the oxidation of olefins into ketones with FeCl_2 (10–20 mol%) as pre-catalyst in the presence of over-stoichiometric quantities of PMHS (PMHS = polymethylhydrosiloxane) as reducing agent at 80 °C in ethanol solution under air atmosphere (Scheme 7). The catalysis was compatible with other type of iron precursors such as $\text{Fe}(\text{acac})_2$ (acac = acetylacetonate) as well as other hydrosilane reagents [$(\text{EtO})_3\text{SiH}$] and alcohol solvents ($t\text{BuOH}$). Traces of aldehydes resulting from the anti-Markovnikov selectivity were encountered in some cases. The catalysis was amenable to internal olefins as well and it tolerated many sensitive functional groups. Several control experiments were conducted to study the reaction mechanism that would explain the Markovnikov selectivity. In contrast to the reaction mechanisms leading to anti-Markovnikov products which are based on the formation of $\text{LFe}^{\text{IV}}=\text{O}$ species, the proposed mechanism here involves an

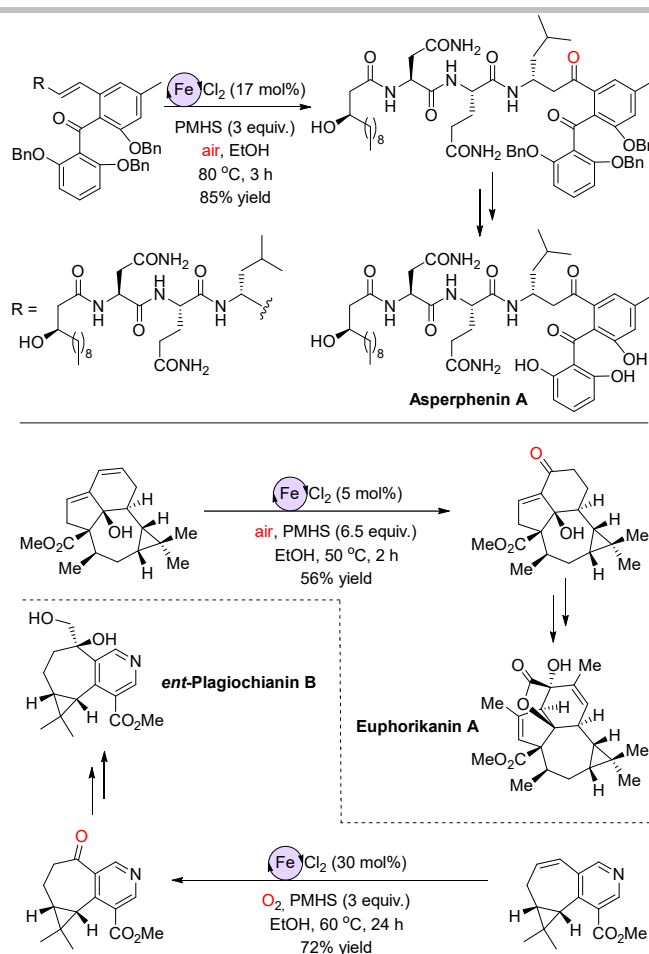
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original set of elementary steps (Scheme 7, framed). It starts with the olefin substrate reacting with an *in situ* formed Fe(III)-hydride arising from the combination of Fe(II) precursor and the hydrosilane under O₂ atmosphere yielding an Fe(III)-alkyl intermediate that further recombines with O₂ to afford a carbon-centered radical intermediate and simultaneous formation of Fe(III)-peroxide species. Next, a concerted processes involving both O-O and C-H bond cleavage leads to the ketone product and Fe(III)-hydroxide species. The latter undergoes reduction with hydrosilane by regenerating the Fe(II) active species.



Scheme 7. Markovnikov-selective Wacker-type iron-catalyzed oxidation of terminal and internal olefins to ketones and its postulated reaction mechanism (framed, the ligands around iron are not depicted). Si-H = PMHS or other hydrosilane reducing agent.

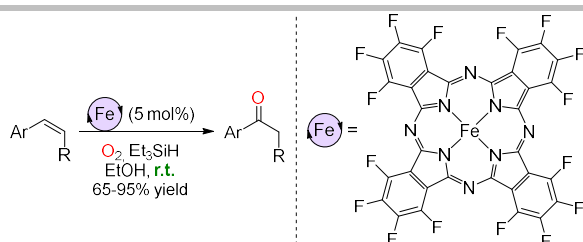
The robustness of this methodology was demonstrated by applying it in the late-stage functionalization of complex small molecules, thereby establishing its reliability for implementation total synthesis.^[23] Other research groups have implemented the iron-catalyzed Wacker-type Markovnikov reaction in the total synthesis of biologically relevant molecules such as Asperphenin A,^[24] Euphorikanin A,^[25] and *ent*-Plagiochianin B (Scheme 8).^[26] In these examples, the palladium-catalyzed Wacker oxidation processes were either unselective or unreactive, whereas Han's reaction conditions are milder, selective and compatible with the many functional groups found in the molecules of interest. Although a high iron catalyst loading was needed, these challenging functionalizations were achieved in excellent isolated yields considering the complexity of the targeted products.



Scheme 8. Application of the Markovnikov-selective Wacker-type iron-catalyzed oxidation of olefins to ketones in the total synthesis of Asperphenin A (top), Euphorikanin A (bottom, right) and *ent*-Plagiochianin B (bottom, left).

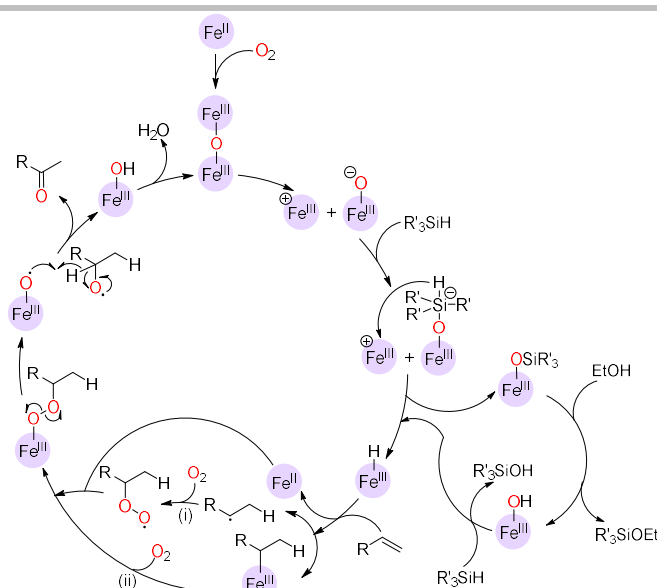
The development of Wacker-type iron-catalyzed oxidations with Markovnikov selectivity witnessed a second breakthrough in 2018 with the contribution by Knölker's group (Scheme 9).^[27] They accomplished the oxidation of aromatic olefins into ketones at room temperature and with a relatively low catalyst loading (5 mol%) compared to Han's contribution. Decreasing the temperature from 80 °C to room temperature while keeping the Markovnikov selectivity was possible by using the hexadecafluorinated iron(II) phthalocyanine complex as the pre-catalyst. The hydrosilane loading was reduced to 2 equivalents by using Et₃SiH as the reducing agent. In this case, there were no traces of epoxydes or aldehydes as side-products but from alcohols with the same Markovnikov selectivity. The uniqueness of this iron catalyst was demonstrated by the poor reactivity encountered in the analogous non-fluorinated iron(III) phthalocyanine and perfluorinated iron(III) tetraphenylporphyrin complexes.

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Scheme 9. Wacker-type oxidation of terminal aromatic olefins to ketones catalyzed by an hexadecafluorinated iron(II) phthalocyanine using O_2 as the oxidant at room temperature.

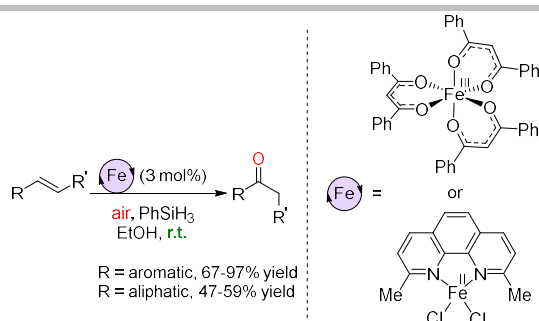
The mechanism has been studied experimentally in detail by combining different spectroscopic techniques (Mössbauer spectroscopy, UV-vis, magnetic susceptibility, HRMS, etc.), kinetic studies and isotopic labeling experiments (with C_2D_5OD , Et_3SiD , and $^{18}O_2$).^[28] The plausible reaction mechanism appears in Scheme 10, which establishes the initial formation of a μ -oxo bridged diiron(III) species *via* oxidation of the iron(II) phthalocyanine pre-catalyst, which undergoes dissociation towards a cationic Fe(III) species and an anionic oxido-Fe(III) complex. The latter reacts with hydrosilane leading to a pentavalent silicon intermediate that transfers the hydride to the cationic Fe(III) species forming a postulated Fe(III)-hydride species. Note that an ethanol-mediated pathway may also operate to form the Fe(III)-hydride species, which is likely involved in the rate-determining step of the catalysis. The Fe(III)-hydride species could further react with the olefin substrate and O_2 leading to an alkylperoxy-Fe(III) complex *via* two possible pathways: (i) a “naked” carbon-centered radical species or (ii) a Fe(III)-alkyl species (Scheme 10). The final step is the homolytic fragmentation of the alkylperoxy-Fe(III) complex and rearrangement towards the ketone product while the Fe(III)-hydroxide species regenerates the μ -oxo bridged diiron(III) complex. The formation of alcohol by-products was rationalized by the presence of side-reactions involving $\cdot OH$ radical transfer between intermediates, Russel fragmentation within peroxide species or formal reduction of ketone to alcohol with iron-hydride species.



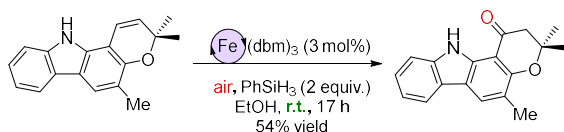
Scheme 10. Postulated reaction mechanism for the Wacker-type oxidation of terminal olefins to ketones catalyzed by an hexadecafluorinated iron(II) phthalocyanine (the phthalocyanine ligand around iron is not depicted for the sake of clarity).

Pushing the boundaries of sustainable Wacker-type oxidations, the Knölker group reported in 2021 the first examples of iron catalysts operating under air atmosphere and at room temperature with Markovnikov selectivity.^[29] The pre-catalysts are based on an hexacoordinated iron(III) complex comprising three O,O-chelating dibenzoylmethanato (dbm) ligands or an *in situ* combination of $FeCl_2$ and the *N,N*-chelating neocuproine ligand (Scheme 11). $PhSiH_3$ was the hydrosilane that performed the best and variable amounts of alcohols side-products were formed depending on the nature of the substrate. The iron catalysts did not only work for aromatic olefins but also for aliphatic olefins including internal ones. In addition, the application towards the late-stage functionalization of Girinimbine, a natural product, was successfully achieved at room temperature under ambient pressure (Scheme 12). Its application in the total synthesis of structurally-related Euchrestifoline was demonstrated as well.^[30] The reaction mechanism that was postulated according to labelling studies undoubtedly established that O_2 from air was the source of oxygen and that the hydrosilane delivered the hydrogen atom found in the ketone product. Most of the reaction intermediates are the same to those represented in Scheme 10. The main difference is the formation of the catalytically productive species. This time, a ligand exchange by ethanol at the iron complex may lead to an Fe(III)-ethoxide which is supposed to react with the hydrosilane ($PhSiH_3$) in order to form the key Fe(III)-hydride (Scheme 13, left). The remaining catalytic cycle is the same as depicted in Scheme 10 with the catalyst regeneration occurring by a reaction between the Fe(III)-hydroxide and ethanol forming water and the catalytically active Fe(III)-ethoxide or by reaction with the hydrosilane to form the key Fe(III)-hydride (Scheme 13, right).

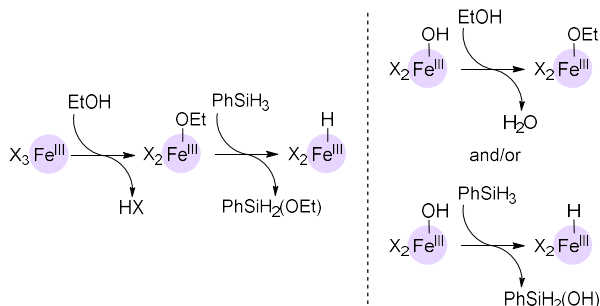
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Scheme 11. Wacker-type oxidation of olefins to ketones catalyzed by iron catalysts using air as the oxidant at room temperature.

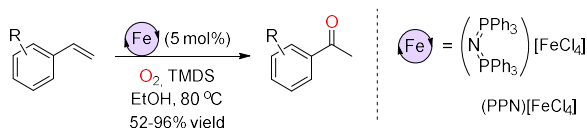


Scheme 12. Application of the Markovnikov-selective Wacker-type iron-catalyzed oxidation of olefins to ketones under air atmosphere at room temperature in the late-stage functionalization of Girinimbine. dbm = dibenzoylmethanato.



Scheme 13. Catalyst formation (left) and catalyst regeneration pathways (right) in the Markovnikov-selective Wacker-type oxidation of olefins to ketones catalyzed by iron catalysts using air as the oxidant at room temperature. X = dibenzoylmethanato.

Similarly, Yamaguchi and co-workers developed an iron-catalyzed Wacker-type oxidation of styrenes to ketones by utilizing 5 mol% of a ferrate Fe(III) complex as pre-catalyst (Scheme 14).^[31] The reaction conditions are similar to those reported by Han and Knölker, independently. They consist of TMDS (TMDS = 1,1,3,3-tetramethyldisiloxane) as the reducing agent in ethanol at 80 °C under O₂ atmosphere. This catalytic system is less active than the previous ones as shown by the lack of reactivity towards internal olefins and aliphatic ones as well as the impossibility to operate under air atmosphere. Importantly, they noted that FeCl₃ was not a suitable pre-catalyst but it becomes active once it is associated to the cation PNN⁺.



Scheme 14. Wacker-type oxidation of styrenes to ketones catalyzed by an iron(III) ionic catalyst using O₂ as the oxidant and TMDS.

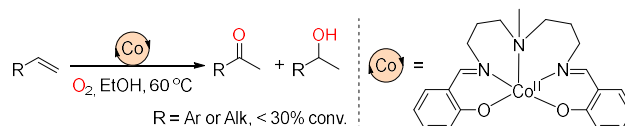
Overall, the above-stated examples of iron-catalyzed Wacker-type processes demonstrate that Fe(III) species are the

active ones and that the role of the Fe(II) or Fe(III) precursor complex has a strong effect on the final outcome of the catalysis. In addition, the key role of the Fe(III)-hydride intermediate has been evidenced although its characterization remains elusive to date. The manifold reaction mechanisms than can be devised with appropriate ligands engineered at the molecular level for coordinating iron are responsible for the formation of Markovnikov or anti-Markovnikov oxidation products. It is well-established that the current state-of-the-art iron catalysts for Wacker-type oxidations compete, and even outperform in some cases, the most reactive palladium catalysts as regards of the broad functional group tolerance and ease of operability at room temperature under ambient pressure.

3. Wacker-type Reactions with First Row Transition Metal Catalysts Different from Iron

3.1. Wacker-type Reactions with Cobalt-based Catalysts

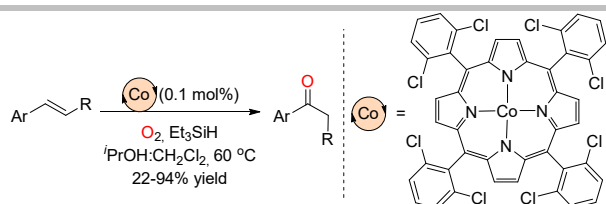
Besides the preponderance of iron catalysts to replace palladium ones in Wacker-type oxidations, other base metals from the first row of the periodic table have been studied. In this respect, it is worthy to note the pioneering contribution by Drago and co-workers in the 80's who reported a cobalt complex behaving as catalyst for the oxidation of terminal olefins in the presence of O₂ in ethanol solution (Scheme 15).^[32] Although the reaction displayed excellent Markovnikov selectivity, almost equimolar amounts of ketone and alcohol were observed with very modest isolated yields. This inspired a number of research groups to develop protocols, typically based on a two-step sequence involving first formation of hydroperoxides followed by acetylation transformation to the ketone.^[33] These methodologies are beyond the scope of this minireview since they suffer from low step- and atom-economy.



Scheme 15. Lack of chemoselectivity found in the Markovnikov-selective Wacker-type oxidation of olefins catalyzed by a cobalt catalyst under O₂.

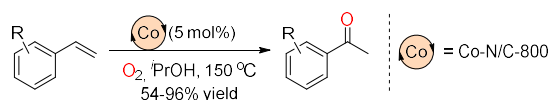
On the other hand, and similar to the preliminary observations by Drago, the Matsushita's group found, back in 1992, that an hexachlorinated Co(II)-porphyrin behaved as an excellent catalyst for the Markovnikov-selective Wacker-type oxidation of olefins into ketones with a catalyst loading as low as 0.1 mol% (Scheme 16).^[34] The reaction conditions were similar to those reported by Han and Knölker, independently, for the iron-catalysed version with the same regio-selectivity. Et₃SiH was employed as reducing agent in the presence of O₂ atmosphere in a 1:1 mixture of *iso*-propanol and dichloromethane as the solvents.

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Scheme 16. Markovnikov-selective Wacker-type oxidation of olefins catalyzed by a cobalt(II)-porphyrin catalyst using O_2 as the oxidant.

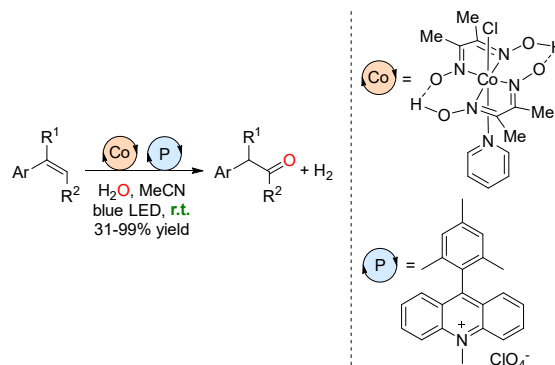
Recently, An and co-workers reported a heterogeneous cobalt catalyst enabling the Markovnikov-selective Wacker-type oxidation of styrenes to acetophenones (Scheme 17).^[35] The catalyst was formed upon pyrolysis of mixtures of $Co(OAc)_2$ with phenantroline (N) in ethanol supported in activated charcoal (C). The most active and selective heterogeneous catalyst was the Co-N/C-800 (synthesized by pyrolysis at 800 °C) that afforded the Markovnikov products in *iso*-propanol solution. The latter is both the hydrogen source of the reaction and the solvent. The catalysis occurs in the absence of any additional reducing agent, but at elevated temperatures (150 °C) and high pressures of O_2 (40 bar). Monodisperse cobalt atoms appear to be the catalytically active species rather than nanoparticles.



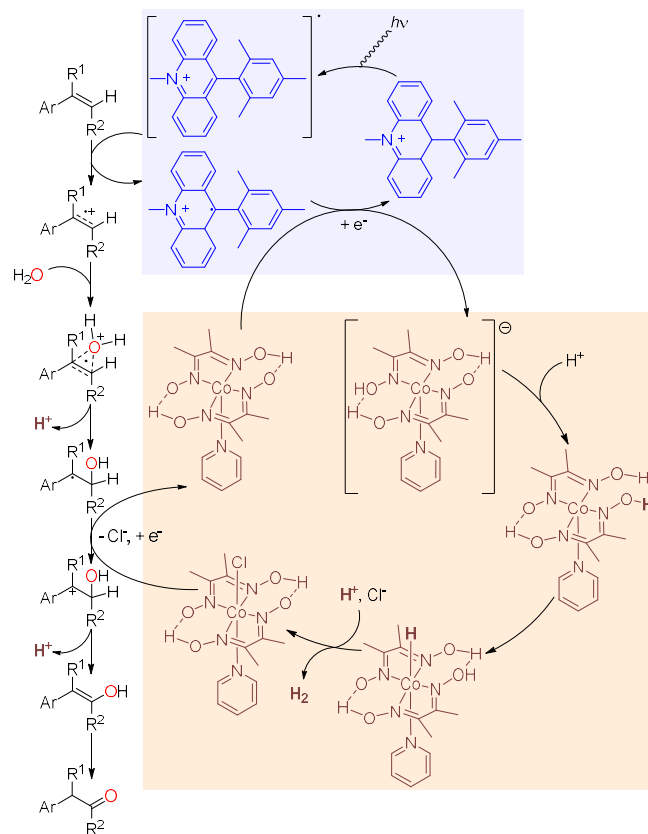
Scheme 17. Markovnikov-selective Wacker-type oxidation of styrenes to acetophenones catalyzed by a heterogeneous cobalt-based system under O_2 pressure.

Dual catalysis has emerged in the last decades as a powerful approach to generate sustainable processes and most importantly, to access fundamentally new transformations.^[36] In particular, the combination of transition metal catalysts and photochemical processes has reached tremendous interest nowadays.^[37] In this respect, Lei and co-workers reported a photocatalytic anti-Markovnikov oxidation of olefins with the participation of a cobalt-based proton-reducing catalyst, namely $Co(dmgH)_2pyCl$ ($dmgH$ = dimethylglyoximate monoanion; py = pyridine).^[38] The reaction design considers water as the source of oxygen and dihydrogen is liberated with a perfect atom economy (Scheme 18). The reactions were conducted in acetonitrile solution under blue LED irradiation with an acridinium photosensitizer at room temperature during 24 hours. The catalysis was applicable only to aromatic olefins since the aliphatic ones were unreactive due to their high oxidation potential. Based on labelling studies, kinetic isotopic effect and CV analysis, a catalytic cycle was proposed (Scheme 19). The photosensitizer generates a radical cation in the olefin that undergoes anti-Markovnikov water addition with a deprotonation leading to a carbocation after oxidation with the cobalt complex. The ketone is formed after proton elimination and the corresponding keto-enol tautomerism. H_2 is produced in the cobalt catalytic cycle while the photocatalytic form of acridinium is regenerated. It is worthy to mention that the Milstein group reported a procedure for the Markovnikov oxidation of styrenes by water with H_2

liberation with a noble-metal ruthenium complex as pre-catalyst in the presence of a Lewis acid.^[39]



Scheme 18. Photocatalytic anti-Markovnikov Wacker-type oxidation of β -alkyl styrenes by water with dihydrogen liberation. P = photosensitizer.



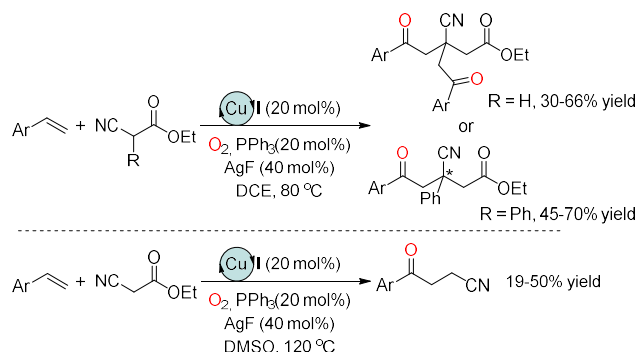
Scheme 19. Postulated reaction mechanism of the photocatalytic anti-Markovnikov Wacker-type oxidation of β -alkyl styrenes by water with dihydrogen liberation.

3.2. Wacker-type Reactions with Copper-based Catalysts

A unique copper-catalyzed oxidation of olefins was reported by Zhang and co-workers when applied in a multicomponent transformation.^[40] Specifically, α -cyanoesters reacted with styrenes in the presence of air to access γ -ketoesters resulting from mono- or bis α -enolation (Scheme 20, top). Alternatively, γ -ketonitriles were formed in a chemo-selective manner and short reaction time by changing the solvent and increasing the reaction temperature (Scheme 20, bottom). These transformations might be regarded as an oxidative enolate-olefin

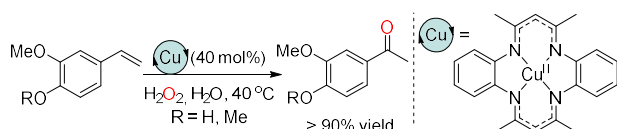
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cross-coupling. CuI was identified as the optimal pre-catalyst in the presence of triphenylphosphine (PPh₃) ligand and sub-stoichiometric amounts of AgF, whose role was attributed to be as co-oxidant. However, one can speculate that silver could play also the role of iodide scavenger to generate cationic copper species, which are typically more active than the neutral ones.^[41] The γ -ketoester products bear a stereogenic quaternary α -center, which paves the way for searching asymmetric variants.



Scheme 20. Simultaneous copper-catalyzed Wacker-type oxidation of styrenes and enolate cross-coupling with cyanoesters under O₂ atmosphere.

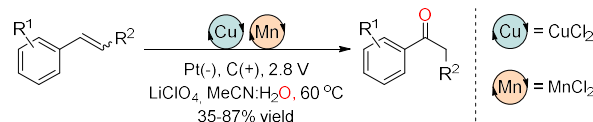
The above stated examples demonstrate the ability of Fe, Co and Cu complexes to be engaged as homogeneous catalysts in Wacker-type oxidation of olefins. They share in common the need to use chlorinated or alcohol solvents as well as different types of additives. Consequently, the quest for more benign reaction conditions has been explored too. Using water as media and/or reagent is clearly an appealing as well as challenging approach to bring Wacker-type reactions close to the green chemistry principles.^[42] In this context, a first contribution appeared in 2017 by Meng's group who developed a copper-catalyzed Wacker-type oxidation of styrenes to ketones in the presence of H₂O₂ as oxidant (Scheme 21).^[43] A high catalyst loading was required and no rational or mechanistic studies were performed to understand the exact role of the catalyst.



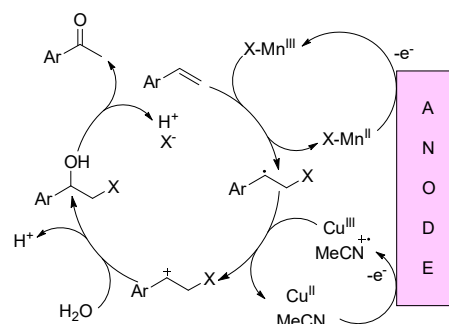
Scheme 21. Copper-catalyzed Wacker-type oxidation of styrenes into ketones with H₂O₂ as the oxidant.

In 2020, Pericàs and co-workers reported on the electrochemical Wacker-type reaction in the presence of catalytic amounts of both copper and manganese salts with water being the source of oxygen in the absence of any external chemical oxidant (Scheme 22).^[44] The reactions were suitable for styrenes with excellent Markovnikov selectivity delivering the corresponding ketones at 60 °C. The procedure was carried out in an undivided cell at a constant potential of 2.8 V with acetonitrile as co-solvent and LiClO₄ salt. From a mechanistic point of view, several redox processes as depicted in Scheme 23. First, the electrochemically formed Mn(III)-halide transfers a halogen atom to the terminal olefin, leading to an radical intermediate that

undergoes oxidation to a carbocation by *in situ* electrogenerated Cu(III) and/or acetonitrile radical cation. After hydration, halohydrin is formed followed by dehydrohalogenation towards the ketone product *via* keto-enol tautomerism. Note that all this redox events take place in the anode whereas in the cathode, protons are reduced to dihydrogen (H₂). This contribution shows one of the possible advantages of combining two different transition metals from the first row of the periodic table.



Scheme 22. Mn/Cu co-catalysed electrochemical Wacker-type oxidation of styrenes without any external chemical oxidant.

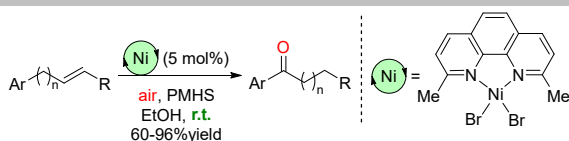


Scheme 23. Postulated reaction mechanism for the Cu/Mn co-catalysed electrochemical Wacker-type oxidation of styrenes. The elementary steps related to the anode are shown, reduction of protons to H₂ occurs in the cathode. X = Cl or Br.

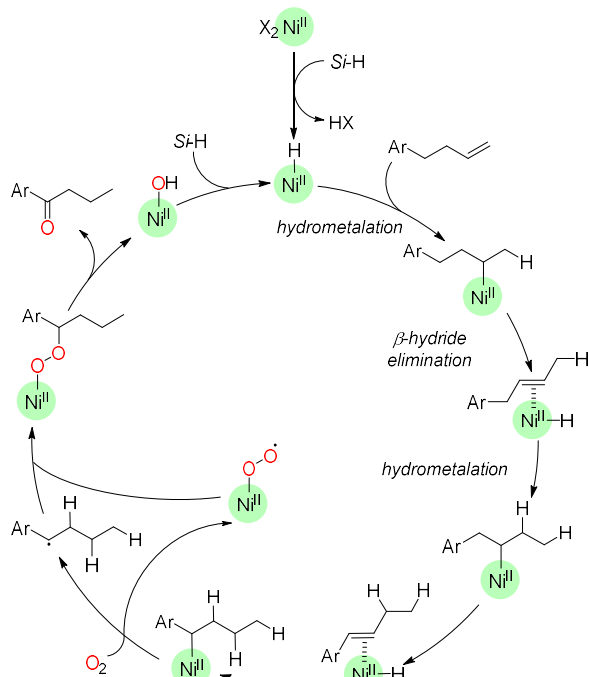
3.3. Wacker-type Reactions with Nickel-based Catalysts

Han's group reported in 2019 the only known example of a nickel-catalyzed Wacker-type oxidation (Scheme 24).^[45] Starting from internal aliphatic olefins, the reaction design aimed at forming catalytically active nickel-hydride species that undergo a chain-walking mechanism (iterative hydrometalation and β -hydride elimination by nickel, Scheme 25) prior to a nickel(II)-catalyzed oxidation with Markovnikov selectivity. In this case, the catalyst precursor is formed by a combination of NiBr₂ complex and neocuproine ligand. PMHS hydrosilane is used as both the reducing agent and the source of hydrogens in the final product. The catalysis takes place at room temperature under air atmosphere with ethanol being the solvent of choice. Although the reaction is limited in scope to substrates containing aromatic motifs that stabilize the final intermediate from the nickel-catalyzed chain-walking mechanism (Scheme 25), this transformation shows that nickel catalysts promote Wacker-type oxidations and that they could be employed in one-pot multi-step sequences, which is relevant in the context of sustainability.^[46]

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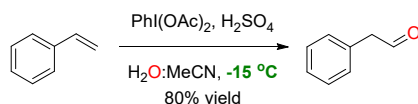
Scheme 24. Aerobic nickel-catalyzed remote Wacker-type oxidation of olefins at room temperature.



Scheme 25. Postulated reaction mechanism of the aerobic nickel-catalyzed remote Wacker-type oxidation of olefins exploiting a chain walking mechanism (the neocuproine ligand around nickel is not depicted for the sake of clarity). X = Br or OEt, Si-H = PMHS or other hydrosilane.

4. Wacker-type Reactions in the Absence of Metal-Catalysts

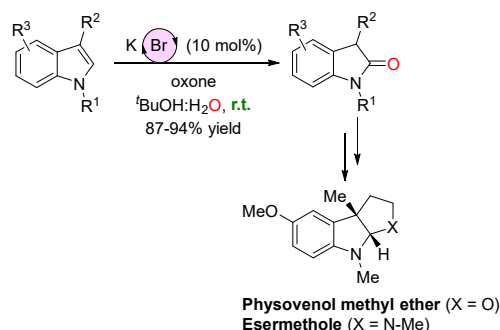
Avoiding any metal species in Wacker-type oxidation of olefins remained a challenge until the beginning of the 21st century. In two seminal contributions, Yusubov and co-workers showed the ability of the hypervalent iodine compound PhI(OAc)₂ to react with styrene forming phenylacetaldehyde in the absence of any metal species (Scheme 26).^[47] The product resulted from an anti-Markovnikov selectivity-determining step. The reaction proceeded at -15 °C in the presence of the strong Brønsted acid H₂SO₄ and a mixture of solvents (H₂O and MeCN). The role of iodonium species as oxidizing species was evoked,^[48] but the exact reaction mechanism was not studied.



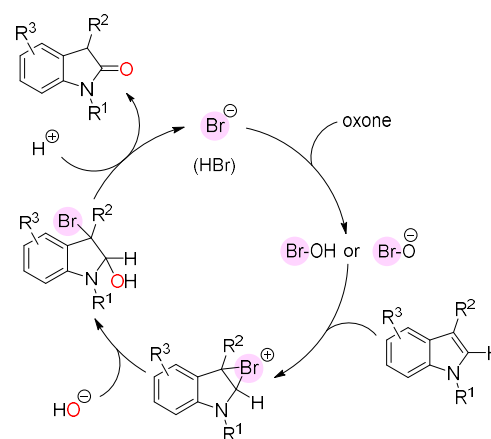
Scheme 26. Metal-free oxidation of styrene to acetaldehyde in the presence of PhI(OAc)₂ reagent.

Considering the growing interest to develop metal-free catalysts, for which halide(III) species occupy a place of choice,^[49] Tong and co-workers developed a methodology for the oxidation of the olefinic bond of indoles by catalytically forming bromonium

species provided that oxone (potassium peroxymonosulfate) was employed as stoichiometric oxidant (Scheme 27).^[50] The reaction development identified KBr as the source of bromide ions and ^tBuOH/water as the solvents. The substrate scope was restricted to 3-alkyl-substituted indoles furnishing the corresponding 2-oxindoles. Many functional groups were tolerated in different positions of the backbone including the challenging free N-H indoles. The applicability of this methodology was demonstrated in the total synthesis of two natural products: Physovenol (isolated as the methyl ether derivative) and Esermethole (Scheme 27). From a mechanistic point of view, firstly, bromide reacts with oxone forming hypobromite that reacts with the olefin leading to a cyclic bromonium cation which undergoes ring-opening by nucleophilic hydroxyl attack (Scheme 28). Debromination in the resulting intermediate affords the ketone product and oxone further converts the remaining bromide anion into the catalytically active hypobromite species (Scheme 28).



Scheme 27. Oxidation of indoles to 2-oxindoles in the presence of catalytic amounts of KBr assisted by oxone at room temperature, and its application in the total synthesis of two natural products.

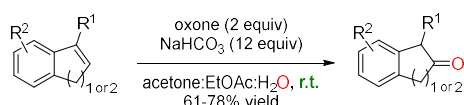


Scheme 28. Proposed reaction mechanism of the oxidation of indoles to 2-oxindoles in the presence of catalytic amounts of KBr assisted by oxone.

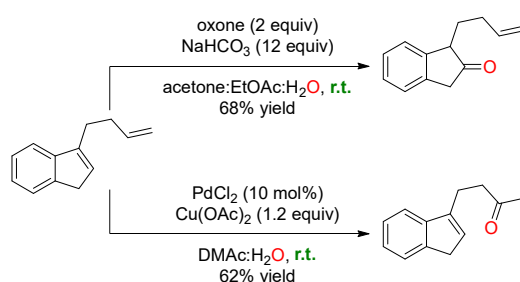
In the previous example, oxone was employed as oxidizing agent to generate the catalytically productive halonium species. Alternatively, Ramana and co-workers described an oxidation of olefins to ketones that employs oxone as the single reagent.^[51] The methodology, which is based on the use of NaHCO₃ as additive in large amounts and a ternary mixture of solvents (acetone, ethyl acetate and water), is compatible to indenes and 1,2-dihydronaphthalenes, affording the anti-Markovnikov products 2-indanones and 2-tetralones, respectively (Scheme 29). This

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protocol reversed the site-selectivity encountered in the classical palladium-catalyzed Wacker-type Markovnikov oxidation of an allyl-containing indene substrate (Scheme 30). The current protocol oxidized in a selective manner the indene core leaving the allyl group unreacted whereas the palladium-catalyzed process oxidized the allyl moiety keeping intact the indene core. Preliminary investigations indicate that neither the epoxyde nor the acetonide are involved in the mechanism and the presence of trace impurities of metals was ruled out by a metal scavenger test. However, the overall mechanism of this reaction remains to be addressed. Compared to metal-based catalysts, the current metal-free systems for Wacker-type reactions display lower functional group tolerance due to the strong oxidizing power associated to the reagents.



Scheme 29. Anti-Markovnikov-selective oxidation of indene and 1,2-dihydronaphthalene derivatives mediated by oxone.



Scheme 30. Comparison of site-selective oxidations mediated by oxone (top) versus a palladium catalyst (bottom) for an allyl-containing indene substrate. DMAc = *N,N*-dimethylacetamide.

5. Conclusions and Perspectives

Since the first report on Wacker-type oxidation of olefins more than 60 years ago, such transformation has stimulated the creativity of chemists to design more sustainable protocols. Due to its atom-economic nature and the highly-value added carbonyl-containing products formed, tremendous efforts have been devoted for developing regioselective catalysts. Besides the acknowledgeable breakthroughs reached by noble palladium catalysts,^[52] recent advances have shown the ability of first row transition metals to replace the scarce and costly palladium while still affording excellent levels of reactivity with absolute control of the regioselectivity. This is particularly true for aromatic olefins and less pronounced for terminal olefins, not to mention the challenge of internal olefins, in which statistical mixture of ketones can form. Moreover, mild reactions conditions have been developed by avoiding the use of both copper co-catalyst and strongly acidic media to make the catalysis compatible with sensitive functional groups, which is relevant for fine chemical synthesis. In addition, reducing the reaction temperature to 20-30 °C and replacing high pressures of O₂ by ambient air makes these methodologies attractive for implementation in any type of laboratories.

The most widely exploited metal to replace palladium in Wacker-type oxidations is iron and the efficiency of these

methodologies is exemplified by its application in the total synthesis of natural products. All the examples above described highlight that the steric and electronic effects of the ligands attached to the metal center play a key role in controlling the reaction coordinate towards the selective formation of the Markovnikov or anti-Markovnikov carbonyl products. Most of the catalysts based on first row transition metal catalysts concern purely homogeneous systems, albeit promising results have been obtained with heterogeneous and bio-catalysts, especially for asymmetric versions. A common feature of the first row catalysts is that they can stabilize metal-oxo and metal-peroxo species as well as metal-hydride species that facilitate metal-alkyl intermediates. Such mechanistic considerations are different from those established for palladium catalysts in Wacker-type reactions and they complement each other. Studying in more detail the plausible elementary steps of the catalytic cycles should translate into the design of more powerful catalysts in the near future. It might be even reasoned that such a field is still in its infancy when considering the many other first row transition metal catalysts that could be envisaged. Interestingly, the conceptualization of reaction designs considering cooperative mechanisms, electrocatalysis, photocatalysis and hypervalent halides should enlarge the possibilities in order to provide ketones (or aldehydes) from olefins in a more benign manner.

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Conflict of Interest

The authors declare no conflict of interest.

Keywords: oxidation • olefins • green chemistry • ketones • aldehydes

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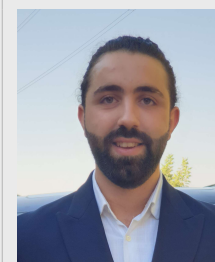
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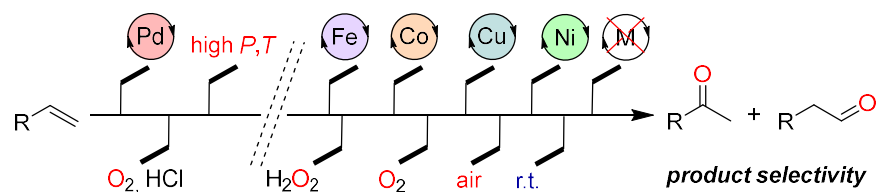


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Wacker-type oxidations afford highly-value added carbonyl compounds starting from readily available olefins by using scarce and expensive palladium catalysts at high pressures of dioxygen and elevated temperatures. The last years has witnessed a paradigm shift by developing procedures that operate at mild conditions as discussed in this Minireview. They are based on more abundant and affordable, first row transition metals including metal-free processes.

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