

Recent Advances in Wacker Oxidation: from Conventional to Oxidative Rearrangement of 1,1-disubstituted Alkenes to Ketones

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ABSTRACT

The functionalization of olefins represents one of the most essential synthetic transformations in organic chemistry. We here conceive a review emphasizing the recent developments in the Wacker oxidation process, homogeneous olefin oxidation by Pd^{II} catalysts, from conventional to oxidative rearrangement of 1,1-disubstituted alkenes to ketones. Wacker oxidation uses palladium catalysis to produce aldehydes or ketones from olefins and water. The generally accepted mechanism relies on a β -H elimination via a Pd^{II}/Pd⁰ catalytic cycle. Previously, the reaction worked particularly well for monosubstituted alkene, which nowadays can have great regioselectivity. The extension to the intramolecular aza-Wacker reaction is a new dimension for the site-selective amination of olefins. In contrast, Wacker oxidation of 1,1-disubstituted alkenes remains mostly unexplored. Recently, Zhu *et al.* reports report a method to promote intramolecular carbon migration by oxidizing a catalyst intermediate to the Pd^{IV} state, compatible with a broad range of functional groups and great regioselectivity. The wide applicability of newer modes, along with the conventional conditions of the Wacker oxidation process for the synthesis of natural products and valuable compounds, is another recent dimension that has been covered to validate the potential of this well-known reaction.

1 INTRODUCTION

The multiple oxidation states of transition metals permit their use in the field of catalysis for many organic functional group transformations in comparison to non-transition metals. This is evident from the enormous growth in catalysis observed in past years. Among all the transition metals, palladium is perhaps the most active and versatile metal employed in catalysis, with an appropriate ionic radius and the number of valence electrons.[1] The craze for the Pd-catalyzed synthetic procedures of carbonyl compounds from oxidation of alkenes finds its origin in the study by Francis C. Phillips of the PdCl₂-mediated oxidation of ethylene to acetaldehyde, published in 1894.[2] This report sank into oblivion until the stoichiometric to catalytic evolution of the reaction by researchers from Wacker Chemie GmbH Company, leading to an industrial process.[3] The reaction was named as ‘Wacker Process’ or ‘Hoechst-Wacker Process’ since it opened up the field of catalytic palladium chemistry.

The Wacker process and related processes have been a staple for organic and organometallic chemistry for half a century.[4] An

acidic aqueous solution of catalytic amounts of both PdCl₂ and CuCl₂ or CuCl under oxygen was mainly used and effective for a large panel of olefins. However, a controversy centered on the oxidation mechanisms mode of nucleophilic attack has persisted for decades. The widely accepted general mechanism of Wacker oxidation involves the coordination of Pd^{II} salt with the η^2 -olefin, followed by the subsequent key step (Hydroxypalladation) based on Markovnikov or anti-Markovnikov addition, which causes the formation of two regioisomers of the carbonyl compound, and beta-H elimination. The widely accepted general mechanism of Wacker oxidation involves the coordination of Pd^{II} salt with the η^2 -olefin, followed by the subsequent key step (Hydroxypalladation) based on Markovnikov or anti-Markovnikov addition, which causes the formation of two regioisomers of the carbonyl compound, and β -H elimination. (Figure 1)[5] The mechanistic studies show that the formation of the product, whether an aldehyde or a ketone, solely depends on the pathway of hydroxypalladation and the stereochemistry of the hydroxylalkane–palladium complex formed.[6]

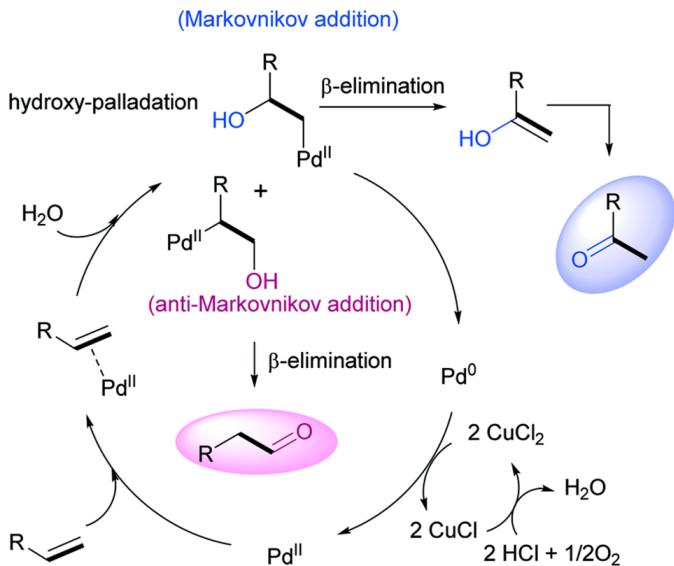
There are a number of other inorganic oxidants such as Fe₂(SO₄)₃·nH₂O,[7] CrO₃,[8] KBrO₃,[9] H₂O₂,[10][11] and oxone[12] that have been investigated for the replacement of Cu^{II} salts. Similarly, there are many reports documented in which organic oxidants such as benzoquinone (BQ),[13] t-BuOOH,[14][15] and selectfluor[16] have marked their significance as notable oxidants for this transformation and as remarkable substitutes for Cu^{II} salts.

Since Wacker oxidation is an active area of research, we compiled our review, which only concerns the methods and related mechanisms. We have discerned that during this span of time, there have been noticeable developments in the catalytic reaction conditions and substrate scope.

2 PALLADIUM-BASED WACKER OXIDATION

2.1 Synthesis of Ketones or Aldehydes from Monosubstituted Olefins

Since hydroxypalladation causes the formation of two regioisomers of the carbonyl compound, it is not difficult to control the conditions to form the Markovnikov products (ketones), like the original discovery of the ‘Wacker Process.’ To increase the anti-Markovnikov/ Markovnikov products ratio, various modifications of the experimental conditions, especially the use of other oxidants

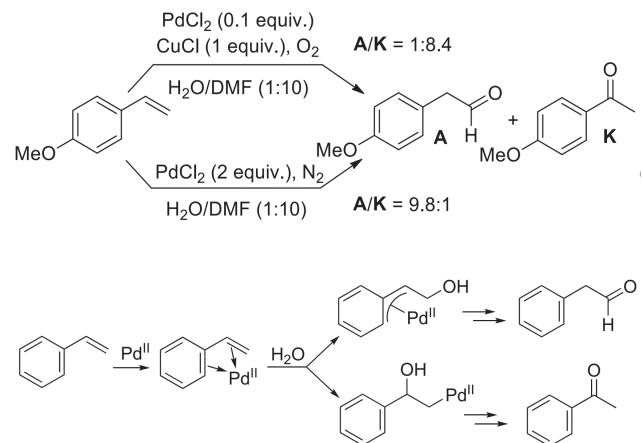
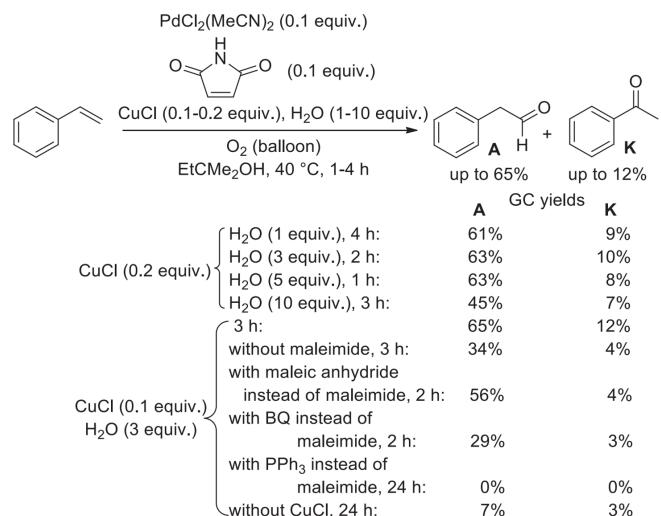
**Fig. 1.** General mechanism of Wacker oxidation for monosubstituted alkene

and oxygenated nucleophilic species, have been reported. Thus, the present review only concerns the methods leading to some anti-Markovnikov products in this subsection.

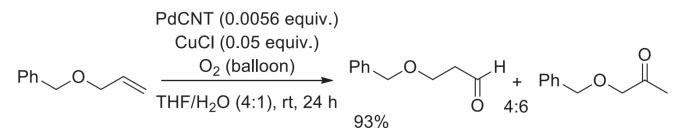
In 2006, Spencer's team reported that PdCl_2 -catalyzed oxidation of 4-methoxystyrene in the presence of 1 equiv. of CuCl under oxygen in aqueous DMF led to the 1:8.4 mixture of corresponding arylacetaldehyde and methyl ketone while the aldehyde was the main product with 2 equiv. of PdCl_2 in the absence of reoxidants.[17] (**Figure 2, top**) Comparison with the stoichiometric Wacker reaction of vinyladamantane showed the crucial role of the aryl group on the regioselectivity, leading the authors to propose that the stoichiometric Wacker reaction of styrenes involves a η^4 -complex formed from coordination of the substrate to palladium. (**Figure 2, bottom**) Subsequent attack of water at the terminal carbon rather than at the 2-position would be favored by the formation of η^3 -benzylpalladium complex more stabilized than η^1 -complex. Both complexes undergo β -H elimination to provide the aldehyde and ketone, respectively. Under catalytic conditions with different palladium salts and reoxidants, the authors observed aldehyde/ketone ratios depending on the coordination sphere of Pd.

In 2016, Ura's team[18] obtained phenylacetaldehyde in up to 88% selectivity from the reaction of styrene with catalytic amounts of $\text{PdCl}_2(\text{MeCN})_2$, CuCl and maleimide in aqueous tert-amyl alcohol at 40°C under oxygen atmosphere. Changing maleic anhydride for maleimide or benzoquinone decreased the yield, while PPh_3 inhibits the oxidation. No catalytic character of the reaction was observed in the absence of the Cu salt. (**Figure 3**)

Ura and co-workers stated that maleimide could "operate as a ligand to stabilize the in situ formed Pd^0 species". Citing above Spencer's report, the authors nevertheless proposed reaction intermediates similar to those of **Figure 2**, but noted that maleimide and maleic anhydride "possibly stay on palladium during the whole catalytic cycle". Coordination of both maleimide and a η^4 -ligand to PdCl_2 would however lead to a rather unusual 18 electron palladium complex.

**Fig. 2.** Initial Anti-Markovnikov Wacker Oxidation and η^4 -Palladium complex reactivity**Fig. 3.** Maleimide-assisted Catalytic Wacker Oxidation of Styrene

Similarly, inspired by η^4 coordination and chelation-controlled regioselectivity, Doris's team disclosed that coordination of the allylic oxygen, which causes water to attack the terminal position, could also be involved in the $\text{PdCl}_2/\text{CuCl}$ -catalyzed oxidation of allyl benzyl ether at room temperature under oxygen atmosphere.[19] (**Figure 4**)

**Fig. 4.** Anti-Markovnikov Wacker Oxidation of Terminal Olefins directed by allylic oxygen atom

2.2 Synthesis of Ketones or from Internal Alkenes

Internal alkenes have also been examined. However, the reaction generally affords a mixture of two regioisomeric ketones unless a neighboring chelating group can direct the hydroxypalladation process. For example, Grubbs's group[20] and Sigman's group[21] demonstrated that directing group is essential in regioselectivity in two catalytic systems. (**Figure 5**)

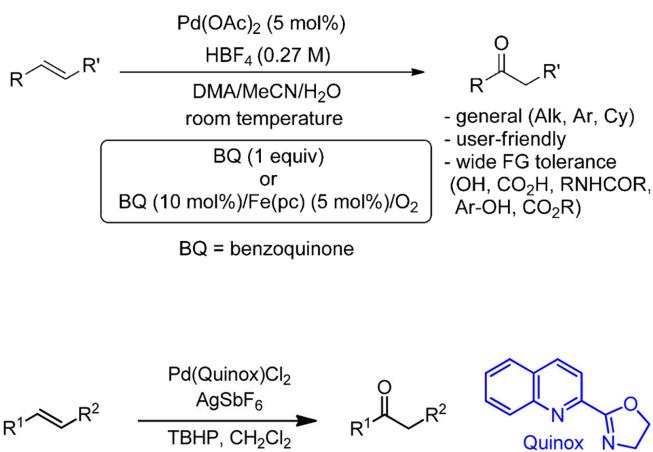


Fig. 5. Synthesis of Ketones or from Internal Alkenes

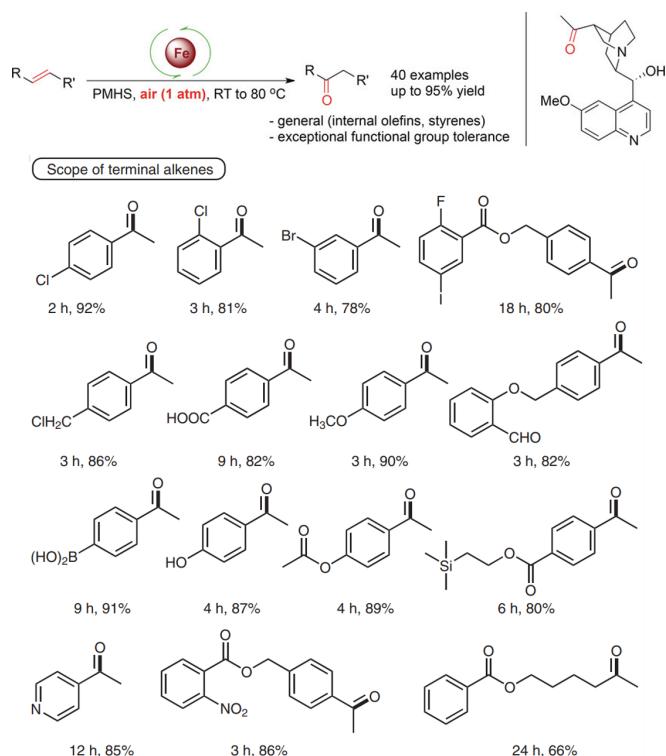


Fig. 6. Han's Fe-catalyzed aerobic Wacker-type oxidation

3 OTHER METAL-BASED WACKER OXIDATION

3.1 Iron-based Wacker Oxidations

However, in recent years, many other metals have shown the potential to replace Pd in Wacker oxidation, resulting in cheaper and efficient alternatives. Han and co-workers, based on Baran's work,[22] hypothesized that hydrosilane could reduce the Fe^{III} species to iron hydride that adds to olefins and generates carbon radicals, which are oxidized by molecular oxygen. In 2017, they[23] developed the oxidative system involving FeCl₂ or Fe(acac)₂ as the catalyst, polymethylhydrosiloxane (PMHS) as the reductant, ambient air as the sole oxidant, and alcoholic solvent for the aerobic oxidation of styrenes, internal olefins, and electron-deficient aryl olefins to ketones (**Figure 6**). A wide range of electron withdrawing, electron neutral, electron rich, and heteroatom substrates delivered ketones in good to excellent yields.

The iron-catalyzed methodology was then applied to oxidize the natural products or compounds with high complexity due to mild reaction conditions using t-BuOH as the solvent (**Figure 7**) to provide the corresponding methyl ketones.[24]

3.2 Cobalt-based Wacker-type Oxidations

Wang and co-workers[25] presented the first example of a heterogeneous cobalt-based catalytic system for the Wacker type oxidation, involving the single atom dispersed Co–N/C catalyst, using isopropanol as the hydrogen source under oxygen atmosphere. (**Figure 8**) With the optimized conditions involving Co–N/C-800 in i-PrOH, various styrene derivatives were converted into arylmethyl

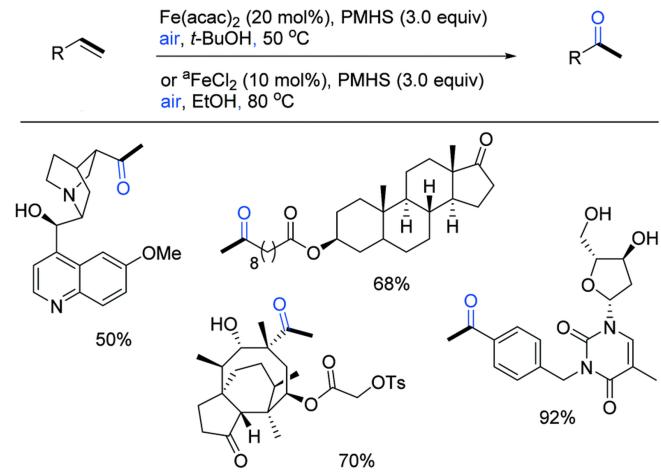


Fig. 7. Han's iron-catalyzed aerobic Wacker-type oxidation of complex molecules

ketones under aerobic reaction conditions. Substrates with ortho substitutions resulted in lower yields than the meta and para substitutions on the aryl ring. However, the regioselectivity was excellent. It was also concluded that the monodisperse cobalt atoms provided the active sites for Wacker oxidation.

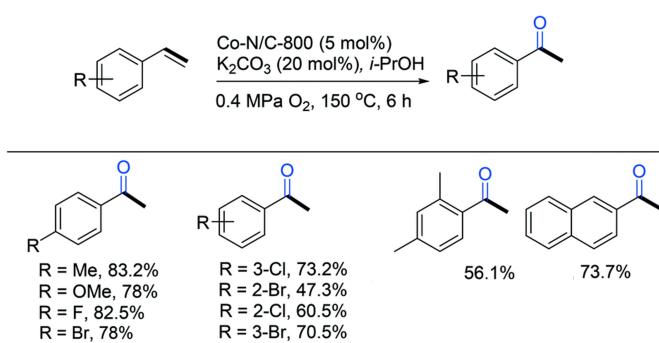


Fig. 8. Wang's Wacker-type Oxidation of styrenes catalyzed by Co-N/C-800

3.3 Mn/Cu co-catalysed electrochemical Wacker Oxidations

In yet another recent (2020) report, Lai and Pericàs^[26] developed the electrochemical Wacker–Tsuji-type oxidation of aryl-substituted alkenes using cheap, environment-friendly MnBr₂ and CuCl₂ as the co-catalysts at the carbon felt anode in the undivided cell with Pt as the cathode. In the optimization study, they found that the combined use of MnBr₂ and CuCl₂ led to the oxidation reaction to a very significant yield. After the optimization of other factors, such as the amount of MnBr₂/CuCl₂, and solvents, a library of aryl-substituted alkenes were converted into the corresponding ketones with good functional group tolerance to halogen or ester groups and as well as electron withdrawing substituents. (**Figure 9**) However, the method was sensitive to ortho-substituents and nitro group. Although the Wacker oxidation of aryl olefins has been known, this new method based on the electrochemical process provided α -aryl ketones in palladium-free conditions.

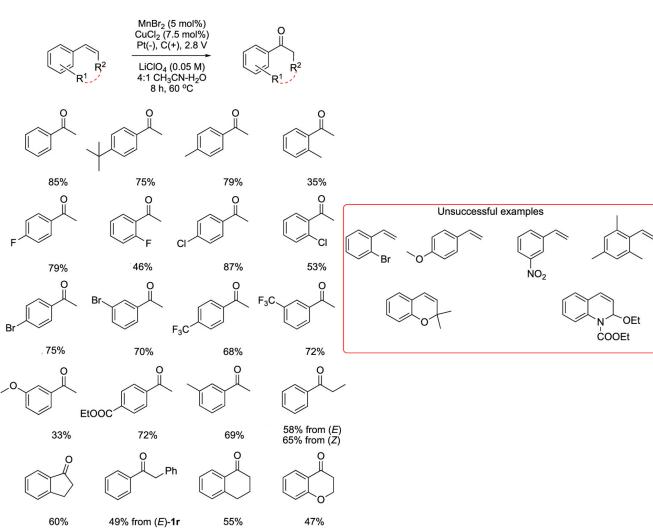


Fig. 9. Pericàs' Mn/Cu co-catalysed electrochemical Wacker Oxidation of aryl-substituted alkenes

3.4 Metal-free Wacker-type Oxidation

An interesting report in 2015 by Ramana *et al.*[27] disclosed a novel application of the oxone–acetone combination for the Wacker-type oxidation of indenes and dihydronaphthalenes leading, respectively, to indan-2-ones and 2-tetralones, along with NaHCO₃. (**Figure 10**) While oxone is known in the epoxidation reactions along with NaHCO₃, the present paper disclosed the unusual reactivity of oxone, depending on the amount of the base (NaHCO₃) used. While 3 equivalents resulted in diolacetonide formation, the use of excess of 12 equivalents resulted in the Wacker oxidation products. Control experiments suggest that the reaction is not proceeding via the epoxide or diol-acetonide route and also that there is no role of trace amounts of metals present in the reagents on the current oxidation. Various indan-2-ones and 2-tetralones were obtained in good yields, compatible with many functional groups, for example, azide group and p-tolyl.

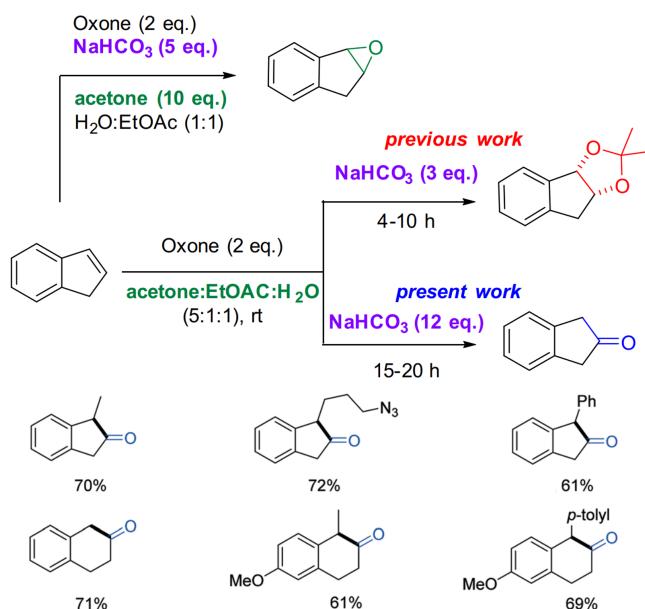


Fig. 10. Ramana's Metal-free Wacker-type oxidation of indenes and dihydronaphthalenes by the oxone-acetone combination

4 AZA-WACKER-TYPE REACTION

Aerobic Pd^{II} -catalyzed oxidative coupling of nonbasic nitrogen nucleophiles provides a powerful strategy for the synthesis of nitrogen-containing molecules. The reactions are initiated by intra- or intermolecular aminopalladation of the alkene.

4.1 Intramolecular Oxidative Amination of Alkenes

Catalysis was first achieved in intramolecular oxidative amination reactions, which benefit from a significantly lower entropic penalty than intermolecular reactions. Initial work demonstrated the ability of anilines to undergo oxidative cyclization (**Figure 11, top**),^[28] but later work highlighted the benefit of nonbasic nitrogen

nucleophiles such as sulfonamides[29] (**Figure 11, bottom**) and ureas,[30] which are less susceptible to catalyst poisoning because they are poor ligands for Pd^{II}.

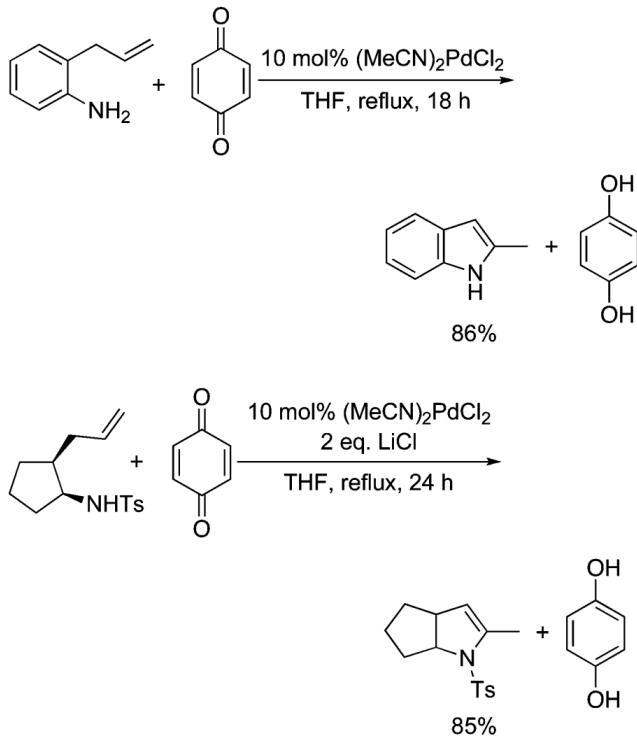


Fig. 11. Initial aza-Wacker-type oxidation and nonbasic nitrogen nucleophiles

Detailed mechanistic studies of these oxidative amination reactions have not been performed; however, the catalytic cycle in **Figure 12** provides a framework for future investigation.[31] Several valuable insights can be gained from our investigation of Pd(OAc)₂/pyridine-catalyzed aerobic alcohol oxidation. These coupling reactions proceed through a similar aminopalladation intermediate but diverge in their subsequent reactivity: β -hydride elimination produces enamides or allylic amides.

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In 2012, Zhang and co-workers disclosed a highly enantioselective aza-Wacker cyclization which furnishes isoindolinones bearing quaternary stereocenters (**Figure 13**).[32] After testing a variety of quinox and pyrox ligands in combination with Pd^{II} salts, they discovered that the reagent manifold of Pd(TFA)₂/tBu-pyrox under 1 atm of O₂ in CH₃CN furnished products with excellent yields and enantioselectivities (ee up to 99%). Importantly, they found that the

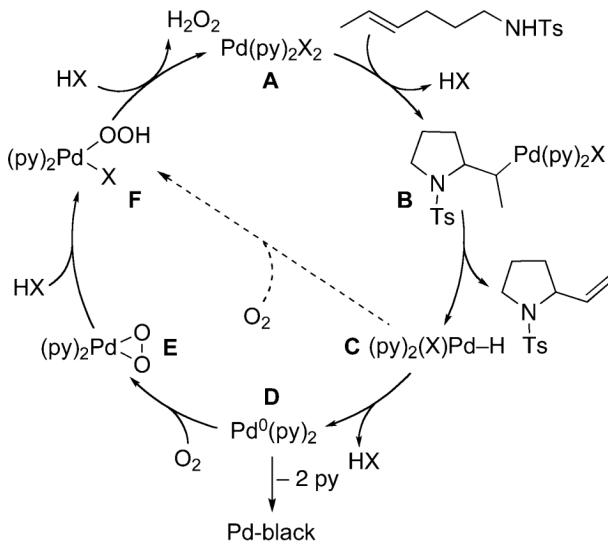


Fig. 12. Mechanism of Intramolecular Oxidative Amination

N-OMe is cleaved facilely using SmI₂ yielding N-unfunctionalized amide products.

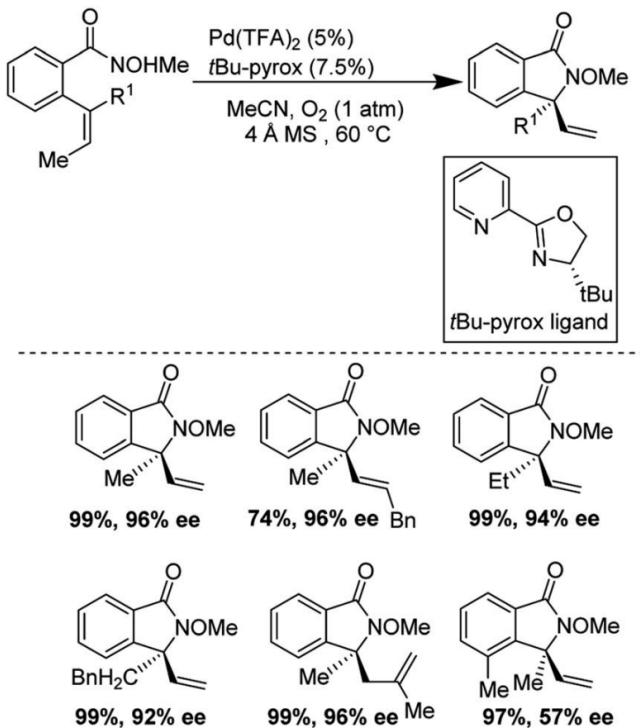


Fig. 13. Zhang's enantioselective synthesis of isoindolinones

4.2 Intermolecular Oxidative Amination of Alkenes

The initial precedent for intermolecular aza-Wacker reactions consisted of the formal oxidative conjugate addition of cyclic amides and carbamates to electron-deficient alkenes.[33] (**Figure 14**)

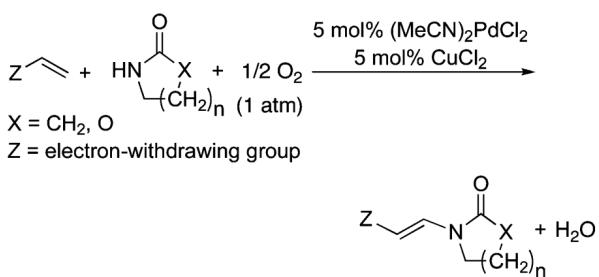


Fig. 14. Initial Intermolecular Oxidative Amination of Alkenes

Recently, Sigman and co-workers presented the enantioselective N-Alkylation of Indoles via an Intermolecular Aza-Wacker-Type Reaction.[34] Allylic and homoallylic alcohols with a variety of functional groups are compatible with the reaction in high enantioselectivity. (**Figure 15**)

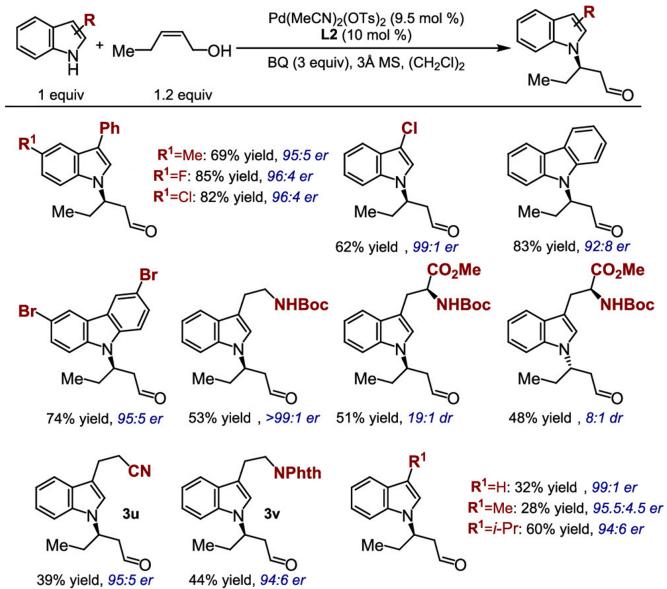


Fig. 15. Enantioselective N-Alkylation of Indoles via an Intermolecular Aza-Wacker-Type Reaction

5 OXIDATIVE REARRANGEMENT OF 1,1-DISUBSTITUTED ALKENES TO KETONES

Since 1,1-disubstituted alkenes generally lack directing group and obey the Markovnikov rule, Wacker Oxidation is inapplicable to the synthesis of ketones from the 1,1-disubstituted alkenes. The mechanistic scenario ($\text{Pd}^{\text{II}}/\text{Pd}^{\text{0}}$) becomes much more difficult on 1,1-disubstituted alkenes due to the lack of β -H.

5.1 Scarce Reports on the Wacker Reaction of 1,1-disubstituted Olefins

Currently, reports on the Wacker reaction of 1,1-disubstituted olefins remain scarce. Grigg and co-workers[35] reported that methylenecyclobutane was converted to cyclopentanone under typical Wacker conditions. (**Figure 16, top**) Wahl *et al.*[36] have very recently reported optimized conditions using tert-butyl nitrite (*t*-BuONO) as a terminal oxidant under mild conditions. (**Figure 16, bottom**) However, they are both methylenecyclobutanes that undergo Wacker oxidation towards cyclopentanones based on the *semi-pinacol*-type rearrangement of Pd^{II} intermediates proposed to be responsible for the intermediary 1,2-shift.

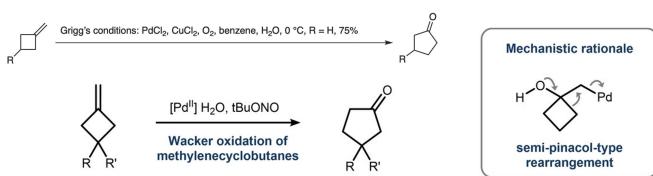


Fig. 16. Wacker reaction of 1,1-disubstituted terminal alkenes using Grigg's and Wahl's previous work on ring expansion of the methylenecyclobutanes.

5.2 Zhu Lab's Previous Work on Dyotropic Rearrangement of Pd^{IV} Species

In their previous works, neopentyl σ - Pd^{II} complex can be oxidized *in situ* to Pd^{IV} species, and Pd^{IV} species have great potential to undergo dyotropic rearrangement.[37][38][39] (**Figure 17**) It's worth noting that generation of each product has its own driving force. For example,[39] the ring strain releasing going from 5- to 6-membered ring and the presence of the stabilizing β -agostic effect in F could indeed provide the desired driving forces. (**Figure 18**)

5.3 Reaction Design & Screening of Conditions

To address the generality of oxidation of 1,1-disubstituted olefins to the rearranged ketones, Zhu and co-workers moved from the $\text{Pd}^{\text{II}}/\text{Pd}^{\text{0}}$ catalytic cycle of Wacker conditions to $\text{Pd}^{\text{II}}/\text{Pd}^{\text{IV}}$ chemistry. (**Figure 19**) Their working hypothesis exploits the dyotropic rearrangement. Hydroxypalladation of alkenes following Markovnikov's rule would afford a reasonably stable neopentyl σ - Pd^{II} complex that would be oxidized *in situ* to Pd^{IV} species in the presence of an appropriate oxidant. A 1,2-alkyl/ Pd^{IV} dyotropic rearrangement of the latter and then the C-X bond-forming reductive elimination process. Further elimination of HX from α -X species would provide ketone, assuming that X is a reasonably good nucleophile. The generation of the ketone is thought to be the driving

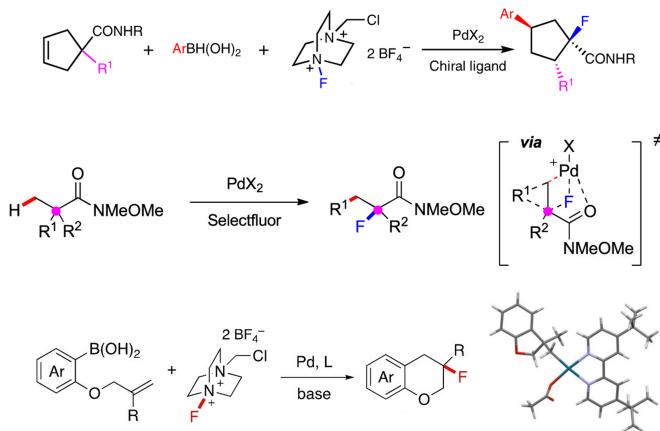


Fig. 17. Previous works of Zhu's lab on dyotropic rearrangement

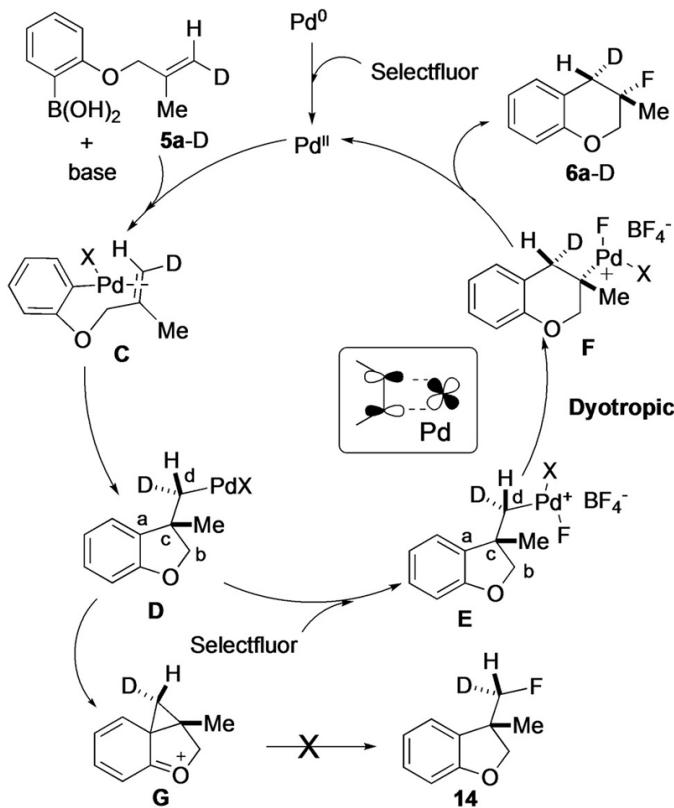


Fig. 18. Proposed reaction mechanism of one of Zhu's works

force for the proposed dyotropic rearrangement. Alternatively, a *semi*-pinacol rearrangement[40] of the Pd^{IV} intermediate could afford the rearranged ketone directly. To streamline the proposed reaction sequence, the choice of oxidant would be of utmost importance; it must satisfy at least the following two criteria: (i) Chemoselectively oxidize the *in situ* generated AlkylPd^{II} species rather than the Pd^{II} salt; (ii) Generate a relatively stable alkylPd^{IV}-X species to avoid the premature C-X bond-forming reductive elimination or a *S*_N2 substitution reaction.

In the optimization study, they found that selectfluor, a frequently used oxidant in their previous reports, led to the oxidation reaction to a very significant yield. After the systematic optimization of other factors, such as the Pd^{II} sources, the temperature, the solvents, and the ligands. Performing the reaction in MeCN/H₂O (v/v = 4:1) at room temperature in the presence of Selectfluor (1.2 equiv.) and a catalytic amount of Pd(MeCN)₄(BF₄)₂ (10 mol%) afforded the modeled rearranged ketone the best yield. Hence, they consider these conditions as their standard conditions.

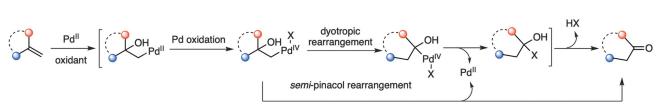


Fig. 19. Reaction Design

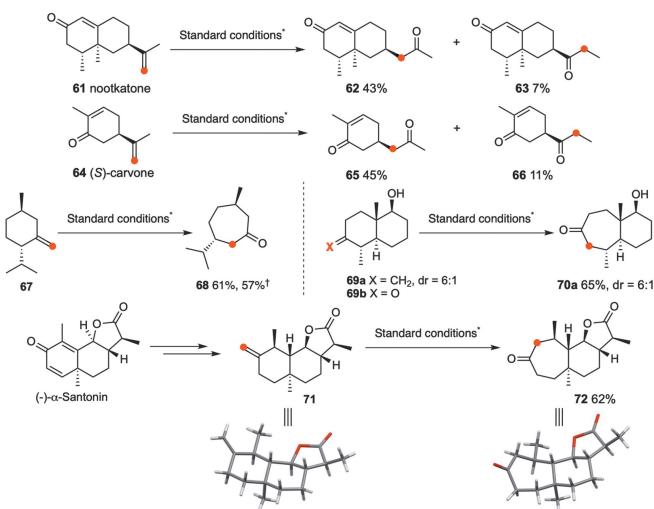
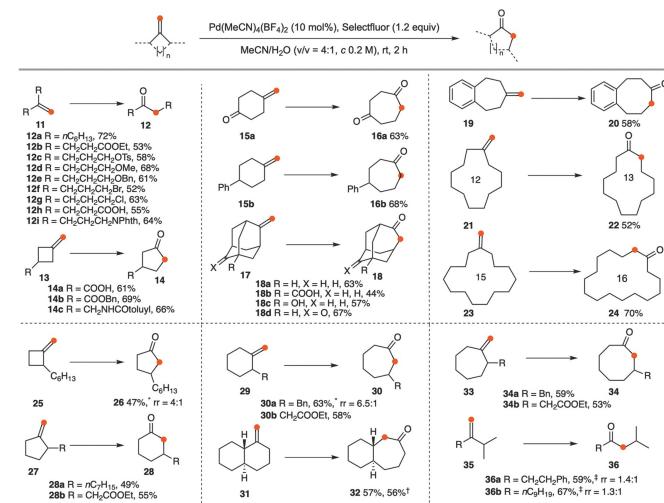
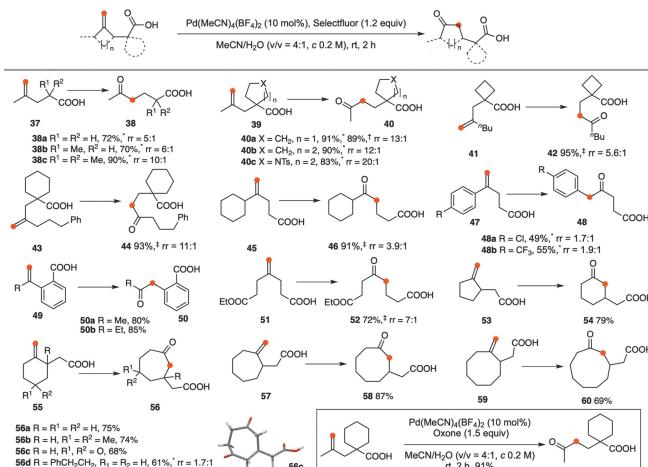
5.4 Reaction scope

With the optimum conditions thus determined, the reaction scope was examined. A range of symmetric 1,1-disubstituted alkenes (**Figure 20, top**) bearing diverse functional groups such as ester, tolylsulfonate, alkyl ethers (MeO, BnO), alkyl halides (Cl, Br), carboxylic acid, and phthalimide and hydroxyl groups, were successfully transformed to the rearranged ketones in good yields. Beyond one-carbon ring expansion of strained methylenecyclobutanes[35] affording the cyclopentanones as expected, ring expansion of functionalized methylenecyclohexanes with low strain proceeded equally well to afford seven-membered cycloheptanones in good yields. All symmetric 1,1-disubstituted alkenes can proceed smoothly including ring expansion of macrocycles.

Unsymmetric 1,1-disubstituted alkenes were next examined. (**Figure 20, bottom**) Cycloalkane underwent ring expansion to the corresponding products resulting from selective migration of the more substituted carbon. However, linear unsymmetrical terminal alkenes were oxidatively rearranged to ketones in low selectivity.

They examined the directing effect of common organic functional groups to address the low regioselectivity observed with the linear unsymmetrical terminal alkenes. (**Figure 21**) When a compound with an adjacent (β position) carboxyl group was submitted to the standard conditions, acid resulting from the migration of the chain with the carboxyl group was formed as a major product. However, styrene derivatives 47a and 47b sometimes were converted to a mixture of two regiosomeric ketones, 48a and 48b, with low selectivities caused by the intrinsically high migratory aptitude of the phenyl group.

To demonstrate the generality of their protocol, the proceeded the reaction on natural products and their derivatives. ((**Figure 22**)) Under the standard conditions, nootkatone and (S)-carvone was converted to corresponding ketones with relatively high selectivity. Ring expansion of derivative of L-menthone, and bicyclic compound provided relatively high selectivity and yield in contrast to traditional protocol (Tiffeneau-Demjanov reaction), respectively, resulting from the selective migration of the tertiary alkyl groups.

**Fig. 21.** From 1,1-disubstituted Alkenes to Rearranged Ketones

5.5 Conclusion

In summary, Zhu et al. have developed a Pd^{II}-catalyzed oxidative conversion of 1,1-disubstituted alkenes to the rearranged ketones via a Pd^{IV}/Pd^{II} catalytic cycle. The reaction is compatible with a wide range of functional groups, including alkyl halides, aryl halides, alkyl tosylate, hydroxyl, carboxylic acid, ester, lactone, amide, and ketone and α , β -unsaturated ketone and has a broad reaction scope. The substrates they selected are representative, and they did not blindly increase the workload to glory their work.

However, linear unsymmetric terminal alkenes without a directing group cannot have high selectivity. Furthermore, the scope of directing group is relatively narrow, only including carboxylic acid, and the position of the directing group is locked (β position). We deem the next step for Zhu's lab, and other organic chemists are optimizing their condition to achieve high selectivity in linear unsymmetric terminal alkenes and finding versatile directing groups in diverse positions to figure out the problems.

6 SUMMARY

In summary, developing new synthetic methodologies and further refinement through modifications is an unending quest in organic synthesis and method development. A developed method is validated for its synthetic potential, general applicability, usefulness, and operational simplicity. Wacker oxidation is one such method that has grown enormously in terms of its modifications, mainly directed towards alternative oxidants, a replacement for Pd in recent years, and versatile regioselectivity and reaction type. In this review, we conclude the progress of Wacker oxidation and give the gist of these crucial developments. Future directions could be to develop more benign processes based on non-toxic and cheaper metals, use oxygen as an oxidant or other easily accessible oxidants, and have scalability and applications in complex molecule synthesis.

AUTHOR CONTRIBUTIONS

Kecheng Wang completed this review independently.

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