

Carbonyl Desaturation: Where does Catalysis Stand?

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ABSTRACT: There is a strong parallel between simple alcohol oxidation and carbonyl desaturation from both strategic and tactical vantage points. As they both seek to extract hydrogen from an organic substrate, they are deceptively simple looking transformations that have been addressed over the past 70+ years through stoichiometric means. The past decade has seen an intensifying level of interest in rendering both of these simple reactions catalytic. In this perspective recent advances from the past five years are highlighted featuring both transition-metal catalyzed and metal-free approaches to carbonyl desaturation. Through a historical overview and a detailed look at each of these new developments we seek to address the question of in what context a catalytic strategy emerges as ideal.

Introduction and Historical Perspective

Carbonyl desaturation is one of the most oft-employed transformations in modern organic chemistry.^{1,2} From a synthetic perspective, the sheer variety of tools available to the practitioner to achieve this simple conversion bears a striking resemblance to alcohol oxidation. As with the basic oxidation of an alcohol to a carbonyl group, the oxidative formation of an unsaturated carbonyl from its reduced precursor opens up a large realm of new reactivity and options for downstream functionalization. As with alcohol oxidation, it took almost 70 years and the combined efforts of several chemistry research groups to develop more efficient, chemoselective and greener reaction conditions to achieve this transformation.³⁻⁴ Figure 1A presents a truncated timeline of some milestone events in desaturation but the perceptive reader will recognize some parallels of these developments with contemporaneous breakthroughs in alcohol oxidation. The examples procured in this Figure have found significant applications in synthesis or as inspiration for future developments. The initial impetus to search for new oxidants (both for alcohols and carbonyls) started in the 1950s largely due to the burgeoning interest in the chemistry of steroids. Desaturation in those days relied on strong oxidizing reagents such as 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ)⁵ or SeO₂.⁶ The high temperatures that had to be employed with these reagents often afforded low yields and poor selectivity. To control the regioselectivity, an α -halogenation/elimination sequence was developed. However, the harsh conditions needed to achieve the elimination of the halide reduced the broad uptake of this approach.⁷ Thereafter, in the 1970s, syn-eliminations of selenoxide and sulfoxide intermediates were developed by Sharpless,⁸ Reich⁹ and Trost¹⁰ allowing milder elimination

conditions (especially with organoselenium) based on the pericyclic nature of the reaction (retro-2,3 fragmentation). However, these methodologies still presented several drawbacks such as the number of steps required to introduce, oxidize, and subsequently eliminate the corresponding organoselenium or organosulfur as well as the inherent toxicity and smell associated with the reagents and intermediates. Later on, using similar logic, Mukaiyama reported the exposure of enolates to *N*-tert-butyl phenylsulfonimidoyl chloride **1** to deliver the unsaturated product in a single step *via* the elimination of the C-sulfonimidoylated intermediate at low temperature, overcoming some of the previously observed limitations.¹¹ In 1977, the Jung group introduced the oxidation of silyl enol ethers by vinylogous hydrogen abstraction under mild conditions (*via* a two-electron or single electron transfer (SET) mechanism). In such cases, the use of DDQ or trityl tetrafluoroborate was found to be essential to afford the desired desaturated product.¹² In 2000, a unique approach was uncovered by Nicolaou using hypervalent iodine reagents such as IBX **2** to afford the desired desaturated aldehyde or ketone in good to excellent yields.¹³ The reaction proceeds through intramolecular SET and use of DMSO as solvent or co-solvent is essential to obtain high yield. Numerous variants of this I(V)-based approach have also been developed and even applied to the desaturation of enol-ethers.¹⁴ Finally, the Iwabuchi group has reported the use of hindered *N*-oxoammonium salts, such as AZADO **3**, to achieve enol ether dehydrogenation through ene-type mechanism.¹⁵

One of the main breakthroughs in the search for new carbonyl desaturation tools was the introduction of transition-metal based dehydrogenation processes. In 1971, Theissen¹⁶ reported that stoichiometric Pd(II) salts in presence of oxygen and Cu(II) salts or *para*-benzoquinone

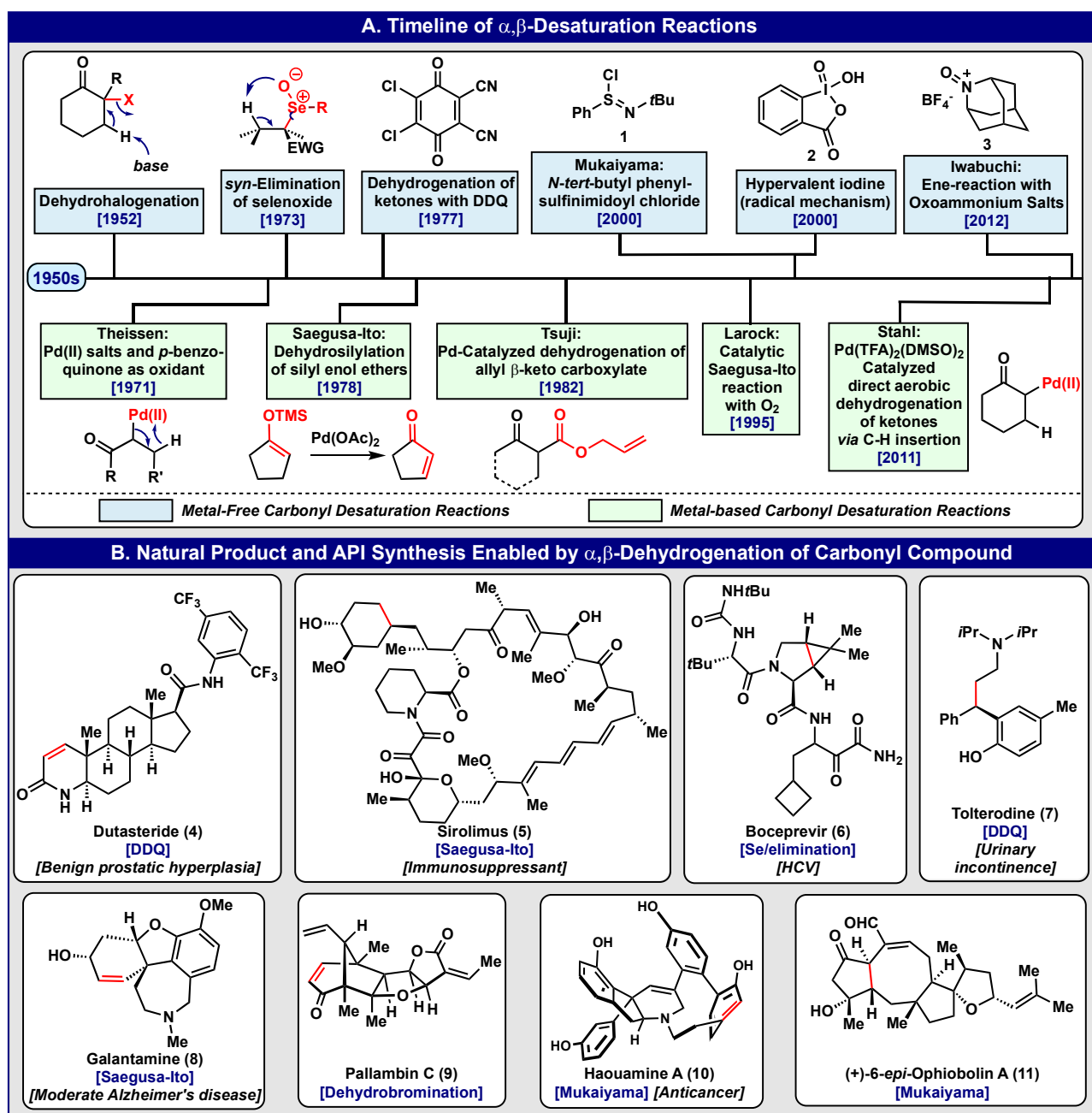


FIGURE 1. A) Timeline of α,β -desaturation reactions. B) Application of desaturation reactions in total synthesis.

additives generate a Pd-enolate species that readily undergoes β -H elimination affording the desired unsaturated product in low yields along with over-oxidized and regioisomer by-products. Advances in the regiochemical outcome of the reaction were made by Saegusa and co-workers in 1978.¹⁷ Indeed, starting from a simple enol ether enabled precise control of the regioselectivity under similar reaction conditions affording a broad range of enones in excellent yields. Generally, even in the modern era, a high loading of Pd(II) is required to achieve serviceable yields due to the coordination of Pd(0) to the enone moiety which inhibits the reoxidation step.¹⁸ In 1982, Tsuji demonstrated that lower palladium loadings (to 5 mol%) could be achieved by simply using allyl β -ketocarboxylates. The latter

acts as an oxidant in the reaction mixture to form a π -allyl-palladium complex. Based on this preliminary finding the reaction conditions were then further optimized to broaden the scope of this transformation.¹⁹ In 1995, a significant advance was made by the Larock group when they performed net desaturation of enol ethers (*via* dehydrosilylation) under an oxygen atmosphere thereby allowing the use of a catalytic amount of Pd(OAc)₂.²⁰ In 2011, Stahl and co-workers reported the direct access to enones from the corresponding ketones without preactivation enabled by a Pd(DMSO)₂(TFA)₂ catalyst under aerobic conditions.²¹ The meticulous choice of ligand limited the formation of higher-oxidation-state byproducts (arenes). As briefly highlighted above, a plethora of methodologies were reported in the blossoming field of desaturation chemistry

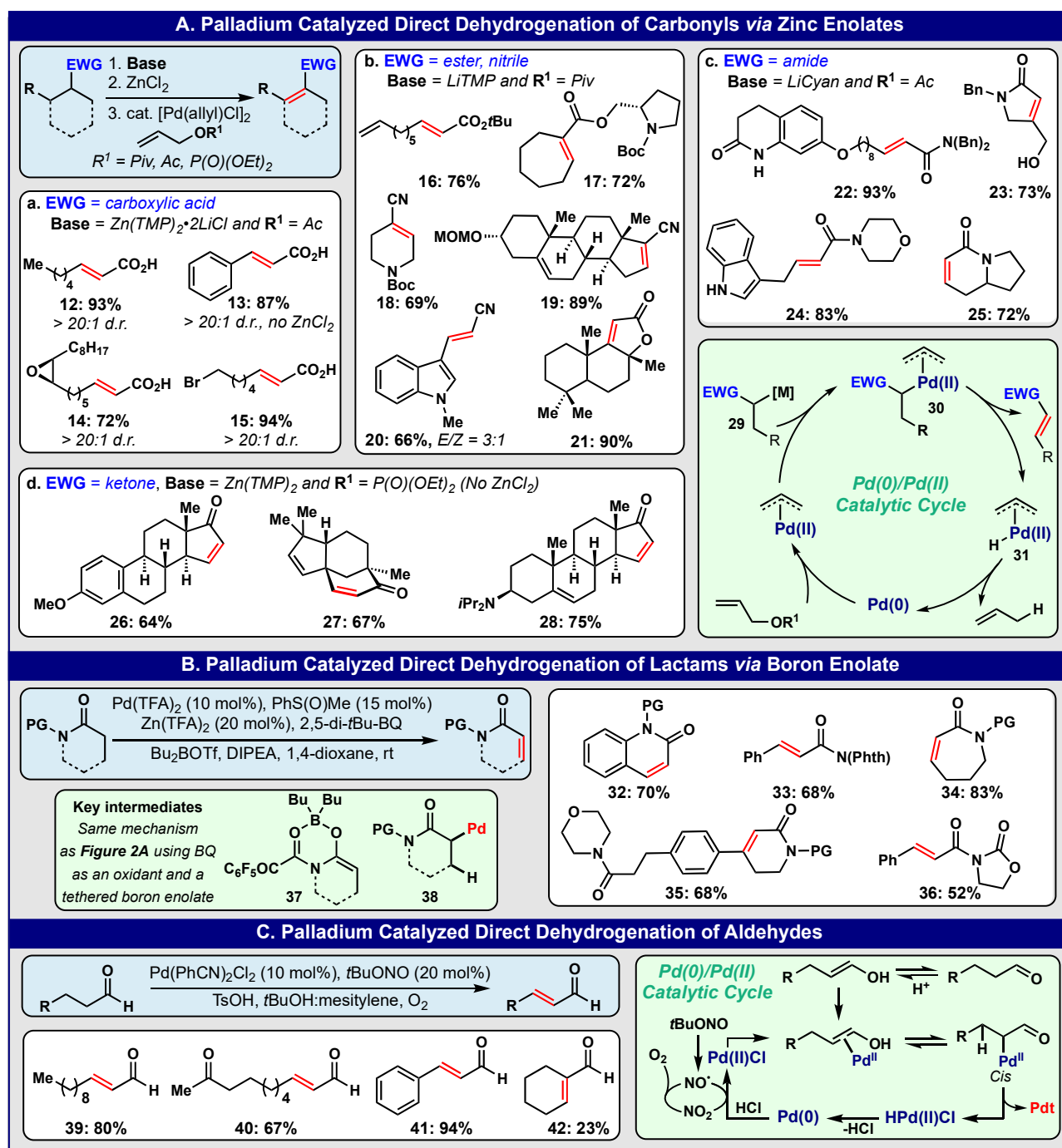


FIGURE 2. Palladium-catalyzed dehydrogenation reactions over the past few decades and have been summarized in various book chapters and review articles.^{1-4,22} Figure 1B serves to highlight how some of these classic methods have been leveraged in complex natural product total synthesis and pharmaceutical development (4-11).²³ This Perspective therefore, summarizes recent advances reported for the α,β -desaturation of carbonyl since 2015, which are largely enabled by the power of catalysis. Given that this field is in a constant state of evolution, it is particularly useful to identify the logical progressions, current limitations, and emerging future directions.

Pd-based desaturation

The majority of previously mentioned desaturation methods are mainly applicable with ketones and aldehydes. A breakthrough in this field was disclosed by Newhouse and co-workers, in a series of four papers, which describe a general and direct α,β -desaturation of carbonyl compounds (Figure 2A) that overcome this limitation.²⁴⁻²⁷ Inspired by the pioneering work of Tsuji with silyl enol ethers, they first reported the direct dehydrogenation of esters and nitriles (16-21).²⁴ Under the reaction conditions, a broad substrate scope containing acyclic compounds (16, 20), lactones (21), and various

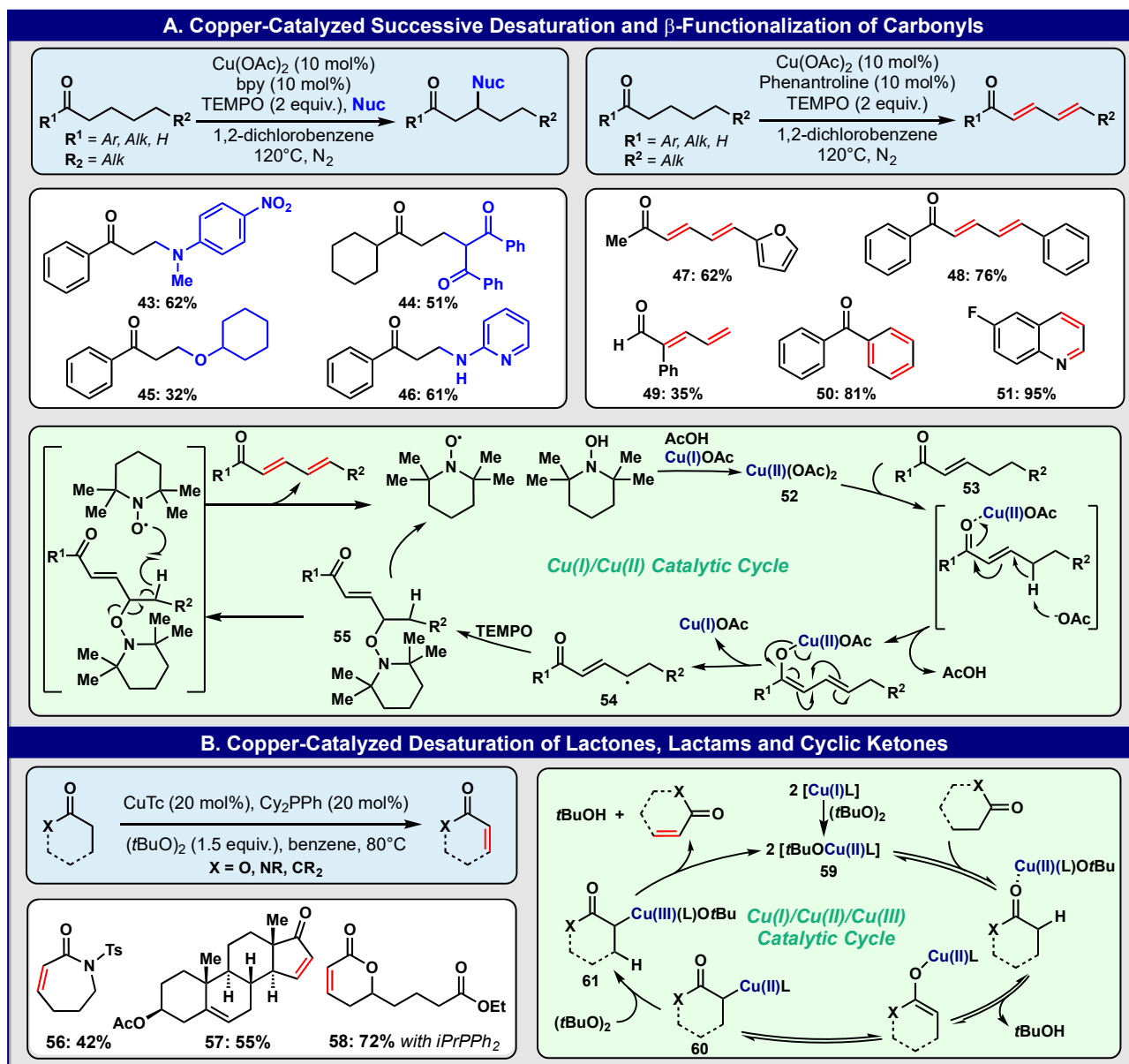


FIGURE 3. Copper-catalyzed dehydrogenation reactions.

steroid skeletons were desaturated (**19**, **21**). In addition, a variety of protic moieties such as alcohols, amines, anilines and amides were tolerated; demonstrating an exceptional functional group compatibility.²⁸ From a mechanistic standpoint, the reaction is initiated by the *in-situ* formation of a zinc enolate (**29**), followed by the addition of catalytic Pd(II) to form the corresponding palladium enolate (**30**). This enolate undergoes β -hydride elimination to afford the desired product and an allylpalladium hydride (**31**) which generates Pd(0) after reductive elimination. A final oxidative addition step of the Pd(0) with the allyl pivalate completes the catalytic cycle. In this study, Newhouse and co-workers have highlighted the crucial role of the zinc enolate intermediate in suppressing the Tsuji-Trost allylation and Claisen side reaction pathways. They later extended this mechanistic paradigm to ketones (**26–28**), amides (**22–25**), and carboxylic acids (**12–15**). Accordingly, the desired α,β -dehydrogenated product can be obtained using the right combination of base and allyl-based oxidant (Figure 2A). In the

case of amide and lactams, the nature of the substituents attached to the amide nitrogen dictate the selectivity of the dehydrogenation reaction.²⁶ It has been shown that mono *N*-substituted amides cannot be dehydrogenated under the reaction conditions compared to fully substituted substrates. Similarly, dehydrogenation adjacent to tosyl or carbamate-protected amides is not possible under the reported conditions. Finally, this elegant methodology was successfully applied to the total synthesis of (+)-Granatumine A²⁹ and (-)-Xylogranatopyridine B.³⁰

In 2017, Dong and co-workers reported the α,β -desaturation of lactams *via* the union of soft enolization and Pd-catalyzed enolate oxidation processes (Figure 2B).³¹ In their design, they reported that the Lewis acid/base pair ($\text{Bu}_2\text{BOTf}/\text{DIPEA}$) efficiently promotes the enolization step allowing for the reaction to be conducted at room temperature. The reaction conditions are applicable to both cyclic (**32**, **34**, and **35**) and acyclic amides (**33**, **36**)

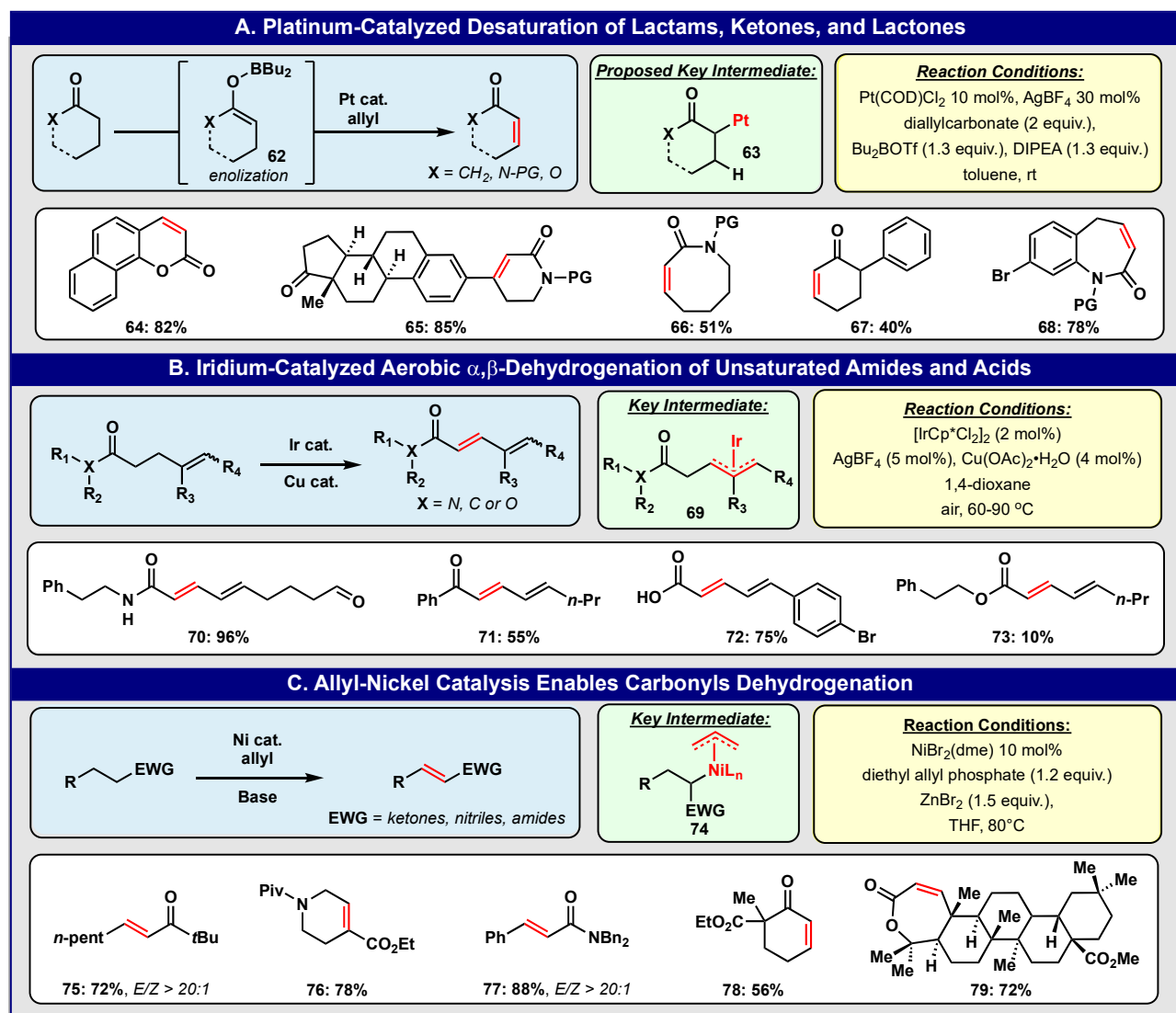


FIGURE 4. Other transition metal-catalyzed dehydrogenation reactions.

and are compatible with a variety of functional groups, especially base-sensitive moieties. From a mechanistic standpoint, a Pd(II) enolate intermediate (**38**) is formed *via* transmetalation of an *in-situ* generated amide enolate (**37**). Subsequent β-H elimination leads to the desired α,β-unsaturated amide. The resulting Pd(0) species is oxidized back to the active Pd(II) catalyst using 2,5-di-*t*Bu-benzoquinone. It worth mentioning that the high chemoselectivity observed during this process stems from the lactam protecting group which allows for the formation a cyclic 6-membered transition state between the substrate and the boron Lewis acid prior to enolization (**37**).

While the aforementioned conditions made great strides in overcoming the scope of desaturation, acyclic aldehydes were still challenging substrates. In 2017, Kang *et al.* reported (Figure 2C) a direct desaturation method of aldehydes using catalytic *t*BuONO as a redox co-catalyst under aerobic conditions.³² The methodology provides access to various types of linear non-aromatic α,β-unsaturated aldehydes (**39–42**). The use of *p*-toluenesulfonic acid (TsOH) in a non-coordinating solvent (mesitylene) proved essential for the enolization step. The authors proposed a similar reaction mechanism to those above. Based on the same concept, other research groups reported direct desaturation methods of aryl ketones and aldehydes.³³

Cu-based desaturation

In 2016, the first copper catalyzed direct β-functionalization of saturated ketones was reported by Su *et al.*³⁴ The reaction involves a selective ketone dehydrogenation leading to the *in situ* formation of an α,β-unsaturated ketone, followed by a Michael addition wherein amine, oxygen and carbon nucleophiles are compatible (Figure 3A). Both steps are catalyzed by an inexpensive first row transition metal (Cu(OAc)₂) using bipyridine (bpy) as ligand, and TEMPO as stoichiometric oxidant. Due to the mild oxidative conditions, a broad substrate scope containing pyridines (**46**), anilines (**43**) and aliphatic alcohols (**45**) has been reported. However, the reaction only affords access to *trans*-enone products and is limited to acyclic substrates. Another limitation of this method is the use of a relatively large excess of the ketone (1.5 to 3.0 equiv) to obtain satisfactory yields.

A year later, the same research group reported the construction of diverse stereo defined conjugated dienes (**47–49**), arenes (**50**), and nitrogen-containing heteroarenes

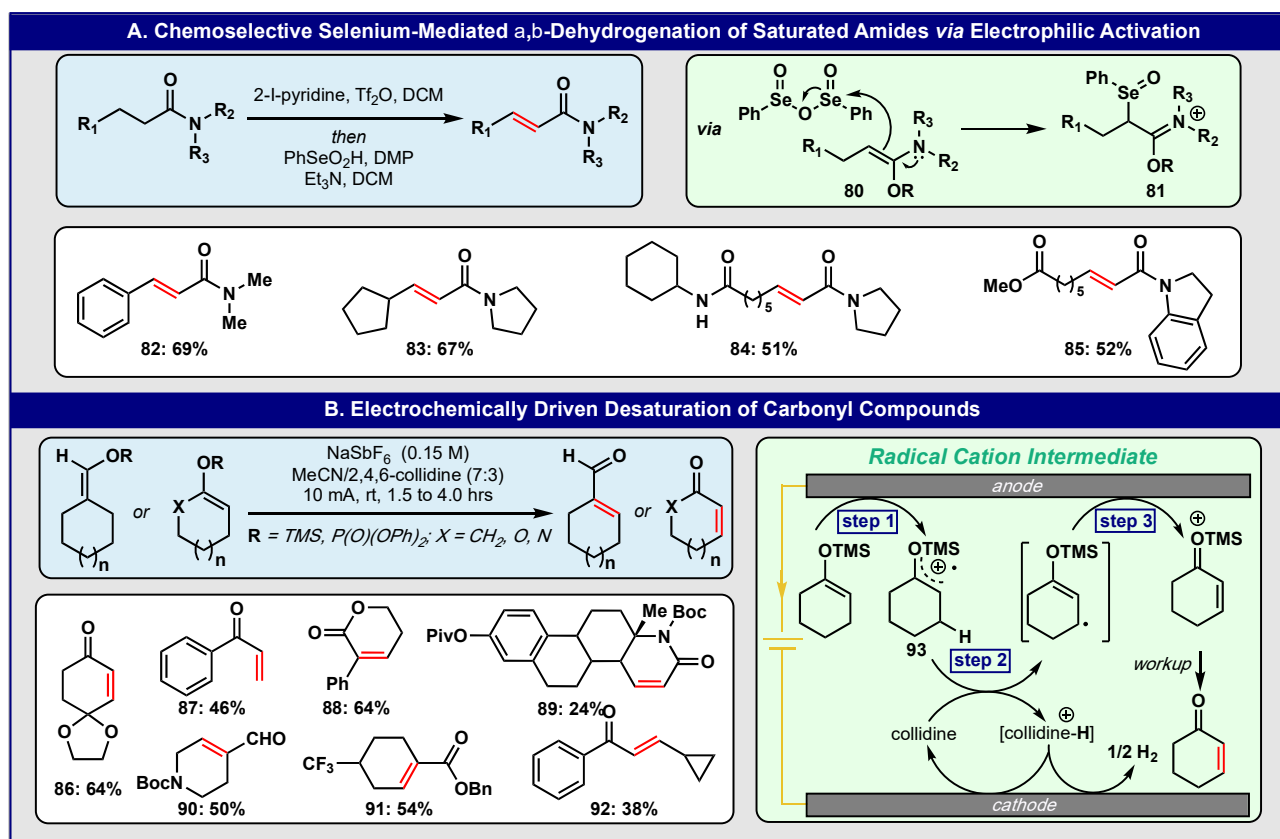


FIGURE 5. Metal-free dehydrogenation reactions.

(51) by simply switching the bipyridine ligand to phenanthroline (Figure 3A).³⁵ Starting from ketones, aldehydes, alcohols, α,β -unsaturated diesters, and *N*-heterocycles it was demonstrated that the ligand mainly modulates the Lewis acidity and the redox properties of the copper catalyst allowing for the desaturation pathway to occur efficiently. As revealed by mechanistic studies, the catalytic cycle starts with the formation of an α -radical (54) upon treatment of the ketone/enone (53) with the copper catalyst (52) following by trapping with a molecule of TEMPO to afford intermediate 55. A subsequent TEMPOH-elimination affords the desired desaturated product and the Cu(II) catalyst is regenerated upon oxidation (by TEMPO). It worth noting that the authors have isolated and characterized the corresponding TEMPO adduct which afforded the desaturated product once resubmitted to the standard reaction conditions. Similarly, Fan and co-workers further studied the copper-TEMPO system to achieve the direct formation of 3-acylquinolines and acylpyrazoles starting from acyclic ketones. Comparable to the Su design, the enone is formed *in-situ* followed by 1,4-addition of *N*-based nucleophiles to access heteroaromatic structures.³⁶

In an elegant report, Dong and co-workers demonstrated the direct copper-catalyzed conversion of lactones (58), lactams (56), and cyclic ketones (57) to their α,β -unsaturated counterparts (Figure 3B).³⁷ The reported protocol uses an inexpensive catalyst (Cu(I)Tc), a mild oxidant (di-*tert*-butyl peroxide, DTBP), and exhibits extensive functional group compatibility. However, the reaction is mainly limited to five and six membered ring systems. Inspired by Stahl's seminal mechanistic studies (on the palladium catalyzed desaturation reaction), Dong *et al.* envisioned that copper could form the desired organocopper ketone intermediate (60) by acting as a Lewis acid and later favor the β -hydride elimination process. Based on

control experiments and side products observed, the authors proposed that the reaction initiates by oxidative formation of the catalyst Cu(II)OTBu (59) via oxidation of Cu(I) with DTBP. The Cu(II)OTBu species then coordinates to the carbonyl moiety and promotes the subsequent reversible deprotonation of the α -proton to form the Cu(II)-enolate intermediate (60). This species is then directly oxidized by a second molecule of DTBP to form a highly reactive Cu(III) intermediate (61) which readily undergoes oxidative elimination to afford the desaturated product and ultimately regenerate the active Cu(II)OTBu catalyst (59).

Other transition metal-based desaturations

Until recently, the field of transition metal catalyzed carbonyl desaturation has been dominated by palladium and copper-based methods. However, in recent years, other transition metal-based such as platinum, iridium, and nickel have been used to achieve similar transformations. In 2018, the Dong group reported the first platinum-catalyzed direct desaturation reaction of lactams, ketones and lactones (64-68, Figure 4A).³⁸ The reaction proceeds *via* the *in situ* formation of a boron enolate using Bu₂BOTf (62), followed by transmetalation with the Pt(II) active catalyst (63). Subsequent β -H elimination leads to the desired α,β -unsaturated product. The resulting Pt species is oxidized back to the active catalyst using diallyl carbonate (DAC). This method is similar conceptually to the Pd catalyzed method published by the same research group (Figure 3B).

Thereafter, Huang and co-workers reported an iridium-dimer catalyzed aerobic dehydrogenation reaction to access conjugated diene-carbonyl compounds (70-73, Figure 4B).³⁹ Direct α,β -desaturation of γ,δ -unsaturated acyclic amides, acids, and ketones was disclosed using catalytic amount of [Cp*IrCl₂]₂ (2 mol%), AgBF₄ (5 mol %), and Cu(OAc)₂·H₂O (4 mol %) under air in 1,4-dioxane. However, the reaction conditions could not

be translated to the desaturation of esters and nitriles. It is worth noting that the reaction proceeds following a different mechanistic pathway than all of the previously reported methods since it commences with the insertion of the iridium catalyst into the β -C-H bond to form the allyl-Ir intermediate (**69**). Direct hydride elimination or ketone tautomerization, followed by 1,5-hydrogen shift, leads to the desired dehydrogenated product.

In 2019, Newhouse *et al.* reported the α,β -dehydrogenation of carbonyls using the *in-situ* generation of an allyl-nickel catalyst (**74**, Figure 4C).⁴⁰ As with their previously reported Pd catalyzed desaturation methods, allyl phosphate is used as an oxidant and the zinc enolate is formed by either using LiCyan with ZnBr₂ or Zn(TMP). The reaction conditions are applicable to both cyclic and acyclic ketones, amides, nitriles and esters (**75-79**). Analogously, the same group reported early this year a nickel catalyzed benzylic dehydrogenation of electron deficient heteroarenes.⁴¹ This group has gone on to show that such intermediates in desaturation can be intercepted to form new C-C bonds through intramolecular cycloalkenylation.⁴⁰

Transition metal-free desaturation

Since the first report by Theissen in 1971, transition metals have played a significant role in the expansion of the carbonyl desaturation toolbox. However, with the constant need to develop greener processes, interesting metal-free α,β -dehydrogenation methods have emerged over the past 3 years.

In 2019, the Maulide group reported a metal free chemoselective desaturation of amides (**82-85**, Figure 5A).⁴² This method exhibits good functional group compatibility and enables the selective desaturation of amides in the presence of cyclic and acyclic ketones, esters (**85**), and nitriles. Moreover, tertiary amides can be selectively converted to the corresponding dehydrogenated product over their primary and secondary analogs. Although the precise mechanism remains unclear, it was postulated that the reaction proceeds *via* an electrophilic amide activation to generate a keteniminium species, followed by the formation of an enamine/enol hybrid (**80**). The latter species reacts with phenyl seleninic anhydride to generate the desired α -selenoxide intermediate (**81**) followed by α,β -elimination and hydrolysis to afford the desired desaturated product. In a similar fashion, the Maulide research group has expanded the scope of the previously reported method leading to the *in-situ* formation of an α,β -unsaturated of α -branched amides, followed by a Michael addition of thiol, or alternatively epoxidation of the formed double bond.⁴³

Earlier this year, our group reported an electrochemically driven desaturation (EDD) method to address this challenge (Figure 5B).⁴⁴ Notably, this method exhibits a broad scope across an array of carbonyl derivatives such as ketones (**86**, **87** and **92**), aldehydes (**90**), esters (**88**, **91**) and lactams (**89**). In addition, this oxidation protocol can simply be performed in an undivided cell, without strict removal of air or water, and in the absence of expensive metals, ligands, or stoichiometric chemical oxidants. Furthermore, the method is easily scalable (1-100g) using both batch and flow electrochemical setups. Regarding the mechanism, it was proposed that EDD proceeds *via* a single electron pathway that can be divided in three elementary steps. First, direct anodic oxidation of the enol-ether leads to the formation of the radical cation intermediate (**93**). This radical cation undergoes β -proton elimination, and finally a second oxidation takes place to form the desired enone product (Figure 5B). It's worth noting that as part of this study, a simple

¹H-NMR-based rubric was created to allow users to experimentally or computationally predict which substrates are suitable for EDD.

Conclusion and future outlook

As mentioned in the introduction, the desaturation of carbonyls to yield α,β -unsaturated systems is reminiscent to the oxidation of alcohols. Both methods are foundational transformations that are found in countless total syntheses and are employed in all sectors of industry. The strategies used to render alcohol oxidation catalytic or more inexpensive are also similar to those seen employed in the modern era for carbonyl dehydrogenation. From a sustainability standpoint, although catalytic systems are amongst the most valuable, one also needs to consider the source of the net oxidation which often comes from stoichiometric co-oxidants, additives, or even atmospheric oxygen. These facets are summarized along with the substrate scope of the innovative emerging methods highlighted in this perspective in Figure 6. It is interesting to note that only in 2019 were the first catalytic dehydrogenation conditions identified using inexpensive transition metals like Ni and Cu. One of the most valuable lessons from the development of catalytic methods may stem from learning new methods to activate carbonyls for downstream functionalization (e.g. Newhouse-type cyclization⁴⁰) or to achieve unprecedented chemoselectivity in complex settings. In those instances, catalytic strategies may be ideal for the control of reactivity.

Oxidants Used in Desaturation Reactions				
Metal-catalyzed desaturation reactions				
Group	Metal	Scope	Oxidant	Ref.
Newhouse	Pd	Ketone	Allyl phosphate	[24]
Newhouse	Pd	Amide	Allyl acetate	[25]
Newhouse	Pd	Ester, nitrile	Allyl pivalate	[26]
Newhouse	Pd	Carboxylic acid	Allyl acetate	[27]
Dong	Pd	Amide	2,5-di- <i>t</i> Bu-BQ	[31]
Kang	Pd	Aldehyde	O ₂	[32]
Su	Cu	Ketone, Aldehyde	TEMPO	[34, 35]
Dong	Cu	Ketone, lactone, lactam	DTBP	[37]
Dong	Pt	Ketone, lactone, lactam	Diallyl carbonate	[38]
Huang	Ir	Ketone, amide, carboxylic acid	Air (O ₂)	[39]
Newhouse	Ni	Ketone, ester, amide, nitrile	Allyl phosphate	[40]
Metal-free desaturation reactions				
Group	Scope		Oxidant	Ref.
Maulide	Amide		DMP	[42]
Baran	Ketone, ester, lactam, aldehyde		Electrons	[43]

FIGURE 6. Oxidants used in desaturation reactions. 2,5-di-*t*Bu-BQ = 2,5-di-*t*Bu-benzoquinone. DTBP = di-*tert*butyl peroxide. DMP = Dess-Martin periodinane.

At the same time, if nothing more than dehydrogenation is required, it may be wise to consider non-canonical oxidation methods such as electrochemistry that can exhibit broad substrate scope and efficiency on scale using inexpensive electrons as the oxidant. Perhaps in the future, hybrid approaches will emerge that benefit from the low cost of electrochemical methods and the exquisite control enabled by catalytic systems. Direct approaches that do not require enolate or enol derivatives that exhibit a wide scope are still in need of further development and it is likely that catalysis will play a pivotal role.

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Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

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