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Synthesis of Cyclic Enones by Allyl-Palladium-Catalyzed α,β-Dehydrogenation

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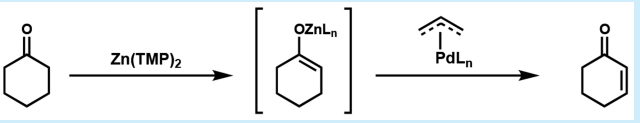
Supporting Information

ABSTRACT: The use of allyl-palladium catalysis for the one-step α,β-dehydrogenation of ketones via their zinc enolates is reported. The optimized protocol utilizes commercially available $Zn(TMP)_2$ as base and diethyl allyl phosphate as oxidant. Notably, this transformation operates under salt-free conditions and tolerates a diverse scope of cycloalkanones.

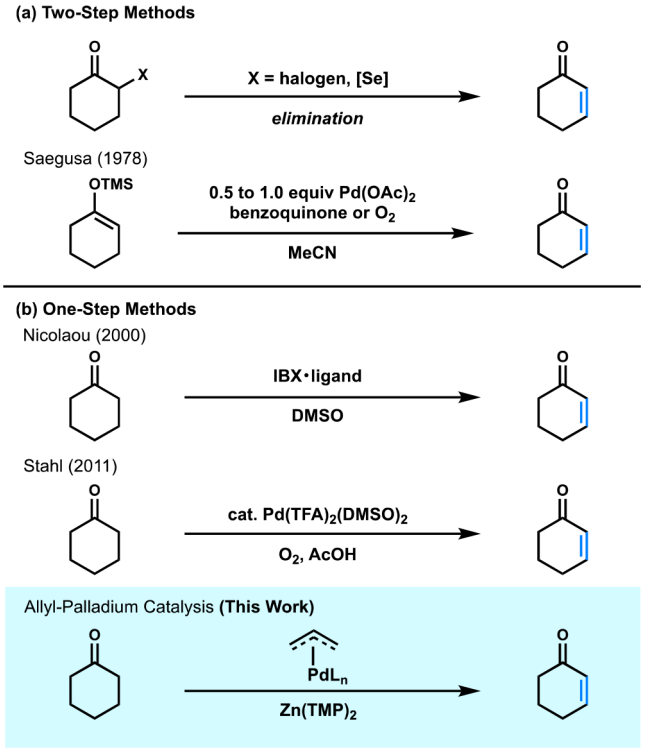


The conversion of ketones to the more versatile enone functionality is an important transformation in organic synthesis due to the utility of enones as intermediates in multistep production of pharmaceuticals and biologically active compounds. The introduction of an alkene adjacent to a ketone is well-precedented in the literature and can be broadly categorized into two main areas: two-step methods that proceed via an α-functionalized intermediate (Scheme 1a) and one-step methods that directly access enones from ketones in a single operation (Scheme 1b).[1]

While two-step ketone dehydrogenations are widely employed and reliable, the suboptimal step economy associated with these processes leads to significant ancillary waste and excessive production times. One of the earliest strategies for the synthesis of enones involves the prefunctionalization of the ketone α-position with a halogen, which can be eliminated upon treatment with base at high temperatures.[2] This strategy remains an important instrument in multistep synthesis owing to the low cost and limited byproducts produced. The utilization of α-selenide intermediates is similarly broad in scope as these species can be formed under mild conditions through trapping of a lithium enolate with PhSeX.[3,4] The second step entails conversion of the selenide moiety to the corresponding selenoxide, which allows for spontaneous generation of α,β-unsaturated products via a 2,3-sigmatropic rearrangement.[5] Another reliable two-step methodology for ketone to enone conversion is the Saegusa oxidation, wherein an initially formed enoxysilane undergoes palladium-mediated dehydrosilylation in a separate step. While benzoquinone or O_2 can be employed as terminal oxidants to enable the use of catalytic quantities of palladium, substoichiometric loadings are typically required to achieve synthetically useful yields.[6]

The two most practical one-step methodologies that have emerged are Nicolaou's dehydrogenation and Stahl's palladium-catalyzed dehydrogenation. Nicolaou demonstrated that the use of a stoichiometric hypervalent iodine oxidant, 2-iodoxybenzoic acid (IBX), can effect the α,β-dehydrogenation of ketones and aldehydes. This process can be further promoted through the addition of catalytic *p*-TsOH, or *N*-oxide or sulfoxide ligands to generate an I(V) oxidant. As a result of its generality and practical ease of application, the IBX oxidation is one of the principle methods for ketone dehydrogenation.[7] Stahl reported the direct aerobic dehydrogenation of ketones via the use of palladium catalysis and O_2 as oxidant. The intermediate palladium enolates needed for β-hydride elimination are accessed by oxidative functionalization of the ketone α-position

Scheme 1. Overview of Strategies for the α,β-Dehydrogenation of Ketones



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under acidic conditions for cyclic ketones[8] and neutral conditions for acyclic substrates.[9]

Despite these advances in the practical application of this transformation, recourse to two-step methods is common. Our group has previously reported the formation of unsaturated carboxylic acids and their derivatives using allyl-palladium catalysis.[10] Precedent for this approach originates with Tsuji's pioneering studies of allyl-palladium enolates derived by oxidative decarboxylation of allyl-β-keto esters that were reported to undergo β-hydride elimination to form enones.[6c] For carboxylic acids and their derivatives, allyl-palladium enolates were formed via deprotonation with a lithium amide, transmetalation with $ZnCl_2$, and a subsequent transmetalation with an allyl-palladium catalyst.

It was found that changing the identity of the metal enolate from lithium to zinc crucially avoided typical Tsuji–Trost allylation products.[10] It is postulated that the less reactive zinc enolate is less prone to undergo nucleophilic substitution with an electrophilic allyl-palladium species. Thus, a transmetalation pathway could proceed instead to provide the necessary allyl-palladium enolate for β-hydride elimination. Alternatively, the presence of a zinc additive may be responsible for altering the structure of the allyl-palladium enolate to favor β-hydride elimination over reductive elimination to give enones rather than α-allylated products.[11] After β-hydride elimination, the resulting allyl-palladium hydride species then undergoes rate-determining reductive elimination to generate propene gas. The catalytic cycle is completed after palladium(0) undergoes oxidative addition with an allyl oxidant.

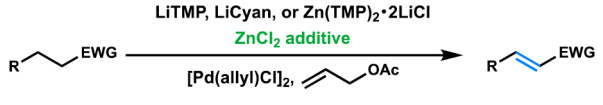
More recently we demonstrated that the use of allyl-palladium catalysis can enable a telescoped process for the vicinal difunctionalization of ketones via their enone intermediates.[12] Herein, we report the effective allyl-palladium-catalyzed dehydrogenation of ketones as a standalone method to access a broad range of enones with varied structural complexity through the formation of zinc enolates under salt-free conditions.

Table 1 describes our efforts to optimize the α,β-dehydrogenation of (+)-nopinone (**1a**) to form (+)-apoverbenone (**2a**); previous synthesis of bioactive compounds relied on two-step approaches for this challenging transformation.[13] We determined that the optimized protocol for allyl-palladium-catalyzed ketone dehydrogenation requires the specific combination of commercially available $Zn(TMP)_2$ as base[14] and diethyl allyl phosphate as oxidant[6g] (Table 1, entry 1). In contrast to our previous reports of carbonyl dehydrogenation, which were conducted in the presence of in-situ-generated LiCl salts and externally added $ZnCl_2$ salts, salt-free conditions are optimal for ketone dehydrogenation, which underscores the complex role that these additives play in transition metal catalysis with enolates.[15]

Alternative conditions led to inferior results. The use of allyl acetate as oxidant led to a substantial loss in reaction efficiency (entry 2), thereby emphasizing the significance of the leaving group on the allyl oxidant, which may play a role in perturbing enolate aggregation states or influencing the ligand sphere on palladium to alter its reactivity.[16] The addition of $ZnCl_2$ as an additive also led to a sharp decline in the yield of product **2a** (entry 3) and indicates that the presence of metal halide salts are detrimental to the reaction efficiency. The use of $Zn(TMP)_2{\cdot}2LiCl$, prepared according to Knochel's procedure,[17] provided **2a** in moderate yield (entry 4) and suggests that while in-situ-generated LiCl is also unfavorable, $Zn(TMP)_2{\cdot}2LiCl$ conveniently prepared from LiTMP and $ZnCl_2$ can still provide synthetically useful yields of enone product. Lastly, attempts to use the bases and additives optimized for carboxylic acid, ester, nitrile, and amide dehydrogenation ($Zn(TMP)_2{\cdot}2LiCl$, LiTMP, or LiCyan with added $ZnCl_2$) all led to significant depreciations in yield (entries 5–7) and highlights that the structure and identity of the base plays an intimate role in determining reaction efficiency.

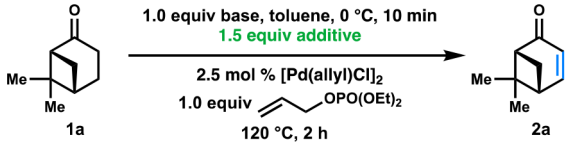
Table 1. Optimization of Ketone α,β-Dehydrogenation

(a) α,β-Dehydrogenation of Carboxylic Acid Derivatives **(Previous Work)**



EWG = ester, nitrile, amide, carboxylic acid

(b) α,β-Dehydrogenation of Ketones **(This Work)**



entry	base	additive	NMR yield (%)[a]
1	**$Zn(TMP)_2$**	**none (salt-free)**	**80 (70)[b]**
2	$Zn(TMP)_2$	none	11[c]
3	$Zn(TMP)_2$	$ZnCl_2$	27
4	$Zn(TMP)_2{\cdot}2LiCl$	none	56
5	$Zn(TMP)_2{\cdot}2LiCl$	$ZnCl_2$	44
6	LiTMP	$ZnCl_2$	33
7	LiCyan	$ZnCl_2$	29

[a] ^{1}H-NMR yields were obtained using 1,3,5-trimethoxybenzene as an internal standard. Complete conversion was observed in all entries. [b] Isolated yield. [c] 1.0 equiv of allyl acetate was used instead of diethyl allyl phosphate.

With the optimized conditions in hand, the scope of cyclic ketones that can undergo dehydrogenation was explored (Scheme 2). (+)-Nopinone **1a** was dehydrogenated to give (+)-apoverbeneone **2a** in 70% isolated yield. 4-*tert*-Butylcyclohexanone was also successfully dehydrogenated to give enone **2b** in 72% yield with only 18% of the overoxidized phenol product observed. Although this is an effective preparation of the γ-substituted enone, it also highlights a key challenge in this arena. (−)-Menthone was also readily dehydrogenated on gram scale to give the β-substituted enone product (+)-piperitone (**2c**) in 60% yield, and remarkably, without epimerization of the isopropyl group,[18] which indicates that enolate transfer is not competitive with dehydrogenation in this case. A series of other monocyclic (**2d**), bicyclic (**2e**, **2f**), and tricyclic (**2g**–**2j**) 5-, 6-, and 7-membered cycloalkanones were all smoothly dehydrogenated under the standard conditions. Additionally, a variety of steroidal substrates could also be desaturated to give enones **2k**–**2o**. Notably, the standard conditions allowed dehydrogenation in the presence of a range of acid-sensitive functionality, including TBS (**2d**) and MOM (**2i**, **2k**) protected alcohols, acetals (**2f**), strained cyclobutanes (**2g**) and cyclopropanes (**2j**, **2l**), and readily oxidizable functionality such as a tertiary amine (**2n**).

The application of the optimized ketone dehydrogenation conditions to an acyclic ketone substrate such as butyrophenone (**1p**) was ineffective and led to a complex mixture of products, therefore highlighting a challenge and limitation to the current protocol (Scheme 3).[19]

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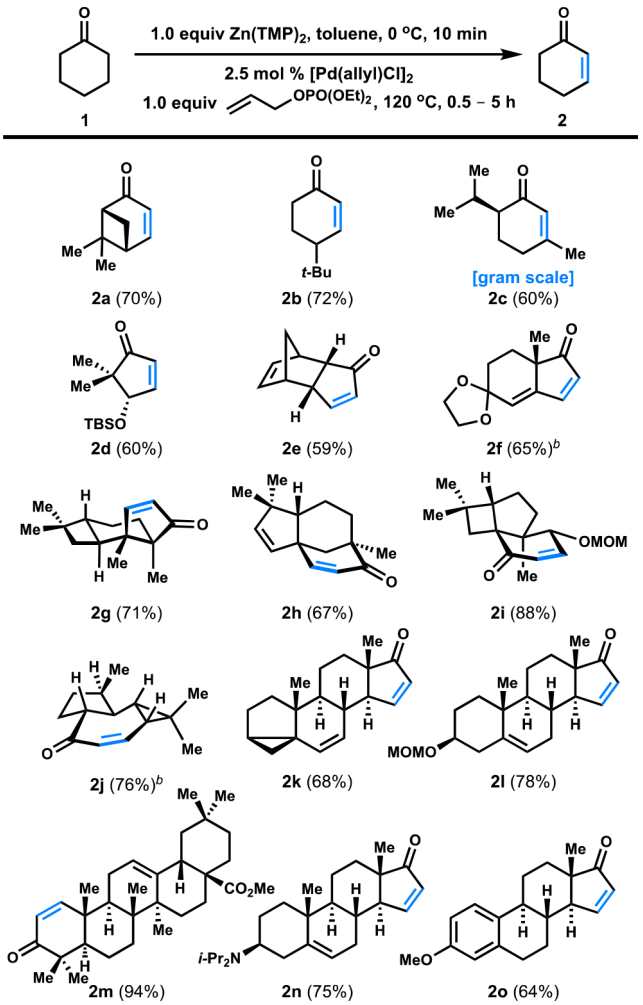
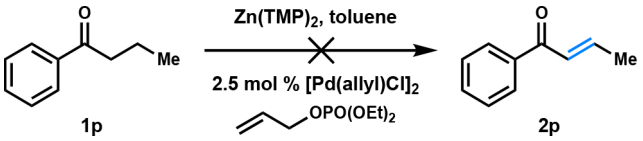
Scheme 2. Scope of Ketone α,β-Dehydrogenation[a]



[a]Isolated yields. [b]1.3 equiv of $Zn(TMP)_2$ was used.

Scheme 3. Dehydrogenation of Acyclic Ketones



In conclusion, we have developed a general method for the α,β-dehydrogenation of cyclic ketones via their zinc enolates. The use of a less basic zinc amide and a nonelectrophilic allyl phosphate oxidant was crucial to achieving a broad scope of architecturally diverse ketone substrates with acid-sensitive functional groups. This approach for enone synthesis is expected to be broadly useful because it initiates mechanistically with deprotonation, which is facile and reliable in complex chemical settings. This one-step dehydrogenation of cyclic ketones that operates under basic conditions represents an orthogonal procedure to existing one-step methodologies that operate under acidic conditions and is amenable to tandem functionalizations of the enone by reactions that employ basic conditions.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b03818.

Experimental procedures and spectroscopic data for all compounds (**2a**–**2o**) including ^1H and ^{13}C NMR spectra (PDF)

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Author Contributions

The manuscript is the product of contributions by all authors.

Notes

The authors declare no competing financial interest.

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