JACS
JOURNAL OF THE AMERICAN CHEMICAL SOCIETY

Communication

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Palladium-Catalyzed α,β-Dehydrogenation of Esters and Nitriles

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Supporting Information

ABSTRACT: A highly practical and general palladium-catalyzed methodology for the α,β-dehydrogenation of esters and nitriles is reported. Generation of a zinc enolate or (cyanoalkyl)zinc species followed by the addition of an allyl oxidant and a palladium catalyst results in synthetically useful yields of α,β-unsaturated esters, lactones, and nitriles. Preliminary mechanistic investigations are consistent with reversible β-hydride elimination and turnover-limiting, propene-forming reductive elimination.

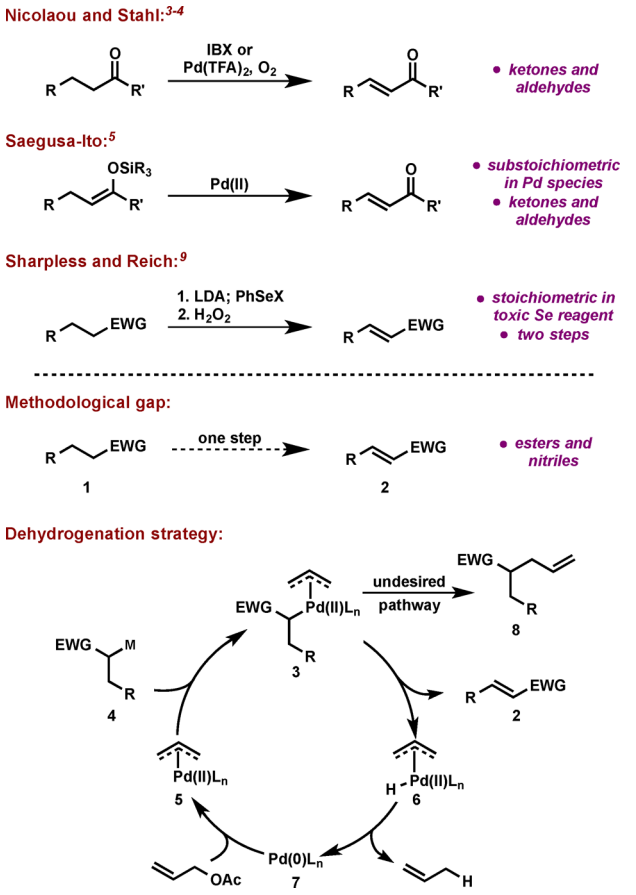
Electronically polarized alkenes are useful functional groups in organic synthesis because of the abundance of methods by which they can be regioselectively manipulated. Consequently, synthetic access to enones and enals from the corresponding ketones and aldehydes has been studied since the 1930s (Scheme 1).[1−9] Early approaches to carbonyl α,β-dehydrogenation utilized nonselective oxidants, such as 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) and SeO_2, that suffer from limited functional group compatibility.[2] The range of substrates that can be oxidized has been broadened through the introduction of *o*-iodoxybenzoic acid (IBX)[3] as a dehydrogenation reagent; Stahl and co-workers have recently reported a versatile palladium-catalyzed protocol that leverages an α-C−H cleavage mechanism to oxidize aldehydes and ketones to the unsaturated derivatives.[4] Recourse to two-step methodologies has been most widely employed, including the Saegusa oxidation, which necessitates the synthesis of an unstable enoxysilane as the first step.[5] The ensuing oxidation mediated by palladium has been reported with catalytic loadings, yet stoichiometric quantities of precious metal are frequently needed to avoid the formation of the proto-desilylation byproduct, which is difficult to chromatographically separate from the unsaturated product.[6]

Despite these advances in dehydrogenation adjacent to the relatively acidic aldehydes and ketones, practical methods for the direct dehydrogenation of less acidic substrates, including aliphatic esters and nitriles, remains an unmet challenge.[7,8] For less acidic nitrile and ester substrates, approaches involving α-phenylselenide synthesis followed by a second oxidation step are most commonly employed; however, this approach requires multiple operations in addition to stoichiometric quantities of the expensive and toxic phenylselenyl halide.[9] This Communication details the implementation of a strategy to directly effect α,β-dehydrogenation of esters and nitriles that likely operates via transmetalation of an enolate from Zn to Pd and subsequent β-hydride elimination (Scheme 1).

It was envisioned that a palladium enolate or cyanoalkyl species (**3**)[10] could be accessed via deprotonation with a suitable base[11] and transmetalation with a palladium(II) catalyst (**5**). The resulting palladium intermediate **3** could undergo β-hydride elimination[12] to form the desired product **2** and an allylpalladium hydride species (**6**), which would undergo reductive elimination to generate propene and a Pd(0) intermediate (**7**).[13] The catalytic cycle would be complete after oxidative addition with an allyl electrophile, such as allyl acetate. Initial attempts highlighted the difficulty of suppressing the formation of the α-allyl byproduct (**8**), which may have proceeded via the pathway depicted in Scheme 1 or via direct nucleophilic attack of the enolate at one of the terminal carbon atoms of the (π-allyl)palladium complex.[14,15]

We determined the most favorable parameters for the α,β-dehydrogenation of esters through a series of experiments summarized in Table 1. Formation of the lithium ester enolate of

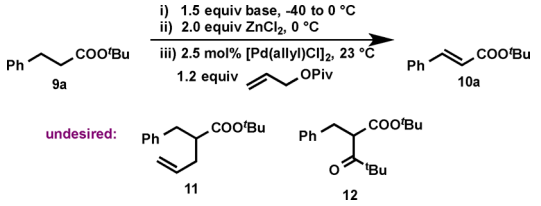
Scheme 1. Overview of α,β-Dehydrogenation



Received: March 2, 2015
Published: April 28, 2015

DOI: 10.1021/jacs.5b02243
J. Am. Chem. Soc. 2015, 137, 5875−5878

Table 1. Dehydrogenation Optimization



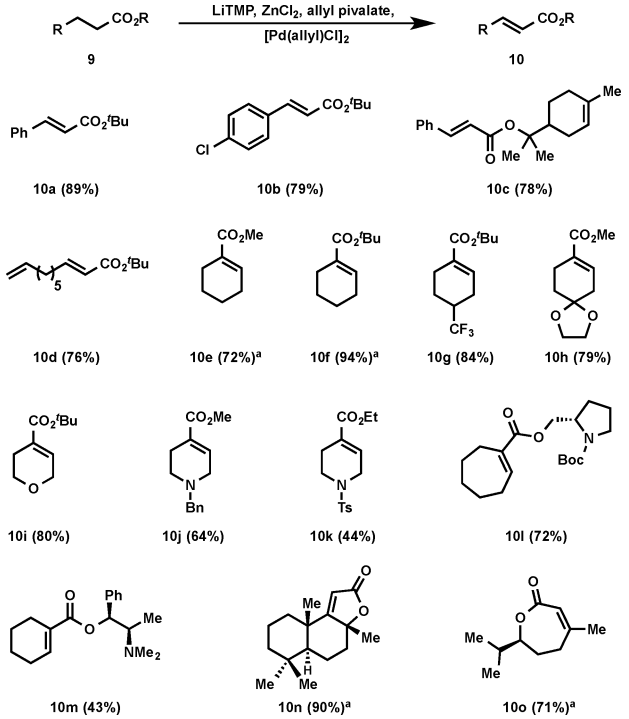
entry	base	additive	**10a** (%)[a]	**11** (%)[a]	**12** (%)[a]
1	LiTMP	–	20 (62)	20	17
2	LiTMP	$ZnCl_2$	90 (95)	nd	nd
3	$LiNCy_2$	$ZnCl_2$	69 (94)	nd	nd
4	LDA	$ZnCl_2$	89 (92)	nd	nd
5	TMPZnCl·LiCl	–	75 (84)	nd	nd
6[b]	LiTMP	$ZnCl_2$	83 (84)	nd	nd
7[c]	LiTMP	$ZnCl_2$	98 (>98)	nd	nd

[a]Determined by ^{1}H NMR analysis using 1,3,5-trimethoxybenzene as an internal standard. The conversions of **9a** are shown in parentheses. nd = not detected. [b]Allyl acetate was used instead of allyl pivalate as the oxidant. [c]$ZnCl_2$ was added at −40 °C. The isolated yield was 89%.

9a using lithium 2,2,6,6-tetramethylpiperidine (LiTMP) followed by treatement with (π-allyl)palladium chloride dimer and allyl pivalate as the oxidant delivered the desired dehydrogenation product **10a** in 20% yield (entry 1). Although the product was obtained under these conditions, incomplete conversion prevented chromatographic isolation from the starting material, which is of similar polarity. Furthermore, the undesired π-allyl substitution product, α-allyl ester **11**, was formed in a similar yield as the desired enoate. The lithium enolate also reacted directly with allyl pivalate, which afforded the Claisen condensation side product **12** in comparable yield. Reasoning that the condensation byproducts could be eliminated through the utilization of a less reactive metal enolate, $ZnCl_2$ was added at low temperature before the addition of allyl pivalate. Under these conditions, the condensation byproduct **12** was not observed by GC−MS or ^{1}H NMR spectroscopy after aqueous workup. Additionally, the α-allylation pathway was also suppressed by the inclusion of $ZnCl_2$,[16] and the dehydrogenated product was formed in 90% yield (entry 2). Attempts at optimization of the amide species resulted in less efficient oxidation (entries 3 and 4), which could be due to the possibility that the amide base alters the coordination sphere of the catalytically active Pd center. Alternatively, the speciation of the zinc enolate may be perturbed through the use of different bases. Utilization of the Knochel reagent TMPZnCl·LiCl resulted in a depreciation of the yield (entry 5). For the case of the cinnamyl substrate **9a**, allyl acetate was a competent but slightly less efficient oxidant (entry 6). Finally, when the enolate formation and transmetalation were conducted at −40 °C instead of at 0 °C, complete conversion was observed by ^{1}H NMR analysis, and the ^{1}H NMR yield was greater than 98%. The isolated yield for the formation of *tert*-butyl cinnamyl ester (**10a**) was 89%.[17]

With optimization of the reaction conditions complete, the scope of this process was explored (Scheme 2). Aryl chloride substrate **9b** also underwent efficient dehydrogenation. The dehydrogenation of the α-terpineol-derived ester **9c**, bearing a trisubstituted cyclic alkene, proceeded in 78% yield. A terminal alkene (**9d**) was also tolerated, resulting in a 76% yield of the desired unsaturated compound. The formation of cyclic alkenes was feasible in the cases of the methyl- and *tert*-butylcyclohexane carboxylates **10e** and **10f**. The marginally acidic trifluoromethyl-

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



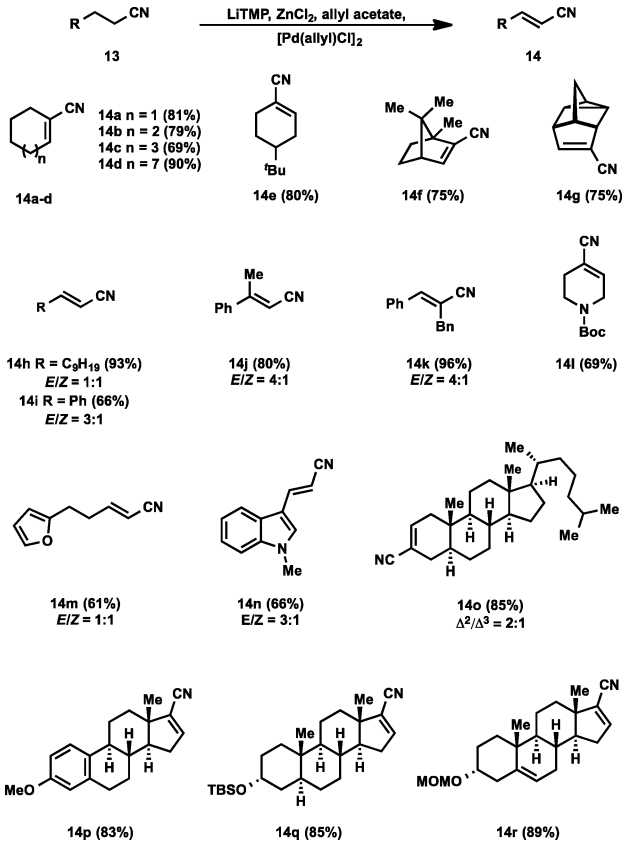
[a]Allyl acetate was used as the oxidant instead of allyl pivalate.

substituted cyclohexane ester (**9g**) was suitable, and the difluorosubstituted alkene side product was not observed under the standard reaction conditions. The ethereal ketal and tetrahydropyranyl functionality did not interfere, as observed by the formation of the α,β-unsaturated products **10h** and **10i** in 79 and 80% yield, respectively. The relatively basic *N*-benzylpiperidine functionality (**10j**) did not inhibit the dehydrogenation reaction. Likewise, the *N*-tosylpiperidine sulfonamide **10k** and the *N*-Boc-protected prolinol product **10l** could be obtained in moderate to good yields. Dehydrogenation of the *N*-methylpseudophedrine-derived ester **9m** proceeded smoothly. Although there are a few examples of one-step dehydrogenations of more acidic lactones, general synthetic methods have not emerged;[18] β-substituted lactones remain a particularly challenging substrate class.[19] Under the optimized conditions, sclareolide and menthone lactone were oxidized in good yields (**10n** and **10o**).

Complete conversion was also observed for a number of nitriles using a similar oxidation system; utilization of readily available allyl acetate provided slightly better results than allyl pivalate (Scheme 3).[20] Normal-, medium-, and large-sized cyclic alkanes were suitable substrates (**13a−e**), and the oxidation of strained bicyclic structures (**13f** and **13g**) also proceeded smoothly using the optimized procedure. Even the more challenging primary and secondary acyclic substrates can be dehydrogenated (**13h−k**) without the observation of condensation byproducts. Heterocyclic motifs, including a Boc-protected piperidine (**14l**), furan (**14m**), and indole (**14n**), were tolerated. A number of other functionalities remained intact under the basic reaction conditions, including a fused carbocycle (**14o**), protected phenol (**14p**), silyl ether (**14q**), and methoxymethyl ether (**14r**). Our observations to date indicate that a wide variety of functionalities can be tolerated under the moderately basic reaction conditions, in part because this

DOI: 10.1021/jacs.5b02243
J. Am. Chem. Soc. 2015, 137, 5875−5878

Scheme 3. Scope of Nitrile α,β-Dehydrogenation



dehydrogenation can proceed at ambient temperature. On larger scales a reduced loading of Pd could be used; **14a** could be produced in comparable yield on a 10 mmol scale with 0.5 mol % palladium catalyst.[21]

To gain insight into which step is turnover-limiting in order to improve the scope and efficiency of this transformation, we conducted parallel and intramolecular kinetic isotope effect (KIE) studies (Figure 1). If a turnover-limiting step were to involve either β-hydride elimination or reductive elimination, a primary KIE would be anticipated for the parallel oxidation of **9a** and the corresponding β,β-dideuterio substrate **9a**-d_2. Thus, in separate reaction vessels, **9a** and **9a**-d_2 were subjected to identical dehydrogenation conditions (Figure 1A); it was observed that **9a** was oxidized to **10a** at a greater rate than the corresponding dideuterio substrate. The KIE value determined from the average of three runs via the method of initial rates was 2.3 ± 0.1 (Figure 1A).[22] The observation of a primary parallel KIE rules out isotope-insensitive steps,[23] such as transmetalation and product dissociation, as turnover-limiting steps and instead requires that C−H bond cleavage or formation occurs in the turnover-limiting step or steps (i.e., β-hydride elimination[24] or reductive elimination).[25] Given the results of the parallel KIE experiments, if a smaller value were observed for the intramolecular KIE experiment, then the product-determining step, namely, the β-hydride elimination, could not be the turnover-limiting step. The intramolecular competition experiment with **9a**-d_1 (Figure 1B) exhibited a KIE value of 1.0 ± 0.1. The lack of a primary intramolecular KIE suggests that a reversible β-hydride elimination is followed by a turnover-limiting reductive elimination.[26] However, further theoretical and experimental mechanistic investigations are ongoing and will be reported in due course.

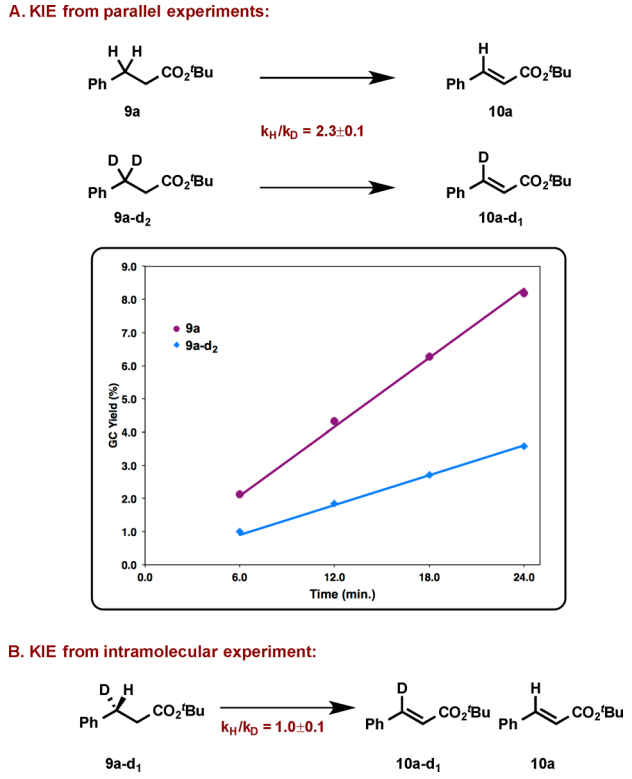


Figure 1. Kinetic isotope effect study.

This report details a mode of reactivity for (π-allyl)palladium catalytic intermediates that has facilitated the development of a methodology for the α,β-dehydrogenation of esters, lactones, and nitriles that features low catalyst loadings, an inexpensive oxidant, and ready purification of the products. Significant challenges remain in carbonyl α,β-dehydrogenation, including complementary methodologies to directly introduce unsaturation into other electron-withdrawing-group-containing substrates and selective dehydrogenation of substrates with multiple groups prone to oxidation. Studies along these lines and further exploration of catalysis using (π-allyl)palladium intermediates are underway.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental procedures and spectroscopic data for all new compounds, including ^{1}H and ^{13}C NMR spectra. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.5b02243.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

Financial support for this work was provided by Yale University and the NSF (GRFP to J.P.R.). The authors thank Prof. Robert Crabtree, Prof. Jonathan Ellman, Prof. Seth Herzon, Prof. Nilay Hazari, Prof. Patrick Holland, Prof. James Mayer, and Prof. Scott Miller for helpful discussions and the use of equipment and chemicals. We gratefully acknowledge Ms. Aneta Turlik for a

DOI: 10.1021/jacs.5b02243
J. Am. Chem. Soc. 2015, 137, 5875−5878

protocol check and Mr. Alexander Thompson for early experiments.

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(10) (a) Palladium cyanoalkyl complexes may exist as C- or N-bound monomers or higher-order aggregates. See: Culkin, D. A.; Hartwig, J. F. *J. Am. Chem. Soc.* **2002**, *124*, 9330 and references therein. (b) Palladium ester enolates usually exist as C-bound monomers or higher-order aggregates. See: Tian, G.; Boyle, P. D.; Novak, B. M. *Organometallics* **2002**, *21*, 1462.

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(13) Product dissociation may occur before or after the reductive elimination step. See: Porth, S.; Bats, J. W.; Trauner, D.; Giester, G.; Mulzer, J. *Angew. Chem., Int. Ed.* **1999**, *38*, 2015.

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(20) See the Supporting Information for selected reaction conditions for the α,β-dehydrogenation of nitriles.

(21) With the reported reaction conditions some functionality was not tolerated, including lactones that lack substitution at the β-position, protected amino acids, and α-aryl-substituted nitriles. Additionally, substrates were generally selected such that regioisomers could not be formed during the β-hydride elimination.

(22) In order to obtain initial rate data, the catalyst loading was decreased to 0.125 mol %. See the Supporting Information for details.

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DOI: 10.1021/jacs.5b02243
J. Am. Chem. Soc. 2015, 137, 5875−5878