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Letter

Aerobic Oxidative Dehydrogenation of Ketones to 1,4-Enediones

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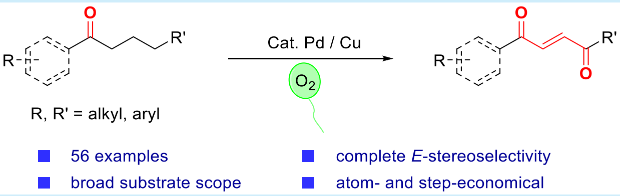
ABSTRACT: An efficient and unprecedented strategy for the synthesis of 1,4-enediones from saturated ketones has been developed via palladium-catalyzed oxidative dehydrogenation. The protocol employs molecular oxygen as the sole oxidant and represents an atom- and step-economic process. The approach showed broad substrate scope, good functional group tolerance, and complete *E*-stereoselectivity. The reaction mechanism has been investigated through deuterium-labeling experiments and intermediate experiments.



1,4-Enediones constitute a privileged structural motif of many bioactive natural products and pharmaceuticals (Figure 1).[1]

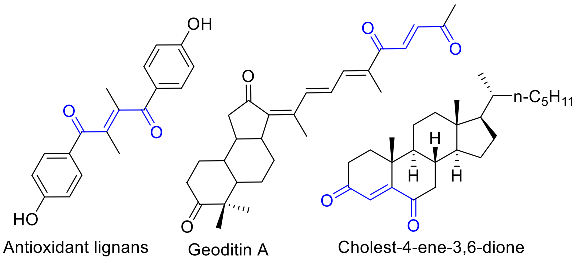
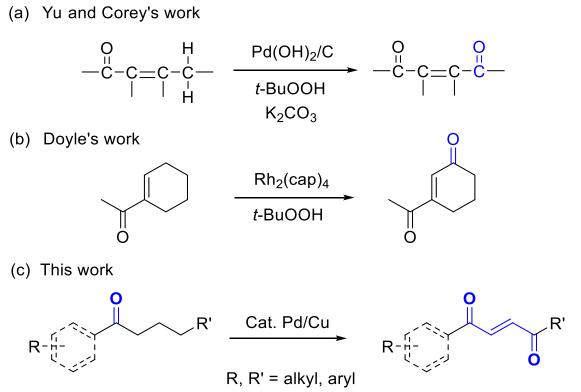


Figure 1. Examples of natural products with 1,4-enediones.

1,4-Enediones also serve as versatile precursors in the construction of various heterocycles such as furans, thiophenes, pyrroles, pyrazines, and indolizines.[2] In addition, by virtue of their distinctive electrophilicity and electron affinity, they have been used as highly reactive electrophiles and dienophiles to construct complex molecules.[3] Owing to their importance, the synthetic methodologies of 1,4-enediones have attached considerable attention, and remarkable progress has been made over the past decades.[4−9] Traditionally, 1,4-enediones were synthesized by oxidative ring opening of furan and thiophene derivatives,[5] decomposition of *α*-diazo carbonyl compounds,[6] and Wittig reaction.[7] In 2003, Yu and Corey developed an oxidative protocol to synthesize 1,4-enediones from *α*,*β*-enones utilizing a Pd(OH)$_2$-on-C/K$_2$CO$_3$/*t*-BuOOH system (Scheme 1a).[10] Later, Doyle et al. reported a dirhodium(II) caprolactamate catalyzed allylic oxidation protocol that also enabled the preparation of 1,4-enediones from *α*,*β*-enones (Scheme 1b).[11] Compared to the traditional methods, the oxidation dehydrogenative protocol of *α*,*β*-enones is much more concise, efficient, and atom- and step-economic.[12] Herein, we reported the first direct aerobic oxidative dehydrogenation of saturated ketones into 1,4-enediones (Scheme 1c).

Scheme 1. Oxidative Synthesis of 1,4-Enediones



Ketone is very common, cheap, and readily accessible substrate. Therefore, it would be a more valuable synthetic route to construct 1,4-enedione directly from ketone. However, the protocol is extremely challenging due to the selective cleavage of four inert C−H bonds in one step. Our study commenced with 1,4-diphenylbutan-1-one (**1aa**) as the model substrate. We initially chose Pd(OAc)$_2$ (10 mol %) as the catalyst and trifluoroacetic acid (TFA, 5.0 equiv) as the additive in DMSO at 80 °C for 48 h under O$_2$. To our delight, the desired product 1,4-enedione was obtained in 21% yield and with complete *E*-stereoselectivity (Table 1, entry 1).

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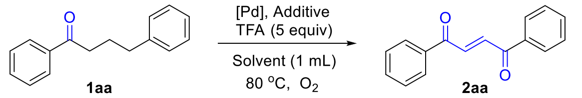
Table 1. Optimization of Reaction Conditions[a]



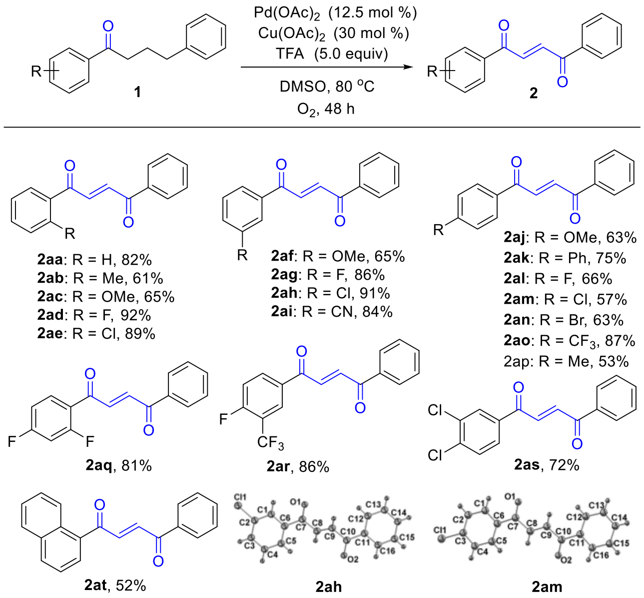
entry	Pd source	additive	TFA (equiv)	solvent	yield[b] (%)
1	$Pd(OAc)_2$		5.0	DMSO	21
2	$Pd(OAc)_2$	$Cu(OAc)_2$	5.0	DMSO	61
3	$Pd(TFA)_2$	$Cu(OAc)_2$	5.0	DMSO	58
4	$PdCl_2$	$Cu(OAc)_2$	5.0	DMSO	17
5	$Pd(PPh_3)_4$	$Cu(OAc)_2$	5.0	DMSO	47
6	$Pd(OH)_2$	$Cu(OAc)_2$	5.0	DMSO	57
7	$Pd_2(dba)_3$	$Cu(OAc)_2$	5.0	DMSO	59
8	-	$Cu(OAc)_2$	5.0	DMSO	NR
9[c]	$Pd(OAc)_2$	$Cu(OAc)_2$	5.0	other solvents	<20
10	$Pd(OAc)_2$	$Cu(OAc)_2\cdot H_2O$	5.0	DMSO	52
11	$Pd(OAc)_2$	Cu(OAc)	5.0	DMSO	57
12	$Pd(OAc)_2$	$CuSO_4$	5.0	DMSO	51
13	$Pd(OAc)_2$	$FeSO_4$	5.0	DMSO	50
14	$Pd(OAc)_2$	AgOAc	5.0	DMSO	16
15[d]	$Pd(OAc)_2$	$Cu(OAc)_2$	5.0	DMSO	8
16[e]	$Pd(OAc)_2$	$Cu(OAc)_2$	5.0	DMSO	<65
17[f]	$Pd(OAc)_2$	$Cu(OAc)_2$	5.0	DMSO	65
18[f]	$Pd(OAc)_2$	$Cu(OAc)_2$	-	DMSO	trace
19[f]	$Pd(OAc)_2$	$Cu(OAc)_2$	1.0	DMSO	15
20[f]	$Pd(OAc)_2$	$Cu(OAc)_2$	2.0	DMSO	53
21[f]	$Pd(OAc)_2$	$Cu(OAc)_2$	10.0	DMSO	64
22[f,g]	$Pd(OAc)_2$	$Cu(OAc)_2$	5.0	DMSO	82
23[f,h]	$Pd(OAc)_2$	$Cu(OAc)_2$	5.0	DMSO	83

[a] Reaction conditions: **1aa** (0.25 mmol), [Pd] (10 mol %), additive (10 mol %), solvent (1 mL), 80 °C for 48 h. [b] Isolated yield. [c] Other solvents: H_2O, acetone, CH_3CN, HOAc, EtOAc, DMF, formamide, piperidine, 1,4-dioxane, toluene, xylene, benzene, MeOH, EtOH, HFIP, $CHCl_3$, THF. [d] Without O_2. [e] Amount of $Cu(OAc)_2$: 1 mol % (48%), 5 mol % (54%), 50 mol % (64%), 1.0 equiv (59%), 2.0 equiv (57%). [f] 30 mol % $Cu(OAc)_2$ was used. [g] $Pd(OAc)_2$ (12.5 mol %). [h] $Pd(OAc)_2$ (15 mol %).

Gratifyingly, when $Cu(OAc)_2$ (10 mol %) as the co-catalyst was added into the reaction system, the yield was greatly improved to 61% (entry 2). We then carefully investigated other Pd sources such as $Pd(TFA)_2$, $PdCl_2$, $Pd(PPh_3)_4$, $Pd(OH)_2$, and $Pd_2(dba)_3$. $Pd(OAc)_2$ was proved to be more effective (entries 3−7). Subsequently, various solvents were screened, and DMSO provided a better yield (entry 9). Then with $Pd(OAc)_2$ as the catalyst and DMSO as the solvent, the other co-catalysts were investigated (entries 10−14). It should be mentioned that $Cu(OAc)_2\cdot H_2O$, CuOAc, $CuSO_4$, $FeSO_4$, and AgOAc were effective co-catalysts for the reaction, while $Cu(OAc)_2$ was still the best choice. Next, the amount of $Cu(OAc)_2$ and TFA was investigated. $Cu(OAc)_2$ (30 mol %) and TFA (5.0 equiv) provided the best results (entries 16−21). The yield was improved to 82% when the loading of $Pd(OAc)_2$ was increased to 12.5 mol % (entry 22), while a further increase to $Pd(OAc)_2$ (e.g., 15 mol %) did not improve the yield obviously (entry 23). It is worth mentioning that replacing O_2 with other hydrogen acceptors such as H_2O_2, 3-chloroperbenzoic acid, or allyl acetate led to inferior yields (see the Supporting Information). A series of control experiments were performed. The reaction could not proceed well in the absence of the $Pd(OAc)_2$, $Cu(OAc)_2$, O_2, or TFA (see the Supporting Information). Accordingly, the reaction conditions were optimized as follows: $Pd(OAc)_2$ (12.5 mol %), $Cu(OAc)_2$ (30 mol %), and TFA (5.0 equiv) under an oxygen atmosphere in DMSO at 80 °C.

With the optimal conditions in hand, we first investigated the effect of the substituents on the left aromatic ring (Scheme 2, **2aa**−**2at**). Both electron-donating and electron-withdrawing groups were well tolerated, furnishing the desired products in 52−92% yields. Notably, the substrates bearing electron-withdrawing groups (F, Cl, Br, CF_3, CN) exhibited much higher reactivity than that with electron-donating groups (Me, OMe, Ph). Substituents at the *otho*, *meta*, or *para* positions had no obvious effect on the reactions, although the substitution on the *otho* position possessed larger steric hindrance. Disubstitution was also well tolerated (**2aq**−**2as**). These functional substituent groups offered versatile handles for further transformations. Moreover, the naphthyl substrate afforded the desired product in 52% yield (**2at**). It is noteworthy that, in all cases, only *E*-isomers were obtained, and no *Z*-isomers could be detected by analyzing the reaction mixtures. The structures of **2ah** and **2am** were confirmed by single-crystal X-ray diffraction (see the Supporting Information).

Scheme 2. Substituents on the Left Aromatic Ring[a,b]

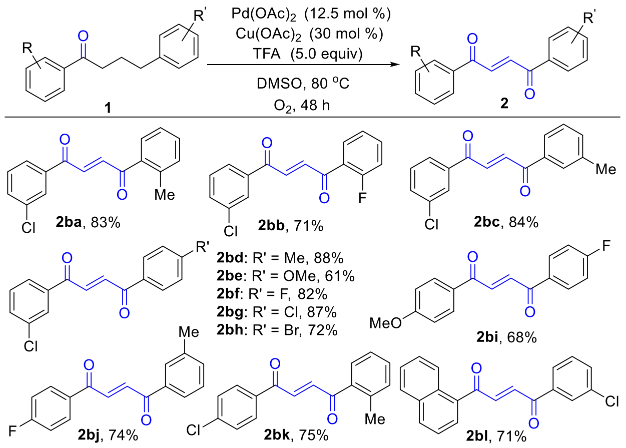


[a] Reaction conditions: **1** (0.5 mmol), $Pd(OAc)_2$ (12.5 mol %), $Cu(OAc)_2$ (30 mol %), and TFA (5.0 equiv) in DMSO (2 mL) at 80 °C for 48 h. [b] Isolated yields.

Next, we investigated the substituents on the right aromatic ring (Scheme 3). Delightfully, the reaction also exhibited good compatibility of various substituent groups. Substrates bearing Me, OMe, F, Cl, and Br all performed well, giving the desired 1,4-enediones with complete *E*-stereoselectivity in good to excellent yields (61−88%, **2ba**−**2bl**).

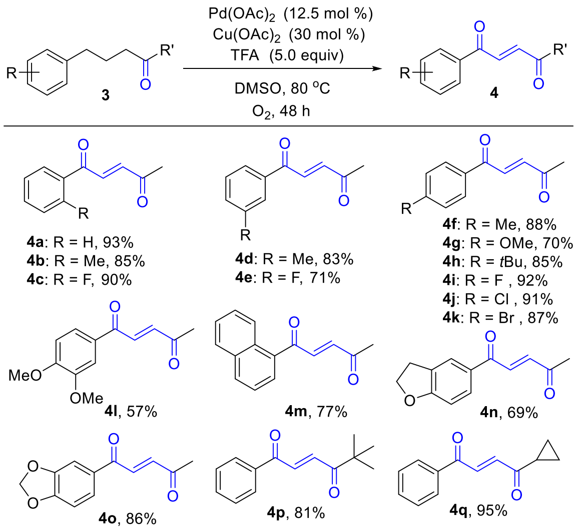
Then, we turned our attention to another kind of ketones, 5-arylpentan-2-ones (Scheme 4). As expected, these ketones were suitable substrates. These reactions were not sensitive to the electronic property and the position of substituent groups on aromatic rings. A broad range of functional groups such as Me, ^{t}Bu, OMe, F, Cl, and Br were compatible with these reaction conditions, and all of the substrates delivered the desired products in good to excellent yields (70−93%, **4a**−**4k**).

Scheme 3. Substituents on the Right Aromatic Ring[a,b]



[a]Reaction conditions: **1** (0.5 mmol), $Pd(OAc)_2$ (12.5 mol %), $Cu(OAc)_2$ (30 mol %), and TFA (5.0 equiv) in DMSO (2 mL) at 80 °C for 48 h. [b]Isolated yields.

Scheme 4. Scope of Ketones with a Monoaromatic Ring[a,b]



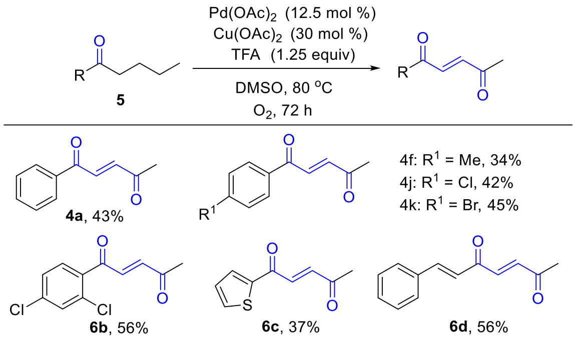
[a]Reaction conditions: **3** (0.5 mmol), $Pd(OAc)_2$ (12.5 mol %), $Cu(OAc)_2$ (30 mol %), and TFA (5.0 equiv) in DMSO (2 mL) at 80 °C for 48 h. [b]Isolated yields.

Note that active cyclopropane ring was intact in the reaction, demonstrating the reaction conditions were mild (**4q**). Again, complete *E*-stereoselectivity for the C=C double bond was exhibited.

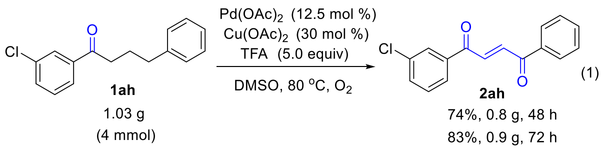
Finally, more challenging substrates, 1-arylpentan-1-ones, were investigated. Pleasingly, these substrates afforded the corresponding 1,4-enediones in 34–56% yields (Scheme 5).[13] A heterocyclic substrate, such as 1-(thiophene-2-yl)pentan-1-one (**5c**), was also suitable for the transformation. It was interesting that vinyl ketone, 1-phenylhept-1-en-3-one (**5d**), reacted well to give the desired product **6d** in 56% yield. However, under the current reaction conditions, 2-hexanone, 2-octanone, and cyclohexanone gave messy reactions.

To test the practicality of this method, a gram-scale reaction was carried out. On a 4 mmol scale, the desired product **2ah** was obtained in 74% yield for 48 h. With a longer reaction time, the yield could reach 83% (eq 1).

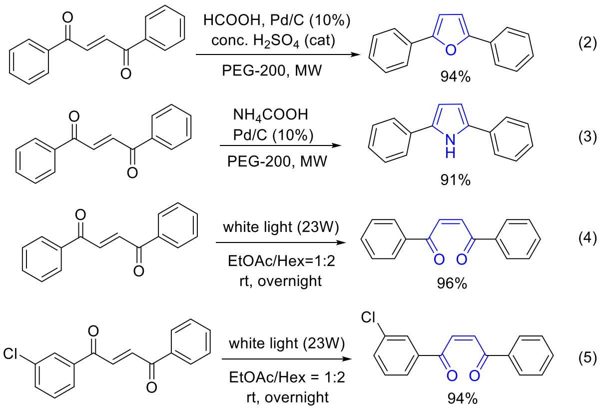
Scheme 5. Scope of Other Ketones[a,b]



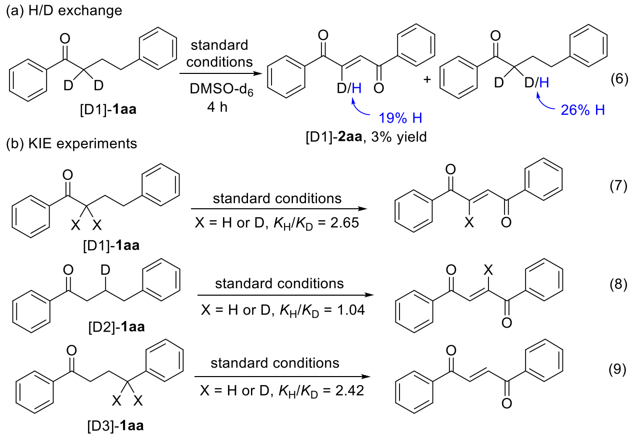
[a]Reaction conditions: **5** (0.5 mmol), $Pd(OAc)_2$ (12.5 mol %), $Cu(OAc)_2$ (30 mol %), and TFA (1.25 equiv) in DMSO (2 mL) at 80 °C for 72 h. [b]Isolated yields.



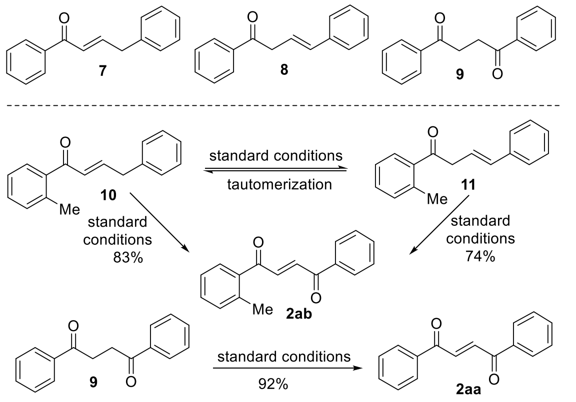
To further demonstrate the synthetic utilities of this protocol, the direct dehydrogenation products were further transformed into 2,5-diphenylfuran and 2,5-diphenylpyrrole (eqs 2 and 3).[2b,c] The (*E*)-1,4-enediones were also transformed into the corresponding *Z*-isomers by irradiation with white light (eqs 4 and 5).[4e]



To gain insight into the reaction mechanism, we carried out a series of deuterium-labeling experiments. We conducted the experiment with DMSO-d_6 under the standard reaction conditions, delivering the deuterium-labeling product in 3% yield with 19% H incorporation at the α position. In addition, the recovered [D1]-**1aa** was found to contain 26% H at the α position (eq 6). The occurrence of H/D exchange in [D1]-**1aa** indicated that the ketone underwent the enolization. Additionally, kinetic isotope effect (KIE) experiments were carried out. The KIE values of two parallel reactions of the α and γ positions were found to be 2.65 and 2.42, respectively (eqs 7 and 9). The intramolecular KIE value for the reaction of the β position was 1.04 (eq 8). These results indicated that the cleavage of the α-C–H and γ-C–H bond should be involved in the rate-determining step, while the elimination of β-C–H bond was not rate limiting. In the reaction system of compound **1**, we successively detected α,β-unsaturated ketone (**7**), vinyl ketone (**8**), and diketone (**9**) (Scheme 6). Then we



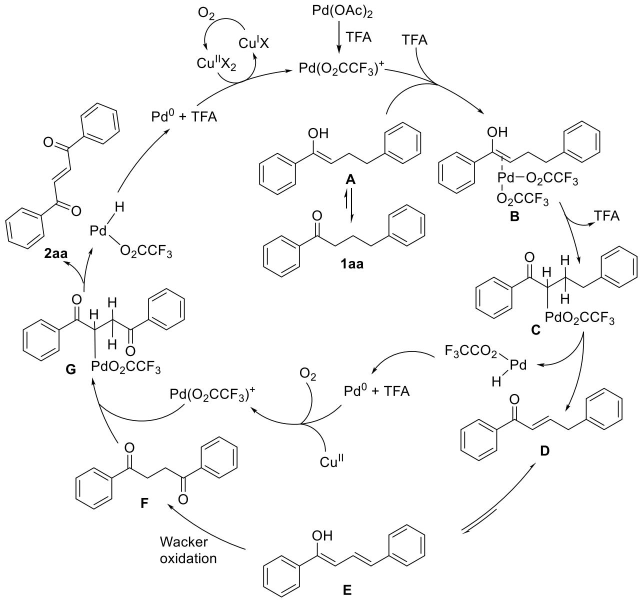
Scheme 6. Syntheses of 1,4-Enediones from Other Ketones



prepared compounds **9**, **10**, and **11**, respectively. Under the standard reaction conditions, α,β-unsaturated ketone (**10**) and vinyl ketone (**11**) could tautomerize and both could generate 1,4-enedione (**2ab**) in 83% and 74% yields, respectively. Diketone (**9**) also underwent the dehydrogenation into 1,4-enedione (**2aa**) in 92% yield under the standard reaction conditions.

On the basis of these results and the related literature,[12,14−18] a tentative mechanism for the Pd-catalyzed dehydrogenation of ketones to produce 1,4-enediones was proposed, as shown in Scheme 7. The active $Pd(O_2CCF_3)^+$ is generated in situ by the treatment of $Pd(OAc)_2$ with TFA.[14] Simultaneously, the ketone undergoes enolization, formation of palladium enolate, and β-hydride elimination to afford the α,β-unsaturated ketone **D** and Pd^{II}-hydride intermediate that eliminates a TFA and then is reoxidized to $Pd(O_2CCF_3)^+$ by O_2 in the presence of TFA.[12g−i,15] Cu^{II} can facilitate the catalytic cycle of Pd^0 to Pd^{II}.[16] Then α,β-unsaturated ketone **D** isomerizes into diene **E**. The right C═C double bond of diene **E** undergoes similar Wacker oxidation[17,18] and thereby generates 1,4-diketone **F** which then proceeds the same palladium enolate and β-hydride elimination to produce 1,4-enedione. The great *E*-stereoselectivity of the C═C double bond was ascribed to *syn* β-hydride elimination of palladium enolate.[12n] Pd^{II} hydride intermediate proceeds by the same process to regenerate $Pd(O_2CCF_3)^+$ and complete the catalytic cycle.

Scheme 7. Proposed Mechanism



In conclusion, we have developed an unprecedented and concise protocol for the synthesis of 1,4-enediones via palladium-catalyzed oxidative dehydrogenation of saturated ketones. The protocol employs molecular oxygen as the sole oxidant and represents an atom- and step-economic process. The reaction is completely *E*-stereoselective and possesses broad substrate scope and good tolerance of functional groups. In addition, the products can be readily transformed into 2,5-diarylfuran, 2,5-diarylpyrrole, and the corresponding *Z*-isomers. Further studies to expand the reaction and their applications as well as investigations of the detailed mechanism are now in progress.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c04174.

Experimental details, characterization data, copies of ^1H, ^{13}C NMR spectra, and the original HRMS analysis reports (PDF)

Accession Codes

CCDC 2017898 and 2038537 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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