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Direct Aerobic α, β-Dehydrogenation of Aldehydes and Ketones with a $Pd(TFA)_2$/4,5-Diazafluorenone Catalyst†

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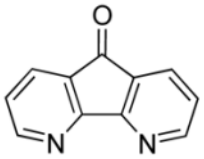
Abstract

The direct α, β-dehydrogenation of aldehydes and ketones represents an efficient alternative to stepwise methods to prepare enal and enone products. Here, we describe a new $Pd(TFA)_2$/4,5-diazafluorenone dehydrogenation catalyst that overcomes key limitations of previous catalyst systems. The scope includes successful reactivity with pharmaceutically important cyclopentanone and flavanone substrates, as well as acyclic ketones. Preliminary mechanistic studies compare the reactivity of this catalyst to previously reported dehydrogenation catalysts and reveal that cleavage of the α-C–H bond of the ketone is the turnover-limiting step of the catalytic mechanism.

Enones and other α,β-unsaturated carbonyl compounds are important intermediates in the synthesis of pharmaceuticals and other complex organic molecules.[1] Such compounds are frequently prepared via stepwise protocols, including α-bromination-dehydrobromination,[2] α-selenylation followed by oxidation to a selenoxide and elimination, [3,4] and formation of a silyl enol ether, followed by Pd^{II}-mediated dehydrosilylation ("Saegusa" oxidation). [5] Direct α,β-dehydrogenation of ketones and aldehydes has also been achieved using stoichiometric reagents, such as 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ)[6] and 2-iodoxybenzoic acid (IBX).[7,8] Pd^{II}-catalyzed direct dehydrogenation of carbonyl compounds with O_2 as the oxidant represents an appealing atom-economical alternative to these methods.[9,10] Here, we report the discovery of a new $Pd(TFA)_2$/4,5-diazafluorenone (TFA = trifluoroacetate) catalyst system that overcomes key limitations of previously reported catalysts for these reactions. Comparison between this catalyst system and other catalysts, as well as preliminary mechanistic insights into these reactions are described below.



4,5-diazafluoren-9-one

Early studies of Pd-catalyzed dehydrogenation reactions focused on cyclohexanone derivatives;[11] however, low yields and/or limited substrate scope restricted the synthetic utility of these methods. We recently reported a $Pd(DMSO)_2(TFA)_2$ catalyst system that overcomes many of these limitations and enables aerobic dehydrogenation of a variety of substituted cyclohexanones and other cyclic ketones, including heterocycles (Scheme 1). [12] Independently, we discovered a different Pd^{II} catalyst system, $Pd(TFA)_2$/2-Me_2Npy (2-Me_2Npy = 2-(*N*,*N*-dimethylamino)pyridine), that affords substituted phenols via aerobic

†Electronic supplementary information (ESI) available: Experimental procedures and compound characterization data.

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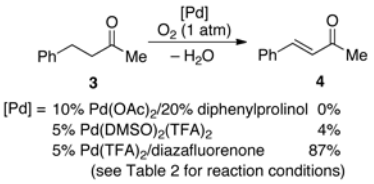
dehydrogenation of cyclohexanone and cyclohexenone derivatives (Scheme 1).[13] Subsequent efforts in our lab to apply these methods to specific target molecules of interest have revealed limitations. In particular, the bicyclic cyclopentanone derivative **2** is a key precursor to a pharmaceutically important anatagonist of the metabotropic glutamate receptor (mGluR) (Scheme 2).[14] This molecule was previously prepared from **1** using IBX as the oxidant.[14b] An aerobic dehydrogenation method could provide a scalable route to this molecule,[15] but efforts to apply the $Pd(DMSO)_2(TFA)_2$ and $Pd(TFA)_2$/2-Me_2Npy catalyst systems to this reaction resulted in unsatisfactory yields (≤37%, Scheme 2). Dehydrogenation of acyclic aldehydes and ketones have less precedent than reactions of cyclic ketones. 3-Arylpropanal (i.e., hydrocinnamaldehyde) derivatives were recently shown to undergo $Pd(OAc)_2$-catalyzed aerobic dehydrogenation in the presence of an amine cocatalyst, possibly via *in situ* formation of an enamine intermediate (Scheme 3).[16] Analogous ketones (e.g., R = Me) were unreactive, however.

Efforts to address these limitations were initiated by exploring possible Pd catalysts for aerobic dehydrogenation of cyclopentanone **1** at 80 °C under 1 atm of O_2. As noted above, the previously reported $Pd(DMSO)_2(TFA)_2$ catalyst exhibited poor reactivity (Table 1, entry 1). Use of the $Pd(TFA)_2$/2-Me_2Npy catalyst system in DMSO or $Pd(TFA)_2$ in the absence of an added ligand led to a slightly improved result (37% and 32% yield, respectively; entries 2 and 3). Other Pd^{II} sources were less effective than $Pd(TFA)_2$ (entries 4–7), and no reactivity was observed with traditional heterogeneous Pd catalysts (entries 8 and 9). A number of ancillary ligands were tested in combination with $Pd(TFA)_2$ (entries 10–19). In general, the ancillary ligands had little benefit or were deleterious relative to the reactivity of $Pd(TFA)_2$ alone. The best yield was observed with 4,5-diazafluorenone as a ligand; however, the yield maximized at 40% when the reaction was performed under 1 atm O_2 (entry 20). We reasoned that catalyst stability and turnover numbers could be improved by increasing the pressure of O_2 (used as a mixture of 9% O_2 in N_2 to minimize safety risks). Upon testing this hypothesis, a 61% yield of cyclopentenone product **2** was obtained with the $Pd(TFA)_2$/2-Me_2Npy catalyst system when the reaction was carried out under 7.2 atm O_2 (entry 21). The optimal yield, however, was achieved with the 4,5-diazafluorenone ligand (85% GC, 79% isolated yield; entry 22). The beneficial effect of diazafluorenone in this reaction complements our recent discovery of the utility of this ligand in other Pd-catalyzed aerobic oxidation reactions (allylic C–H oxidation and direct biaryl coupling).[17]

The success of $Pd(TFA)_2$/4,5-diazafluorenone in the dehydrogenation of **1** prompted us to explore the utility of this catalyst system in reactions of acyclic ketones. As noted above, previously reported catalyst systems were essentially unreactive in the dehydrogenation of benzylacetone (**3**, Eqn. (1)): 0% yield of **4** with $Pd(OAc)_2$/diphenylprolinol[16a] and 4% yield with $Pd(DMSO)_2(TFA)_2$.[12] The poor reactivity of ketone **3** relative to hydrocinnamaldehyde (cf. Scheme 3) probably reflects the higher pK_a of the α-C–H bond of ketones relative to aldehydes (see further discussion below).[18] In contrast, use of the optimized $Pd(TFA)_2$/diazafluorenone catalyst system to the dehydrogenation of **3** afforded enone **4** in 87% isolated yield (eqn (1)). With this substrate, the reaction was compatible with 1 atm O_2. To the best of our knowledge, this reaction represents the first example of aerobic dehydrogenation of acyclic ketones.



(1)

Apigenin is a flavone natural product that has attracted considerable interest as a cancer chemopreventative agent.[19] The saturated precursor, naringenin, and related analogs can be readily obtained via condensation of simple benzaldehyde and *o*-acetylphenol precursors (Scheme 4).[20] An apigenin analog was recently prepared in 66% yield by DDQ-promoted dehydrogenation of the corresponding naringenin derivative.[21] The $Pd(DMSO)_2(TFA)_2$ catalyst system was completely unreactive in an attempted dehydrogenation of naringenin, whereas the $Pd(TFA)_2$/4,5-diazafluorenone catalyst afforded the desired product in 81% yield (Scheme 4).

A number of related acyclic β-arylaldehyde and -ketone substrates and chroman-4-one and flavanone derivatives underwent successful aerobic dehydrogenation with this catalyst system (Table 2). Hydrocinnamaldehyde underwent facile dehydrogenation to afford cinnamaldehyde in 91% yield (entry 1). A small amount of benzaldehyde (8%) was formed as a byproduct in this reaction. Other benzyl acetone derivatives, including those with electron-donating and electron-withdrawing substituents, and a phenyl ketone derivative underwent successful dehydrogenation (Table 2, entries 2–5). Dehydrogenation of methyl 3-benzoylpropanoate afforded the expected alkene in a 13:1 *trans:cis* isomeric ratio (entry 6). Chromones [22] and flavones [23] have important biological activities, and the $Pd(TFA)_2$/4,5-diazafluorenone catalyst exhibits excellent reactivity in the dehydrogenative synthesis of these compounds (Table 2, entries 7–10), including chloro- and fluoro-substituted derivatives.

Preliminary efforts to expand the substrate scope beyond that indicated above have revealed some limitations. Acyclic substrates lacking an aryl group in the β position are susceptible to further dehydrogenation at the γ,δ-position, resulting in a mixture of enone and dienone products. For example, an unoptimized reaction of 2-octanone afforded oct-3-en-2-one in 17% yield and octa-3,5-dien-2-one in 6% yield after 18 h, with 35% recovered starting material. The reaction of propyl phenyl ketone, which cannot undergo a second dehydrogenation step, afforded the enone in only low yield (20%) after 48 h. The low substrate conversion in this reaction possibly reflects deactivation of the catalyst by formation of an inactive Pd-π-allyl species. Finally, esters such as ethyl hydrocinnamate were unreactive under the optimized conditions and increasing the reaction temperature to 100 °C failed to promote reactivity. This lack of reaction probably reflects the reduced acidity of the α-C–H bond of esters relative to ketones and aldehydes.[18]

Future efforts to expand the scope of these reactions will benefit from mechanistic insights, and a thorough study of the different aerobic dehydrogenation catalysts has been initiated. A few preliminary results are worth noting. The $Pd(TFA)_2$/4,5-diazafluorenone catalyst was evaluated in the dehydrogenation of 4-*tert*-butylcyclohexanone (Table 3) in order to compare its reactivity with the recently reported $Pd(DMSO)_2(TFA)_2$[12] and $Pd(TFA)_2$/2-Me_2Npy catalyst systems.[13] Analysis of the reaction time courses for each of these reactions shows that the $Pd(TFA)_2$/4,5-diazafluorenone catalyst behaves similarly to the $Pd(TFA)_2$/2-Me_2Npy catalyst.[24] Both of these catalysts show a preference for formation of the phenol

product, owing to faster dehydrogenation of the cyclohexenone to the phenol relative to the initial dehydrogenation step to afford the enone. In contrast, the first dehydrogenation step (k_1) is much faster than the second (k_2) when $Pd(DMSO)_2(TFA)_2$ is used as the catalyst, resulting in high selectivity for the enone product. The basis for these reactivity differences remains to be elucidated, but the results are consistent with the observation of single and double dehydrogenation products in the reaction of 2-octanone with the $Pd(TFA)_2$/4,5-diazafluorenone catalyst system (see above).

Deuterium kinetic isotope effects in the reaction of benzylacetone were evaluated by comparing the reaction rate of the parent substrate **3** with those of the α- and β-deuterated derivatives **3-*d*$_5$** and **3-*d*$_2$** (Scheme 5).[25] A primary kinetic isotope effect (k_H/k_D = 2.6) was observed with the α-deuterated substrate, whereas a negligible isotope effect was observed from deuteration of the β position. This observation suggests that cleavage of the α-C–H bond is the turnover-limiting step of the catalytic reaction while β-hydride elimination from a presumed Pd-enolate intermediate is comparatively fast. These results are consistent with the correlation between the acidity of the α-C–H bond of the substrate and catalytic reactivity: aldehydes > ketones ≫ esters. A proposed catalytic cycle is shown in Scheme 6. The reaction is initiated by turnover-limiting "activation" (i.e., deprotonation) of the α-C–H bond. Subsequent fast β-hydride elimination from a Pd^{II}-enolate intermediate affords the enone product and a Pd^{II}–hydride intermediate.[26] The latter species can be oxidized by O_2 to regenerate the Pd^{II} catalyst (Scheme 6).[27]

In summary, we have identified a new catalyst, $Pd(TFA)_2$/4,5-diazafluorenone, that significantly expands the utility of direct aerobic dehydrogenation of carbonyl compounds. Noteworthy results include the first demonstration of aerobic dehydrogenation of acyclic ketones and the application of this catalyst to pharmaceutically important target molecules that were unreactive with previously reported catalysts.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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24. The reactions were monitored for 24 h, during which > 50% conversion was achieved for each reaction. The rate constants were obtained by kinetic simulation of the reaction timecourses to a simple A → B → C sequential kinetic model. See Supplementary Information for kinetic profiles.
25. Oxidation of the 3-d_5 was carried out in DMSO-d_6 to avoid background α–H/D exchange.
26. A Pd^0 species, formed from a Pd^{II}–H intermediate, has been isolated from a “Saegusa”-type oxidation reaction: Porth S, Bats JW, Trauner D, Giester G, Mulzer J. Angew Chem Int Ed. 1999; 38:2015.
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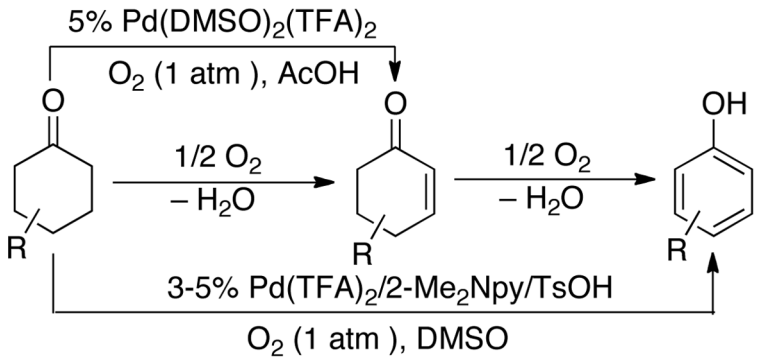
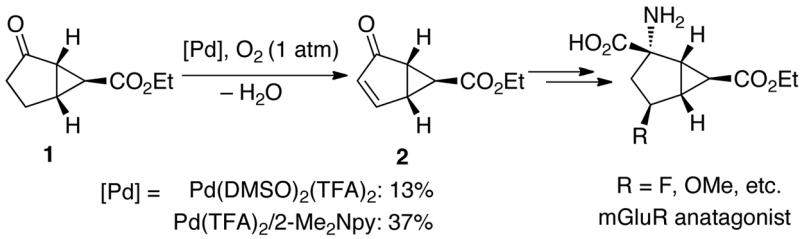
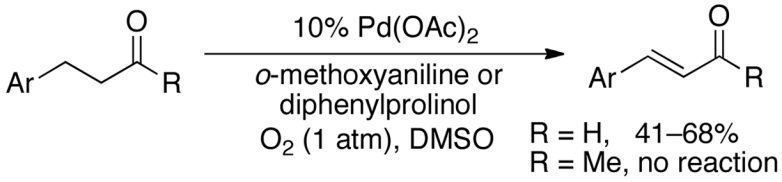


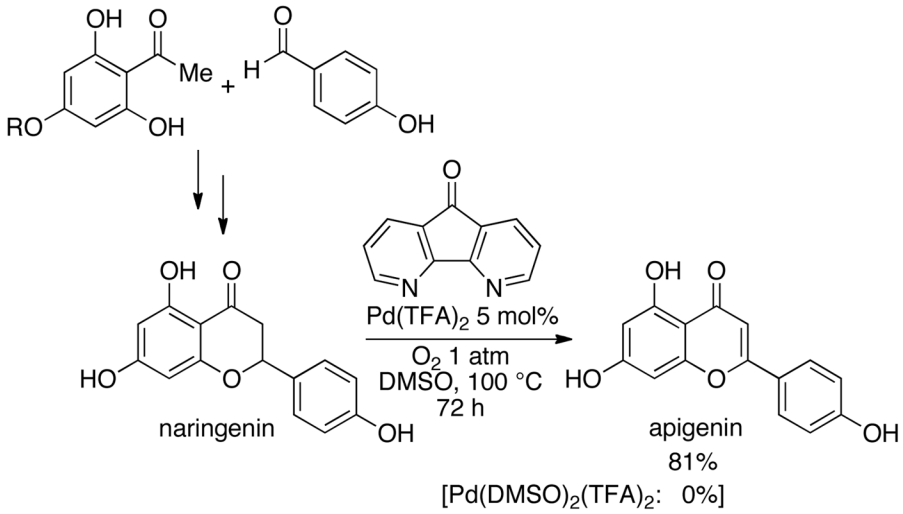
Scheme 1.
Palladium-catalyzed dehydrogenation of cyclohexanones



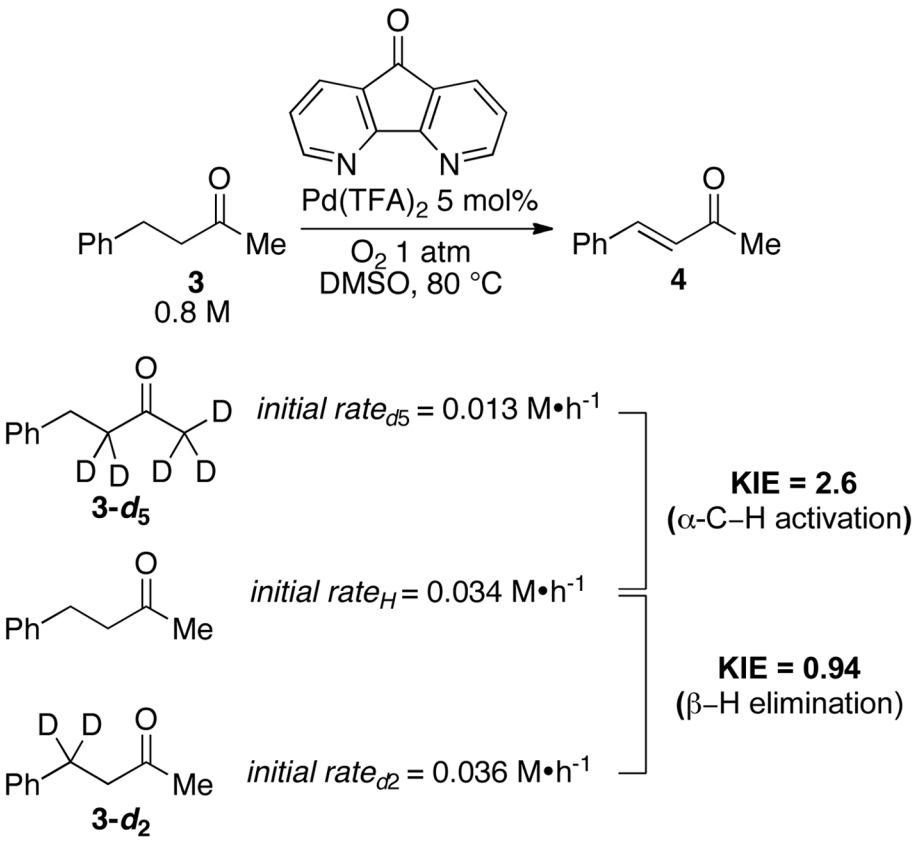
Scheme 2.
Attempted dehydrogenation of a pharmaceutically important cyclopentanone derivative



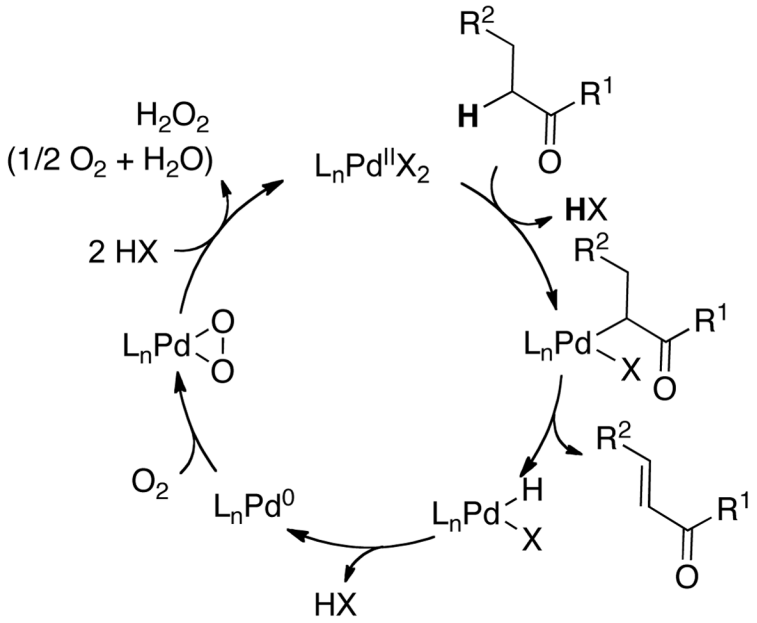
Scheme 3.
Dehydrogenation of β-aryl carbonyl compounds



Scheme 4.
Aerobic dehydrogenation of naringenin with the $Pd(TFA)_2$/diazafluorenone catalyst system.



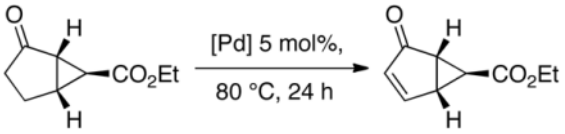
Scheme 5.
Kinetic isotope effects based on independent initial-rate measurements



Scheme 6.
Proposed catalytic cycle for Pd-catalyzed α,β-dehydrogenation of carbonyl compounds

Table 1

Catalyst optimization for the aerobic dehydrogenation of **1**[a]



1 **2**

entry	Pd source	ligand	solvent	yield (%)[b]
1	$Pd(TFA)_2$	DMSO	HOAc	13
2	$Pd(TFA)_2$	2-Me_2Npy/TsOH	DMSO	37
3	$Pd(TFA)_2$	none	DMSO	32
4	$Pd(OAc)_2$	none	DMSO	21
5	$Pd(BF_4)_2(CH_3CN)_4$	none	DMSO	21
6	$PdCl_2$	none	DMSO	6
7	$Pd_2(dba)_3$	none	DMSO	8
8	Pd/C	none	DMSO	0
9	$Pd(OH)_2$/charcoal	none	DMSO	0
10	$Pd(TFA)_2$	pyridine	DMSO	27
11	$Pd(TFA)_2$	2-F pyridine	DMSO	31
12	$Pd(TFA)_2$	2-MeO-pyridine	DMSO	32
13	$Pd(TFA)_2$	3-NO_2-pyridine	DMSO	21
14	$Pd(TFA)_2$	2,2′-bipyridine (bpy)	DMSO	33
15	$Pd(TFA)_2$	6,6′-Me_2bpy	DMSO	15
16	$Pd(TFA)_2$	5,5′-Me_2bpy	DMSO	12
17	$Pd(TFA)_2$	phenanthroline	DMSO	36
18	$Pd(TFA)_2$	2,9-Me_2phenanthroline	DMSO	14
19	$Pd(TFA)_2$	bipyrimidine	DMSO	19
20	$Pd(TFA)_2$	4,5-diazafluorenone	DMSO	40
21	$Pd(TFA)_2$	2-Me_2Npy/TsOH	DMSO	61[c]
22	**$Pd(TFA)_2$**	**4,5-diazafluorenone**	**DMSO**	**85[c][79][d]**

[a]Conditions: [**1**] = 0.2 M (16.8 mg, 0.1 mmol), 5% catalyst (0.005 mmol), solvent (0.5 mL), 1 atm O_2, 80 °C, 24 h.

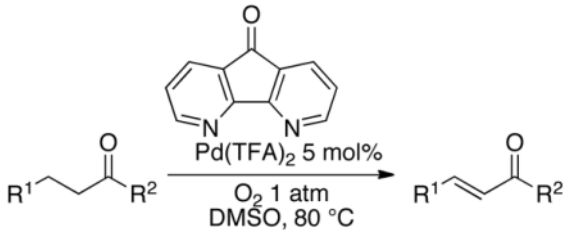
[b]Determined by GC.

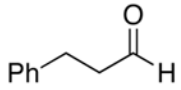
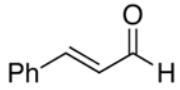
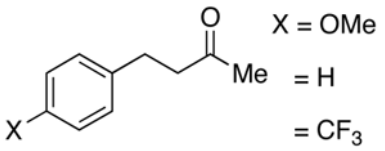
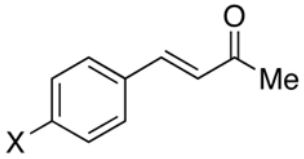
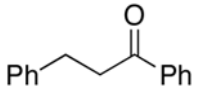
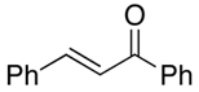
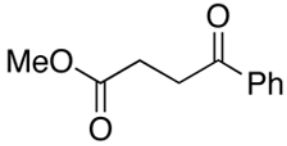
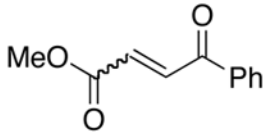
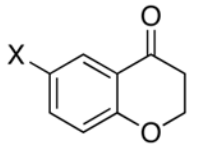
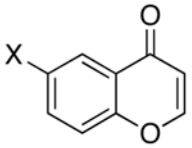
[c]7.2 atm O_2 (9% in N_2), 48 h.

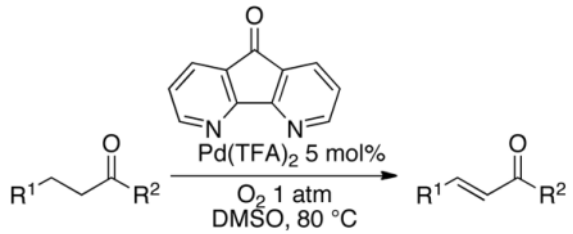
[d]Isolated yield.

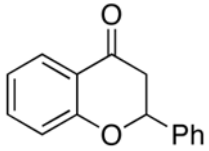
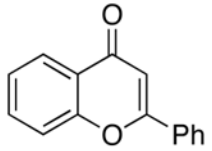
Table 2

Pd-catalyzed aerobic dehydrogenation of aldehydes and ketones[a]



entry	substrate	time (h)	temp (°C)	enone	yield (%)[b]
1		8	80		91
2	 X = OMe	48	80		83
3	= H	48	80		87
4	= CF_3	48	100		86
5		36	100		87
6		48	100	 *trans : cis* = 13 : 1	74
7	 X = H	32	80		96
8	= Cl	32	80		94
9	= F	32	80		94



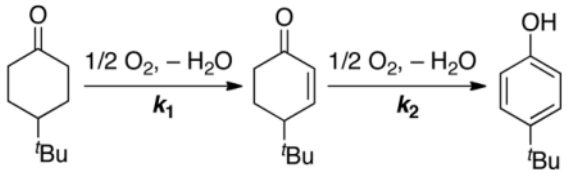
entry	substrate	time (h)	temp (°C)	enone	yield (%)[b]
10		24	100	 Flavone	88

[a] Conditions: [substrate] = 0.8 M (0.4 mmol), $Pd(TFA)_2$ (6.6 mg, 0.02 mmol), 4,5-diazafluorenone (3.6 mg, 0.02 mmol), DMSO (0.5 mL), 1 atm O_2.

[b] Isolated yield.

Table 3

Comparison of Pd catalysts in the oxidation of 4-*tert*-butylcyclohexanone[a]



Catalyst	k_1 (h^{-1})	k_2 (h^{-1})	k_1/k_2
$Pd(TFA)_2$/2-Me_2Npy/TsOH	0.086	0.14	0.61
$Pd(DMSO)_2(TFA)_2$	0.19	0.0057	33
$Pd(TFA)_2$/4,5-diazafluorenone	0.036	0.099	0.36

[a]Conditions: [substrate] = 0.2 M (15.4 mg, 0.1 mmol), [catalyst] = 0.05 M (0.005 mmol), solvent (0.5 mL), 1 atm O_2, 80 °C.