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Synthesis of Cyclic Enones via Direct Palladium-Catalyzed Aerobic Dehydrogenation of Ketones

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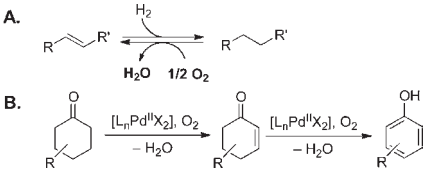
Supporting Information

ABSTRACT: α,β-Unsaturated carbonyl compounds are versatile intermediates in the synthesis of pharmaceuticals and biologically active compounds. Here, we report the discovery and application of $Pd(DMSO)_2(TFA)_2$ as a catalyst for direct dehydrogenation of cyclohexanones and other cyclic ketones to the corresponding enones, using O_2 as the oxidant. The substrate scope includes heterocyclic ketones and several natural-product precursors.

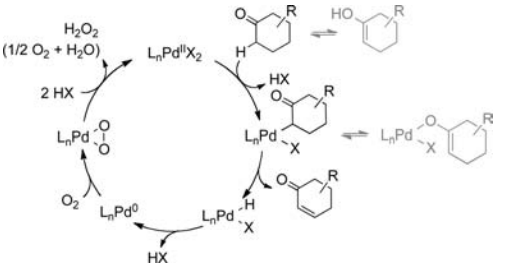
Molecular hydrogen and oxygen are the quintessential reducing and oxidizing agents, respectively. Whereas hydrogenation reactions are commonplace in multistep organic synthesis, aerobic oxidation reactions are seldom used. For example, numerous highly selective methods and sophisticated catalysts exist for the hydrogenation of alkenes;[1] however, complementary aerobic dehydrogenation methods for alkene synthesis are unavailable[2] (Scheme 1A). We recently reported a method for Pd^{II}-catalyzed aerobic dehydrogenation of cyclohexanones to phenols.[3] These reactions proceed via a cyclohexenone intermediate that undergoes further dehydrogenation to the phenol under the reaction conditions (Scheme 1B). Here, we report the identification of a different Pd catalyst system that enables selective dehydrogenation of cycloketones to afford enones rather than phenols. Cyclohexenones and related α,β-unsaturated carbonyl compounds are key intermediates in the synthesis of pharmaceuticals and other biologically active compounds.[4] Their preparation typically requires two or more steps[5−7] and/or the use of stoichiometric reagents, such as 2-iodoxybenzoic acid (IBX)[8,9] or 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ).[10] Catalytic methods for aerobic dehydrogenation of ketones to enones would provide appealing, atom-economical alternatives to these stoichiometric methods.

The synthesis of enones via Pd^{II}-mediated dehydrosilylation of silyl enol ethers was reported by Ito and Saegusa in 1978.[6a] In some cases, these reactions have been achieved with catalytic Pd^{II},[6b,c] but the use of ≥0.5 equiv of Pd^{II} is commonly required to obtain good yields of products.[4b,c,11] Methods for direct Pd^{II}-catalyzed dehydrogenation of ketones have been pursued as an alternative to Saegusa reactions; however, previous examples exhibit quite limited substrate scope.[12−15] Both Saegusa-type dehydrosilylation and direct dehydrogenation reactions are expected to be initiated by formation of a Pd^{II}-enolate, followed by β-hydride elimination to afford the enone product (Scheme 2).[16] The resulting Pd^{II}—hydride intermediate can be oxidized by O_2 to regenerate the Pd^{II} catalyst.[17,18] Recent advances in Pd^{II}-catalyzed aerobic oxidation and C—H functionalization reactions[19] provided useful starting points for our investigation of dehydrogenation catalysts.

Scheme 1. Hydrogenation/Dehydrogenation of C—C Bonds (A) and Pd-Catalyzed Dehydrogenation of Cyclohexanones (B)



Scheme 2. Proposed Mechanism for Pd^{II}-Catalyzed Dehydrogenation of Cyclic Ketones



Our initial catalyst screening efforts focused on the dehydrogenation of 4-*tert*-butylcyclohexanone **1** under relatively mild conditions: 1 atm O_2, 80 °C, 12 h (Table 1).[20] Use of the recently reported Pd^{II} catalyst, $Pd(TFA)_2$/2-*N*,*N*-dimethylaminopyridine (2-Me_2Npy), for conversion of cyclohexanones to phenols[3] resulted in incomplete conversion and, as expected, favored formation of phenol **3** over the enone **2** (entry 1). The best previous catalyst for the conversion of cyclohexanone to cyclohexenone, reported by Tsuji and co-workers,[12e] forms enone **2** selectively, but only in 19% yield under these conditions (entry 2). Improved results were obtained by using catalytic $Pd(OAc)_2$ in DMSO,[21,22] affording a mixture of enone and phenol products in 63% and 14% yield, respectively (entry 3). The best results were obtained by using DMSO as a ligand (10 mol %) with $Pd(TFA)_2$ (5 mol %; TFA = trifluoroacetate) in acetic acid (entry 7). This catalyst system led to a 91% yield of the desired enone **2**. Replacing DMSO with other monodentate and bidentate

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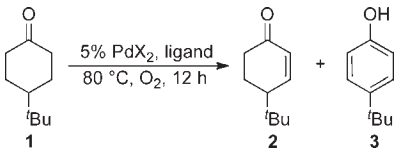
ligands led to inferior results (entries 13−19; see also Table S1).[23] The benefit of using DMSO as a catalytic ligand, rather than a solvent, has been observed recently in two other Pd-catalyzed aerobic oxidation reactions, including chelate-directed C−H arylation of anilides[24] and oxidative amination of alkenes.[25]

The high selectivity for formation of the enone with the $Pd(DMSO)_2(TFA)_2$ catalyst system is noteworthy in light of the preferential formation of phenols with a $Pd(TFA)_2$/2-Me_2Npy catalyst system.[3] A comparison of time courses for reactions with the two catalyst systems (Figure 1) highlights the significant differences between the relative rates of the corresponding dehydrogenation steps (cf. Scheme 1B). Fitting of the time-course data to a simple sequential kinetic model, A → B → C,[26] reveals that the first dehydrogenation step is 33-fold *faster* than the second step when $Pd(DMSO)_2(TFA)_2$ is used as the catalyst. In contrast, the first step is nearly 2-fold *slower* than the second step with the $Pd(TFA)_2$/2-Me_2Npy catalyst system.[27] Further mechanistic studies are ongoing, but these observations have important implications for use of the present catalyst system in the synthesis of enones (Table 2).

Table 1. Catalyst Optimization of Aerobic Oxidative Dehydrogenation of 4-*tert*-Butylcyclohexanone 1[a]



entry	PdX_2	ligand (mol %)	solvent	2 (%)[b]	3 (%)[b]
1	$Pd(TFA)_2$	2-Me_2N-pyridine (10)/ TsOH(20)	DMSO	23	33
2	$Pd(TFA)_2$	5,5′-Me_2bpy (5)/ 4 Å MS	PhCl	19	0
3	$Pd(OAc)_2$		DMSO	63	14
4	$Pd(TFA)_2$		DMSO	34	56
5	$Pd(TFA)_2$		HOAc	24	1
6	$Pd(OAc)_2$	DMSO (10)	HOAc	86	8
7	**$Pd(TFA)_2$**	**DMSO (10)**	**HOAc**	**91**	**8**
8	$Pd(TFA)_2$	DMSO (10)	Toluene	67	3
9	$Pd(TFA)_2$	DMSO (10)	THF	66	8
10	$Pd(TFA)_2$	DMSO (10)	Dioxane	84	10
11	$Pd(TFA)_2$	DMSO (10)	EtOAc	30	6
12	$Pd(TFA)_2$	DMSO (10)	PhCl	11	0
13	$Pd(TFA)_2$	pyridine (10)	HOAc	55	2
14	$Pd(TFA)_2$	2-Me_2N-pyridine (10)	HOAc	3	1
15	$Pd(TFA)_2$	2-F-pyridine (10)	HOAc	37	2
16	$Pd(TFA)_2$	bipyridine (5)	HOAc	0	0
17	$Pd(TFA)_2$	5,5′-Me_2bpy (5)	HOAc	0	0
18	$Pd(TFA)_2$	phenanthroline (5)	HOAc	0	0
19	$Pd(TFA)_2$	1,2-bis(phenylsulfinyl)ethane (5)	HOAc	9	4

[a] Conditions: [**1**] = 0.2 M (15.4 mg, 0.1 mmol), 5% PdX_2 (0.005 mmol), 10% ligand (0.01 mmol), Solvent (0.5 mL), 1 atm O_2, 80 °C, 12 h. [b] Determined by GC, external standard = tetradecane.

A number of 4-substituted cyclohexanone derivatives underwent dehydrogenation in good yields with the $Pd(DMSO)_2(TFA)_2$ catalyst (Table 2, entries 1−5). Substrates with electron-deficient substituents (entries 2 and 3) exhibited somewhat faster rates, and the conditions tolerated various functional groups, including trifluoromethyl and siloxy groups (entries 2 and 5). The parent cyclohexanone (entry 1) decomposed under the acidic conditions, but a good yield of enone was obtained by performing the reaction in ethyl acetate.[28] Dehydrogenation of 2- and 3-substituted cyclohexanones can afford two enone regioisomers, and reactions of 2- and 3-phenylcyclohexanone proceeded with modest (~3:1) regioselectivity (entries 6 and 7). The ability to achieve highly regioselective dehydrogenation was demonstrated in the reactions of two steroid derivatives (entries 8 and 9), each of which afforded one of two possible cyclohexenones in excellent yield. In both cases, the regioselectivity favored formation of the less substituted alkene. No dehydrogenation of the cyclopentanone fragment was observed in the reaction leading to 5α-androst-1-ene-3,17-dione (entry 9). The lower reactivity of cyclopentantones was also evident in the dehydrogenation of indanone, which afforded the corresponding enone in 54% yield, with toluene as the optimal solvent (entry 10). In contrast, 1-benzosuberone underwent dehydrogenation in good yield (81%, entry 11). Cycloheptanone and cyclooctanone led to a mixture of dehydrogenation products, with 2,6-cycloheptadien-1-one and 2,7-cyclooctadien-1-one formed as the major products in 26 and 25% yields, respectively, based on GC−MS and ^{1}H NMR spectroscopic analysis.

Chromones[29] and flavones have important biological activity,[30] and the saturated dihydrobenzopyranones are readily prepared via condensation of simple precursors.[31] Aerobic dehydrogenation reactions to form chromone, 6-fluorochromone,[32] and flavone[33] proceeded in good yield (entries 12−14). Related *N*-methyl- and *N*-Boc-piperidone derivatives underwent successful dehydrogenation to the corresponding dihydro-4-pyridone derivatives (entries 15 and 16).

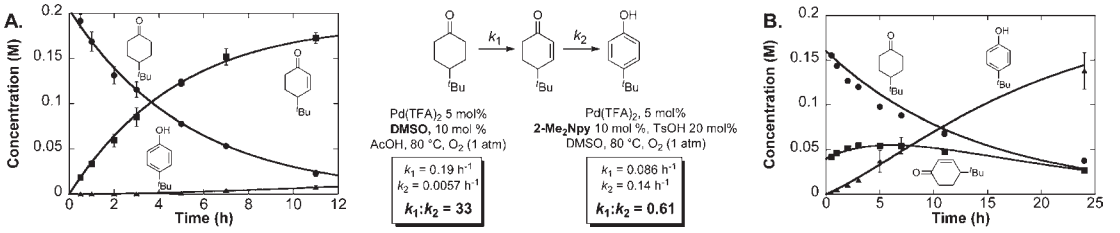


Figure 1. Comparison of kinetic profiles of $Pd(DMSO)_2(TFA)_2$- and $Pd(TFA)_2$/2-Me_2Npy-catalyzed dehydrogenation of **1**. Reaction conditions: (A) [**1**] = 0.2 M (0.1 mmol), $Pd(TFA)_2$ (5 μmol), DMSO (10 μmol), AcOH (0.5 mL), 1 atm O_2, 80 °C; (B) [**1**] = 0.2 M (0.1 mmol), $Pd(TFA)_2$ (5 μmol), 2-Me_2Npy (10 μmol), TsOH (20 μmol), DMSO (0.5 mL), 1 atm O_2, 80 °C. Int. std. = 1,4-dimethoxybenzene. Error bars represent std. dev. from 3 indep. measurements.

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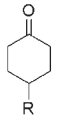
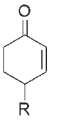
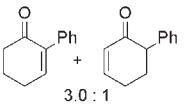
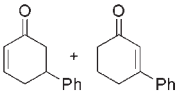
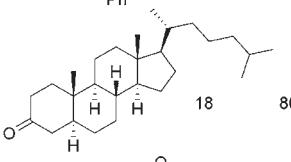
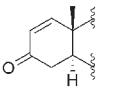
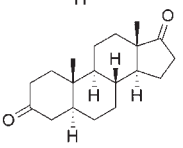
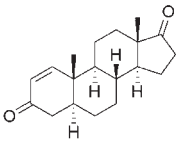
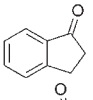
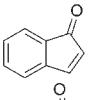
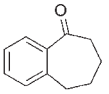
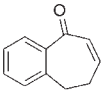
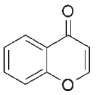
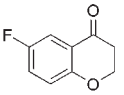
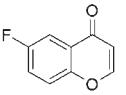
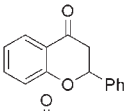
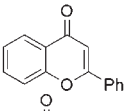
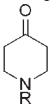
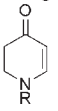
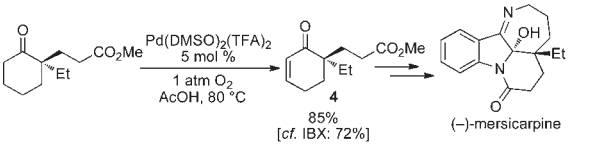
Table 2. Pd-Catalyzed Aerobic Dehydrogenation of Diverse Cycloketones[a]

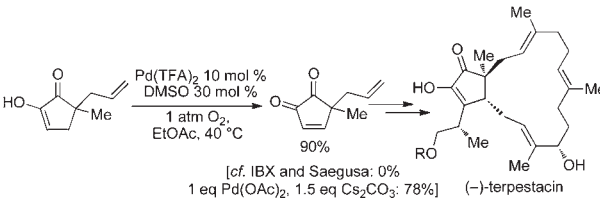
Entry	Substrate	Reaction time (h)	Temp. (°C)	Enone	Yield (%)[b]
1	 R = H	24	60		72[c]
2	= CF_3	5	80		81
3	= Ph	6	80		83
4	= *tert*-Bu	12	80		91
5	= OTBS	20	80		76
6		24	60	 3.0 : 1	84[c]
7		24	60	 2.7 : 1	86[c]
8		18	80		94
9		12	80		93
10		48	60		54[d]
11		36	80		81[d]
12		48	100		80
13		36	80		78
14		32	100		66
15	 R = Me	24	60		74[c]
16	R = Boc	48	80		72[e]

[a] Reactions conditions: [substrate] = 0.2 M (0.8 mmol), [$Pd(TFA)_2$] = 0.01 M (0.04 mmol =5 mol %), [DMSO] = 0.02 M (0.08 mmol), solvent = HOAc (4 mL), 1 atm O_2. [b] Isolated yield. [c] Ethyl acetate was used as solvent to prevent product decomposition in acetic acid, [substrate] = 0.8 M (0.8 mmol), ethyl acetate (1 mL). [d] [substrate] = 0.4 M (0.8 mmol), [$Pd(TFA)_2$] = 0.02 M, [DMSO] = 0.2 M, solvent = toluene (2 mL). [e] In DMSO; no additional ligand.

Cyclic enones are common intermediates in the synthesis of natural products, and the aerobic dehydrogenation reactions described here could find broad utility in this context. For example, α,α-disubstituted cyclohexenone **4** has been used as an intermediate in the synthesis of (−)-mersicarpine.[34] This enone was obtained in 85% yield using the $Pd(DMSO)_2(TFA)_2$ catalytic method (eq 1); the original protocol employed stoichiometric IBX and proceeded in 72% yield.[34] Catalytic Saegusa-type[6c] and stoichiometric IBX[8] oxidation methods failed in the synthesis of a cyclopentene-α-dione precursor to the natural product (−)-terpestacin, and stoichiometric $Pd(OAc)_2$ was used instead.[35] Application of an aerobic $Pd(TFA)_2$/DMSO catalyst system to this reaction afforded the enedione in 90% yield (eq 2).



(1)



(2)

In summary, we have identified a Pd^{II} catalyst system that enables direct dehydrogenation of cyclic ketones to the corresponding enones with a number of important substrates. The high selectivity for enone rather than phenol formation sharply contrasts other Pd^{II}-catalyzed dehydrogenation methods[3,13] and warrants further mechanistic investigation. The ability to replace stoichiometric reagents (e.g., Br_2, organoselenium reagents, and IBX) with O_2 as an oxidant has important implications for large-scale applications of these methods in pharmaceutical and fine-chemical synthesis.[36]

■ ASSOCIATED CONTENT

Supporting Information. Reaction procedure and spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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■ ACKNOWLEDGMENT

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■ REFERENCES

(1) (a) Nishimura, S. *Handbook of Heterogeneous Catalytic Hydrogenation for Organic Synthesis*; John Wiley & Sons: New York, 2001. (b) *The Handbook of Homogeneous Hydrogenation*; de Vries, J. G., Elsevier, C. J., Eds.; Wiley-VCH: Weinheim, 2007.

(2) Transfer-dehydrogenation methods are currently the most effective methods for dehydrogenation of saturated carbon−carbon bonds; however, the application of these methods in organic synthesis is rare. For leading references to these methods, see the following recent review articles: (a) Dobereiner, G. E.; Crabtree, R. H. *Chem. Rev.* **2010**, *110*, 681.

(b) Choi, J.; MacArthur, A. H. R.; Brookhart, M.; Goldman, A. S. *Chem. Rev.* **2011**, *111*, 1761.

(3) Izawa, Y.; Pun, D.; Stahl, S. S. *Science* **2011**, *333*, 209.

(4) Numerous examples of cyclohexanone dehydrogenation in natural product synthesis exist. For recent examples, see: (a) Herzon, S. B.; Lu, L.; Woo, C. M.; Gholap, S. L. *J. Am. Chem. Soc.* **2011**, *133*, 7260. (b) Yokoe, H.; Mitsuhashi, C.; Matsuoka, Y.; Yoshimura, T.; Yoshida, M.; Shishido, K. *J. Am. Chem. Soc.* **2011**, *133*, 8854. (c) Petronijevic, F. R.; Wipf, P. *J. Am. Chem. Soc.* **2011**, *133*, 7704.

(5) For reviews of methods for α,β-dehydrogenation of carbonyl compounds, see: (a) Buckle, D. R.; Pinto, I. L. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, U.K., 1991; Vol. 7, pp 119−149. (b) Larock, R. C. In *Comprehensive Organic Transformations*; John Wiley & Sons: New York, 1999; pp 251−256.

(6) For Pd-catalyzed dehydrogenation of silyl enol ethers ("Saegusa reactions"), see: (a) Ito, Y.; Hirao, T.; Saegusa, T. *J. Org. Chem.* **1978**, *43*, 1011. (b) Larock, R. C.; Hightower, T. R.; Kraus, G. A.; Hahn, P.; Zheng, D. *Tetrahedron Lett.* **1995**, *36*, 2423. (c) Yu, J. Q.; Wu, H. C.; Corey, E. J. *Org. Lett.* **2005**, *7*, 1415.

(7) Common methods include bromination/dehydrobromination and selenoxide and sulfoxide elimination reactions. See the following leading references: (a) Miller, B.; Wong, H.-S. *Tetrahedron* **1972**, *28*, 2369. (b) Stotter, P. L.; Hill, K. A. *J. Org. Chem.* **1973**, *38*, 2576. (c) Trost, B. M.; Salzmann, T. N.; Hiroi, K. *J. Am. Chem. Soc.* **1976**, *98*, 4887. (d) Sharpless, K. B.; Lauer, R. F.; Teranishi, A. Y. *J. Am. Chem. Soc.* **1973**, *95*, 6137. (e) Reich, H. J. *Acc. Chem. Res.* **1979**, *12*, 22.

(8) (a) Nicolaou, K. C.; Zhong, Y. L.; Baran, P. S. *J. Am. Chem. Soc.* **2000**, *122*, 7596. (b) Nicolaou, K. C.; Montagnon, T.; Baran, P. S.; Zhong, Y. L. *J. Am. Chem. Soc.* **2002**, *124*, 2245. (c) Nicolaou, K. C.; Montagnon, T.; Baran, P. S. *Angew. Chem., Int. Ed.* **2002**, *41*, 993. (d) Nicolaou, K. C.; Gray, D. L. F.; Montagnon, T.; Harrison, S. T. *Angew. Chem., Int. Ed.* **2002**, *41*, 996.

(9) For a method employing catalytic 2-iodoxybenzene sulfonate (IBS) in combination stoichiometric Oxone, see: Uyanik, M.; Akakura, M.; Ishihara, K. *J. Am. Chem. Soc.* **2009**, *131*, 251.

(10) (a) Walker, D.; Hiebert, J. D. *Chem. Rev.* **1967**, *67*, 153. (b) Buckle, D. R. 2,3-Dichloro-5,6-dicyano-1,4-benzoquinone. In *Encyclopedia of Reagents for Organic Synthesis*; John Wiley & Sons, Inc.: New York, 2010. (c) Bhattacharya, A.; DiMichele, L. M.; Dolling, U. H.; Douglas, A. W.; Grabowski, E. J. J. *J. Am. Chem. Soc.* **1988**, *110*, 3318.

(11) The requirement for large amounts of Pd^{II} in these reactions may arise from inhibition of catalyst reoxidation, arising from enone coordination to Pd^0: Porth, S.; Bats, J. W.; Trauner, D.; Giester, G.; Mulzer, J. *Angew. Chem., Int. Ed.* **1999**, *38*, 2015.

(12) (a) Theissen, R. J. *J. Org. Chem.* **1971**, *36*, 752. (b) Muzart, J.; Pete, J. P. *J. Mol. Catal.* **1982**, *15*, 373. (c) Wenzel, T. T. *J. Chem. Soc., Chem. Commun.* **1989**, 932. (d) Park, Y. W.; Oh, H. H. *Bull. Korean Chem. Soc.* **1997**, *18*, 1123. (e) Tokunaga, M.; Harada, S.; Iwasawa, T.; Obora, Y.; Tsuji, Y. *Tetrahedron Lett.* **2007**, *48*, 6860.

(13) For a recent review of reactions of this type, see: Muzart, J. *Eur. J. Org. Chem.* **2010**, 3779.

(14) Pd^{II}-catalyzed dehydrogenation of β-aryl aldehydes has been explored recently; however, the current substrate scope is rather limited: (a) Zhu, J.; Liu, J.; Ma, R. Q.; Xie, H. X.; Li, J.; Jiang, H. L.; Wang, W. *Adv. Synth. Catal.* **2009**, *351*, 1229. (b) Liu, J.; Zhu, J.; Jiang, H. L.; Wang, W.; Li, J. *Chem.—Asian J.* **2009**, *4*, 1712.

(15) Direct dehydrogenation of 3,3-dimethylcyclohexanone was reported recently with 1−5 mol % of an Ir-pincer catalyst and *t*Bu-ethylene as the H_2 acceptor. Other cyclohexanone substrates lacking *gem*-disubstitution undergo stoichiometric deydrogenation, forming an Ir-phenoxide product. Zhang, X. W.; Wang, D. Y.; Emge, T. J.; Goldman, A. S. *Inorg. Chim. Acta* **2011**, *369*, 253.

(16) The mechanism could proceed via *C*- and/or *O*-bound Pd enolates, although β-hydride elimination is expected to occur from the *C*-bound enolate. For the formation of a *C*-bound Pd-enolate under relatively similar conditions, see: Fuchita, Y.; Harada, Y. *Inorg. Chim. Acta* **1993**, *208*, 43.

(17) Recent studies suggest that aerobic oxidation of Pd^{II}-hydrides proceeds via Pd^0, as shown in Scheme 2. See: (a) Konnick, M. M.; Stahl, S. S. *J. Am. Chem. Soc.* **2008**, *130*, 5753. (b) Popp, B. V.; Stahl, S. S. *Chem.—Eur. J.* **2009**, *15*, 2915.

(18) Gas update experiments show that the product/O_2 stoichiometry is 2:1, consistent with Pd-mediated disproportionation of H_2O_2 under reaction conditions. For previous characterization of Pd-mediated H_2O_2 disproportionation under related conditions, see the Supporting Information for the following reference: Steinhoff, B. A.; Fix, S. R.; Stahl, S. S. *J. Am. Chem. Soc.* **2002**, *124*, 766.

(19) (a) Stahl, S. S. *Angew. Chem., Int. Ed.* **2004**, *43*, 3400. (b) Gligorich, K. M.; Sigman, M. S. *Chem. Commun.* **2009**, 3854. (c) Chen, X.; Engle, K. M.; Wang, D.-H.; Yu, J.-Q. *Angew. Chem., Int. Ed.* **2009**, *48*, 5094.

(20) See Supporting Information for further details.

(21) $Pd(OAc)_2$/DMSO catalyst systems for aerobic oxidation reactions were pioneered by the groups of Hiemstra and Larock. For initial reports, see: (a) Larock, R. C.; Hightower, T. R. *J. Org. Chem.* **1993**, *58*, 5298. (b) van Benthem, R. A. T. M.; Hiemstra, H.; Michels, J. J.; Speckamp, W. N. *J. Chem. Soc., Chem. Commun.* **1994**, 357.

(22) For mechanistic characterization of this catalyst system, see: Steinhoff, B. A.; Stahl, S. S. *J. Am. Chem. Soc.* **2006**, *128*, 4348.

(23) The other ligands, such as pyridine (entry 13), 2-F-pyridine (entry 15), and the bis-sulfoxide ligand (entry 19), were selected on the basis of their utility in other recent Pd-catalyzed oxidation reactions. See, for example: (a) Nishimura, T.; Onoue, T.; Ohe, K.; Uemura, S. *J. Org. Chem.* **1999**, *64*, 6750. (b) Izawa, Y.; Stahl, S. S. *Adv. Synth. Catal.* **2010**, *352*, 3223. (c) Chen, M. S.; Prabagaran, N.; Labenz, N. A.; White, M. C. *J. Am. Chem. Soc.* **2005**, *127*, 6970.

(24) Brasche, G.; García-Fortanet, J.; Buchwald, S. L. *Org. Lett.* **2008**, *10*, 2207.

(25) McDonald, R. I.; Stahl, S. S. *Angew. Chem., Int. Ed.* **2010**, *49*, 5529.

(26) Kinetic fitting was carried with COPASI software: Hoops, S.; Sahle, S.; Gauges, R.; Lee, C.; Pahle, J.; Simus, N.; Singhal, M.; Xu, L.; Mendes, P.; Kummer, U. *Bioinformatics* **2006**, *22*, 3067.

(27) The kinetics of phenol formation (Figure 1B) show that this reaction is more complicated than a simple sequential A → B → C process. Specifically, a kinetic "burst" is evident during the first catalytic turnover that leads to the early rapid conversion of cyclohexanone to cyclohexenone. The fit in Figure 1B reflects a fit of the data after this burst phase. Mechanistic studies to elucidate the origin of these observations are ongoing.

(28) Catalyst decomposition appears to be more rapid when ethyl acetate is used as the solvent rather than acetic acid. Vigorous agitation of the reaction mixture to ensure good gas−liquid mixing, or the use of higher O_2 pressure, improves the outcome. When using elevated O_2 pressures, we employed a dilute mixture of O_2 in N_2 (9%) as the gas source to reduce flammability hazards. See Supporting Information for details.

(29) Si, D.; Wang, Y.; Zhou, Y. H.; Guo, Y.; Wang, J.; Zhou, H.; Li, Z. S.; Fawcett, J. P. *Drug Metab. Dispos.* **2003**, *37*, 629.

(30) Cermak, R.; Wolffram, S. *Curr. Drug Metab.* **2006**, *7*, 729.

(31) (a) Loudon, J. D.; Razdan, R. K. *J. Chem. Soc.* **1954**, 4299. (b) Choudary, B. M.; Ranganath, K. V. S.; Yadav, J.; Lakshmi Kantam, M. *Tetrahedron Lett.* **2005**, *46*, 1369.

(32) Kurono, M.; Yamaguchi, T.; Usui, T.; Fukushima, M.; Mizuno, K.; Matsubara, A. EP0193415 (A2), 1986.

(33) Kondo, T.; Oyama, K.-I.; Yoshida, K. *Angew. Chem., Int. Ed.* **2001**, *40*, 894.

(34) Nakajima, R.; Ogino, T.; Yokoshima, S.; Fukuyama, T. *J. Am. Chem. Soc.* **2010**, *132*, 1236.

(35) Trost, B. M.; Dong, G.; Vance, J. A. *Chem.—Eur. J.* **2010**, *16*, 6265.

(36) Dehydrogenation of substrate **1** has been carried out on a 10-g scale using a prototype flow reactor donated to UW-Madison by Eli Lilly. See Supporting Information and the following reference for details: Ye, X.; Johnson, M. D.; Diao, T.; Yates, M. H.; Stahl, S. S. *Green Chem.* **2010**, *12*, 1180.