Published in final edited form as:
Science. 2011 July 8; 333(6039): 209–213. doi:10.1126/science.1204183.

Palladium-Catalyzed Aerobic Dehydrogenation of Substituted Cyclohexanones to Phenols

Yusuke Izawa, **Doris Pun**, and **Shannon S. Stahl**
Department of Chemistry, University of Wisconsin-Madison, 1101 University Avenue, Madison, Wisconsin 53706

Abstract

Aromatic molecules are key constituents of many pharmaceuticals, electronic materials and commodity plastics. The utility of these molecules directly reflects the identity and pattern of substituents on the aromatic ring. Here, we report the discovery of a palladium(II) catalyst system, incorporating an unconventional *ortho*-dimethylaminopyridine ligand, for the conversion of substituted cyclohexanones to the corresponding phenols. The reaction proceeds via successive dehydrogenation of two saturated carbon-carbon bonds of the six-membered ring and uses molecular oxygen as the hydrogen acceptor. This reactivity demonstrates a versatile and efficient strategy for the synthesis of substituted aromatic molecules with fundamentally different selectivity constraints from the numerous existing synthetic methods that rely on substitution of a pre-existing aromatic ring.

Phenols are common precursors and core structures of industrial chemicals, ranging from pharmaceuticals to polymers. The introduction of chemical functional groups with specific patterns around the aromatic ring represents a key challenge in the preparation of these (*1*). Electrophilic aromatic substitutions are classical chemical reactions that remain among the most versatile methods for the synthesis of substituted phenols; however, strong electronic directing effects associated with these reactions limit their utility to the preparation of *ortho*- and *para*-substituted derivatives. This limitation has inspired extensive efforts to identify complementary routes to substituted phenols, such as a recent two-step arene C–H borylation/oxidation procedure for the introduction of a hydroxyl group into an aromatic ring, guided by steric rather than electronic effects (*2*). Recent advances in palladium-catalyzed aerobic oxidation reactions (*3-5*) suggested to us that diverse phenol derivatives, including those with *meta* substitution, could be accessed by dehydrogenation of cyclohexanones via sequential Pd-mediated C–H activation/β-hydride elimination steps, followed by tautomerization of the resulting dienone product (Fig. 1A). This strategy is appealing because Pd^{II}–hydride intermediates formed in this mechanism could be oxidized by molecular oxygen (*6,7*), thereby enabling the overall process to be catalytic in Pd with water as the sole byproduct (Fig. 1B). Successful catalysts for this class of reactions could find broad utility owing to the numerous straightforward chemical reactions that provide access to substituted cyclohexanones, including enolate arylation and alkylation methods, conjugate addition to cyclohexenones, and Robinson annulation and Diels-Alder reactions (Fig. 1C).

Supporting Online Material
Materials and Methods
Tables S1 and S2
Characterization Data of New Compounds
References 31-43

The preparation of phenols from ketone precursors have been explored previously (*8-16*). Condensation reactions of acyclic ketones, for example, with β-ketoaldehydes or β-diketones, enab le direct access to substituted phenols (*8*), but low product yields, limited access to starting materials and/or formation of isomeric products have restricted the utility of these procedures. Methods for formation of phenols via dehydrogenation of cyclohexenones have been pursued (*8-13*), but reactions of this type typically employ undesirable stoichiometric reagents, such as DDQ (2,3-dichloro-5,6-dicyano-1,4-benzoquinone) (*17*), utilize stepwise procedures, such as bromination/dehydrobromination, or require harsh reaction conditions (≥ 200 °C) that limit functional group compatibility. In contrast, no effective methods for dehydrogenation of substituted cyclohexanones exist, with relevant precedents almost exclusively limited to reactions of unsubstituted cyclohexanone and yields of ≤ 30 % (mostly < 5%) (*12-16*). Iridium complexes bearing tridentate "pincer" ligands are among the most effective catalysts for the dehydrogenation of saturated hydrocarbons (*18,19*). These reactions are typically are typically carried out in the presence of a sacrificial hydrogen acceptor, such as norbornene or *tert*-butylethylene, and a recent investigation of the reaction of an Ir-pincer complex with cyclohexanone resulted in stoichiometric dehydrogenation. Catalytic turnover was inhibited by the formation of an Ir-phenoxide product, (pincer)Ir(H)(OPh) (*20*). In order to explore prospects for the proposed Pd-catalyzed dehydrogenation methods, we investigated the reactivity of 3-methylcyclohexenone (**1a**) and 3-methylcyclohexanone (**1b**) under 1 atm of O_2 with various Pd^{II} catalysts. Preliminary analysis of Pd^{II} sources, solvents and reaction conditions revealed that 3-methylphenol (*meta*-cresol) could be obtained in modest yields from **1a** and **1b** (28-52%) with 3 mol % $Pd(OAc)_2$ or $Pd(TFA)_2$ (TFA = trifluoroacetate) in dimethylsulfoxide (DMSO) as the solvent under 1 atm of O_2 at 80 °C (Table 1, entries 1 and 2) (*21, 22*). Brønsted bases, such as sodium acetate, and traditional monodentate and bidentate nitrogen ligands (pyridine, bipyridine, phenanthroline) failed to increase the yield of the phenol product (entries 3–6; for expanded screening results, see Table S2). 4,5-Diazafluorenone (*23*) led to a substantial increase in the yield of *m*-cresol from **1a** (78%, entry 7); however, conversion to phenol from the saturated cyclohexanone **1b** was still unsatisfactory. Both key steps in the C–H activation and β-hydride elimination (Fig. 1A), should benefit from a more-electrophilic catalyst, and recent success with 2-fluoropyridine (^{2F}py) as an electron-deficient ligand in aerobic oxidative coupling reactions (*24*) prompted us to evaluate ligands of this type in the dehydrogenation reactions (entries 8–15). The use of ^{2F}py as a ligand led to a modest improvement in the yield of **2** from **1b** (44%, entry 10); however, the best results were obtained when 2-(*N*,*N*-dimethylamino)pyridine (^{2NMe2}py) was used in combination with *p*-toluenesulfonic acid (TsOH) (entry 18). We speculate that the improved results obtained with the ^{2NMe2}py/TsOH combination relative to those with ^{2NMe2}py alone (cf. entries 15 and 18) reflect the ability of TsOH to protonate the tertiary amine of the coordinated pyridine and thereby afford a more electron-deficient pyridine ligand. The position of the dimethylamino group on the pyridine ligand is important, as reveale d by the inferior results obtained with 4-(*N*,*N*-dimethylamino)pyridine in place of the 2-substituted ligand (entries 19 and 20). Common heterogeneous palladium catalysts failed to afford the desired *m*-cresol (entries 21-24).

The optimized catalytic conditions (Table 1, entry 18) proved to be effective in the preparation of a number of substituted phenol derivatives (Table 2). Varying the position of the methyl substituent on the cyclohexanone had little effect on the outcome of the reaction; the corresponding *ortho*-, *meta*-, and *para*-cresols were each obtained in good yield (Table 2, entries 1–3). Aryl-substituted phenols, including a number of *meta*-substituted derivatives, were accessed via the dehydrogenation of the corresponding arylcyclohexanone derivatives (entries 4–11). The 3-arylcyclohexanones were readily obtained via conjugate addition of aryl boronic acids to cyclohexenone, and both electron-donating and electron-withdrawing groups were tolerated in the dehydrogenation reaction. Substrates with aryl

groups bearing a *para* bromide and iodide afforded only low yields of the desired phenol (28% and 16%, respectively; data not shown). Diels-Alder cycloaddition and Robinson annulation represent classical and widely used synthetic organic reactions that provide efficient routes to cyclohexenones bearing multiple substituents on the 6-membered ring. The aerobic oxidation method described here provide an attractive alternative to the use of stoichiometric reagents, such as DDQ, which have been used previously in the dehydrogenation of cyclohexenones (*17*), and such substrates underwent very effective dehydrogenation under the optimized catalytic conditions, including those bearing alkyl, aryl and/or ester substituents (entries 12–17).

3,5-Disubstituted cyclohexenones were pursued further because the corresponding phenol derivatives exhibit important biological activity, and products of this type cannot be readily prepared by classical aromatic-substitution, metal-catalyzed cross-coupling, or related synthetic methods. As a representative example, *O*-terphenylcarbamate **5** was recently identified as a potent in-vitro allosteric inhibitor of the human luteinizing hormone receptor, which has been implicated in fertility and ovarian cancer (*25*). This compound was prepared by traditional Suzuki coupling methods using 3,5-dibromophenol as the starting material; however, introduction of the unsymmetrical aryl substitution pattern results in low yields of the biaryl intermediate **6** and the desired 3,5-diarylphenol **4** (30% and 62% yields, respectively; Fig. 2). In contrast, the 3,5-diarylcyclohexenone derivative **3** is obtained readily from very inexpensive starting materials (4-methylacetophenone, benzaldehyde and acetone) via sequential aldol condensation/Robinson annulation. Subsequent Pd-catalyzed dehydrogenation of **3** afforded phenol **4** in excellent yield.

Preliminary mechanistic analysis of these dehydrogenation reactions were performed by monitoring the conversion of cyclohexanone to phenol by gas chromatography. The kinetic time course revealed the formation and disappearance of the partially dehydrogenated intermediate, cyclohexenone (Fig. 3A). This result is consistent with the overall catalytic mechanism in Fig. 1B, in which the substrate dissociates from the catalyst after each dehydrogenation step. A fit of the kinetic data based on a simple sequential reaction model reveals that the two dehydrogenation steps have similar rate constants, $k_1 = 0.12(2)\ h^{-1}$ and $k_2 = 0.33(4)\ h^{-1}$ (Fig. 3B). The dehydrogenation of cyclohexenone, monitored independently, exhibits a rate constant somewhat lower than that obtained from the fit of the sequent reaction, $k_2' = 0.19(2)\ h^{-1}$. Accurate interpretation of these results will require further investigation; however, the higher concentration of cyclohexenone in the latter reaction may slow the catalytic turnover via alkene coordination to Pd.

The joint application of catalyst screening and mechanistic studies will play an important role in extending these reactions to different product classes. For example, catalysts that can effect the first step significantly more rapidly than the second step (k_1:k_2 > 10:1) would enable selective formation of the enone products rather than phenols. Moreover, it should be possible to develop efficient catalysts for dehydrogenative aromatization of other substrate classes, such as substituted cyclohexenes (*26-28*). Substrates of this type are readily accessed via Diels-Alder cycloaddition reactions, and their dehydrogenation could proceed via sequential allylic C–H activation/β-hydride elimination steps (Fig. 3C). Toward this end, preliminary studies reveal that cyclohexene derivative **7** undergoes efficient dehydrogenation to the trisubstituted arene **8** in near-quantitative yield.

Methods for selective dehydrogenation of saturated carbon-carbon bonds represent an important class of C–H functionalization (*18,29*), and the reactions presented above highlight the prospective utility of such methods in the synthesis of substituted aromatic molecules. These reactions achieve high conversions and product yields, they are capable of using O_2 as the hydrogen acceptor, and the catalyst tolerates useful substrate functional

groups, including aromatic and heteroatom substituents. With the development of improved methods for safe and scalable aerobic oxidation reactions (*30*), dehydrogenation methods of this type could have an important impact on laboratory- and industrial-scale chemical synthesis.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

We are grateful to the NIH (RC1-GM091161), Mitsubishi Chemical Corporation and NSF (CHE-1041934; to DP) for financial support of this work.

References

1. Tyman, JHP. Synthetic and Natural Phenols. Elsevier; New York: 1996.
2. Maleczka RE Jr. Shi F, Holmes D, Smith MR III. J. Am. Chem. Soc. 2003; 125:7792. [PubMed: 12822984]
3. Stahl SS. Angew. Chem., Int. Ed. 2004; 43:3400.
4. Gligorich KM, Sigman MS. Chem. Commun. 3854. 2009
5. Chen X, Engle KM, Wang D-H, Yu J-Q. Angew. Chem. Int. Ed. 2009; 48:5094.
6. Konnick MM, Stahl SS. J. Am. Chem. Soc. 2008; 130:5753. [PubMed: 18393426]
7. Denney MC, Smythe NA, Cetto KL, Kemp RA, Goldberg KI. J. Am. Chem. Soc. 2006; 128:2508. [PubMed: 16492014]
8. Bamfield P, Gordon PF. Chem. Soc. Rev. 1984; 13:441.
9. Horning EC, Horning MG. J. Am. Chem. Soc. 1947; 69:1359.
10. Fu PP, Harvey RG. Chem. Rev. 1978; 78:317.
11. Moriuchi T, Kikushima K, Kajikawa T, Hirao T. Tetrahedron Lett. 2009; 50:7385.
12. Yi CS, Lee DW. Organometallics. 2009; 28:947. [PubMed: 20119477]
13. Schuda PF, Price WA. J. Org. Chem. 1987; 52:1972.
14. Muzart J, Pete JP. J. Mol. Catal. 1982; 15:373.
15. Wenzel TT. J. Chem. Soc., Chem. Commun. 1989; 932
16. Muzart J. Eur. J. Org. Chem. 2010; 20:3779.
17. Buckle, DR. Encyclopedia of Reagents for Organic Synthesis. John Wiley & Sons, Inc.; New York: 2010. 2,3-Dichloro-5,6-dicyano-1,4-benzoquinone.
18. Choi J, MacArthur AHR, Brookhart M, Goldman AS. Chem. Rev. 2011; 111:1761. [PubMed: 21391566]
19. Ahuja R, Punji B, Findlater M, Supplee C, Schinski W, Brookhart M, Goldman AS. Nat. Chem. 2011; 3:167. [PubMed: 21258391]
20. Zhang XW, Wang DY, Emge TJ, Goldman AS. Inorg. Chim. Acta. 2011; 369:253.
21. Larock RC, Hightower TR. J. Org. Chem. 1993; 58:5298.
22. van Benthem RATM, Hiemstra H, Michels JJ, Speckamp WN. J. Chem. Soc., Chem. Commun. 1994; 357
23. Campbell AN, White PB, Guzei IA, Stahl SS. J. Am. Chem. Soc. 2010; 132:15116. [PubMed: 20929224]
24. Izawa Y, Stahl SS. Adv. Synth. Catal. 2010; 352:3223. [PubMed: 21399704]
25. Heitman LH, Narlawar R, De Vries H, Willemsen MN, Wolfram D, Brussee J, Ijzerman AP. J. Med. Chem. 2009; 52:2036. [PubMed: 19296599]
26. Sheldon RA, Sobczak JM. J. Mol. Catal. 1991; 68:1.
27. Bercaw JE, Hazari N, Labinger JA. J. Org. Chem. 2008; 73:8654. [PubMed: 18821804]
28. Bercaw JE, Hazari N, Labinger JA, Oblad PF. Angew. Chem., Int. Ed. 2008; 47:9941.

29. Dobereiner GE, Crabtree RH. Chem. Rev. 2010; 110:681. [PubMed: 19938813]
30. Ye X, Johnson MD, Diao T, Yates MH, Stahl SS. Green Chem. 2010; 12:1180. [PubMed: 20694169]
31. Itooka R, Iguchi Y, Miyaura N. J. Org. Chem. 2003; 68:6000. [PubMed: 12868939]
32. Lin SH, Lu XY. Tetrahedron Lett. 2006; 47:7167.
33. Hayashi T, Sasaki K. Chem Lett. 2008; 37:842.
34. Srinivasan B, Johnson TE, Lad R, Xing C. J. Med. Chem. 2009; 52:7228. [PubMed: 19883086]
35. Kamata, T.; Moriguchi, K.; Harimoto, T. 2000. JP Patent 169400
36. Al-Zoubi RM, Marion O, Hall DG. Angew. Chem. Int. Ed. 2008; 47:2876.
37. Luche JL, Petrier C, Lansard JP, Greene AE. J. Org. Chem. 1983; 48:3837.
38. Nakao Y, et al. J. Am. Chem. Soc. 2007; 129:9137. [PubMed: 17602629]
39. Kondo Y, Komine T, Fujinami M, Uchiyama M, Sakamoto T. J. Comb. Chem. 1998; 1:123.
40. Qi S, Shi K, Gao H, Liu Q, Wang H. Molecules. 2007; 12:988. [PubMed: 17873834]
41. Martin SF, Desai SR. J. Org. Chem. 1978; 43:4673.
42. Shmink JR, Holcomb JL, Leadbeater NE. Org. Lett. 2009; 11:365. [PubMed: 19072323]
43. Hoops S, et al. Bioinformatics. 2006; 22:3067. [PubMed: 17032683]

Summary
A palladium(II) catalyst system has been discovered for aerobic dehydrogenation of saturated carbon-carbon bonds in cyclohexanones, enabling efficient preparation of phenols and demonstrating an important strategy for the synthesis of selectively substituted aromatic molecules.

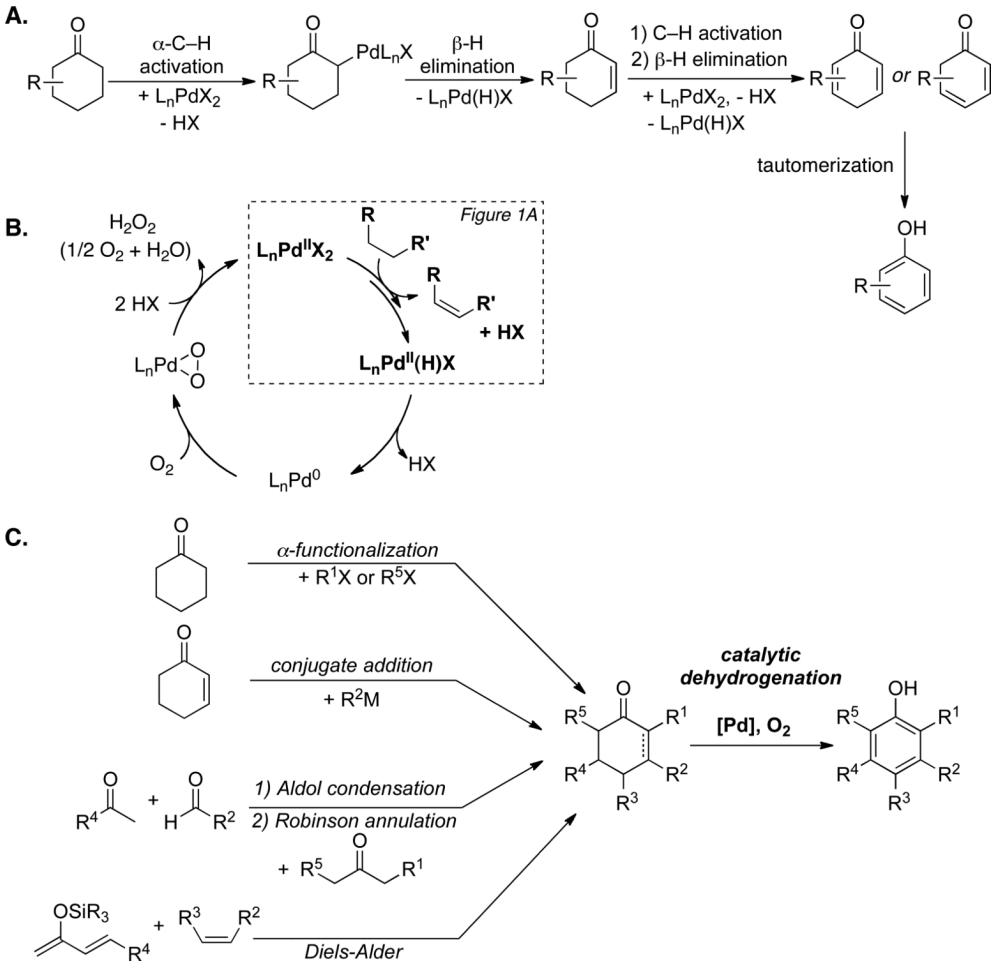


Figure 1.

Strategy for the synthesis of phenols via aerobic oxidative dehydrogenation of cyclohexanone derivatives. (A) Stepwise sequence for Pd-mediated dehydrogenation of cyclohexanone. (B) Catalytic mechanism whereby cyclohexanone dehydrogenation can be achieved with O_2 as the terminal oxidant. (C) Representative synthetic methods that afford facile access to substituted cyclohexanone derivatives.

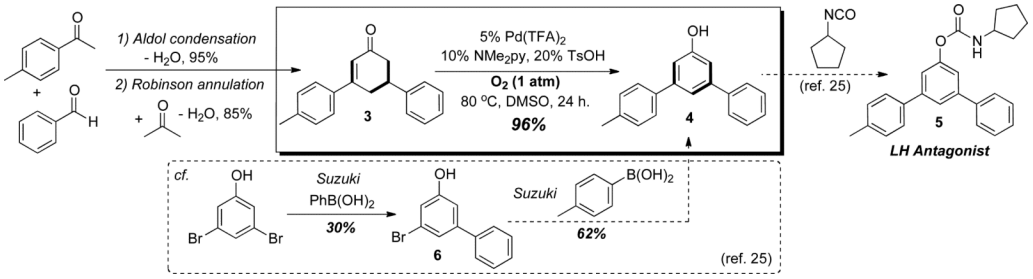


Figure 2.

Application of palladium-catalyzed aerobic oxidative dehydrogenation in the preparation of a terphenyl-derived allosteric inhibitor of the luteinizing hormone receptor.

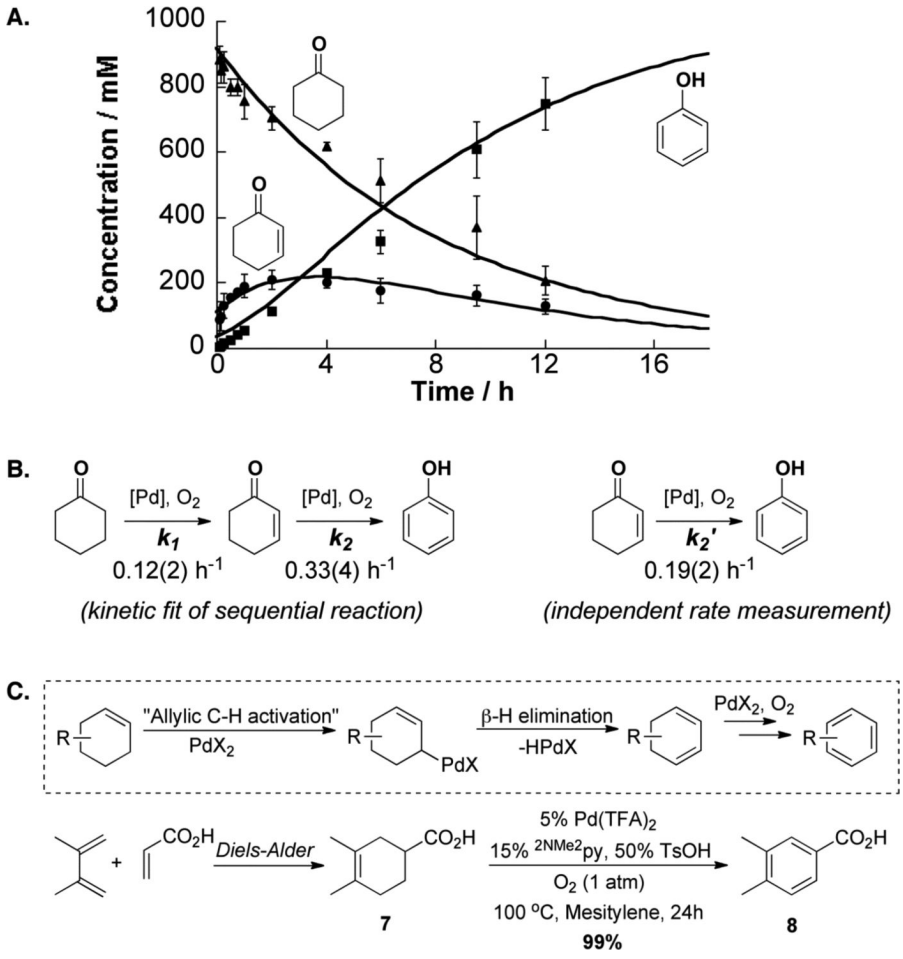
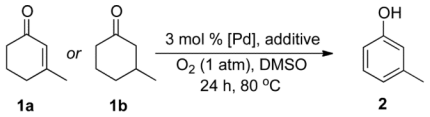


Figure 3.

(A) Kinetic profile of Pd^{II}-catalyzed aerobic dehydrogenation of cyclohexanone and cyclohexenone, showing the formation and decay of cyclohexenone as an intermediate in the reaction. Reaction conditions: Cyclohexanone (0.5 mmol), $Pd(TFA)_2$ (0.025 mmol), 2-(*N*,*N*-dimethylamino)pyridine (0.05 mmol), TsOH (0.10 mmol), DMSO (0.5 mL), 1 atm O_2, 80 °C. Error bars represent standard deviations from 5 independent measurements. (B) Comparison of the rate constants obtained for the dehydrogenation steps in the sequential conversion of cyclohexanone to phenol and in the direct dehydrogenation of cyclohexenone. (C) General strategy and a specific example of Pd-catalyzed aerobic dehydrogenation of cyclohexenes.

Table 1

Catalyst Optimization for Aerobic Oxidative Dehydrogenation of Cyclohexanone Derivatives **1a** and **1b**. Reaction conditions: cyclic ketone (1.0 mmol), PdX_2 (0.03 mmol), ligand/TsOH (mol % indicated), DMSO (0.4 mL), 80 °C, 1 atm O_2, 24 h.



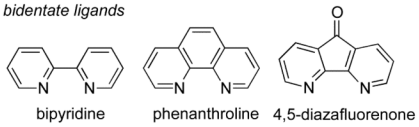
1a **1b** **2**

entry	catalyst/ligand/additive	reagent:	1a	1b
			Yield of *m*-cresol (%)	
1	$Pd(OAc)_2$		30	40
2	$Pd(TFA)_2$		52	28
3	$Pd(TFA)_2$/NaOAc (1 equiv)		13	21
4	$Pd(TFA)_2$/pyridine (6%)		39	16
5	$Pd(TFA)_2$/bipyridine (3%)		26	18
6	$Pd(TFA)_2$/phenanthroline (3%)		15	18
7	$Pd(TFA)_2$/4,5-diazafluorenone (3%)		78	25
8	$Pd(TFA)_2/^{3CO2Et}py$ (6%)		60	14
9	$Pd(TFA)_2/^{3NO2}py$ (6%)		64	24
10	$Pd(TFA)_2/^{2F}py$ (6%)		59	44
11	$Pd(TFA)_2/^{2OH}py$ (6%)		68	32
12	$Pd(TFA)_2/^{2OMe}py$ (6%)		64	24
13	$Pd(TFA)_2/^{2NH2}py$ (6%)		65	8
14	$Pd(TFA)_2/^{2NHMe}py$ (6%)		72	22
15	$Pd(TFA)_2/^{2NMe2}py$ (6%)		53	24
16	$Pd(TFA)_2/^{2NH2}py$ (6%)/TsOH (12%)		65	45
17	$Pd(TFA)_2/^{2NHMe}py$ (6%)/TsOH (12%)		70	65
18	**$Pd(TFA)_2/^{2NMe2}py$ (6%)/TsOH (12%)**		**74 (100)**†	**79 (84)**†
19	$Pd(TFA)_2/^{4NMe2}py$ (6%)		57	55
20	$Pd(TFA)_2/^{4NMe2}py$ (6%)/TsOH (12%)		68	28
21	Pd/C		1.5	< 1
22	Pd/Al_2O_3		< 1	0
23	$Pd/CaCO_3$		0	0
24	$Pd(OH)_2$/C		0	0

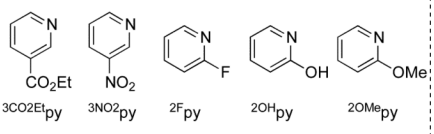
†Yield in parentheses based on 5 mol % Pd.

Ligands:

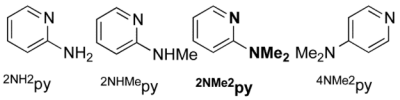
bidentate ligands



electron-deficient pyridines



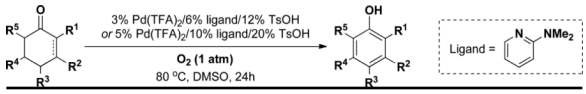
aminopyridines

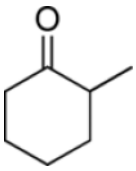
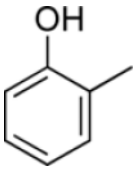
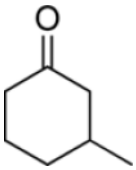
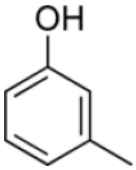
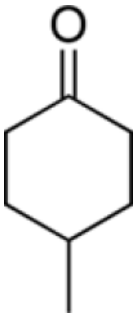
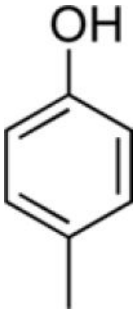
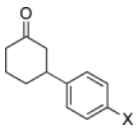
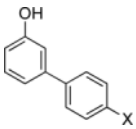


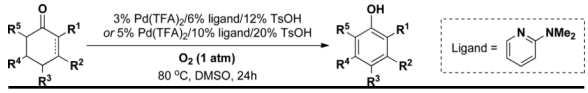
Abbreviations: OAc = acetate; TFA = trifluoroacetate; TsOH = *p*-toluenesulfonic acid. Yields determined by gas chromatography.

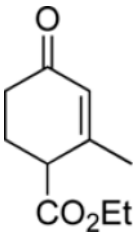
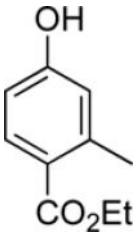
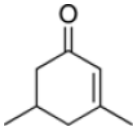
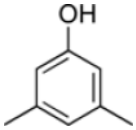
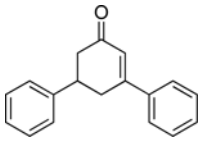
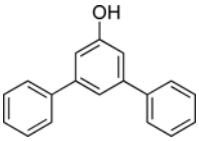
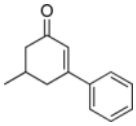
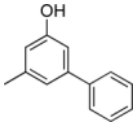
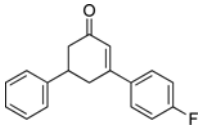
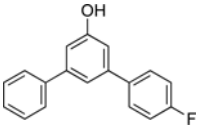
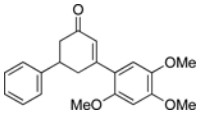
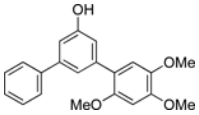
Table 2

Palladium-catalyzed aerobic dehydrogenation of cyclic ketones. Reaction conditions: cyclic ketone (1.0 mmol), $Pd(TFA)_2$ (0.03 or 0.05 mmol), 2-(*N*,*N*-dimethylamino)pyridine (0.06 or 0.10 mmol), TsOH (0.12 or 0.20 mmol), DMSO (0.4 mL), 1 atm O_2, 80 °C, 24 h. Isolated product yields are reported.



entry	substrate	phenol	% yield
1			70*
2			76*
3			86*
4			83*
5		 X = H	78*
6		Ph	85†
7		OMe	96*



entry	substrate	phenol	% yield
8		CF_3	93*
9		CO_2Me	75†
10		F	65†
11		Cl	57†
12			79†
13			76*
14			95†
15			73†
16			91†
17			85†

*3% Pd/6% ligand/12% TsOH.

†5% Pd/10% ligand/20% TsOH.