Pd-Catalyzed Wacker Cyclizations

Palladium-Catalyzed Oxidative Wacker Cyclizations in Nonpolar Organic Solvents with Molecular Oxygen: A Stepping Stone to Asymmetric Aerobic Cyclizations**

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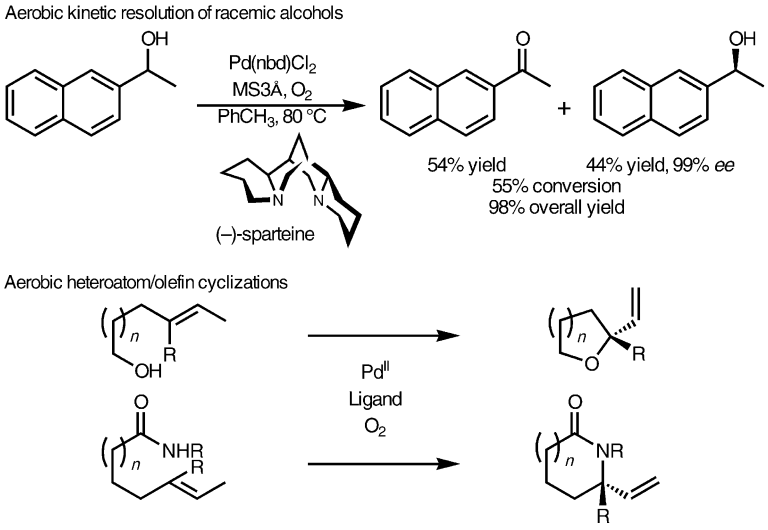
Catalytic asymmetric oxidation-chemistry involving heteroatom transfer from a reagent to a substrate is perhaps unparalleled in synthetic utility for the construction of enantioenriched materials.[1] Conversely, there is a significant deficiency of asymmetric two-electron oxidations that do not involve heteroatom transfer. Some potentially valuable reactions of this type include the oxidation of secondary alcohols and oxidative heterocyclizations (Scheme 1). The design of efficient processes of this nature requires an abundant, inexpensive, and effective stoichiometric oxidant, and a solvent that is amenable to asymmetric catalysis. To begin to address this general synthetic problem, we recently developed a Pd-catalyzed oxidative kinetic resolution of secondary alcohols in toluene that uses molecular oxygen as the terminal oxidant (Scheme 1).[2,3] Herein we demonstrate the utility of this simple system (Pd catalyst, ligand, $PhCH_3$, O_2) for the construction of a range of heterocycles by catalytic oxidative cyclization. We also demonstrate for the first time that aerobic cyclizations of this type are amenable to asymmetric catalysis, and thereby establish a critical proof of concept for the further development of catalytic asymmetric oxidative cyclizations that use molecular oxygen as the sole stoichiometric oxidant.



Scheme 1. Some aerobic oxidation reactions.

Palladium-catalyzed bond-forming constructions have become indispensable in organic chemistry.[4] A favorable property of palladium is that it can serve as both a nucleophile (i.e., Pd^0) and an electrophile (i.e., Pd^{II}), which produces many opportunities for catalysis. Although both modes are prevalent, electrophilic oxidative catalysis by Pd^{II} has garnered less attention in the asymmetric arena. Adding to the disparity is the fact that until recently, cocatalysts (e.g., copper salts) or organic oxidants (e.g., benzoquinone) were necessary for the reoxidation of Pd^0 to Pd^{II}, thus creating a nearly intractable situation for asymmetric catalysis. For example, the use of the traditional copper/O_2 reoxidation system introduces a secondary catalytic cycle, while the benzoquinone system requires the removal of stoichiometric quantities of organic compounds at the end of the reaction. In contrast, reactions that proceed under direct dioxygen coupled catalysis produce H_2O as the sole byproduct. Despite the difficulties of the traditional systems, seminal works by Hosokawa and Murahashi,[5] Hayashi,[6] Sasai,[7] and Bäckvall[8] have established the potential for enantioselective Pd^{II}-catalyzed oxidative cyclizations and dialkoxylations.[9] To the best of our knowledge, however, there were no examples of direct dioxygen-coupled enantioselective Pd^{II}-catalyzed cyclizations prior to this report. In fact, the work on the enantioselective oxidation of secondary alcohols stands as the benchmark for copper-free aerobic asymmetric palladium catalysis.[2,3]

To address this general problem in asymmetric catalysis, we needed to establish the feasibility of aerobic cyclizations under conditions that would eventually be amenable to the introduction of chiral ligands for palladium. Thus, we began our investigation of aerobic oxidative cyclizations with $Pd(OAc)_2$, pyridine, O_2, and MS3Å in $PhCH_3$ at 80 °C (Table 1).[10] We intentionally avoided the more common DMSO-based conditions because of the highly donating nature of DMSO as a ligand for palladium and its use as solvent in such reactions.[11] This would preclude the use of chiral ligands and thus prevent a general entry into asymmetric catalysis.

Treatment of phenol **1** under a range of aerobic oxidation conditions in $PhCH_3$ led to the discovery that the electron-deficient $Pd(TFA)_2$ in conjunction with Na_2CO_3 as a stoichiometric base rapidly produces dihydrobenzofuran **2** in excellent yield (entry 5). Similar to the reactivity observed in the oxidation of secondary alcohols,[9a,c] the absence of pyridine causes a pronounced rate deceleration, and reactions typically proceed to low conversion (entry 6).

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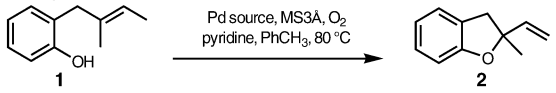
Table 1: Optimization studies.[a]



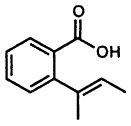
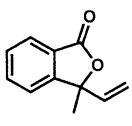
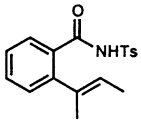
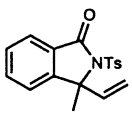
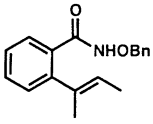
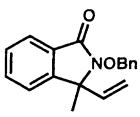
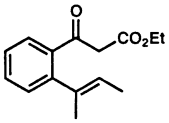
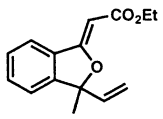
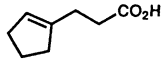
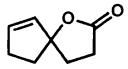
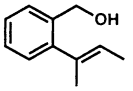
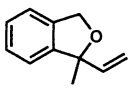
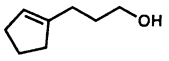
Entry	Pd source	Additive	Time	Yield
1	$Pd(nbd)Cl_2$	None	24 h	7%
2	$PdCl_2$	None	24 h	27%
3	$Pd(OAc)_2$	None	24 h	76%
4	$Pd(TFA)_2$	None	60 min	87%
5	$Pd(TFA)_2$	Na_2CO_3 (2 equiv)	20 min	95%
6	$Pd(TFA)_2$	Na_2CO_3 (2 equiv), no pyridine	24 h	39%

[a] All reactions were carried out with 0.25 mmol of **1**, 5 mol% Pd (0.0125 mmol), 20 mol% pyridine (0.05 mmol), 0.5 mmol additive, 125 mg MS3Å (500 mg mmol^{-1} substrate), and 1 atm O_2 in 2.5 mL $PhCH_3$ (0.1 M in substrate). All yields are based on the isolated product.

Under our optimized conditions, oxidative cyclization of a variety of substituted phenols occurs readily (Table 2). Cyclizations of electron rich phenols are particularly facile, and provide the isolated products with high yields in under 30 min (entries 2–4 and 6–9). Electron deficient phenols serve as excellent substrates as well, although they react more slowly (entry 5). Additionally, dihydropyran systems are accessible under identical conditions (entry 11). Finally, high yields and reasonable rates persist with reduced catalyst loading (2 mol%, entry 12).

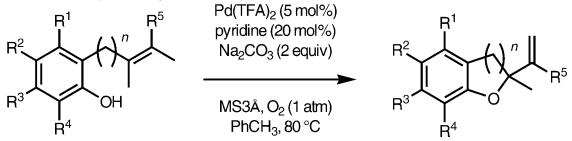
In addition to phenols, we have investigated a number of other nucleophile/alkene oxidative cyclizations. For carboxylic acid derivatives, the addition of stoichiometric amounts of an external base was found to be unnecessary, and exposure simply to $Pd(TFA)_2$, O_2, pyridine, and MS3Å, in $PhCH_3$ at 80 °C leads to a variety of oxidatively cyclized products (Table 3). Importantly, the scope of the cyclization is not limited to benzoic acid derivatives (entries 4 and 5). Moreover, we have shown that oxidative cyclization of primary alcohols is feasible and appears to proceed without significant oxidation to the aldehyde under the optimal conditions (entries 6 and 7).

Table 3: Aerobic oxidative heteroatom/alkene cyclizations.[a]

Entry	Substrate	Product	Time, yield
1[b]			8 h, 90% yield
2[b]			8 h, 88% yield
3[b]			4 h, 82% yield
4[b]			48 h, 63% yield[c,d]
5			48 h, 62% yield[e]
6[b]			3 h, 87% yield[f]
7			10 h, 93% yield[f]

[a] Unless noted, reactions were carried out using 0.25 mmol of starting material, 5 mol% $Pd(TFA)_2$ (0.0125 mmol), 20 mol% pyridine (0.05 mmol), 0.5 mmol additive, 125 mg MS3Å (500 mg mmol^{-1} substrate), and 1 atm O_2 in 1.0 mL (entries 1–5) or 2.5 mL (entries 6–7) $PhCH_3$ at 80 °C. All yields are based on isolated product. [b] The starting material was used as a mixture of *E* and *Z* alkenes. [c] 10 mol% $Pd(TFA)_2$, 40 mol% pyridine, 2 equiv LiOAc. [d] 3:1 *Z*:*E*. [e] 10 mol% $Pd(TFA)_2$, 40 mol% pyridine. [f] 2 equiv Na_2CO_3 were added.

Table 2: Pd-catalyzed aerobic phenol/alkene cyclizations.[a]

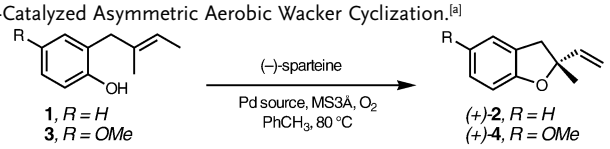


Entry	R^1	R^2	R^3	R^4	R^5	*n*	Time, yield
1	H	H	H	H	H	1	20 min, 95% yield
2	H	Me	H	H	H	1	20 min, 99% yield
3	H	*t*Bu	H	H	H	1	25 min, 90% yield
4	H	OMe	H	H	H	1	15 min, 89% yield
5	H	$COCH_3$	H	H	H	1	25 h, 93% yield
6	H	Me	H	Me	H	1	20 min, 85% yield
7	H	H	H	H	Me	1	25 min, 80% yield
8	OMe	OMe	OMe	H	H	1	10 min, 86% yield
9	H	OMe	H	OMe	H	1	40 min, 80% yield
10	H	OMe	H		H	1	2 h, 93% yield
11[b]	H	H	H	H	H	2	75 min, 85% yield
12[c]	H	H	H	H	H	1	14 h, 86% yield

[a] Unless noted, reactions were carried out with 0.25 mmol of starting material, 5 mol% Pd (0.0125 mmol), 20 mol% pyridine (0.05 mmol), 0.5 mmol additive, 125 mg MS3Å (500 mg mmol^{-1} substrate), and 1 atm O_2 in 2.5 mL $PhCH_3$ (0.1 M in substrate). All yields are based on isolated product. [b] The starting material was used as a 3.6:1 mixture of alkene isomers. [c] 2 mol% $Pd(TFA)_2$, 8 mol% pyridine.

With the success of the racemic aerobic oxidative cyclizations described above, we could then investigate the feasibility of the asymmetric counterpart as a proof of concept that such aerobic cyclizations are amenable to asymmetric catalysis. Thus, we chose to explore the cyclization of phenols, similar to those reported by Hayashi and co-workers,[6] as a test for our catalytic system. Table 4 shows some of the results we have obtained for the asymmetric oxidation of phenols **1** and **3** to ethers

Table 4: The Pd-Catalyzed Asymmetric Aerobic Wacker Cyclization.[a]



1, *R* = *H*
3, *R* = *OMe*

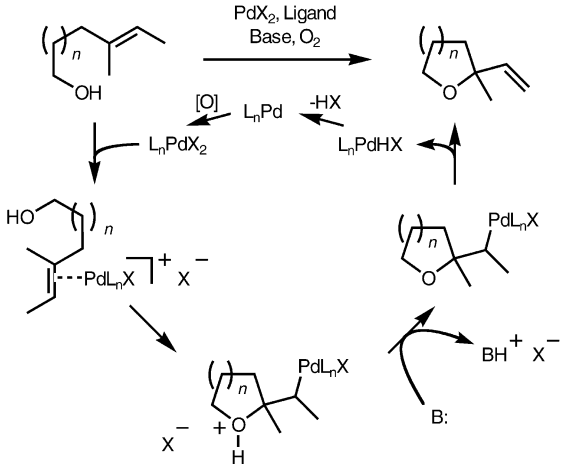
(+)-**2**, *R* = *H*
(+)-**4**, *R* = *OMe*

Entry	Compd	Pd source	Additive	Time	Yield[b]	*ee*
1	**1**	$Pd(nbd)Cl_2$[c]	None	36 h	68%	12%
2	**1**	$PdBr_2$	None	36 h	32%	8%
3	**1**	$PdCl_2$	None	36 h	2%	12%
4	**1**	$Pd(CH_3CN)_2Cl_2$	None	36 h	53%	12%
5	**1**	$Pd(OAc)_2$	None	36 h	18%	51%
6	**1**	$Pd(TFA)_2$	None	36 h	72%	76%
7	**1**	$(sp)Pd(TFA)_2$[d]	None[e]	36 h	83%	77%
8	**1**	$(sp)Pd(TFA)_2$	Na_2CO_3 (2 equiv)[f]	36 h	53%	76%
9	**1**	$(sp)Pd(TFA)_2$	$Ca(OH)_2$ (2 equiv)[f]	36 h	87%[g]	81%
10	**3**	$(sp)Pd(TFA)_2$	$Ca(OH)_2$ (2 equiv)[f]	24 h	64%[g,h]	88%
11	**3**	$(sp)Pd(TFA)_2$	$Ca(OH)_2$ (2 equiv)[f]	60 h@55 °C	57%[g,h]	90%

[a] Entries 1–8 were carried out by using 0.10 mmol of starting material, 10 mol% Pd (0.01 mmol), 40 mol% sparteine (0.04 mmol), 50 mg MS3Å (500 mg mmol^{-1} substrate), and 1 atm O_2 in 1.0 mL $PhCH_3$ (0.1 M in substrate) at 80 °C. Entries 9–11 were carried out using 0.25 mmol of starting material, 10 mol% $(sp)Pd(TFA)_2$ (0.025 mmol), 0.50 mmol $Ca(OH)_2$, 125 mg MS3Å (500 mg mmol^{-1} substrate), and 1 atm O_2 in 2.5 mL $PhCH_3$ (0.1 M in substrate) at 80 °C. [b] Measured by GC. [c] nbd = norbornadiene. [d] sp = (−)-sparteine. [e] 30 mol% (−)-sparteine. [f] 100 mol% (−)-sparteine. [g] Isolated yield. [h] Produced with a dimeric byproduct, see Supporting Information.

(+)-**2** and (+)-**4**, respectively. There is a great deal of disparity in enantioselectivity among palladium sources and additives, as all of the results presented in Table 4 use (−)-sparteine as the sole chiral ligand. Simply changing from $Pd(nbd)Cl_2$ to $Pd(TFA)_2$ results in an increase from 12% *ee* to 76% *ee* (entries 1 and 6). A significant counterion dependence was also observed in our work on the oxidative kinetic resolution of secondary alcohols[2] and points to exceedingly subtle reasons for the general reactivity and enantioselectivity of intermediates in these catalytic reactions. As in the racemic series, we have found that addition of certain bases can accentuate the catalytic activity. Finally, the use of excess (−)-sparteine results in highly enantioselective cyclizations that reach 90% *ee* (entries 8–11).

A plausible mechanism for the aerobic oxidative cyclizations presented herein is outlined in Scheme 2. Initial alkene binding to the electron deficient $L_nPd(TFA)_2$ serves to activate the alkene toward intramolecular nucleophilic attack. Deprotonation of the oxonium ion is facilitated by stoichiometric quantities of the base or by pyridine (or sparteine) through a proton shuttle-type mechanism. In either case, this mechanism accounts for the base-mediated acceleration that is observed in both the racemic and asymmetric cyclizations. Subsequent β-hydride elimination produces $L_nPd(H)X$ that eliminates acid (HX) and L_nPd^0, which, after oxidation by molecular oxygen, reenters the catalytic cycle. Details of the reoxidation steps have been elegantly worked out by Stahl and coworkers.[12]



Scheme 2. Potential mechanism for the Pd-catalyzed aerobic oxidative Cyclizations.

In conclusion, we have demonstrated that several Pd-catalyzed oxidative cyclizations proceed in excellent yield under simple aerobic conditions. Importantly, this system provided entry into enantioselective catalysis with a readily available Pd-sparteine system similar to that used in the previously reported enantioselective alcohol dehydrogenation.[2,3] Although our asymmetric results are somewhat limited in scope at this juncture, we have established for the first time that aerobic cyclizations of this kind are feasible with high levels of enantioselectivity. With this proof of principle established, efforts to expand the scope of and further understand these non-heteroatom-transfer asymmetric aerobic oxidations are ongoing.

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Keywords: asymmetric catalysis · homogeneous catalysis · oxidation · oxygen · palladium

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