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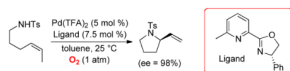
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Enantioselective Pd(II)-Catalyzed Aerobic Oxidative Amidation of Alkenes and Insights into the Role of Electronic Asymmetry in Pyridine-Oxazoline Ligands

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Abstract



Enantioselective intramolecular oxidative amidation of alkenes has been achieved using a (pyrox)Pd(II)(TFA)₂ catalyst (pyrox = pyridine-oxazoline, TFA = trifluoroacetate) and O₂ as the sole stoichiometric oxidant. The reactions proceed at room temperature in good-to-excellent yield (58–98%) and with high enantioselectivity (ee = 92–98%). Catalyst-controlled stereoselective cyclization reactions are demonstrated for a number of chiral substrates. DFT calculations suggest that the electronic asymmetry of the pyrox ligand synergizes with steric asymmetry to control the stereochemical outcome of the key amidopalladation step.

Wacker-type oxidative cyclization reactions provide efficient access to oxygen and nitrogen heterocycles and have been the subject of longstanding interest.¹ Despite extensive efforts, development of enantioselective methods remains a key challenge.^{1i,2–4} Here, we describe a simple catalyst system consisting of Pd(TFA)₂ (TFA = trifluoroacetate) and a pyridine-oxazoline (pyrox) ligand that enables high yields and enantioselectivities in the intramolecular aerobic oxidative amidation of unactivated alkenes bearing tethered sulfonamide nucleophiles. The aliphatic tethers do not require conformational biasing groups (e.g., *gem*-disubstitution or fused cyclic substituents) to achieve efficient cyclization. DFT computational studies provide a preliminary model for the origin of catalyst stereocontrol in these reactions and provide insights into the electronic and steric asymmetry of pyrox ligands.

In 2002, we reported Pd(OAc)₂/pyridine-catalyzed aerobic oxidative cyclization of alkenyl sulfonamides such as **1** (Scheme 1A),^{5a,6} and mechanistic studies of this catalyst system have shown that this reaction proceeds via turnover-limiting *cis*-amidopalladation of the alkene.^{5b,c} This Pd^{II}/pyridine catalyst system has been the starting point for development of other enantioselective aerobic oxidative cyclization reactions;³ however, previous work from our lab suggested that bidentate ligands inhibit the oxidative cyclization of **1** (Scheme 1B).

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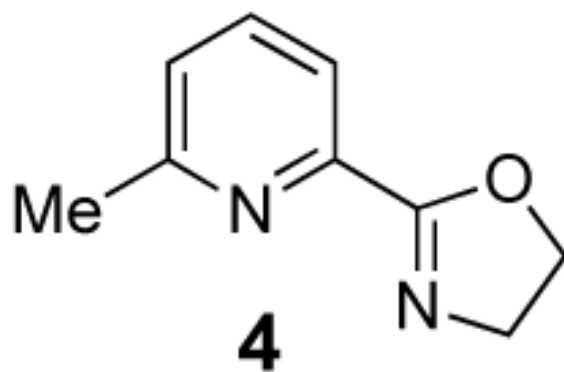
Supporting Information Available: Experimental details, characterization for all new compounds, and chiral HPLC traces, and computational data. This material is available free of charge via the Internet at <http://pubs.acs.org>.

Recently, pyrox and quinoline-oxazoline (quinox) ligands have emerged as an effective class of ligands for enantioselective Pd^{II}-catalyzed reactions. Early applications of these ligands were reported by Widenhoefer in Pd^{II}-catalyzed hydrosilylation/cyclization of 1,6-dienes,⁷ and, more recently, they have been used in enantioselective aerobic oxidative Heck reactions,⁸ C–O bond-forming reactions with *ortho*-vinyl phenols,⁹ oxidative cyclization reactions with *ortho*-allyl anilines,^{3d,f} and other applications.¹⁰ In this context, we tested the aerobic oxidative cyclization of alkenyl sulfonamide **1** in the presence of Pd^{II} salts and the C₁-symmetric Bn-quinox ligand. Use of this ligand in combination with Pd(TFA)₂ and 3 Å molecular sieves (M.S.) in toluene afforded pyrrolidine **2** in 66% enantiomeric excess and 37% yield, substantially better than our earlier results (Scheme 2; cf. Scheme 1B). A similar yield, but lower enantioselectivity, was observed with Pd(OAc)₂ as the Pd source.

The modular nature and ease of synthesis of pyridine-oxazolines enabled a straightforward evaluation of a focused library of ligands. Systematic variation of the pyridine and oxazoline groups revealed that a phenyl glycinol derived oxazoline and a 6-methyl functionalized pyridine provided the highest levels of enantioselectivity (Scheme 3). These subunits were incorporated into ligand **3**, and use of this ligand in the oxidative cyclization reaction resulted in 91% enantiomeric excess and 60% yield. Decreasing the ligand loading from 7.5% to 5.5% led to slightly lower enantioselectivity. In the absence of 3 Å M.S., both the yield and enantioselectivity were reduced. Carrying out the reaction at room temperature resulted in the formation of pyrrolidine **2** in 98% ee and 68% yield. The *cis* alkene was important to the reaction outcome: use of *trans*-**1** as the substrate under the optimized conditions formed **2** in 51% yield and 50% e.e. Both alkene isomers generated the (*R*) enantiomer of the pyrrolidine as the major product with (*S*)-**3** as the ligand.¹¹

A number of other *cis*-alkenes underwent efficient cyclization to afford pyrrolidines with high levels of enantioselectivity (Table 1).¹² Cyclization of ethyl and benzyl substituted alkenes generated products bearing an internal double bond in 97 and 93% ee, respectively (entry 2 and 3), and a *gem*-dimethyl substituted substrate cyclized in 92% ee (entry 4). A symmetrical diene cyclized to provide the desymmetrized product in 93% ee, albeit with moderate diastereoselectivity (entry 5). A sulfamide nitrogen nucleophile was also highly effective, furnishing the corresponding pyrrolidine in 92% ee and 95% yield (entry 6). Use of the more electron-withdrawing nosyl (Ns) *N*-substituent resulted in reduced yield and stereoselectivity (entry 7).

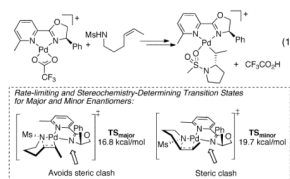
Several enantiomerically pure chiral substrates were investigated to probe the ability of the catalyst to control the stereochemical outcome of the reaction (Table 1, entries 8-19). The intrinsic substrate-controlled diastereoselectivities of these reactions were evaluated by performing the oxidative cyclization reactions with the achiral pyrox ligand **4**, and the reactions were then repeated with a Pd catalyst bearing the (*R*)- or (*S*)-antipode of ligand **3**. The sulfonamide substrate with an α -methyl substituent exhibited a diastereoselectivity of 1:7 favoring the *cis*-2,5-disubstituted pyrrolidine when the reaction was carried out with the *achiral* pyridine-oxazoline ligand **4** (entry 8). The same *cis* diastereomer was formed exclusively when (*R*)-**3** was used as the ligand (entry 9), whereas the *trans* diastereomer was favored (d.r. = 7:1) when (*S*)-**3** was used (entry 10). Although substantial alkene isomerization reduced the yield of the desired product in the latter reaction, these results highlight the ability of the ligand to overcome the substrate-controlled selectivity pattern. Investigation of two substrates with substituents in the β position further highlights the ability to achieve catalyst-controlled stereoselectivity (entries 11–16). When these substrates were tested independently with the two enantiomers of ligand **3**, either diastereomer of the pyrrolidine products could be obtained in very good yield. A substrate with a methyl group adjacent to the alkene was not subject to catalyst control (entries 17–19); the same product diastereomer was obtained in good yield with either enantiomer of the ligand.



Despite the growing success of pyrox and quinox ligands in Pd^{II}-catalyzed reactions, comparatively little fundamental insight has been provided into the origins of enantioselectivity with these ligands. A full mechanistic study of these reactions is the focus of ongoing work, but preliminary DFT computational studies have provided some valuable insights. In our initial work, we have focused on an oxidative amidation pathway that proceeds via *cis*-amidopalladation of the alkene, analogous to that established with the Pd(OAc)₂/pyridine catalyst (Scheme 1). The results reveal that the subtle electronic asymmetry of the two pyrox nitrogen ligands plays an important role in the stereochemical course of the reaction.

Four substrate-binding conformations were optimized for a putative Pd^{II}-(amidate-alkene) intermediate, in which the alkene is *cis* or *trans* with respect to the pyridine (*cis*_{py} and *trans*_{py}) and binds to Pd with *re* or *si* facial selectivity (*re* vs. *si*) (Scheme 4). The calculated free energies of the four ground-state structures reveals a preference for the sulfonamidate to coordinate *cis* to pyridine and with the Ms group *anti* to the oxazoline methyl group. This conformational preference is retained in the transition-state structures. The preference for the *cis*_{py} orientation arises from the electronic asymmetry of the pyrox ligand, which is evident from analogous calculations with an unsubstituted pyrox ligand lacking significant steric effects: the *cis*_{py} orientation is more stable than *trans*_{py} by 1.76 kcal/mol.¹³ The observed electronic asymmetry is a result of the more basic oxazolonyl fragment exerting a stronger *trans* influence, thereby directing substrate orientation.¹³

This analysis was expanded to a more experimentally relevant system by calculating the free energy profile for the reaction of the [(pyrox)Pd(TFA)]⁺ species and (*Z*)-4-hexenylmesylamide, illustrated in eq 1.¹³ The calculated relative free energies of the diastereomeric transition states, **TS_{major}** and **TS_{minor}** ($\Delta\Delta G^{\ddagger}_{\text{cald}} = 2.9$ kcal/mol), match the experimental result remarkably well (at 98% ee, the $\Delta\Delta G^{\ddagger} = 2.7$ kcal/mol). Analysis of the transition state structures **TS_{major/minor}** reveal the vinylic methyl group in **TS_{minor}** is in close proximity to the oxazolonyl phenyl group, whereas the vinylic methyl group in **TS_{major}** is oriented downward, away from the phenyl group. This analysis highlights the synergy between the electronic asymmetry of the pyrox framework, which orients the substrate at the Pd^{II} center, and the steric effects of the oxazoline substituent, which differentiates the two enantiotopic faces of the alkene in the insertion step. These insights resemble principles elaborated by Trend and Stoltz on the electronic and steric influence of (–)-sparteine as a C₁-symmetric ligand in the Pd-catalyzed oxidative kinetic resolution of secondary alcohols.¹⁴



In summary, we have developed highly enantioselective Wacker-type oxidative cyclizations of alkenes with sulfonamides linked via conformationally unconstrained aliphatic tethers. The Pd(pyrox)(TFA)₂ catalyst for these reactions is very efficient, operating at room temperature, and highly selective. Preliminary computation insights into the origin of the enantioselectivity highlight the importance of electronic asymmetry in the pyrox ligand family, and they provide an important foundation for the rational design of new ligands for enantioselective transformations.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

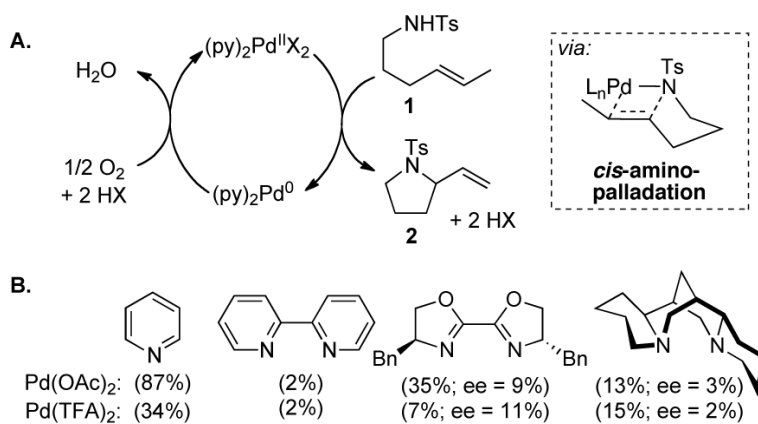
Acknowledgments

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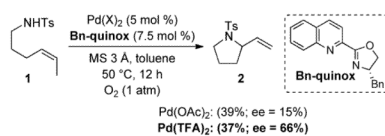
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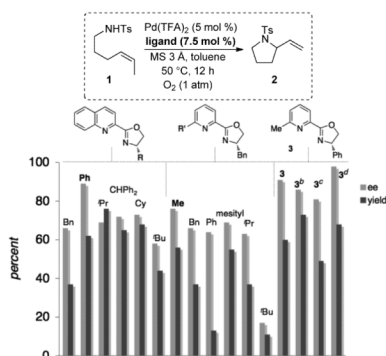
**Scheme 1.**

Pd(OAc)₂/Pyridine-Catalyzed Intramolecular Aerobic Oxidative Amidation of an Alkene and Ligand Effects.

Reaction conditions: 5 mol % PdX₂, 7.5 mol % ligand (10 mol % Py), O₂ (1 atm), molecular sieves 3 Å, toluene (0.1 M), 50 °C, 12 h.

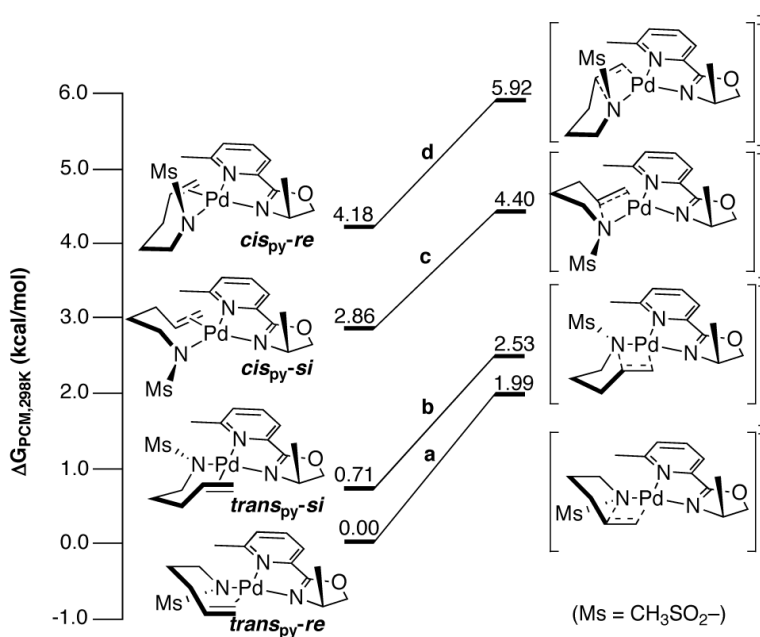


Scheme 2.
Enantioselective Oxidative Amidation Employing Pyridine Oxazoline Ligands.

**Scheme 3.****Ligand Substituent Effects and Reaction Optimization.^a**

^a Conditions: **1** (0.075 mmol), 1 atm O₂, MS 3 Å (20 mg), toluene (0.75 mL), 12 h. Yield determined by ¹H NMR spectroscopy, internal standard = 1,3,5-trimethoxybenzene.

Enantiomeric excess determined by chiral HPLC (see Supporting Information for details). ^b 5.5 mol % ligand. ^c Without MS 3 Å. ^d 25 °C, 24 h. Isolated yield (0.5 mmol scale).

**Scheme 4.**

Calculated Ground- and Transition-State Energies Associated with the *cis*-Amidopalladation of an Alkene at a Pyridine-Oxazoline-Ligated Pd^{II}-Center.^a

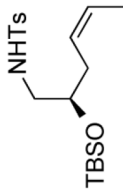
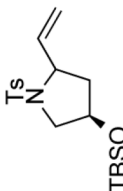
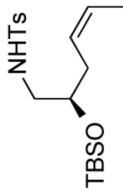
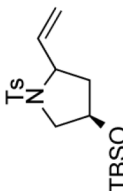
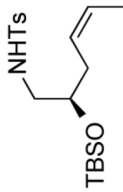
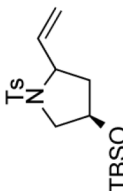
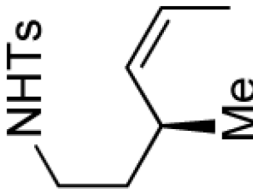
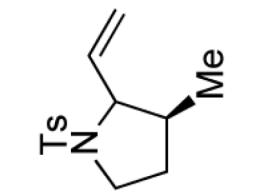
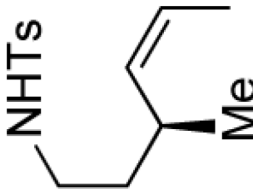
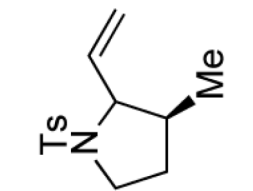
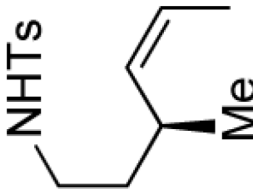
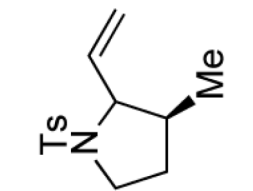
^a The cationic charge on all structures is omitted for clarity. Final structures were optimized with the following method (*Gaussian 03*): B3LYP; Stuttgart RSC 1997 ECP/triple- ζ basis for Pd; 6-311+G (d,p) basis on all other atoms; polarizable continuum solvation model (toluene); see Supporting Information for computational details.

Table 1

Asymmetric Aerobic Oxidative Cyclization.^{a,b}

entry	substrate	product	ligand	yield % ^c	ee % ^d or dr ^b
1			(S)-3	68	98
2			(S)-3	62	97
3			(S)-3	98	93

entry	substrate	product	ligand	yield % ^c	ee % ^d or d.r. ^b
4			(S)-3	58	92
5			(S)-3	86	93 (95) ^f (d.r. = 1.4:1)
6			(S)-3	95	92
7			(S)-3	52	76
8			4	-- ^g	1:7
9			(R)-3	88	<1:20
10			(S)-3	23 (64) ^h	7:1
11			4	-- ^g	1.5:1
12			(R)-3	87	1:17
13			(S)-3	90	>20:1

entry	substrate	product	ligand	yield % ^c	ee % ^d or dr ^b
14			4	-- ^g	1.4:1
15			(R)- 3	97	>20:1
16			(S)- 3	92	<1:20
17			4	-- ^g	>20:1
18			(R)- 3	92	>20:1
19			(R)- 3	77	>20:1

^a Conditions: substrate (0.3 mmol), Pd(TFA)₂ (15 μmol), ligand (22.5 μmol), MS 3 Å (80 mg), toluene (3 mL), 25 °C, 24 h.

^b Entries 8-19; 36 h.

^c Isolated yield.

^d Enantiomeric excess determined by chiral HPLC analysis.

^e Diastereomeric ratio (*anti:syn*) determined by ¹H NMR spectroscopy of the crude reaction mixture.

^f Enantiomeric excess of the minor diastereomer.

^g Substantial alkene isomerization was observed in these reactions, and the reaction yields were not optimized.

^h The number in parentheses refers to a mixture of olefin isomers.