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Pd(II)/^{t}Bu-quinolineoxazoline: An Air-Stable and Modular Chiral Catalyst System for Enantioselective Oxidative Cascade Cyclization

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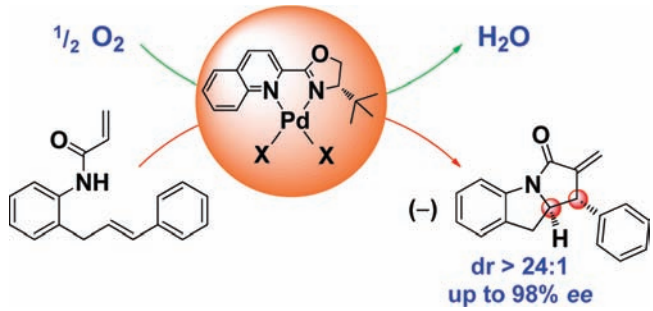
ABSTRACT



An air-stable and structurally tunable chiral ^{t}Bu-quinolineoxazoline/Pd(II) catalyst system has been developed for the enantioselective oxidative cascade cyclization of a variety of disubstituted olefinic substrates, with the apparent advantages of good yields and excellent enantioselectivities (up to 98% ee) and diastereoselectivities (dr >24:1). A transition-state model has also been proposed to account for the excellent stereocontrol.

As integral cores of many bioactive alkaloids, enantioenriched N-heterocycles have attracted tremendous attention for development of new approaches to construct those cyclic skeletons.[1]Numerous examples rely on transition-metal-catalyzed asymmetric C−N bond formations such as allylic substitution[2] and hydroamination.[3] However, these methods are restricted to single bond-forming events, and their cascade variants for constructing several bonds in a single step remain to be developed. We previously reported enantioselective C−N bond and C−C bond tandem cyclization reactions of unsaturated anilides under a (−)-sparteine/Pd(TFA)$_2$ catalyst system.[4] Despite this earlier system's excellent enantioselectivities (up to 91% ee) and easy availability of (−)-sparteine, a new chiral catalyst system (in particular, one adept at oxidative transformations) remains highly desirable because: (1) sparteine is difficult to be chemically engineered, restricting its reaction scope; (2) (+)-sparteine[5] is not naturally occurring, and the preparation of its surrogates invariably requires multistep synthesis;[6,7] and (3) new chiral ligands for Pd(II) that can tolerate oxidizing conditions remain of great demand.[8] More recently, we discovered that in our oxidative cascade cyclization[9] quino-

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(1) For comprehensive reviews, see: (a) Nicolaou, K. C.; Edmonds, D. J.; Bulger, P. G. *Angew. Chem., Int. Ed.* **2006**, *45*, 7134. (b) Tietze, L. F. *Chem. Rev.* **1996**, *96*, 115. For a thematic issue on "Heterocycles", see: Katritzky, A. R. (Ed.), *Chem. Rev.* **2004**, *104*.

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(3) Müller, T. E.; Hultzsch, K. C.; Yus, M.; Foubelo, F.; Tada, M. *Chem. Rev.* **2008**, *108*, 3795.

(4) To the best of our knowledge, this is the only successful example of enantioselective oxidative C−N bond-forming reaction. See: Yip, K.-T.; Yang, M.; Law, K.-L.; Zhu, N.-Y.; Yang, D. *J. Am. Chem. Soc.* **2006**, *128*, 3130.

(5) For the first asymmetric synthesis of (+)-sparteine, see: Smith, B. T.; Wendt, J. A.; Aubé, J. *Org. Lett.* **2002**, *4*, 2577.

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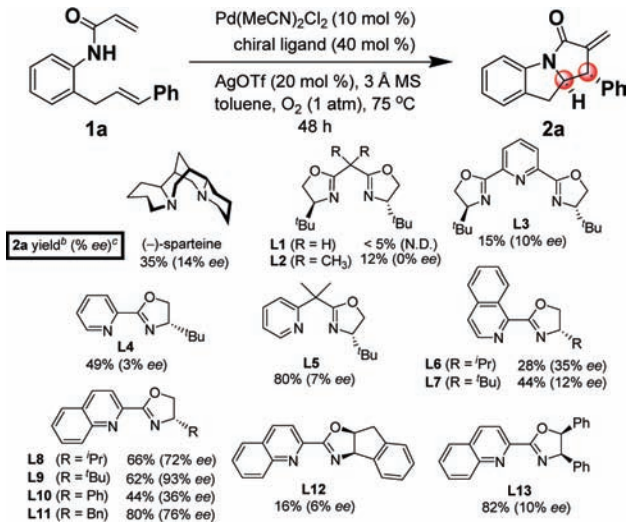
line as an N-ligand is superior to pyridine, a well-established ligand being used extensively in a range of Pd-catalyzed oxidative reactions.[10] These findings prompted us to incorporate readily available chiral elements into the quinoline moiety for the development of new chiral ligands for Pd catalysis as a viable alternative to the (−)-sparteine/Pd(II) system. In contrast to the well-developed asymmetric Pd(0)-catalyzed cyclization reactions,[11] much less attention has been paid to investigate the origins of enantioselectivities in Pd(II)-catalyzed asymmetric nucleopalladation of alkenes.[12] Herein, we present a new chiral Pd catalyst system comprising quinoline and chiral oxazoline units,[13] which catalyzes enantioselective oxidative cascade cyclization of unsaturated anilides to afford enantioenriched indolines[14] with excellent diastereoselectivities (dr >24:1) and enantioselectivities (up to 98% ee). Also, we propose a transition-state model to account for the observed high enantioselectivity attained by the new chiral Pd catalyst system.

Since (−)-sparteine has been previously identified as a good ligand for the oxidative cascade cyclization of monosubstituted olefinic substrates, the disubstituted olefin **1a** was first subjected to the cyclization (Scheme 1). However, this

Scheme 1. Screening of Chiral Ligands[a]



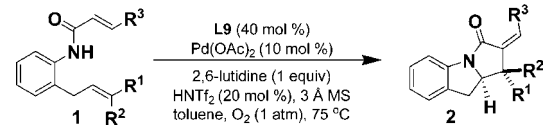
[a] Reaction scale: 1 mmol of substrate **1a**. [b] Isolated yield. [c] Determined by HPLC analysis using a Chiralcel OD column.

resulted in a low observed ee value of only 14%. C_2-symmetric BOX ligands[15] **L1**−**L2** and PyBOX ligand[16] **L3** were not efficient for this reaction. Pyridine-oxazoline ligand **L4** afforded product **2a** in moderate yield but low enantioselectivity (3% ee). We anticipated that placing one more carbon between the pyridine and the oxazoline ring would presumably allow the formation of a six-membered ring chelate with Pd(II) species, thereby creating a distinct chiral environment. Indeed, pyridine-oxazoline **L5** did improve the conversion dramatically, albeit with poor chiral induction.

Isoquinoline-oxazoline **L6** and **L7** were also examined, and only modest enantioselectivities were observed. Interestingly, the ^{i}Pr-quinoline-oxazoline **L8** allowed moderate conversion and enantiomeric excess (72% ee). With these encouraging results, we moved on to evaluate a series of quinoline-oxazoline ligands (QUOX) with different R groups. These air-stable QUOX ligands can be readily synthesized in two steps from their parent carboxylic acids and enantiopure amino alcohols, making this class of ligands structurally versatile and highly modular. Although **L10**, **L12**, and **L13** led to poor enantioselectivities, Bn-QUOX (**L11**) gave good yield (80%) and moderate product ee value (76%). By using ^{t}Bu-QUOX (**L9**),[17] the product enantioselectivity was improved further to 93% ee. The X-ray crystallographic structure of Pd(**L9**)Cl_2 showed the coplanarity of the quinoline and oxazoline units upon chelation with Pd(II).

Further optimization of the reaction conditions led to an improved catalyst system, which was then used to evaluate the scope of a Pd(II)-catalyzed enantioselective cascade cyclization for a number of unsaturated acrylanilides (Table 1). Modest to good product yields were achieved for both

Table 1. Pd(II)-Catalyzed Enantioselective Cascade Cyclization[a]



	substrate **1**					
entry	R^1	R^2	R^3	t (h)	yield of **2** (%)[b]	ee (%)[c]
1	Ph	H	H	48	75 (**2a**)	98
2	p-FC_6H_4	H	H	48	68 (**2b**)	92
3	p-ClC_6H_4	H	H	48	75 (**2c**)	80
4	p-MeC_6H_4	H	H	48	74 (**2d**)	96
5	p-$MeOC_6H_4$	H	H	40	82 (**2e**)	86
6	m-ClC_6H_4	H	H	48	70 (**2f**)	82[d]
7	o-$MeOC_6H_4$	H	H	40	73 (**2g**)	83
8	2-naphthyl	H	H	48	65 (**2h**)	91
9	Ph	H	Ph	60	55 (**2i**)	90
10	Ph	H	p-MeC_6H_4	60	45 (**2j**)	85
11	H	Ph	H	60	73 (**2k**)	80

[a] Unless otherwise indicated, all reactions were carried out at 75 °C with substrate (1 mmol), 2,6-lutidine (1 equiv), $Pd(OAc)_2$ (10 mol %), $HNTf_2$ (20 mol %), and ^{t}Bu-QUOX **L9** (40 mol %) over activated 3 Å molecular sieves (500 mg/mmol substrate) in toluene (10 mL) under O_2 (1 atm). [b] Isolated yield. [c] Determined by HPLC analysis using a Chiralcel OD or OD-H column. [d] The absolute configuration of product **2f** was determined by X-ray crystallography.

electron-rich and electron-poor substrates (entries 1−7), and in particular, the cyclization of **1a** resulted in enantiomeric excesses of up to 98% (entry 1). In addition, X-ray crystallographic analysis of chiral product **2f** also reveals the absolute configuration of the angular carbon center as *R* and that of the chlorophenyl-bearing carbon center as *S*. More bulky substrate **1h** could also be cyclized with excellent chiral induction (91% ee; entry 8). Substrates **1i** and **1j** with a cinnamide group cyclized less efficiently, albeit with good enantioselectivities (entries 9 and 10). Cyclization of *cis*-

(6) For recent efforts, see: O'Brien, P. *Chem. Commun.* **2008**, 655.
(7) For recent applications of (+)-sparteine surrogates in asymmetric catalysis, see: Ebner, D. C.; Trend, R. M.; Genet, C.; McGrath, M. J.; O'Brien, P.; Stoltz, B. M. *Angew. Chem, Int. Ed.* **2008**, *47*, 6367.

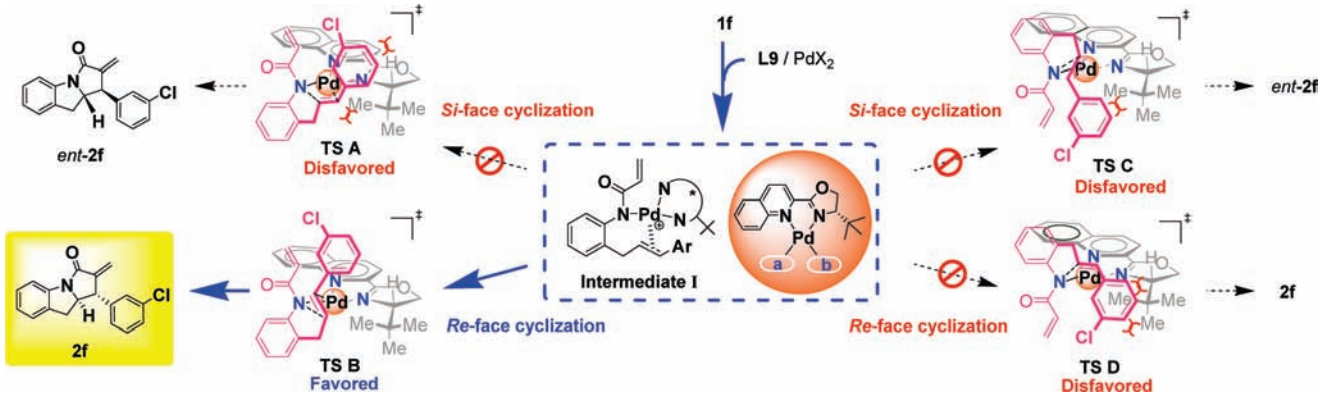


Figure 1. Proposed transition-state model.

olefin-bearing substrate **1k** proceeded to afford **2k** with good yield and enantiomeric excess (entry 11).

It is noteworthy that the oxidative cascade cyclization of all substrates essentially yielded only one diastereomer. A comparison of the cyclizations of **1a** and **1k** revealed the stereospecific nature of the enantioselective cascade cyclizations, in which the olefin geometry of the substrate completely controls the relative stereochemistry of the product. In addition, *the stereochemical outcomes supported the syn-amidopalladation as the only operating pathway in the reaction mechanism.*[18]

The absolute stereochemistry of **2f** can be explained by proposing a transition-state model as shown in Figure 1. Owing to the observed high enantioselectivities, the acrylimide nitrogen (substrate) bound to the Pd center should occupy site **a** instead of site **b** to maximize the interaction of the chiral element of the ligand with the aryl olefin in the formation of the first chiral center. The additional benzene ring of the quinoline moiety is crucial to offer steric bulkiness that constrains the orientation of the Pd-bound substrate. Prior to amidopalladation, site **b** would be released by dissociation of the counterion and occupied by the aryl-substituted olefin (substrate). Since cyclization proceeds through a *syn*-amidopalladation, four different transition states (TS) originating from intermediate **I** are considered. *Si*-face cyclization of **I** leading to TS **A** is disfavored due to steric repulsion between the cinnamyl moiety of substrate and the *tert*-butyl group of **L9**. In contrast, formation of TS **B** is favored through *Re*-face cyclization. In this case, the orientation of the cinnamyl group of the substrate is sterically matched with the chiral environment of **L9**. However, when the substrate is turned upside down, the resulting TS **C** and **D** are disfavored and nonproductive since the cinnamyl group of the substrate would directly clash with the *tert*-butyl group of **L9**, regardless of the orientation of cinnamyl olefin from one side to another (i.e., TS **C** ↔ TS **D**). As a result, only one (TS **B**) out of the four possible transition states is favored, affording the enantioenriched product.

In summary, a novel chiral ^{t}Bu-QUOX (**L9**)/Pd(II) system has been developed for enantioselective oxidative cascade cyclizations. This catalyst system has the advantages of being air stable, structurally tunable, and highly stereoselective for a variety of disubstituted olefinic substrates. A transition-state model has also been proposed to account for the excellent stereocontrol, which provides the basis for designing new asymmetric oxidative systems.

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Supporting Information Available: Preparation and characterization of **1**−**2** and **L9**; HPLC analysis of chiral products **2**; and X-ray crystallographic data of product (−)-**2f** and complex Pd(**L9**)Cl_2. This material is available free of charge via the Internet at http://pubs.acs.org.

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