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Palladium-Catalyzed Highly Diastereoselective Oxidative Cascade Cyclization Reactions

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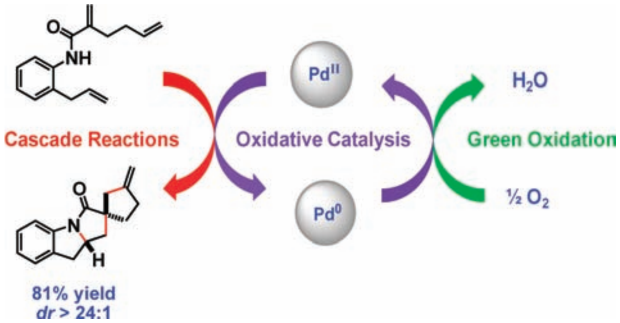
ABSTRACT



Isoquinoline and quinoline have been discovered as novel ligands for palladium-catalyzed oxidative cascade cyclization reactions. With our new catalyst systems (Pd(OAc)$_2$/isoquinoline or quinoline), unsaturated anilides cyclize under an oxygen atmosphere (1 atm) to furnish structurally versatile indoline derivatives in good yields. One C−N bond and two C−C bonds are formed in a single step with excellent diastereoselectivities (dr > 24:1).

Cascade cyclization reactions[1] are powerful and practical strategies for constructing polycyclic ring skeletons, many of which serve as frameworks of natural products with important bioactivities. Over the last few decades, Heck-type cascade cyclization has become one of the most popular methods for the synthesis of multiple ring systems (Scheme 1, top route).[2] However, these cascade cyclization reactions do have their intrinsic drawbacks, including the following: (1) preactivation of cyclization precursors as aryl (or vinyl) halides (or triflates), leading to concomitant formation of stoichiometric amounts of hydrohalic (or triflic) acids; (2) palladium complexes as catalysts that usually feature air-sensitive phosphine ligands; and (3) a reaction scope that is limited to carbon−carbon bond formation, rather than more versatile carbon−heteroatom bond formation.[3] Thus, methodological refinement toward cascade cyclization reactions that are more atom-economical and applicable to carbon−heteroatom bond formation remains a central pursuit in the synthesis of complex polycyclic molecules (Scheme 1; bottom route).

Recently, we reported that palladium-catalyzed oxidative double cyclization of unsaturated anilides can afford a variety of racemic and enantioenriched indoline derivatives with the use of Pd(OAc)$_2$/pyridine and Pd(TFA)$_2$/(−)-sparteine, respectively, as catalyst systems.[4] Importantly, our oxidative double cyclization is free of any

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[1] (a) Nicolaou, K. C.; Edmonds, D. J.; Bulger, P. G. *Angew. Chem., Int. Ed.* **2006**, *45*, 7134–7186. (b) Tietze, L. F. *Chem. Rev.* **1996**, *96*, 115–136.

[2] For excellent reviews, see: (a) de Meijere, A.; Zezschwitz, P. V.; Bräse, S. *Acc. Chem. Res.* **2005**, *38*, 413–422. (b) Link, J. T. *Org. React.* **2002**, *60*, 157–534. (c) Negishi, E.-I.; Copéret, C.; Ma, S.; Liou, S.-Y.; Liu, F. *Chem. Rev.* **1996**, *96*, 365–393.

[3] For reviews of Pd-catalyzed cyclization with an emphasis on natural product synthesis, see: (a) Shibasaki, M.; Vogel, E. M.; Ohshima, T. *Adv. Synth. Catal.* **2004**, *346*, 1533–1552. (b) Dounay, A. B.; Overman, L. E. *Chem. Rev.* **2003**, *103*, 2945–2963. (c) Shibasaki, M.; Boden, C. D. J.; Kojima, A. *Tetrahedron* **1997**, *53*, 7371–7395.

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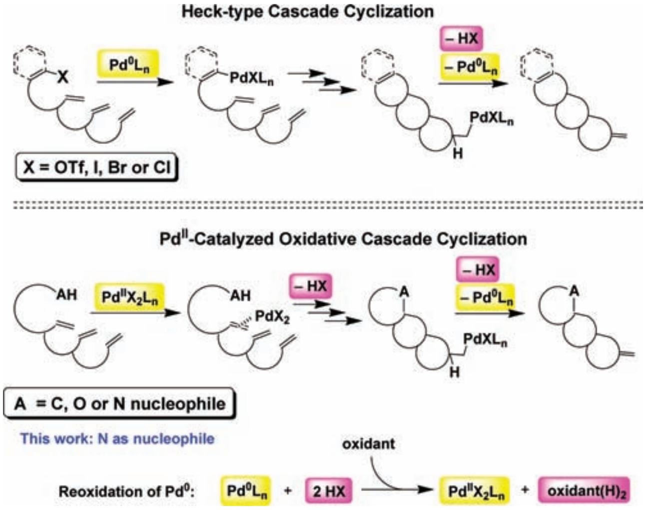
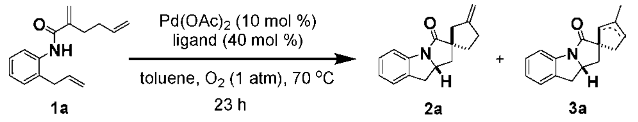
Scheme 1. Top Route: Heck-Type Cyclization Involves Oxidative Addition to Aryl/Vinyl Halides or Triflates (Pre-activated Carbon Nucleophiles), thus Requiring Pd(0) Catalysts. Bottom Route: Oxidative Cyclization Is Initiated through Nucleophilic Attacks on Pd(II)−olefin Complexes, and External Oxidants Are Required To Regenerate Pd(II) from Pd(0) Species



undesired monocyclization products, even in the absence of tandem relays, which are usually required in polycyclization reactions. To the best of our knowledge, no successful examples of palladium-catalyzed oxidative cascade cyclization have been reported for the formation of more than two bonds.[5] Herein we report palladium-catalyzed, highly diastereoselective oxidative cascade cyclization of unsaturated anilides, leading to the formation of three bonds in one step.

We first investigated the cyclization of **1a** under a Pd(OAc)$_2$/pyridine catalyst system (Table 1, entry 1).[6]

Table 1. Screening of *N*-Ligands for the Pd-Catalyzed Oxidative Cascade Cyclization[a]



entry	ligand	convn[b] (%)	% yield (**2a** + **3a**)[b]	product ratio (**2a**:**3a**)[b]
1	pyridine	73	56	1.5:1
2	quinoline	86	70	4.2:1
3	6-methoxyquinoline	43	39	1:8.3
4	8-methylquinoline	42	26	1:3.2
5	acridine	65	24	1:6.3
6	quinoxaline	52	39	1:1.4
7	isoquinoline	89	76	5.6:1

[a] All reactions were performed at 70 °C using **1a** (0.2 mmol), ligand (40 mol %), and Pd(OAc)$_2$ (10 mol %) in toluene (2 mL) under O$_2$ (1 atm). [b] Determined by ^{1}H NMR.

Similar to our oxidative double cyclization,[4] the cascade cyclization of **1a** did not produce any undesired monocyclization products. The reaction afforded a mixture of triple cyclization products **2a** and **3a** (in 1.5:1 ratio) in 54% yield. Further screening of different ligands was proven to be fruitful: using quinoline in place of pyridine as ligand improved both product yield and ratio (entry 2 vs 1). However, other quinoline derivatives did not result in satisfactory reaction conversions (entries 3−6). Interestingly, isoquinoline was found to be the best ligand for the cyclization of **1a**, furnishing **2a** as the major product (in 5.6:1 ratio) in 76% combined yield (entry 7).

A comparison of basicities of these *N*-heteroaromatics indicates a correlation with the reaction conversion and product ratio.[7] Therefore, we hypothesized that the *N*-ligand basicities play a crucial role in suppressing olefin isomerization.

With quinoline and isoquinoline as ligands, we then evaluated the scope of the cascade cyclization, and the results are summarized in Table 2. Substrates **1a**−**c**, which bear different para substituents, underwent triple cyclization smoothly to furnish **2a**−**c** as the sole diastereomers in good yields (entries 1−6). Notably, the triple cyclization reactions were found to be highly diastereoselective (dr > 24:1). Compared with reactions under the Pd(OAc)$_2$/isoquinoline system, the cyclization reactions of **1a**−**c** using the Pd(OAc)$_2$/quinoline system required similar reaction time to reach complete conversion. However, the Pd(OAc)$_2$/isoquinoline system resulted in better yields of products **2a**−**c** by lowering the yields of olefin-isomerized product **3**. For instance, the cyclization of **1c** with the Pd(OAc)$_2$/quinoline system furnished product **2c** in 34% yield and olefin-isomerized product **3c** in 29% yield (entry 6). When the ligand was changed to isoquinoline, **1c** could be converted to **2c** in 55% yield by suppressing the formation of olefin-isomerized product **3c** (5% yield; entry 5). On the other hand, the cyclization efficiency of **1a**−**c** did not correlate strongly with their electronic properties, which differs from the case of our recently reported double cyclization reactions involving unsaturated anilides. The aforementioned system exhibited a significant electronic dependence, allowing electron-withdrawing anilides to cyclize faster than did their electron-donating counterparts.[4] With the Pd(OAc)$_2$/isoquinoline system, substrate **1d**, which possesses a homologated olefinic tethered chain, cyclized in a diastereoselective manner to afford **2d** as the major product (45% yield; entry 7) and trace amounts of olefin-isomerized products (2% combined yield). The yield of

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(4) Yip, K.-T.; Yang, M.; Law, K.-L.; Zhu, N.-Y.; Yang, D. *J. Am. Chem. Soc.* **2006**, *128*, 3130–3131.

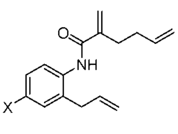
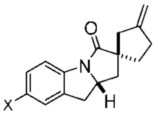
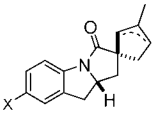
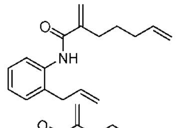
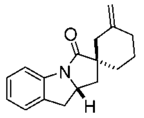
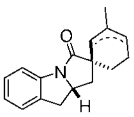
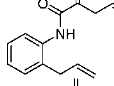
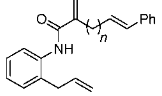
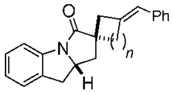
(5) For examples of palladium-catalyzed oxidative cyclizations involving the formation of more than one bond, see: (a) Alexanian, E. J.; Lee, C.; Sorensen, E. J. *J. Am. Chem. Soc.* **2005**, *127*, 7690–7691. (b) Tietze, L. F.; Sommer, K. M.; Zinngrebe, J.; Stecker, F. *Angew. Chem., Int. Ed.* **2005**, *44*, 257–259. (c) Liu, C.; Widenhoefer, R. A. *J. Am. Chem. Soc.* **2004**, *126*, 10250–10251. (d) Arai, M. A.; Kuraishi, M.; Arai, T.; Sasai, H. *J. Am. Chem. Soc.* **2001**, *123*, 2907–2908. (e) Andersson, P. G.; Bäckvall, J.-E. *J. Am. Chem. Soc.* **1992**, *114*, 8696–8698. (f) Tamaru, Y.; Hojo, M.; Higashimura, H.; Yoshida, Z.-I. *J. Am. Chem. Soc.* **1988**, *110*, 3994–4002.

(6) For screening of other reaction parameters, including the effects of solvent, temperature, and oxidant, see the Supporting Information.

(7) For details, see the Supporting Information.

Table 2. Scope of Pd-Catalyzed Oxidative Cascade Cyclization[a]

$$\text{substrate}\ \xrightarrow[\text{toluene, O}_2\text{ (1 atm), 70 °C}]{\text{Pd(OAc)}_2\text{ (10 mol \%)},\ \text{ligand (40 mol \%)}}\ \text{product (dr > 24:1)}^{b}$$

entry	substrate			ligand	t (h)	product (% yield)[c]			
1	**1a**		X = H	isoquinoline	28		**2a** (81)		**3a** (3)
2	**1a**			quinoline	27		**2a** (60)		**3a** (9)
3	**1b**		X = F	isoquinoline	30		**2b** (70)		**3b** (3)
4	**1b**			quinoline	30		**2b** (55)		**3b** (7)
5	**1c**		X = OMe	isoquinoline	26		**2c** (55)		**3c** (5)
6	**1c**			quinoline	25		**2c** (34)		**3c** (29)
7	**1d**			isoquinoline	19		**2d** (45)		**3d** (2)
8	**1d**			quinoline	19		**2d** (59)		**3d** (5)
9	**1e**			quinoline	48				
10	**1f**		***n*** = 1	quinoline	19		**2f** (33)[d]		
11	**1g**		***n*** = 2	isoquinoline	24		**2g** (77)		
12	**1h**		***n*** = 3	quinoline	22		**2h** (55)		

[a] Unless otherwise indicated, all reactions were performed at 70 °C using the substrate (0.3 mmol), ligand (40 mol %), and Pd(OAc)$_2$ (10 mol %) in toluene (3 mL) under O$_2$ (1 atm). [b] Diastereomeric ratio of the crude reaction mixture was determined by ^{1}H NMR, and the major diastereomer was shown. [c] Yield of isolated product. [d] Besides **2f**, other unidentifed products were found.

product **2d** could be improved to 59% when quinoline was used as the ligand (entry 8). We reasoned that the formation of *endo*-olefinic products **3a−d** is most likely due to the secondary addition of palladium hydride to the *exo*-olefin moiety, resulting in olefin isomerization through subsequent iterative β-hydride elimination/palladium migration.[8] *As a result, our examples clearly demonstrate the pronounced ligand effects on the product selectivity (i.e.,* ***2*** *vs* ***3****) and reveal the role of N-ligand in suppressing olefin isomerization.*

Despite the success of the cyclization of trienes **1a−c** (via sequential 5-*exo*;5-*exo*;5-*exo* mode) and **1d** (via sequential 5-*exo*;5-*exo*;6-*exo* mode), substrate **1e** failed to cyclize, and most of the starting material (>90%) was recovered (entry 9). Gratifyingly, substrate **1f** cyclized to afford product **2f** in 33% yield (entry 10). The last cyclization of **1f** was expected to be the most challenging step as it involves a 4-*exo-trig* cyclization.[9] On the other hand, substrates **1g** and **1h** with *trans*-cinnamyl moiety cyclized diastereoselectively to furnish **2g** (with isoquinoline as the ligand; 77% yield; entry 11) and **2h** (with quinoline as the ligand; 55% yield; entry 14) as the sole cyclization products, respectively, and no olefin isomerization products such as **3** were produced.[10]

A transition-state model is proposed here to rationalize the high diastereoselectivity observed in the Pd-catalyzed cascade cyclization reactions (Scheme 2). The unsaturated anilide **1** undergoes reversible intramolecular amidopalladation to generate σ-alkylpalladium intermediate **A**, which cyclizes in 5-*exo-trig* mode through transition state **B** to afford intermediate **C**. In contrast, the cascade cyclization of **1** through transition state **D** becomes severely disfavored because of the steric repulsion between the angular hydrogen and the pendant unsaturated chain (R group). In transition state **B**, the more bulky unsaturated chain (R group) is placed further away from the angular hydrogen, leading to a lower barrier of cyclization pathway than that of **D**. Eventually, sequential olefin insertion of intermediate **C** results in **2** as the sole diastereomer. The catalytic cycle is completed by the reoxidation of Pd(0) to Pd(II) with molecular oxygen as a terminal oxidant.[11]

In summary, we have reported new palladium-catalyzed oxidative cascade cyclization reactions which are highly diastereoselective in constructing three bonds and two

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(8) Cabri, W.; Candiani, I. *Acc. Chem. Res.* **1995**, *28*, 2–7.

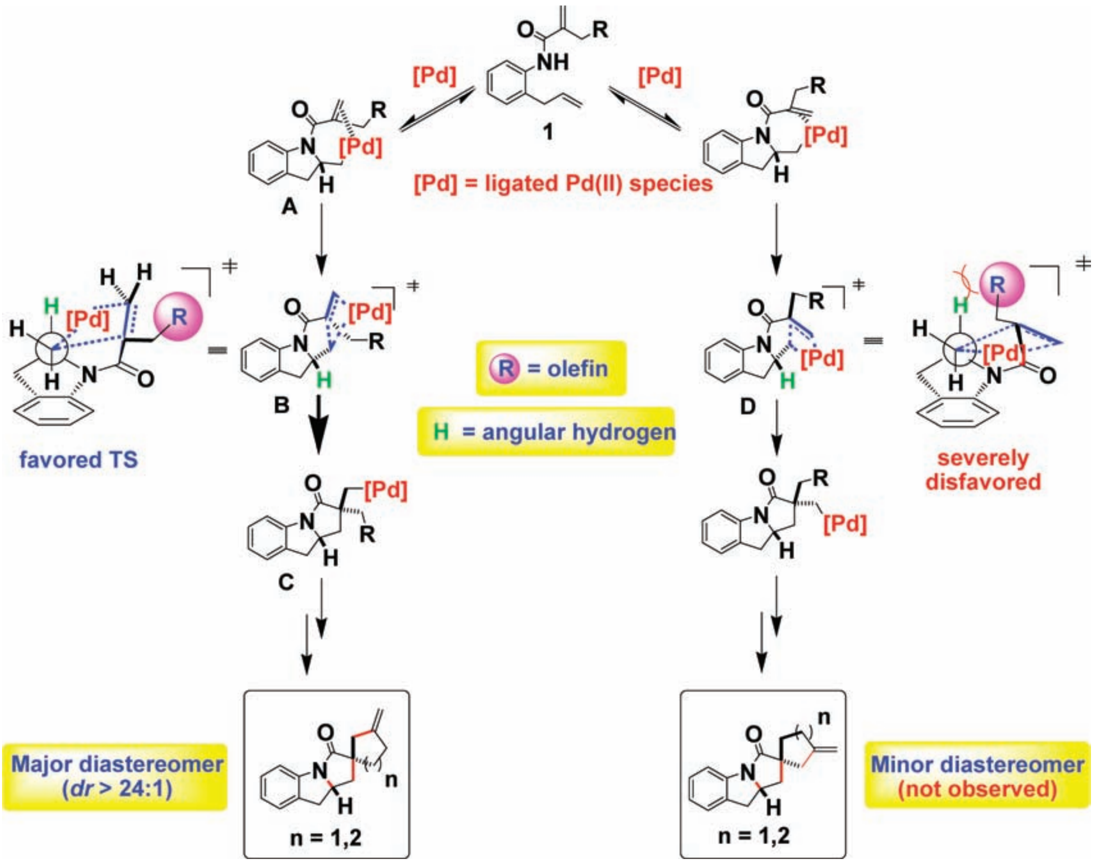
(9) For examples of 4-*exo-trig* cyclization, see: (a) Bräse, S. *Synlett* **1999**, 1654–1656. (b) Larock, R. C.; Han, X. *J. Org. Chem.* **1999**, *64*, 1875–1887.

(10) For the determination of relative stereochemistry of cyclization products, see the Supporting Information.

(11) For reviews of oxidative palladium catalysis, see: (a) Beccalli, E. M.; Broggini, G.; Martinelli, M.; Sottocornola, S. *Chem. Rev.* **2007**, *107*, 5318–5365. (b) Stahl, S. S. *Angew. Chem., Int. Ed.* **2004**, *43*, 3400–3420. (c) Stoltz, B. M. *Chem. Lett.* **2004**, *33*, 362–367. (d) Nishimure, T.; Uemura, S. *Synlett* **2004**, 201–216.

(12) For recent examples using the Pd(II)/pyridine system, see: (a) Trend, R. M.; Ramtohul, Y. K.; Stoltz, B. M. *J. Am. Chem. Soc.* **2005**, *127*, 17778–17788. (b) Zhang, H.; Ferreira, E. M.; Stoltz, B. M. *Angew. Chem., Int. Ed.* **2004**, *43*, 6144–6148. (c) Ferreira, E. M.; Stoltz, B. M. *J. Am. Chem. Soc.* **2003**, *125*, 9578–9579. (d) Trend, R. M.; Ramtohul, Y. K.; Ferreira, E. M.; Stoltz, B. M. *Angew. Chem., Int. Ed.* **2003**, *125*, 2892–2895. (e) Fix, S. R.; Brice, J. L.; Stahl, S. S. *Angew. Chem., Int. Ed.* **2002**, *41*, 164–166. (f) Steinhoff, B. A.; Stahl, S. S. *Org. Lett.* **2002**, *4*, 4179–4181. (g) Nishimura, T.; Kakiuchi, N.; Onoue, T.; Ohe, K.; Uemura, S. *J. Chem. Soc., Perkin Trans. 1* **2000**, 1915–1918. (h) Nishimura, T.; Onoue, T.; Ohe, K.; Uemura, S. *J. Org. Chem.* **1999**, *64*, 6750–6755.

Scheme 2. Origin of Diastereoselection in Pd-Catalyzed Oxidative Cascade Cyclization



chiral centers in a single step (one of which being a quaternary center). This is also the first report to demonstrate that $Pd(OAc)_2$/isoquinoline and $Pd(OAc)_2$/quinoline catalyst systems are more robust (though of comparable degree of simplicity) in comparison with the well-documented $Pd(OAc)_2$/pyridine system.[12] We anticipate that the new catalyst systems will hold good promise for a variety of palladium-catalyzed oxidative transformations. In particular, elucidating the mechanistic roles of isoquinoline in minimizing undesired olefin-isomerization processes[13] would allow better ligand design for oxidative palladium catalysis.

Acknowledgment. This work was supported by the University of Hong Kong and the Hong Kong Research Grants Council (HKU 705807P).

Supporting Information Available: Experimental details for Pd-catalyzed oxidative cascade cyclization; preparation of **1** and characterization data of **2**; NMR spectra of **2**; X-ray structures of **2d** and **2h** (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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[13] In the Heck-type cascade cyclization (see ref 2), olefin-isomerization reactions are a common problem. For examples, see: (a) Abelam, M. M.; Overman, L. E. *J. Am. Chem. Soc.* **1987**, *110*, 2328–2329. (b) Abelman, M. M.; Oh, T.; Overman, L. E. *J. Org. Chem.* **1987**, *52*, 4130–4133.