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Aerobic Oxidative Cyclization under Pd(II) Catalysis: A Regioselective Approach to Heterocycles

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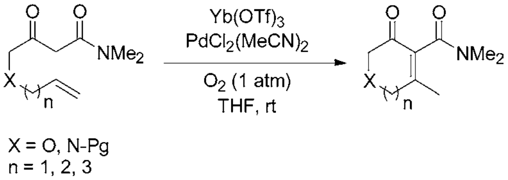
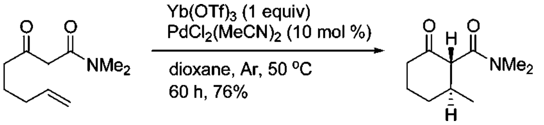
ABSTRACT



An efficient Yb(OTf)$_3$-promoted palladium-catalyzed oxidative cyclization of γ-heteroalkenyl β-keto amides has been developed. Under simple aerobic condition, a variety of six-, seven-, and eight-membered-ring *N*- and *O*-heterocycles were obtained regioselectively in excellent yield.

Six-, seven-, and eight-membered-ring heterocycles are common structural motifs of many drugs and biologically active natural products.[1] Transition-metal-catalyzed cyclization methods have been extensively developed for the synthesis of heterocycles.[2] Among them, Pd(II)-catalyzed oxidative cyclization is considered to be one of the most effective strategies.[3–5] Apart from the oxidative C–X bond formation, the oxidative C–C bond-forming reactions provide an alternative approach to access heterocycles. However, successful examples are rare and the reported approaches are limited to five- and six-membered-ring heterocycles only.[6–7] Herein, we report our regioselective approach toward six- to eight-membered-ring *N*- and *O*-heterocycle synthesis via Yb(OTf)$_3$-promoted and Pd(II)-catalyzed oxidative cyclization under simple aerobic conditions.

Recently, Widenhoefer and co-workers reported the oxidative cyclization of alkenyl β-diketones and some β-keto esters to afford cyclohexenones in the presence of catalytic amounts of PdCl$_2$(MeCN)$_2$ and 2.5 equiv of CuCl$_2$ as the oxidant.[7] Since the use of molecular oxygen, instead of traditional CuCl$_2$ or benzoquinone, as the sole stoichiometric oxidant has emerged as a cheap, efficient, and environmentally benign alternative in the reoxidation of Pd(0) to Pd(II) species,[8] we decided to examine the oxidative cyclization reactions under aerobic condition.



(1)

As the Pd(II)-catalyzed intramolecular hydroalkylations of alkenyl β-keto amides could be further improved in the

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[1] (a) *Comprehensive Heterocyclic Chemistry II*; Katritzky, A. R., Rees, C. W., Scriven, E. F., Eds.; Pergamon: New York, 1996; Vols. 5 and 9. (b) *Handbook of Heterocyclic Chemistry*; Katritzky, A. R., Pozharskii, A. F., Eds.; Pergamon: New York, 1996. (c) Tietze, L. F.; Modi, A. *Med. Res. Rev.* **2000**, *20*, 304.

[2] For general reviews, see: (a) Nakamura, I.; Yamamoto, Y. *Chem. Rev.* **2004**, *104*, 2127. (b) Bates, R. W.; Satcharoen, V. *Chem. Soc. Rev.* **1996**, *96*, 635. For ring-closing metathesis, see: (c) Grubbs, R. H. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Semmelhack, M. F., Eds.; Pergamon: Oxford, 1991; Vol. 5, p 1115. (d) Deiters, A.; Martin, S. F. *Chem. Rev.* **2004**, *104*, 2199. For Fischer carbene reactions, see: (e) Barluenga, J.; Santamaria, J.; Tomás, M. *Chem. Rev.* **2004**, *104*, 2259. For multicomponent approaches, see: (f) Balme, G.; Bossharth, E.; Monteiro, N. *Eur. J. Org. Chem.* **2003**, *21*, 4101.

[3] For recent reviews of Pd-catalyzed oxidative reactions in heterocycles synthesis, see: (a) McDaniel, K. F. In *Comprehensive Organometallic Chemistry II*; Abel, E. W., Stone, F. G. A., Wilkinson, G., Eds.; Pergamon: New York, 1995; Vol. 12. (b) Balme, G.; Bouyssi, D.; Monteiro, N. In *Handbook of Organopalladium Chemistry for Organic Chemistry*; Negishi, E., Ed.; Wiley: New York, 2002; Vol. II, p 2289. (c) Zeni, G.; Larock, R. C. *Chem. Rev.* **2004**, *104*, 2285. (d) Balme, G.; Bossharth, E.; Monteiro, N. *Eur. J. Org. Chem.* **2003**, *21*, 4101.

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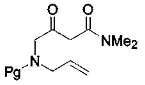
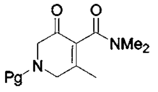
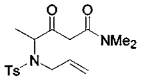
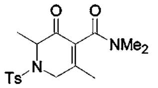
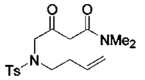
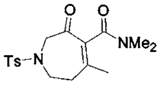
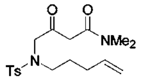
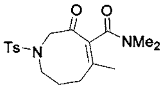
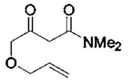
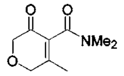
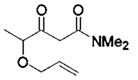
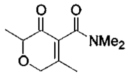
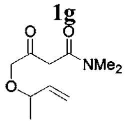
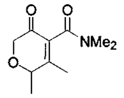
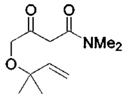
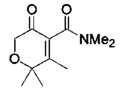
presence of $Yb(OTf)_3$ (eq 1),[9] we utilized $Yb(OTf)_3$ as the Lewis acid in the heterocycle synthesis. Under the optimized conditions, the Pd(II)-catalyzed oxidative cyclization of various *N*- and *O*-alkenyl β-keto amides **1a**−**i** proceeded smoothly to afford the corresponding *N*- and *O*-heterocycles **2a**−**i** in excellent yield (Table 1).[10] For *N*-heterocycles, under the same reaction conditions (30 mol % of $Yb(OTf)_3$ and 10 mol % of $PdCl_2(MeCN)_2$), both Ts- and Boc-protected substrates **1a** and **1b** gave similar product yields (entries 2 and 3). When a stoichiometric amount of $Yb(OTf)_3$ was used, **2a** and **2c** were obtained in excellent yield (entries 1 and 4). Interestingly, even seven- and eight-membered-ring *N*-heterocycles **2d** and **2e** were obtained in 91% and 59% yields, respectively (entries 5 and 6).[11] A comparable yield of heterocycle **2e** resulted when the reaction was scaled up to over 1 mmol scale (entry 7).

Table 1. Palladium-Catalyzed Oxidative Cyclization of γ-Heteroalkenyl Keto Amides (**1a**−**i**) in the Presence of $Yb(OTf)_3$[a]

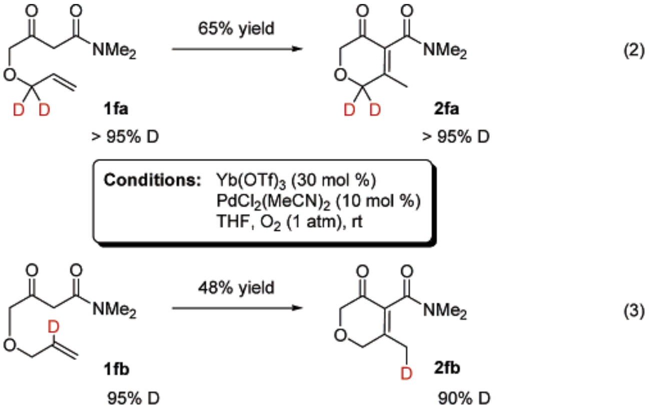
$$\text{substrate} \xrightarrow[\text{THF, } O_2 \text{ (1 atm), rt}]{\text{Yb(OTf)}_3 \text{ (1 equiv)} \quad \text{PdCl}_2\text{(MeCN)}_2 \text{ (10 mol \%)}} \text{heterocycle}$$

entry	substrate	heterocycle	time (h)	yield (%)[b]
1	 Pg- = Ts- **1a**	 **2a**	3.5	98
2[c]			6	69
3[c]	Pg- = Boc- **1b**	**2b**	9	68
4	 **1c**	 **2c**	4	90
5[d]	 **1d**	 **2d**	13	91
6[e]	 **1e**	 **2e**	210	59[f]
7[e]			264	62[g]
8[c]	 **1f**	 **2f**	5	97
9[c]	 **1g**	 **2g**	6.5	96
10[c]	 **1h**	 **2h**	7	54
11[c,d]			6	85
12			4	98
13[d]	 **1i**	 **2i**	4	92

[a] Unless otherwise indicated, all reactions were carried out with **1a** (0.15 mmol), $PdCl_2(MeCN)_2$ (10 mol %), and $Yb(OTf)_3$ (1 equiv) in dry THF (10 mL) under 1 atm O_2. [b] Based on isolated product. [c] 30 mol % of $Yb(OTf)_3$ was used. [d] 20 mol % of $PdCl_2(MeCN)_2$ was added. [e] 30 mol % of $PdCl_2(MeCN)_2$ was added. [f] 0.29 mmol of **1e** was used. [g] 1.23 mmol of **1e** was used.

A series of *O*-heterocycles **2f**−**i** with different substituents were also obtained in good yield (Table 1, entries 8−13). Compared to the *N*-heterocycles, *O*-heterocycles could be formed using smaller amounts of $Yb(OTf)_3$. A general trend is observed relating to the position of substitution. While the presence of a γ-methyl group showed no obvious effect on the reaction rate and yield (entry 9 vs 8), the presence of methyl substituents at the allylic position of the olefin retarded the reaction, and thus higher catalyst loadings were used to ensure excellent yields (entries 10−13). The cyclization reactions of γ-heteroalkenyl β-keto amides with 1,1- or 1,2-disubstituted olefinic group were found unsuccessful.

Although a possible mechanism for the palladium-catalyzed oxidative formation of carbocycles has been suggested by Widenhoefer and co-worker,[7] no intramolecular hydroalkylation products have been isolated in our heterocycle-forming reactions, indicating a good selectivity for the oxidative cyclization pathway over the competing hydroalkylation pathway in our reaction system.[7a] Hence, deuterium-labeling experiments were conducted to probe the reaction mechanism in the heterocycle formation.



The formation of **2fa** from **1fa** without measurable

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(4) For examples of Pd(II)-catalyzed C−O bond-forming reactions, see: (a) Trend, R. M.; Ramtohul, Y. K.; Ferreira, E. M.; Stoltz, B. M. *Angew. Chem., Int. Ed.* **2003**, *42*, 2892. (b) Uozumi, Y.; Kato, K.; Hayashi, T. *J. Am. Chem. Soc.* **1997**, *119*, 5063. (c) Larock, R. C.; Hightower, T. R. *J. Org. Chem.* **1993**, *58*, 5298.

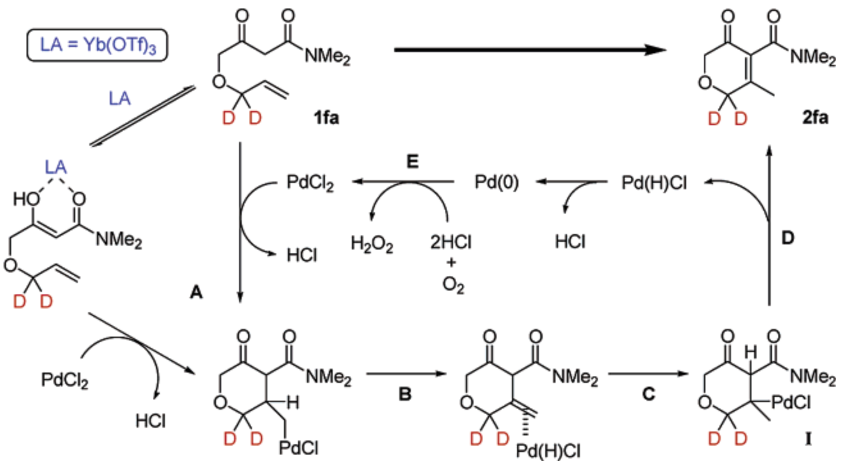
(5) For examples of Pd(II)-catalyzed C−N bond-forming reactions, see: (a) Fix, S. R.; Brice, J. L.; Stahl, S. S. *Angew. Chem., Int. Ed.* **2002**, *41*, 164. (b) Larock, R. C.; Hightower, T. R.; Hasvold, L. A.; Peterson, K. P. *J. Org. Chem.* **1996**, *61*, 3584. (c) Hegedus, L. S. *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 1113.

(6) (a) Zhang, H.; Ferreira, E. M.; Stoltz, B. M. *Angew. Chem., Int. Ed.* **2004**, *43*, 6144. (b) Ferreira, E. M.; Stoltz, B. M. *J. Am. Chem. Soc.* **2003**, *125*, 9578. (c) Franzen, J.; Backvall, J.-E. *J. Am. Chem. Soc.* **2003**, *125*, 6056. (d) Hatano, M.; Mikami, K. *J. Am. Chem. Soc.* **2003**, *125*, 4704.

(7) (a) Liu, C.; Wang, X.; Pei, T.; Widenhoefer, R. A. *Chem. Eur. J.* **2004**, *10*, 6343. (b) Pei, T.; Wang, X.; Widenhoefer, R. A. *J. Am. Chem. Soc.* **2003**, *125*, 648.

(8) Molecular oxygen has been used as the sole oxidant in several Pd(II)-catalyzed reactions. See: (a) Stahl, S. S. *Science* **2005**, *309*, 1824. (b) Stahl, S. S. *Angew. Chem., Int. Ed.* **2004**, *43*, 3400. (b) Brink, G.; Arends, I. W. C. E.; Sheldon, R. A. *Science* **2000**, *287*, 1636.

Scheme 1



D-content loss (eq 2) demonstrates the highly selective β-H elimination in yielding α,β-unsaturation of **2fa** (Scheme 1). This explains the preference of the oxidative cyclization over intramolecular hydroalkylative cyclization.[7b] On the other hand, the conversion of **1fb** into **2fb** was accomplished with a selective D-shift and retention of high D content (eq 3).[12]

On the basis of our deuterium-labeling experiments, a plausible mechanism is shown in Scheme 1. Initially, Yb(OTf)$_3$ serves as a Lewis acid to promote the enol formation of **1fa** and enhance the intramolecular attack of nucleophilic enol toward Pd(II)-activated olefin (step A).[9] With a subsequent β-H elimination (step B) and Pd-migration (step C), intermediate **I** is formed. Finally, a selective β-H elimination of **I** (step D) resulted in product **2fa**. The whole catalytic cycle is completed by the regeneration of active Pd(II) species from Pd(0) using molecular oxygen as the oxidant (step E).[8]

In conclusion, we have developed a mild and efficient method for the synthesis of *N*- and *O*-heterocycles through oxidative formation of the C−C bond using both Yb(OTf)$_3$ and PdCl$_2$(MeCN)$_2$ as catalysts and molecular oxygen as the terminal oxidant. A variety of six-, seven-, and even eight-membered-ring *N*- and *O*-heterocycles have been obtained regioselectively in excellent yield. In addition, the current methodology is selective in yielding oxidative cyclization product, and this is complementary to the recent example of carbocycle formation.[7] Further investigations to expand the scope of this Pd(II)-catalyzed aerobic oxidative cyclization are in progress.

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Supporting Information Available: Experimental details for Pd-catalyzed aerobic oxidative cyclization; preparation of **1** and characterization data of **2**. This material is available free of charge via the Internet at http://pubs.acs.org.

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[9] Yang, D.; Li, J.-H.; Gao, Q.; Yan, Y.-L. *Org. Lett.* **2003**, *5*, 2869.

[10] The condition using a stoichiometric amount of CuCl$_2$ (ref 7) or benzoquinone as reoxidant was attempted for γ-*N*- and *O*-alkenyl β-keto amides **1**. However, the reactions were found messy and no desired heterocycle was obtained. In contrast to **1a**, γ-(*N*-allyltosylamido) β-keto ester did not afford desired heterocyclic product under the aerobic condition.

[11] Formation of seven- and eight-membered-rings by Pd catalysis is rare. For an unusual example, see: Schweizer, S.; Song, Z.-Z.; Meyer, F. E.; Parsons, P. J.; Meijere, A. *Angew. Chem., Int. Ed.* **1999**, *38*, 1452.

[12] We rule out the possibility of the oxidative cyclization of **1** proceeding through a reaction sequence of tandem Wacker oxidation/Knoevenagel condensation because this would result in a significant loss of D content. For example, see: Cornell, C. N.; Sigman, M. S. *J. Am. Chem. Soc.* **2005**, *127*, 2796.