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Lanthanide Triflate-Promoted Palladium-Catalyzed Cyclization of Alkenyl β-Keto Esters and Amides

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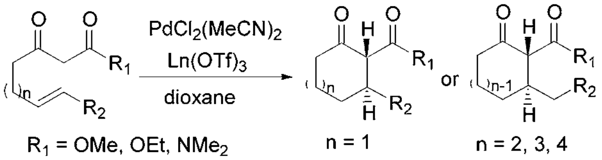
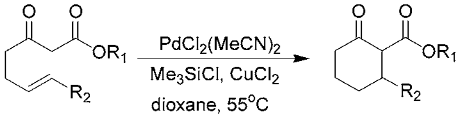
ABSTRACT



Lanthanide triflates were found to promote the palladium-catalyzed cyclization of alkenyl β-keto esters and amides. In the presence of catalytic amounts of $PdCl_2(MeCN)_2$ and $Ln(OTf)_3$, various alkenyl β-keto esters and amides underwent regioselective cyclization reactions to give six-, seven-, or eight-membered-ring carbocycles in moderate to excellent yields.

Six- to eight-membered-ring carbocycles are common structural units of biologically important natural products.[1] Although many methods have been developed for the synthesis of these carbocyclic compounds,[2] transition metal-catalyzed cyclization is considered to be one of the most effective strategies.[3] Recently, Widenhoefer and co-workers reported that alkenyl 1,3-diketones were cyclized to form six-membered ring compounds in the presence of a catalytic amount of $PdCl_2(MeCN)_2$.[4] For unsaturated β-keto esters, the palladium(II)-catalyzed cyclization was efficient in the presence of Me_3SiCl (2 equiv) or Me_3SiCl (2 equiv)/$CuCl_2$ (1 equiv).[5] According to the proposed mechanism for the cyclization reaction,[4,5] the key is to increase the enol population. Me_3SiCl (2 equiv) was believed to form the alkenyl silyl enol ether in situ, thereby increasing the reaction rate and yields (eq 1).



(1)

In our previous work, we found that lanthanide triflates could significantly catalyze the enol formation of β-keto esters.[6] Thus, we expected that the addition of lanthanide triflates might help improve the Pd(II)-mediated cyclization reactions of alkenyl β-keto esters. Indeed, we found that cyclization reactions of various alkenyl β-keto esters and

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[1] (a) Heathcock, C. H.; Graham, S. L.; Pirrung, M. C.; Plavac, W.; White, C. T. In *The Total Synthesis of Natural Products*; Apsimon, J. W., Ed.; Wiley: New York, 1983; Vol. 5, p 333. (b) Rigby, J. H. In *Studies in Natural Products Chemistry*; Atta-ur-Rahman, Ed.; Elsevier Science Publishers B. V.: Amsterdam, 1988; Vol. 12, p 233. (c) Fraga, B. M. *Nat. Prod. Rep.* **1996**, *13*, 307. (d) Dyker, G. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 2223.

[2] (a) *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Semmelhack, M. F., Eds.; Pergamon: Oxford, 1991; Vol. 5. (b) Carruthers, W. *Cycloaddition Reactions in Organic Synthesis*; Pergamon: Oxford, 1990. (c) Hesse, M. *Ring Enlargement in Organic Chemistry*; VCH: Weinheim, 1991. (d) Renaud, P., Sibi, M. P., Eds. *Radicals in Organic Synthesis*; Wiley-VCH: Weinheim, 2001.

[3] (a) Negishi, E.; Copéret, C.; Ma, S.; Liou, S.-Y.; Liu, F. *Chem. Rev.* **1996**, *96*, 365. (b) Ojima, I.; Tzamarioudaki, M.; Li, Z.; Donovan, R. J. *Chem. Rev.* **1996**, *96*, 635. (c) Bates, R. W.; Satcharoen, V. *Chem. Soc. Rev.* **2002**, *35*, 12.

[4] (a) Pei, T.; Widenhoefer, R. A. *J. Am. Chem. Soc.* **2001**, *123*, 11290. (b) Pei, T.; Wang, X.; Widenhoefer, R. A. *J. Am. Chem. Soc.* **2003**, *125*, 648. (c) Qian, H.; Widenhoefer, R. A. *J. Am. Chem. Soc.* **2003**, *125*, 2056.

[5] Pei, T.; Widenhoefer, R. A. *Chem. Commun.* **2002**, 650.

[6] (a) Yang, D.; Ye, X.-Y.; Gu, S.; Xu, M. *J. Am. Chem. Soc.* **1999**, *121*, 5579. (b) Yang, D.; Ye, X.-Y.; Xu, M.; Pang, K.-W.; Cheung, K.-K. *J. Am. Chem. Soc.* **2000**, *122*, 1658. (c) Yang, D.; Yan, Y.-L.; Lui, B. *J. Org. Chem.* **2002**, *67*, 7429. (d) Yang, D.; Gao, Q.; Lee, C.-S.; Cheung, K.-K. *Org. Lett.* **2002**, *4*, 3271.

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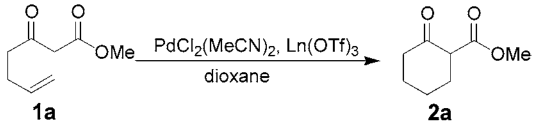
amides took place efficiently in the presence of catalytic amounts of $PdCl_2(MeCN)_2$ and $Ln(OTf)_3$. Here we report the details of those reactions.

The effect of $Ln(OTf)_3$ on the palladium(II)-catalyzed cyclization reaction of **1a** was investigated, and the results are summarized in Table 1. Without the addition of $Ln(OTf)_3$, cyclization of **1a** catalyzed by 10 mol % $PdCl_2(MeCN)_2$ was slow and inefficient (entry 1), similar to the earlier reports.[4a,5] However, the addition of $Yb(OTf)_3$ resulted in a significant increase in rate and yield (entries 2 and 3).[7] While the reaction rate increased with increasing amounts of $PdCl_2(MeCN)_2$ and $Yb(OTf)_3$, the catalyst loadings of both reagents could be reduced without significant compromise in the yield (entries 4, 5, 8, and 9). For example, **1a** was consumed completely after 10 h and afforded 99% yield of **2a** in the presence of 0.3 equiv of $Yb(OTf)_3$ and 5 mol % $PdCl_2(MeCN)_2$ (entry 5).[8] As in the earlier report, both addition of $CuCl_2$ and increase of reaction temperature enhanced the reaction rate to some extent (entries 10 and 11). Finally, other lanthanide triflates such as $La(OTf)_3$ and $Sm(OTf)_3$ (entries 6 and 7) were evaluated and found to promote the cyclization reaction to a similar extent as $Yb(OTf)_3$.[9]

Table 1. $Yb(OTf)_3$-Promoted Cyclization of Methyl 3-Oxohept-6-enoate (**1a**) in the Presence of $PdCl_2(MeCN)_2$[a]

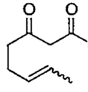
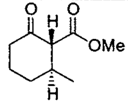
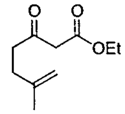
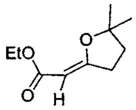
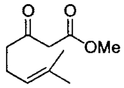
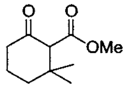
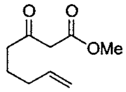
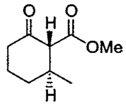
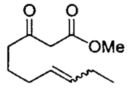
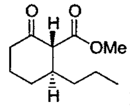
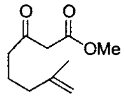
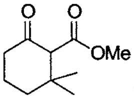
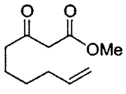
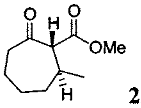
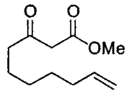
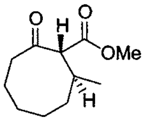
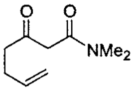
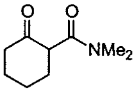
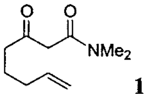
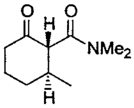
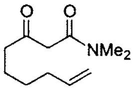
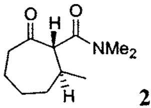
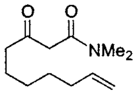
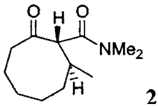


entry	Yb(OTf)$_3$ (equiv)	PdCl$_2$(MeCN)$_2$ (equiv)	time (h)	yield (%)[b]
1		0.10	24	16[c]
2	2.0	0.10	2	90
3	1.0	0.10	5	98
4	1.0	0.05	9	98
5	0.3	0.05	10	99
6[d]	0.3	0.05	10.5	95
7[e]	0.3	0.05	8.5	99
8	0.2	0.05	16	98
9	0.1	0.05	35	92
10[f]	0.3	0.05	5	97
11[g]	0.3	0.05	9	98

[a] Reaction conditions: **1a** (0.7 mmol), $PdCl_2(MeCN)_2$, and $Yb(OTf)_3$ in dioxane (28 mL) at room temperature. [b] Isolated yield. [c] Yield determined by ^1H NMR. [d] $La(OTf)_3$ instead of $Yb(OTf)_3$. [e] $Sm(OTf)_3$ instead of $Yb(OTf)_3$. [f] $CuCl_2$ (1 equiv) was added. [g] At 50 °C.

In the presence of $Yb(OTf)_3$ and $PdCl_2(MeCN)_2$, cyclization reactions of other alkenyl β-keto esters **1b–i** and alkenyl β-keto amides **1j–m** bearing different olefinic groups were carried out smoothly, and the results are summarized in Table 2. In the presence of 0.3 equiv of $Yb(OTf)_3$ and 5 mol % $PdCl_2(MeCN)_2$, **2b** was formed from olefin **1b** after 38 h in 92% yield (entry 1). Increasing the amounts of $Yb(OTf)_3$ and $PdCl_2(MeCN)_2$ to 1.0 equiv and 10 mol %, respectively,

Table 2. Palladium-Catalyzed Cyclization of Alkenyl β-Keto Esters **1b–i** and Amides **1j–m** in the Presence of $Yb(OTf)_3$[a]

entry	substrate	Pd (equiv)	time (h)	product	yield[b] (%)
1[c,d]	 **1b**	0.05	38	 **2b**	92
2[d]		0.10	24		93
3[e]	 **1c**	0.10	14	 **2c**	91
4	 **1d**	0.10	24	 **2d**	<5[f]
5		0.20	5		97
6[c]	 **1e**	0.10	24	 **2b**	91
7			16		94
8[d]	 **1f**	0.10	24	 **2f**	89
9	 **1g**	0.10	24	 **2d**	55
10[c]	 **1h**	0.10	36	 **2h**	80
11			24		78
12	 **1i**	0.10	36	 **2i**	31[g]
13[c]	 **1j**	0.10	48	 **2j**	93
14			36		95
15	 **1k**	0.10	60	 **2k**	76
16	 **1l**	0.20	72	 **2l**	65[g]
17	 **1m**	0.20	72	 **2m**	37[g]

[a] Unless otherwise indicated, all reactions were carried out with **1** (0.7 mmol), $PdCl_2(MeCN)_2$, and $Yb(OTf)_3$ (1 equiv) in dioxane (28 mL) at 50 °C. [b] Isolated yield. [c] Performed with 0.3 equiv of $Yb(OTf)_3$. [d] Both substrates **1b** and **1f** were a mixture of trans and cis isomers. [e] No cyclization occurred in the absence of $PdCl_2(MeCN)_2$. [f] Recovery of **1d** = 95%. [g] Corresponding C=C double bond hydrogenation product was obtained in 47, 15, and 41% yields from **1i**, **1l**, and **1m**, respectively.

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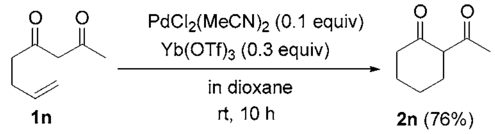
(7) Dioxane was a more effective solvent than THF, ether, CH_2Cl_2, hexane, and toluene.

(8) **Typical Procedure for Cyclization Reactions.** A mixture of $PdCl_2(MeCN)_2$ (9 mg, 0.035 mmol), $Yb(OTf)_3$ (130 mg, 0.21 mmol), and **1a** (109 mg, 0.7 mmol) in dioxane (28 mL) was stirred at room temperature. After the substrate **1a** was consumed (about 10 h) as monitored by TLC, the reaction was quenched with water, diluted with ether, washed with saturated NaCl solution, and then dried over Mg_2SO_4. After removal of the solvent, the crude product was purified by flash column chromatography to give **2a** (107.8 mg, 99% yield).

gave faster reaction but similar yield for the cyclization of **1b** (entry 2). To our surprise, olefin **1c** bearing an internal substituent gave a five- membered-ring product **2c** via oxygen attack on the double bond in 91% yield (entry 3). A similar 5-exo cyclization at the oxygen site of β-keto esters was observed in Lewis acid-catalyzed cation cyclization reactions.[10,6d] However, our control experiment indicated that $PdCl_2(MeCN)_2$ was necessary for the cyclization of **1c** to proceed. The cyclization of trisubstituted olefin **1d** required more $PdCl_2(MeCN)_2$ (entries 4 and 5). In the presence of 1.0 equiv of $Yb(OTf)_3$, a trace amount of **2d** was found after 24 h when 10 mol % $PdCl_2(MeCN)_2$ was added, whereas 97% yield of **2d** was obtained in 5 h using 20 mol % $PdCl_2(MeCN)_2$. With $PdCl_2(MeCN)_2$ (10 mol %) and $Yb(OTf)_3$ (1.0 equiv) as the catalytic system, 7-alkenyl 3-keto esters, **1e** and **1f**, gave their corresponding six-membered-ring products **2b** and **2f** in 94 and 89% yields, respectively (entries 7 and 8). It should be pointed out that olefin **1g**, another olefin bearing an internal substituent, gave the six-membered-ring carbocycle **2d** (55%, entry 9). Most significantly, under the same reaction conditions, 8- and 9-alkenyl 3-keto esters **1h** and **1i** gave the corresponding seven- and eight-membered-ring products **2h** and **2i**, respectively, in moderate to good yields (entries 11 and 12). Compared to alkenyl β-keto esters, alkenyl β-keto amides were less reactive. However, in the presence of $PdCl_2(MeCN)_2$ (10 mol %) and $Yb(OTf)_3$ (1.0 equiv), cyclization of alkenyl β-keto amides **1j−m** could also afford the corresponding carbocycles **2j−m** in moderate to good yields (entries 14−17).

Note that lanthanide triflates functioned as catalysts in the palladium-catalyzed carbocyclization reaction without the help of a reoxidant such as $CuCl_2$. Although prolonged reaction time was required, cyclizations of **1b**, **1e**, **1h**, and **1j** were completed in 10−48 h in the presence of a catalytic amount of $Yb(OTf)_3$ (entries 1, 6, 10, and 13 in Table 2).

$Yb(OTf)_3$ can also promote cyclization of 1,3-diketone **1n**. In the presence of 0.3 equiv of $Yb(OTf)_3$, the reaction time for the conversion of 1,3-diketone **1n** to the corresponding carbocycle product **2n** was shortened from 16 h in the earlier report[4a] to the current 10 h (eq 2).



(2)

Cyclization of **1b**, **1e**, **1f**, **1h**, **1i**, and **1k−m** afforded only trans isomers, whose stereochemistry was determined on the basis of the ^1H NMR coupling constants of the α-hydrogen of the corresponding products. It is likely that the equilibration of the trans and cis isomers via Lewis acid-catalyzed enol formation gives the thermodynamically favored trans products.

In conclusion, we have found an efficient protocol involving the use of catalytic amounts of lanthanide triflates and $PdCl_2(MeCN)_2$ for the regioselective synthesis of six-, seven-, and even eight-membered-ring carbocycles from alkenyl β-keto esters and amides. While the mechanism proposed by Widenhoefer and co-worker[4c] may explain the 6-endo cyclization reactions of substrates **1a**, **1b**, **1d**, and **1j**, the intriguing exo selectivity observed for the cyclization of substrates **1e−i** and **1k−m** requires further mechanistic investigation. In addition, the discovery of Lewis acid catalysis opens up the opportunity of using chiral Lewis acids for enantioselective cyclization. Efforts in those two directions are in progress and will be reported in due course.

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Supporting Information Available: Characterization data of products **2**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(9) For the effect of other lanthanide triflates, see Table S1 in Supporting Information.

(10) Reetz, M. T.; Chatziiosifidis, I.; Schwellnus, K. *Angew. Chem., Int. Ed. Engl.* **1981**, *20*, 687.