

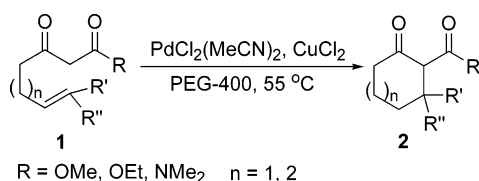
Efficient and Reusable PdCl₂(MeCN)₂/CuCl₂/PEG-400 System for Cyclization of Alkenyl β-Keto Esters and Amides

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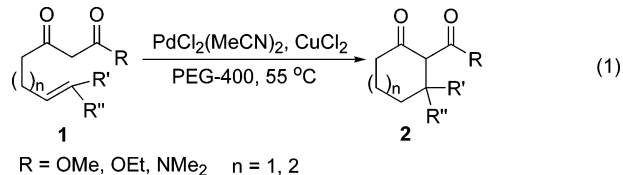
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PEG-400 [poly(ethylene glycol-400)] was found as an effective medium for the PdCl₂(MeCN)₂-catalyzed hydroalkylation cyclization of alkenyl β-keto esters and amides. In PEG-400, no additives such as Me₃SiCl and Ln(OTf)₃ were required for the complete conversion of alkenyl β-keto esters. The results also showed that CuCl₂ could promote the reaction. In the presence of PdCl₂(MeCN)₂, CuCl₂, and PEG-400, various alkenyl β-keto esters and amides underwent a selective cyclization reaction to give good to excellent yields of the desired six-membered-ring carbocycles. Furthermore, the PdCl₂(MeCN)₂/CuCl₂/PEG-400 system could be recycled and reused five times without any loss of catalytic activity.

Six-membered-ring carbocycles are important structural units because of their occurrence in many biologically active natural products and their physiological properties.¹ For these reasons, a number of efficient and selective methods have been developed for the direct synthesis of these carbocyclic compounds.² One of the most effective strategies is the transition metal-catalyzed cyclization reaction transformations.^{3,4} Recently, Widen-

hoefer and co-workers^{4a,e} first reported an effective method for the synthesis of six-membered-ring carbocycles by the palladium-catalyzed hydroalkylation intramolecular cyclization of β-keto esters with unactivated olefins. In the presence of 10 mol % of PdCl₂(MeCN)₂ and a stoichiometric amount of Me₃SiCl or Me₃SiCl/CuCl₂, cyclization of various 6-alkenyl 2-keto esters was carried out to afford the corresponding 2-substituted cyclohexanones in good yields. We have also reported that alkenyl β-keto esters and amides were cyclized efficiently and regioselectively to form six- to eight-membered-ring compounds in the presence of PdCl₂(MeCN)₂ and Ln(OTf)₃.⁵ In these cases, however, some additives such as Me₃SiCl and Ln(OTf)₃ were required to improve the reaction. Besides these, the catalyst systems are very difficult to reuse under the reported reaction conditions. Thus, development of economically as well as environmentally benign reaction conditions would be significant due to the high price of Pd and the additives. To satisfy both recyclability and environmental concerns, a more facile method is to immobilize the catalyst in a liquid phase by dissolving it into a nonvolatile and nonmixing liquid such as PEG.⁶ Here, we report an efficient and selective palladium-catalyzed cyclization of alkenyl β-keto esters and amides method for the synthesis of 2-substituted cyclohexanones in the presence of PdCl₂(MeCN)₂, CuCl₂, and PEG-400 (eq 1). Furthermore, the PdCl₂(MeCN)₂/CuCl₂/PEG-400 system could be recycled five times without any loss of catalytic activity.



As showed in Table 1, the PdCl₂(MeCN)₂-catalyzed cyclization reaction of methyl 3-oxooct-6-enoate (**1a**) was first investigated. The results showed that PEG-400 was an effective solvent for the reaction (entry 1). Without any additive, substrate **1a** could be consumed completely to afford 88% yield of the corresponding cyclized product (**2a**) in the presence of 0.1 equiv of PdCl₂(MeCN)₂ and 2 g of PEG-400. Surprisingly, Yb(OTf)₃ had no effect on the reaction (entry 2). According to the suggestion of Widenhoefer,⁴ the addition of CuCl₂ was expected to improve the palladium cyclization reactions. Indeed,

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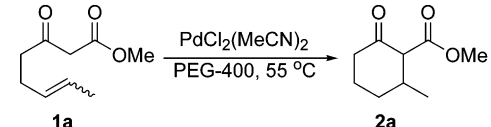
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TABLE 1. Palladium-Catalyzed Hydroalkylation Cyclization Reaction of Olefin **1a in PEG-400^a**


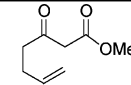
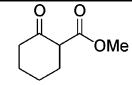
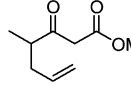
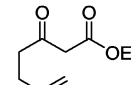
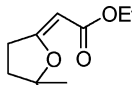
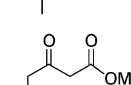
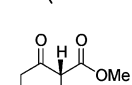
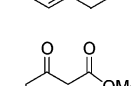
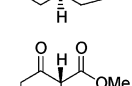
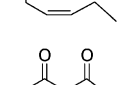
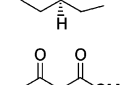
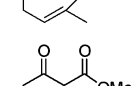
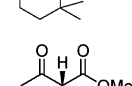
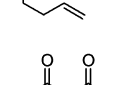
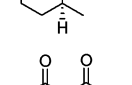
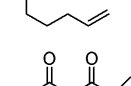
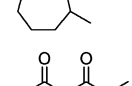
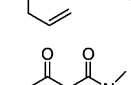
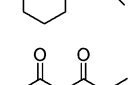
entry	CuCl ₂ (equiv)	PdCl ₂ (MeCN) ₂ (equiv)	time (h)	yield (%) ^b
1	0	0.10	47	88
2 ^c	0	0.10	48	85
3	0.2	0.10	22	94
4	1.0	0.10	4	90
5	2.0	0.10	4	91
6	1.0	0.05	31	96
7	1.0	0.01	44	86
8 ^d	1.0	0	48	0

^a Reaction conditions: **1a** (0.5 mmol), PdCl₂(MeCN)₂, CuCl₂, and PEG-400 (4 g) at 55 °C. ^b Isolated yield. ^c Yb(OTf)₃ (1 equiv). ^d No reaction was observed. >95% of **1a** was recovered.

CuCl₂ could enhance the reaction rate sharply, and 1 equiv of CuCl₂ gave the best results. In the presence of 0.1 equiv of PdCl₂(MeCN)₂, the complete conversion of substrate **1a** required 47 h, whereas the presence of 0.2 equiv of CuCl₂ resulted in the complete conversion in 22 h (entries 1 and 3). In the presence of 0.1 equiv of PdCl₂(MeCN)₂ and 1 equiv of CuCl₂, substrate **1a** was consumed completely after 4 h (entry 4). Identical results were observed even further increasing the loadings of CuCl₂ to 2 equiv (entry 5). It is noteworthy that the loadings of PdCl₂(MeCN)₂ can be decreased to 0.01 equiv in the presence of CuCl₂ and PEG-400 (entries 6 and 7). In the presence of 0.01 equiv of PdCl₂(MeCN)₂ and 1 equiv of CuCl₂, 86% yield of **2a** was obtained after 44 h (entry 7). No reaction was observed in the absence of PdCl₂(MeCN)₂ (entry 8).

In the presence of PdCl₂(MeCN)₂ (0.10 equiv), CuCl₂ (1.0 equiv), and PEG-400 (4 g), cyclization of various alkenyl β-keto esters **1b**, **1d–h**, and amides **1j** were carried out smoothly in good to excellent yields, and the results are summarized in Table 2. The results showed that the reaction tolerated different substituents on the olefinic groups, and both rates and yields of the reaction depended on the structure of the substrates. In the presence of PdCl₂(MeCN)₂ (0.10 equiv), CuCl₂ (1.0 equiv), and PEG-400 (4 g), the desired product **2b** was formed from the olefin **1b** after 4 h in 97% yield (entry 1). Cyclization of the substrates **1e** and **1f**, two isomers bearing a substituent at the terminal position of the carbon–carbon double bond, respectively, afforded the corresponding cyclization product **2e** in good yields (entries 4 and 5). However, the reaction rate of the former (*E*-isomer) was faster than that of the latter (*Z*-isomer). Treatment of substrate **1g**, an olefin having two substituents at the terminal position of the carbon–carbon double bond, with PdCl₂(MeCN)₂ (0.10 equiv) and CuCl₂ (1.0 equiv) gave 96% yield of the desired product **2g** after 16 h (entry 6). Surprisingly, 84% yield of a 5-*exo* hydroalkoxylation product (**2d**) was observed when the olefin **1d** bearing an internal substituent was cyclized (entry 3).^{5,7} It is noteworthy that the reaction of methyl 3-oxooct-

TABLE 2. PdCl₂(MeCN)₂/CuCl₂-Catalyzed Cyclization of Alkenyl 3-Keto Esters and Amides in PEG-400^a

Entry	Substrate	Time (h)	Product	Yield (%) ^b
1	 (1b)	4	 (2b)	97
2 ^c	 (1c)	48	-	-
3	 (1d)	39	 (2d)	84
4	 (1e)	8	 (2e)	90
5	 (1f)	24	 (2e)	98
6	 (1g)	16	 (2g)	96
7	 (1h)	4	 (2a)	80
8 ^d	 (1i)	24	 (2i)	<5%
9	 (1j)	25	 (2j)	94
10 ^d	 (1k)	25	 (2k)	<5%

^a Reaction conditions: **1** (0.5 mmol), PdCl₂(MeCN)₂ (0.10 equiv), CuCl₂ (1.0 equiv), and PEG-400 (4 g) at 55 °C. ^b Isolated yield. ^c No reaction was observed. >95% of **1c** was recovered. ^d >90% of **1** was recovered.

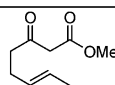
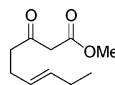
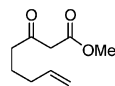
7-enoate (**1h**) afforded an *exo*-hydroalkylation product (**2a**) in 80% yield after 4 h (entry 7). In the presence of PdCl₂(MeCN)₂ (0.10 equiv), CuCl₂ (1.0 equiv), and PEG-400 (4 g), cyclization of the amide **1j** was also carried out smoothly to produce the corresponding desired product (**2j**) in 94% yield (entry 9). Unfortunately, cyclization of substrates **1c**, **1i**, and **1k**, respectively, was not successful (entries 2, 8, and 10).⁸

To check the reusability of the solvent as well as the catalytic system, the cyclization reaction of substrate (**1a**) was first evaluated in the presence of PdCl₂(MeCN)₂

(8) No cyclization reaction of substrates **1c** occurred due to the unfavorable steric hindrance, and the reaction of **1i** or **1k** was not successful presumably because the olefins **1i** and **1k** bind less tightly to transient metals. See: (a) Hartley, F. R. *Chem. Rev.* **1973**, *73*, 163. (b) References 4 and 7.

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TABLE 3. Recovery and Reuse of PdCl₂(MeCN)₂/CuCl₂/PEG-400 for the Cyclization Reactions^a

Entry	Ester	Time (h) ^b	Isolated yield (%)				
			1	2	3	4	5
1	 (1a)	8	90	98	100	100	100
2	 (1d)	12	82	90	88	90	95
3	 (1g)	8	76	78	81	83	90

^a Reaction conditions: **1** (0.5 mmol), PdCl₂(MeCN)₂ (0.10 equiv), CuCl₂ (1.0 equiv), and PEG-400 (4 g) at 55 °C. ^b Average reaction time of five runs

(0.10 equiv), CuCl₂ (1.0 equiv), and PEG-400 (4 g). As demonstrated in Table 3, we were gratified to observe that the PdCl₂(MeCN)₂/CuCl₂/PEG-400 system could be recycled and reused five times without any loss of activity. After initial experimentation the reaction mixture was extracted with dry diethyl ether, and the PEG and PdCl₂(MeCN)₂/CuCl₂ were then solidified and subjected to a second run of the hydroalkylation reaction by charging with the same substrates (alkenyl β-keto esters). The results of five runs showed that they were almost consistent in yields and rates (90%, 98%, 100%, 100%, and 100%, respectively, for 8 h; entry 1). The cyclization reactions of olefins **1d** and **1g**, respectively, could also be recycled and reused five times without any loss of activity in the presence of PdCl₂(MeCN)₂ (0.10 equiv), CuCl₂ (1.0 equiv), and PEG-400 (4 g) (entries 2 and 3).

In summary, a mild and selective PdCl₂(MeCN)₂/CuCl₂-catalyzed cyclization of alkenyl β-keto esters protocol has been developed. In the presence of PdCl₂(MeCN)₂, CuCl₂, and PEG-400, various alkenyl β-keto esters were cyclized efficiently in good to excellent yields. Furthermore, the PdCl₂(MeCN)₂/CuCl₂/PEG-400 system could be recycled and reused five times without any loss of catalytic activity. Currently, further efforts to extend the application of the system in other palladium-catalyzed transformations and investigate the precise mechanism are underway in our laboratory.

Experimental Section

Typical Experimental Procedure for the Palladium-Catalyzed Hydroalkylation Cyclization Reaction in PEG-400. A mixture of **1** (0.5 mmol), PdCl₂(MeCN)₂ (0.10 equiv), and CuCl₂ (1.0 equiv) in PEG-400 (4 g) was added to a sealed tube under N₂, and then the mixture was stirred at 55 °C for the desired time until complete consumption of starting material as judged by TLC. After the mixture was extracted by dry ethyl ether (3 × 10 mL) and evaporated, the residue was purified by flash column chromatography (hexane/ethyl acetate) to afford the desired coupled products **2**.

The mixture of PdCl₂(MeCN)₂, CuCl₂, and PEG-400 were solidified (cooled) and subjected to a second run of the hydroalkylation cyclization reaction by charging with the same substrates (alkenyl β-keto esters and amides).

Acknowledgment. We thank the National Natural Science Foundation of China (No. 20202002) for financial support.

Supporting Information Available: Characterization data and spectra (¹H and ¹³C NMR) of compounds **2**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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