

Palladium-catalyzed cyclization of alkenyl β -keto esters in the presence of chlorotrimethylsilane[†]

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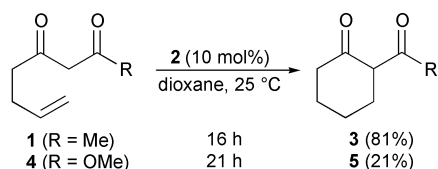
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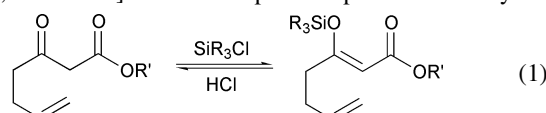
$\text{PdCl}_2(\text{CH}_3\text{CN})_2$ catalyzed the cyclization of alkenyl β -keto esters in the presence of a stoichiometric amount of SiMe_3Cl to form 2-carboalkoxycyclohexanones in good yield with excellent regioselectivity.

We recently reported the palladium-catalyzed cyclization of alkenyl β -diketones to form 2-acylcyclohexanones.¹ For example, treatment of oct-7-ene-2,4-dione (**1**) with a catalytic amount of $\text{PdCl}_2(\text{CH}_3\text{CN})_2$ (**2**) (10 mol %) in dioxane at room temperature for 16 h formed 2-acetylcyclohexanone (**3**) in 81% yield as a single regioisomer (Scheme 1).¹ The palladium-catalyzed cyclization of alkenyl β -diketones represents the first efficient transition metal-catalyzed system for the addition of a stabilized carbon nucleophile to an unactivated olefin and may provide significant advantages relative to free radical² and Lewis acid-catalyzed³ approaches. Our working mechanism for the conversion of **1** to **3** catalyzed by **2** involves intramolecular attack of the pendant enol on the palladium-complexed olefin of intermediate **I** followed by loss of HCl to form the palladium cyclohexyl intermediate **II** (Scheme 2). Protonation of the Pd–C bond of **II** with HCl could then release **3** and regenerate **2**.⁴



Scheme 1

Alkenyl β -keto esters were significantly less reactive toward palladium-catalyzed cyclization than were alkenyl β -diketones. For example, cyclization of methyl 3-oxohept-6-enoate (**4**) catalyzed by **2** (10 mol %) at 25 °C for 21 h formed methyl 2-oxocyclohexanecarboxylate (**5**) in only 21% yield (Scheme 1). We reasoned that the low reactivity of **4** relative to **1** was directly related to the lower equilibrium enol:keto ratio of **4** relative to **1**.⁵ Because both the palladium-mediated addition of silyl enol ethers to alkenes⁶ and the tungsten-catalyzed addition of silyl enol ethers to alkynes has been demonstrated,⁷ we considered that the silyl enol ether of an alkenyl β -keto ester might cyclize in the presence of **2**. Furthermore, generation of the alkenyl silyl enol ether *in situ* from reaction of an alkenyl β -keto ester and a silyl chloride would produce the HCl required to achieve catalysis according to our postulated mechanism [eqn. (1), Scheme 2]. Here we report the palladium-catalyzed

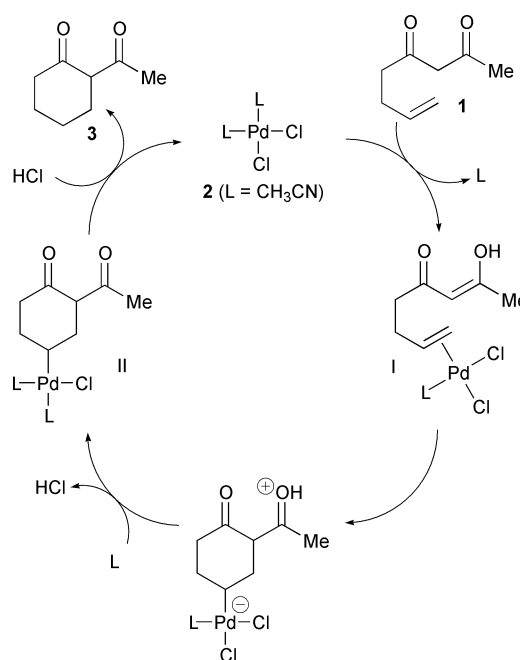


cyclization of alkenyl β -keto esters in the presence of SiMe_3Cl .

[†] Electronic supplementary information (ESI) available: experimental procedures, analytical and spectroscopic data for new compounds and cyclohexanones. See <http://www.rsc.org/suppdata/cc/b1/b111644d/>

The palladium-mediated addition of silyl enol ethers to unactivated olefins was restricted to trimethylsilyl ethers,⁶ and for this reason, we targeted chlorotrimethylsilane as an additive in the cyclization of alkenyl β -keto esters catalyzed by **2**. Significantly, both the rate and efficiency of the palladium-catalyzed cyclization of alkenyl β -keto esters increased dramatically in the presence of SiMe_3Cl . For example, treatment of **4** with a catalytic amount of **2** (10 mol %) and a stoichiometric amount of SiMe_3Cl (2 equiv.) in dioxane at room temperature for 8 h led to complete consumption of **4** and isolation of **5** in 91% yield as a single regioisomer (Table 1, entry 1).[‡] In a similar manner, ethyl (**6**), benzyl (**7**), and isobutyl (**8**) 3-oxohept-6-enoates cyclized in the presence of **2** (10 mol %) and SiMe_3Cl (2 equiv.) to form 2-carboalkoxycyclohexanones **9–11** in >80% yield as single regioisomers (Table 1, entries 2–4).

Palladium-catalyzed cyclization of alkenyl β -keto esters tolerated terminal olefinic substitution. For example, treatment of *trans*-methyl 3-oxonon-6-enoate (*trans*-**12**) with **2** (10 mol %) and SiMe_3Cl (2 equiv.) in dioxane at room temperature for 2 days gave carbocycle **13** in 79% isolated yield (Table 1, entry 5). Increasing the reaction temperature to 55 °C led to the anticipated increase in reaction rate, but also led to catalyst decomposition and incomplete conversion. We reasoned that catalyst decomposition might be initiated by reduction of Pd(II) to Pd(0), and if this were the case, addition of a suitable oxidant to the reaction mixture should prevent catalyst decomposition. Indeed, palladium-catalyzed cyclization of *trans*-**12** in the presence of both SiMe_3Cl (2 equiv.) and CuCl_2 (1 equiv.) at 55 °C for 12 h led to complete consumption of *trans*-**12** to form **13** in 82% isolated yield (Table 1, entry 6).^{†§}



Scheme 2

In addition to *trans*-**12**, alkenyl β -keto esters *cis*-**12** and **14–16**, which possessed either a *cis* or *trans* terminal olefinic substituent, underwent palladium-catalyzed cyclization in the presence of SiMe₃Cl or SiMe₃Cl/CuCl₂ to form carbocycles **13** and **17–19**, respectively, in $\geq 80\%$ yield with excellent regioselectivity (Table 1, entries 7–10). Alkenyl β -keto ester **20**,

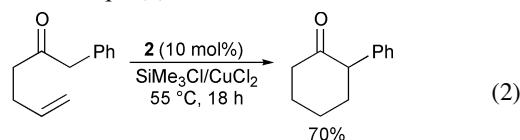
Table 1 Palladium-catalyzed cyclization of alkenyl β -keto esters

Entry	Substrate	Con- ditions ^a	Carbocycle	Yield (%) ^b
1		A		91
2	4 (R = Me)	A	5	91
3	6 (R = Et)	A	9	82 (45)
4	7 (R = Bn)	A	10	83 (32)
4	8 (R = <i>i</i> -Bu)	A	11	82
5		A		79
6	<i>trans</i> - 12	B	13	82
7		A	13	83
7	<i>cis</i> - 12	A	13	83
8		A		93
9	14 (R = Ph)	A	17	93
9	15 (R = Me)	B	18	87
10		B		83
10	16	B	19	83
11		B		62 ^c
11	20	B	21	62 ^c
12		B		72
12	22	B	18	72

^a A = substrate (33 mM), **2** (10 mol%), SiMe₃Cl (2 equiv.), dioxane, 25 °C; B = substrate (33 mM), **2** (10 mol%), SiMe₃Cl (2 equiv.), CuCl₂ (1 equiv.), dioxane, 55 °C. ^b Value in parentheses refers to yield of carbocycle formed in the absence of SiMe₃Cl (ref. 1). ^c Isolated as a 5.8:1 mixture of *trans*:*cis* diastereomers.

which possessed both an olefinic and allylic methyl substituent, cyclized to form carbocycle **21** in 62% yield as a 5.8:1 mixture of *trans*:*cis* diastereomers (Table 1, entry 11). Methyl 3-oxooct-7-enoate (**22**), in which three methylene groups separate the ketone and the olefin, underwent cyclization to form carbocycle **18** in 72% isolated yield (Table 1, entry 12).

Preliminary experiments indicate that a range of carbon pronucleophiles in addition to β -keto esters will undergo palladium-catalyzed intramolecular addition to unactivated olefins in the presence of SiMe₃Cl. For example, treatment of the simple ketone 1-phenylhex-5-en-2-one with **2** (10 mol%), SiMe₃Cl (2 equiv.), and CuCl₂ (1 equiv.) in dioxane at 55 °C for 18 h formed 2-phenylcyclohexanone in 70% isolated yield as a single regioisomer [eqn. (2)].



In summary, PdCl₂(CH₃CN)₂ (**2**) catalyzed the cyclization of alkenyl β -keto esters in the presence of SiMe₃Cl to form 2-carboalkoxycyclohexanones in good yield with excellent regioselectivity. These transformations presumably involve intramolecular attack of an *in situ*-generated silyl enol ether on a palladium-complexed olefin. Our current efforts are directed toward the further utilization of SiMe₃Cl in the palladium-catalyzed addition of carbon pronucleophiles to unactivated olefins.

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Notes and references

‡ Heating a solution of **4** in the presence of excess SiMe₃Cl and/or CuCl₂ at 55 °C in the absence of **2** led to no detectable cyclization after 12 h. The catalytic activity of **2** obtained from Aldrich was indistinguishable from **2** synthesized from PdCl₂.

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