

Cascade Radical Reactions Catalyzed by a Pd/Light System: Cyclizative Multiple Carbonylation of 4-Alkenyl Iodides

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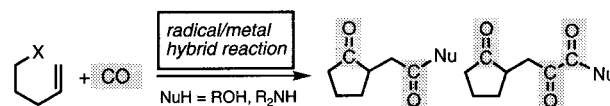
Bond-forming reactions that include cascade steps have gained increasing significance as versatile synthetic methods.¹ Herein we report new cascade reactions, in which five-membered cyclic keto esters and amides are prepared starting from 4-alkenyl iodides via cyclizative multiple CO-trapping reactions (Chart 1). For this purpose, we employed a radical/metal hybrid strategy that relies upon both radical cascades^{2,3} and palladium catalysis. Related cascade transformations including a carbonylation–cyclization–carbonylation sequence have been reported by the Negishi group,⁴ and the Grigg group,⁵ by taking advantage of the reactivity of palladium catalysts with properly substituted *aromatic* and *vinyllic* halides.⁶ Unfortunately, palladium-catalyzed transformations are not applicable to the wider class of aliphatic halides, due to the low reactivity of sp³-carbon–halogen bonds toward oxidative addition with Pd.^{7,8} We believe that the present hybrid strategy provides a viable solution to this problem.

We initially examined the possibility of applying atom transfer carbonylation⁹ to the envisaged cascade reaction. When 4-pentenyl iodide (**1a**) was exposed to standard reaction conditions (irradiation with a xenon lamp through Pyrex under 40 atm of CO pressure),^{9a} the desired cyclic keto ester **2a** was indeed formed, but the yield was only 5% (Scheme 1). It is conceivable that, unlike the case of simple ester synthesis,^{9a} the ionic termination reaction may not be efficient enough to shift the five equilibrium steps (homolysis, carbonylation, cyclization, carbonylation, and iodine atom transfer) to completion. Then, we examined the palladium-catalyzed carbonylation of **1a** under thermal conditions using Pd(PPh₃)₄, but as anticipated, there was no reaction. Interestingly, however, when these two conditions, irradiation and treatment with Pd(0) catalyst, are employed together, the desired keto ester **2a** was obtained in a remarkable 61% yield.¹⁰ The tuning of the conditions by addition of 4-(dimethylamino)pyridine (DMAP) improved the yield up to 82%.

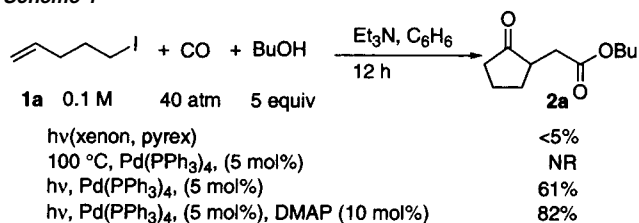
As shown in Table 1, the present cyclizative double carbonylation sequence is applicable to a wide variety of 4-alkenyl iodides having sp³-carbon–iodine bonds. 4-Pentenyl *bromide* (**1a'**) can also be used, but the yield of **2a'** was rather modest. A spirocyclic keto ester **2c** was formed from **1c**. Secondary substrates **1d**, **1e**, **1f**, and **1g** also worked well to give the corresponding cyclic keto esters **2d**, **2e**, **2f**, and **2g** in good yields. The cyclizative double carbonylation of **1h** and **1i** proceeded stereoselectively to give the corresponding bicyclic keto esters **2h** and **2i**, whose pendant methoxycarbonyl group was disposed on the convex face.¹¹

The cyclizative carbonylation, when performed in the presence of diethylamine, provided triply carbonylated α,δ -diketo amides **4**

Chart 1



Scheme 1



as the major products along with the doubly carbonylated γ -keto amides **3** (runs 13–15). Although the formation of vicinal keto amides has many precedents in palladium-catalyzed double carbonylation chemistry,¹² most of them are for aryl, benzyl, vinyl, and allyl halides and we are aware of only two cases with respect to alkyl halides.^{12a,c}

The cascade reactions that we have observed clearly result from the interplay of two reactive species, radicals and organopalladium species. To determine whether the Pd(0)/hv system would effect initiation of radical reactions in our system,¹³ we examined the atom-transfer cyclization of 1-ethyl-5-hexenyl iodide and found that the presence of Pd resulted in a much more efficient reaction and that the observed *cis/trans* ratio (72/28) of the product, 1-ethyl-2-(iodomethyl)cyclopentane, was identical with that observed for a 1-methyl-5-hexenyl radical cyclization.¹⁴ In addition, the observed stereochemical outcomes for the cyclizations of **1e** and **1f** (*cis/trans* = 43/57 and 38/62, respectively) are identical to those obtained in the tin radical-mediated carbonylation of the same substrates,^{2a} providing support for the postulate that a 5-exo-trig acyl radical cyclization of **B** leading to **C** does occur in the present reaction system (Scheme 2). On the other hand, the formation of esters, amides, and keto amides, should be considered to be the products of acylpalladium intermediates. One possibility is that the acyl radical **D**, arising from the second carbonylation, undergoes coupling with Pd(I) to give an acylpalladium intermediate **E**, which may be the precursor for the final product **2**.¹⁵ Mechanistic aspects of palladium-catalyzed single and double carbonylation of organic halides have been extensively investigated.¹⁶ On the basis of the arguments previously advanced by the Yamamoto group and in analogy to the corresponding reactions of double carbonylation of benzyl chloride,^{16b} we propose that (4-oxo-acyl)(carbamoyl)-palladium complexes would be formed in our system, serving as the key precursors for α -keto amides **4** via reductive elimination.

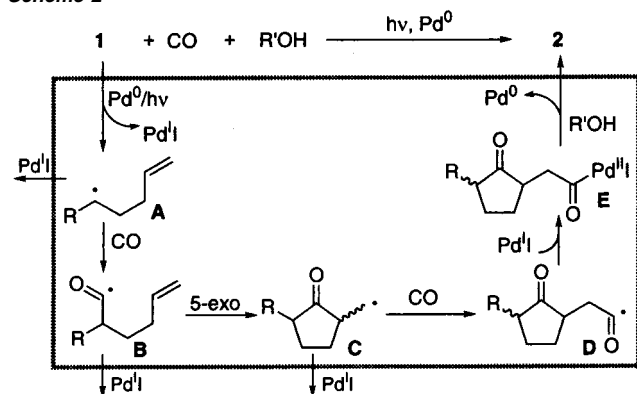
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Table 1. Pd/Light-Induced Cyclizative Carbonylation Reactions of **1**^a

run	substrate	alcohol or amine	product	yield ^b (ratio ^c)
1		BuOH		2a 82%
2		BnOH		2a' 49%
3		MeOH		2b 75%
4		BnOH		2b' 83%
5		EtOH		2c 76%
6		EtOH		2d 64% (41/59)
7		MeOH		2e 67% (43/57)
8		MeOH		2f 68% (38/62)
9		MeOH		2g 72% (44/56)
10		MeOH		78%
11		MeOH		74%
12		MeOH		74% ^d
13 ^e	1a	HNEt ₂		3a 10%
14 ^e	1b	HNEt ₂		3b 22%
				4a 51%
				4b 39%
15 ^e	1i	HNEt ₂		3i 21%
				4i 41%

^a Conditions: **1** (0.5 mmol), Pd(PPh₃)₄ (5 mol %), alcohol (4–30 mmol), Et₃N (0.6 mmol), DMAP (5–10 mol %), CO (40 atm), benzene (5 mL), hν (500 W xenon lamp, Pyrex), 16 h. ^b Isolated yield by silica gel chromatography. ^c Cis/trans ratio determined by ¹H NMR and/or GC analysis. ^d Three minor isomers were also formed in a 78(**2j**)/9/7/6 ratio. ^e Et₂NH (4 mmol), CO (80 atm).

Scheme 2

Further studies to extend this hybrid radical/metal strategy are now in progress.

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Supporting Information Available: Typical experimental procedure and spectroscopy data and analytical data of all products (PDF). This material is available free of charge via the Internet at <http://pubs.acs.org>.

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