

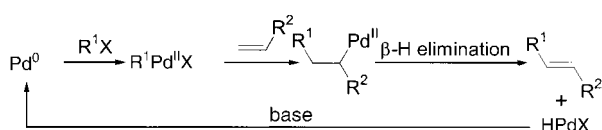
Palladium-Catalyzed Reactions

“Walking” of the C–C π Bond over Long Distances in Pd-Catalyzed Reactions of 2,3-Allenic Acids with ω -1-Alkenyl Halides**

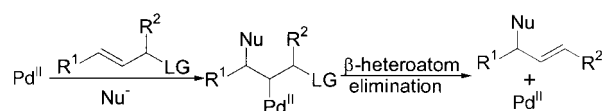
Shengming Ma* and Zhanqian Yu

Transition-metal-catalyzed reactions have proven to be one of the most powerful pathways for the formation of carbon–carbon bonds as well as carbon–heteroatom bonds.^[1] Palladium is a particularly useful and versatile transition metal used for organic synthesis.^[2] Two reaction pathways have been observed in the Pd-catalyzed Heck-type reactions of alkenes (Scheme 1). The catalytic cycle of the Heck reaction was

Pd⁰/Pd^{II}-catalyzed pathway:



Pd^{II}-catalyzed pathway:



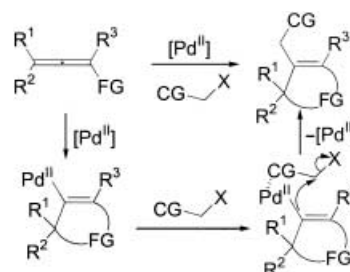
Scheme 1. Possible mechanistic pathways for Pd-catalyzed Heck-type reactions.

based on the Pd⁰–Pd^{II}–Pd⁰ pathway,^[3] whereas in Pd^{II}-catalyzed reactions the catalyst was regenerated through a β -heteroatom elimination.^[4] Herein we report the first example of Pd^{II}-catalyzed “walking” of the carbon–carbon π bond over a carbon chain in which the combination of cyclic oxypalladation–carbopalladation and repeated dehydropalladation/hydopalladation–dehalopalladation are the main steps of a catalytic cycle.

On the other hand, we have recently applied the transition-metal-promoted or -catalyzed cyclizations of 2,3-allenoic acids/esters or salts for the synthesis of several kinds

of butenolides.^[5] In those reactions, we could easily introduce an aryl/vinyl substituent at the β position of the butenolides. Nevertheless, under those established reaction conditions the sp³-hybridized carbon atom could not be introduced into the product by the direct reaction of the allenic acids and sp³-hybridized carbon halides as a result of the intrinsic stability problem of alkyl palladium species. Although we have successfully developed an alternative two-step method for the synthesis of the β -alkyl-substituted butenolides, we wished to develop a new method with which the sp³-hybridized carbon atom could be directly introduced into butenolides.

We observed the formation of unusual products in the Pd^{II}-catalyzed coupling cyclization reaction of 2,3-allenols or 1,2-allenyl ketones with allylic halides^[6] possibly through a coordination-directed direct replacement of the halogen atom by the corresponding palladium species or an oxidative addition–reductive elimination process^[7] (Scheme 2). Based on this hypothesis a Pd-catalyzed cross-coupling cyclization reaction of functionalized allenes with halides bearing a coordination center may be possible.



Scheme 2. Pd^{II}-catalyzed coupling reaction of functionalized allenes with organic halides bearing a group with coordination ability. CG = coordinating group, FG = functional group.

As a first try, we searched for a protocol of the coupling cyclization of functionalized allenes (e.g. allenols, allenic acids) with homoallylic halides, in which the C=C bonds may act as a coordination group. We were pleased to discover that homoallylic bromide **2a** in *N,N*-dimethylformamide (DMF) could react with the 4-phenyl-2-propyl-2,3-butadienoic acid (**1a**) under the catalysis of PdCl₂ to form the desired product **3a** in 41 % yield (Table 1, entry 1). The reaction conditions were further optimized and some typical results are listed in Table 1. Other solvents were also effective. For example, in methanol, dioxane, and hexamethyl phosphoramide (HMPA), comparable yields were observed (Table 1, entries 3–5). Different catalysts showed almost the same results (Table 1, entries 6–11). The reaction was sensitive to temperature. Higher yields were observed at relatively higher temperatures (Table 1, entries 11–13). The best results were obtained when we used 5 mol % of Pd(OAc)₂ and 5 equivalents of the homoallylic bromide in DMF, which provided the product **3a** in 58 % yield (Table 1, entry 13).

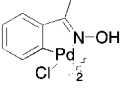
In principle, the presence of the C=C bonds allows two possible pathways for this transformation (Scheme 3). One is the coordination-directed direct substitution pathway (path A), in which PdCl₂ coordinates with the double bond

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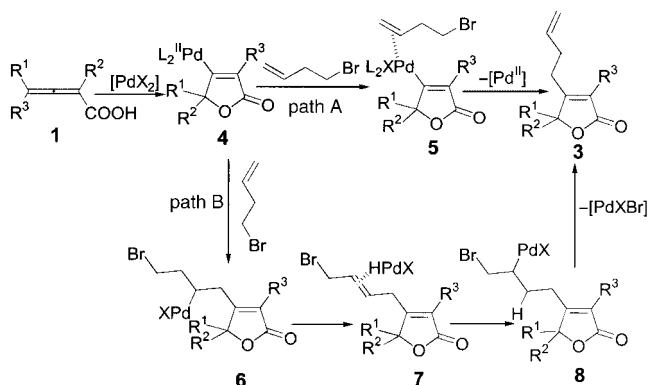
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Table 1: Pd^{II}-catalyzed of coupling cyclization reaction of 4-phenyl-2-propyl-2,3-butadienoic acid **1a** and homoallyl bromide **2a**.

Entry	Catalyst	Solvent	T [°C]	t [h]	Yield [%]
1	PdCl ₂	DMF	50	22	41
2 ^[a]	PdCl ₂	DMF	50	46	44
3	PdCl ₂	ethanol	50	38	44
4	PdCl ₂	HMPA	50	45	40
5	PdCl ₂	dioxane	50	33.5	17
6	PdCl ₂	DMF	80	10.5	46
7 ^[b]		HMPA	50	34.5	40
8	[PdCl ₂ (dppf)]	DMF	50	67	30
9	[PdCl ₂ (PPh ₃) ₂]	DMF	50	110	30
10	[PdCl ₂ (PhCN) ₂]	DMF	80–90	1	51
11	Pd(OAc) ₂	DMF	50	33	43
12	Pd(OAc) ₂	DMF	80	2	51
13	Pd(OAc) ₂	DMF	100	1	58

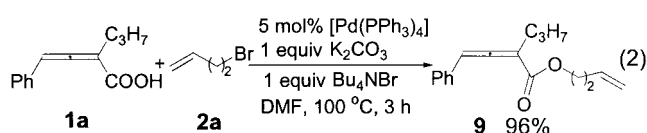
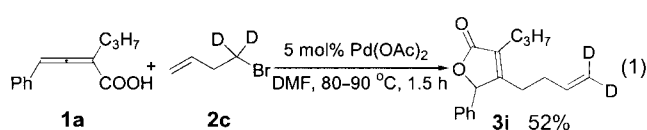
[a] Catalyst: 10 mol %. [b] Catalyst: 5 mol %.



Scheme 3. The possible reaction pathways.

remote from the acid group in 2,3-allenoic acids **1**. Subsequent cyclic oxypalladation affords palladium intermediate **4**, which coordinates with the carbon–carbon double bonds of homoallylic bromide **2a** followed by an oxidative addition–reductive elimination process leading to **3**.^[7] The alternative pathway is the cyclic oxypalladation–carbopalladation pathway with repeated dehydropalladation/hydropalladation–dehalopalladation (path B).

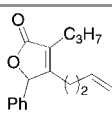
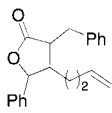
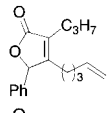
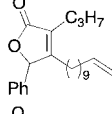
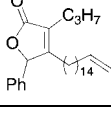
To clarify the mechanism, the reaction of deuterated homoallylic bromide **2c** and **1a** was carried out. Only product **3i** in which the two deuterium atoms located at the terminal carbon atom of the acyclic carbon–carbon double bond was obtained in 52 % yield [Eq. (1)]. When the reaction was carried out in the presence of [Pd(PPh₃)₄], only **9** was obtained in 96 % yield [Eq. (2)].



Those findings illustrated that the reaction proceeded through path B. To the best of our knowledge, this is the first example of a Pd^{II}-catalyzed cycle that combines carbopalladation with repeated dehydropalladation/hydropalladation–dehalopalladation. Based on these results, we were interested to see how far a repeated dehydropalladation and hydropalladation sequence can travel. We prepared ω-bromoalkenes **2a–d** according to a literature method,^[8] and some typical results under the established reaction conditions are shown in Table 2. The substituent of allenoic acids could be aryl, alkyl, and benzyl. The reaction of **1a** with **2d** proceeded smoothly to give the corresponding products **3e** in 18 % yield, an average of 93 % yield for every step (Table 2, entry 5). In this reaction the palladium traveled over 14 carbon atoms!^[9]

In conclusion, we have developed a useful method for the direct introduction of an sp³-hybridized carbon atom at the β position of butenolides through the Pd^{II}-catalyzed coupling cyclization reaction of 2,3-allenoic acids with ω-1-alkenyl halides. The reaction proceeds through a cyclic oxypalladation–carbopalladation with repeated dehydropalladation/hydropalladation–β-dehalopalladation process. The repeated dehydropalladation and hydropalladation sequence can travel through a chain of fourteen carbon atoms.

Table 2: The coupling cyclization of 2,3-allenoic acids and ω-1-alkenyl halides.^[a]

Entry	1 (R ²)	2 (n)	t [h]	Product 3	Yield [%]
1	a (C ₃ H ₇)	a (2)	1		a 58
2	c (PhCH ₂)	a (2)	1.5		b 48
3	a	b (3)	10		c 45
4	a	d ^[b] (9)	21		d 30
5	a	e (14)	9		e 18

[a] The reaction was carried out using **1** (0.25 mmol), **2** (1.25 mmol), and Pd(OAc)₂ in DMF. [b] **2d**: 10 equiv.

Experimental Section

Typical procedure: A mixture of **1a** (50 mg, 0.25 mmol), homoallylic bromide **2a** (170 mg, 1.26 mmol), and Pd(OAc)₂ (3 mg, 0.013 mmol) in DMF (2 mL) was stirred at 100 °C for 1 h. After diluting with diethyl ether, the reaction mixture was washed twice with water, and the organic layer was dried over MgSO₄ and concentrated by evaporation. The residue was purified by column chromatography on silica gel (petroleum ether/ethyl acetate = 10:1) to afford **3a** as an oil (37 mg, 58 %). ¹H NMR (300 MHz, CDCl₃): δ = 7.41–7.30 (m, 3H), 7.22–7.12 (m, 2H), 5.74–5.60 (m, 2H), 5.03–4.91 (m, 2H), 2.57–2.41 (m, 1H), 2.29 (t, *J* = 7.50 Hz, 2H), 2.20–2.00 (m, 3H), 1.66–1.53 (m, 2H), 0.95 ppm (t, *J* = 7.20 Hz, 3H); ¹³C NMR (75.4 MHz, CDCl₃): δ = 13.85, 21.46, 25.56, 25.88, 31.72, 83.69, 116.16, 126.89, 127.51, 128.89, 129.21, 134.85, 136.31, 162.33, 174.36 ppm; EIMS: *m/z* (5): 257 (10.26) [*M*⁺+1], 256 (12.29) [*M*⁺], 105 (100); IR (neat): $\tilde{\nu}$ = 1747, 1668, 1635, 1602 cm⁻¹; HRMS: calcd for C₁₇H₂₀O₂: 256.14633; found: 256.14872.

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