



Palladium(II)-catalyzed coupling of allenic acids and α,β -unsaturated carbonyl compounds through tandem intramolecular oxypalladation and conjugate addition reactions

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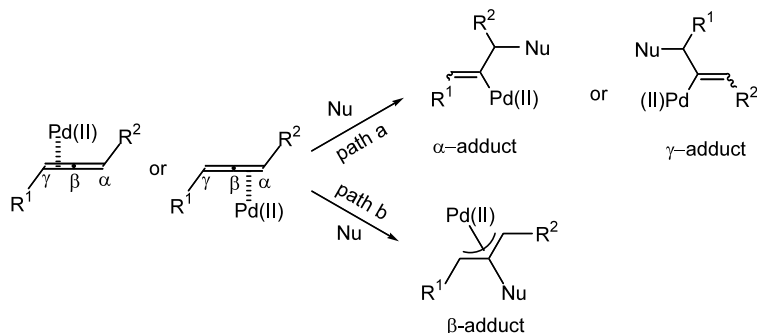
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Abstract—A regioselective divalent palladium-catalyzed tandem coupling reaction of allenic acids with α,β -unsaturated carbonyl compounds was developed. The reaction involves intramolecular oxypalladation of an allene, followed by insertion of the α,β -unsaturated carbonyl compound and protonolysis of the C–Pd bond to regenerate the Pd(II) species in the presence of excess halide ions. Functionalized lactones, tetrahydropyranones and dihydropyranones can be synthesized with high regioselectivity in one step. © 2002 Elsevier Science Ltd. All rights reserved.

The alkenylpalladium species is a versatile reaction intermediate in palladium-catalyzed reactions.¹ Besides the well studied oxidative addition of vinylic halides or triflates to Pd(0) to generate the vinylic palladium species,¹ it can also be obtained from the addition of a nucleophile to divalent palladium coordinated alkynes^{1,2} or allenes^{1a,3} (nucleopalladation). In contrast to the nucleopalladation of alkynes, the nucleopalladation of allenes is more complex, because the nucleophile can react with the palladium-coordinated allenes via two types of pathway due to the different style of coordination of palladium with the allene: (1) the nucleophile attacks the α - or γ -carbon atom to form the vinylic palladium species (the α -adduct or γ -adduct, path a, Scheme 1); (2) the nucleophile attacks the

β -carbon atom to form a π -allylic palladium species (the β -adduct, path b, Scheme 1).³

To our knowledge, nucleophilic addition reactions of allenes catalyzed by divalent palladium without the addition of oxidants has scarcely been reported.⁴ In our previous work, we found that protonolysis of the carbon–palladium bond in the presence of excess halide ions is an effective method quenching the carbon–palladium bond and regenerating the Pd(II) species.⁵ These results prompted us to explore the possibility of a Pd(II)-catalyzed nucleophilic addition reaction of allenes using C–Pd bond protonolysis as the Pd(II) regeneration step. A preliminary communication related to aminopalladation as the initial step has been



Scheme 1.

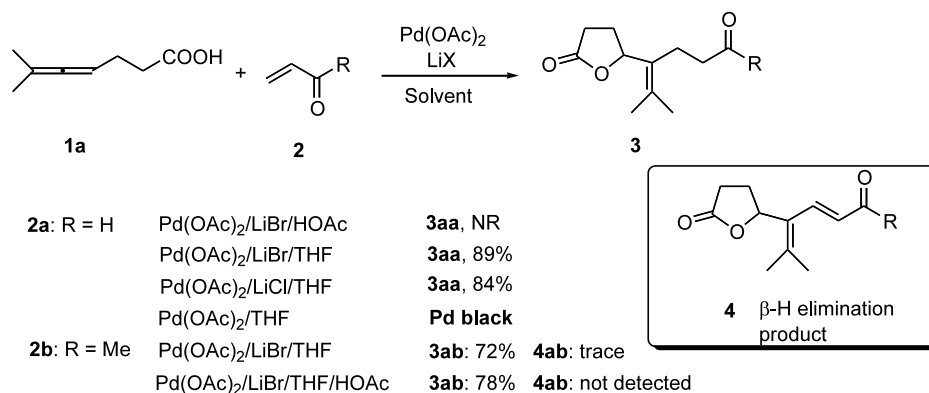
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published.^{6b} Herein, we report the detailed results of the novel palladium(II)-catalyzed nucleophile-allene- α,β -unsaturated carbonyl coupling through tandem intramolecular oxypalladation and conjugate addition reactions.

Reaction of 6-methylhept-4,5-dienoic acid **1a** (0.5 mmol) with acrolein **2a** (2.5 mmol) in the presence of $\text{Pd}(\text{OAc})_2$ (5 mol%) and LiBr (2 mmol) in THF for 2 h at room temperature afforded the product **3aa** regioselectively in 89% yield (Scheme 2). While LiCl gave similar results to LiBr , no coupling reaction occurred, but a Pd black precipitate appeared within a few minutes in the absence of halide ions. When the less active α,β -unsaturated carbonyl compound, methyl vinyl ketone (MVK) **2b**, was used, the reaction gave **3ab** in 72% yield within 18 h accompanied by a trace of the β -H elimination product **4ab** (<5% yield). While no reaction occurred in HOAc, a small amount of HOAc (e.g., THF/HOAc (v/v)=4/1) shortened the reaction time and no β -H elimination product was detected.

Under similar conditions, the reaction of γ -allenoic acids **1c**, **1d** and **1e** also proceeded smoothly with acrolein and methyl vinyl ketone, giving the conjugate addition products **3** in high yield. Furthermore, the reactions of γ -allenoic acid **1d** with phenyl vinyl ketone **2c** or cyclohexyl vinyl ketone **2d** at 50°C also showed good results. However, subjecting 4-allenoic acid **1b** to similar conditions, resulted in the formation of **3ba** and **3bb** in poor yields. The results are listed in Table 1. Most of the reactions gave the *E*-isomer as the major product as substantiated by NOESY studies.

The influence of the substituents on both the allenoic acid and α,β -unsaturated carbonyls seems to exhibit an important effect on the reaction selectivity. When R^1 was a larger group, the reaction stereoselectivity was higher than with less bulky group (Table 1, entries 3, 5 and 4, 6, 9). On the other hand, the substituents on the α,β -unsaturated carbonyls also had an effect on the stereochemical outcome. Changing the substituents



Scheme 2.

Table 1. Palladium(II)-catalyzed intramolecular oxypalladation of 4-allenoic acid and conjugate addition^a

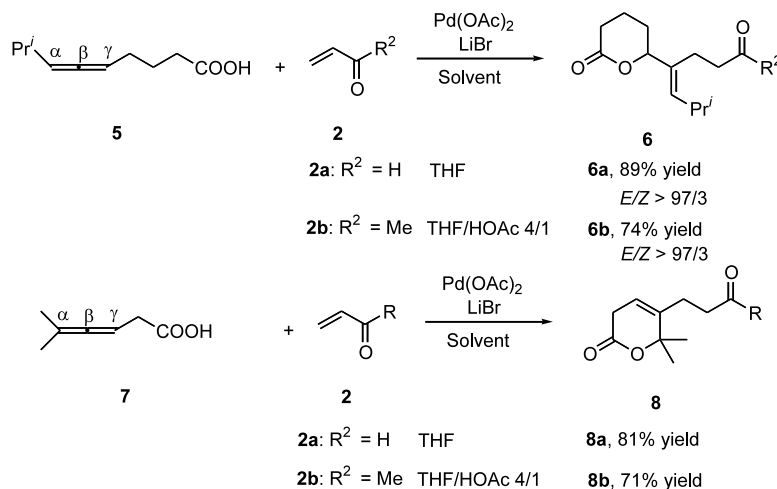
Entry	Allenic acid		α,β -Unsaturated carbonyl compound		Solvent	Time (h)	Product		
	1	R^1	2	R^2			3	Yield (%) ^b	<i>E/Z</i> ^c
1	1b	H	2a	H	THF	48	3ba	44	–
2	1b	H	2b	Me	THF/HOAc 4/1	62	3bb	57	–
3	1c	^{<i>i</i>} Pr	2a	H	THF	2	3ca	90	3.6/1
4	1c	^{<i>i</i>} Pr	2b	Me	THF/HOAc 4/1	8	3cb	81	6.3/1
5	1d	C_5H_{11}	2a	H	THF	2	3da	92	1/1.4
6	1d	C_5H_{11}	2b	Me	THF/HOAc 4/1	8	3db	78	4.0/1
7 ^d	1d	C_5H_{11}	2c	Ph	THF/HOAc 8/1	8	3dc	82	> 19/1
8 ^d	1d	C_5H_{11}	2d	C_6H_{11}	THF/HOAc 8/1	12	3dd	62	11/1
9	1e	CH_2OBn	2b	Me	THF/HOAc 4/1	8	3eb	82	> 19/1

^a Reaction conditions: 4-allenoic acid **1** (0.5 mmol), α,β -unsaturated carbonyl **2** (2.5 mmol), $\text{Pd}(\text{OAc})_2$ (5 mol%) and LiBr (2 mmol) in the specified solvent, rt.

^b Isolated yield.

^c The ratio of *E/Z* was determined by ¹H NMR.

^d **2c** and **2d** (1 mmol, 2 equiv.) were used, 50°C.



Scheme 3.

from H to Me, phenyl and cyclohexyl, the stereoselectivity of **1d** was increased (Table 1, entries 5–8).

To study whether or not the cyclization–conjugate addition could be applied to allenic acids with one more or one less carbon atoms, **5** was treated with **2a** and **2b** under similar conditions, and the reactions gave tetrahydropyranones **6a** and **6b**, respectively (Scheme 3). It is surprising that the formation of **6a** and **6b** is highly stereoselective (*E/Z* > 97/3). Unlike the reactions of **1** and **5**, the reactions of **7** with **2a** or **2b** led to dihydropyranones **8a** and **8b**, respectively, with high regioselectivity.

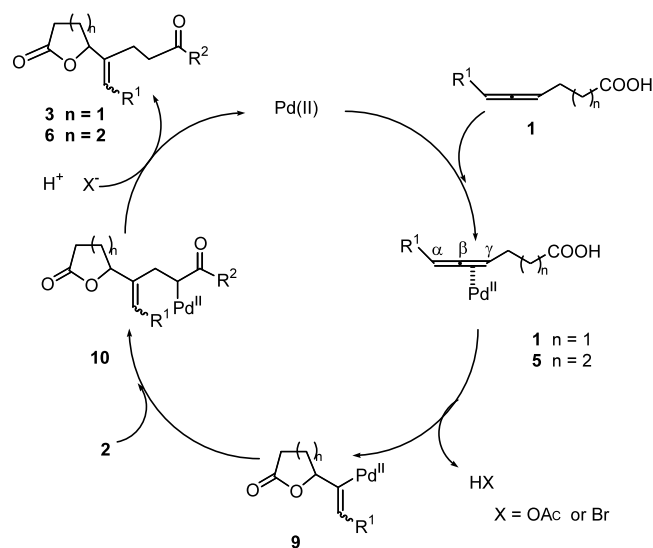
The above results show that the intramolecular nucleopalladation of allenic acids with different carbon atoms led to attack at only the α - or γ -position of the allenic moiety, giving oxygen heterocycles with different ring sizes.

With regard to the mechanism of this reaction, we speculate that it involves a vinyl palladium intermediate as shown in Scheme 4, rather than a π -allyl palladium intermediate as reported in the literature.⁷ First, the carboxylate ion dissociated from the allenic acid in THF, attacks intramolecularly the γ -carbon atom of the $\text{Pd}(\text{II})$ -coordinated allenic acid **1** or **5** to form the vinylic palladium intermediate **9**. This is followed by insertion of the α,β -unsaturated carbonyl compound into the vinylic palladium bond to yield the intermediate **10**, and then the newly formed carbon–palladium bond is protonolyzed in the presence of halide ions to give **3**. For the reaction of **7**, a vinyl palladium intermediate **11** also may be formed by oxypalladation at the α -position of the allene moiety (Scheme 5). Here, the halide ions play a very important role in inhibiting β -H elimination in **10**, allowing the reaction to proceed with high catalytic efficiency and good selectivity.⁸

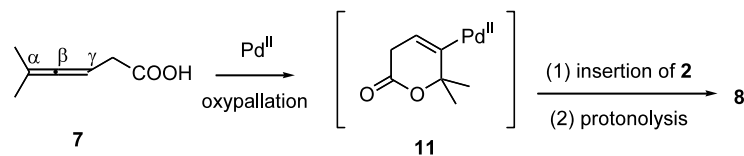
In these reactions, a proton source is important for accelerating the protonolysis of the C–Pd bond, especially for the reactions of the α,β -unsaturated ketones.

The reaction is completely shut down in HOAc possibly due to the suppression of the dissociation of the allenic acid in HOAc, which is important for the oxypalladation to occur. It is obvious that a weakly acidic system is necessary for the reactions of α,β -unsaturated ketones.

In summary, a divalent palladium-catalyzed tandem coupling reaction of allenic acid with α,β -unsaturated carbonyls has been developed. Functionalized lactones, tetrahydropyranones and dihydropyranones can be synthesized with high regioselectivity in one step. This new reaction proceeds via a vinylic palladium intermediate formed from an intramolecular oxypalladation or aminopalladation of an allene, followed by α,β -unsaturated carbonyl compound insertion, and halide-assisted protonolysis to regenerate the $\text{Pd}(\text{II})$ without using oxidants.



Scheme 4.



Scheme 5.

Acknowledgements

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