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Highly Regio- and Stereoselective Synthesis of 2(*E*),4-Alkadienoates via the Pd(0)-Catalyzed Reaction of Aryl Halides with 3,4-Alkadienoates

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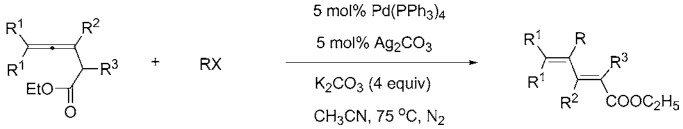
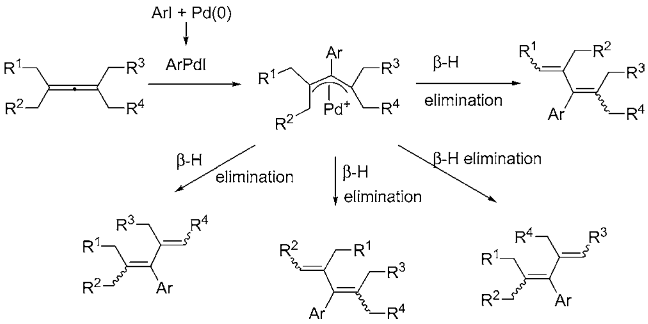
ABSTRACT



2(*E*),4-Alkadienoates were prepared highly stereoselectively via the Pd(0)/Ag_2CO_3-cocatalyzed reaction of 3,4-alkadienoates and aryl halides. The reaction is believed to proceed via the oxidative addition–carbopalladation–*β*-H elimination process. Compared to the other reported methods for the synthesis of 2,4-alkadienoates, in which usually only disubstituted C═C bonds were formed, the current reaction forms the trisubstituted or even tetrasubstituted C═C bond highly stereoselectively.

Stereoselective synthesis of conjugated 1,3-dienes is of current interest[1] since they are very important intermediates in organic synthesis.[2] Recently, much attention has been paid to the transition metal-catalyzed chemistry of allenes.[3−6] After observing high selectivities with allenes bearing an α-functionality,[4] we proposed that carbopalladation of allenes would provide a very convenient entry to π-allyl palladium species, which upon β-H elimination would lead to a convenient formation of conjugated 1,3-dienes (Scheme 1).[7] However, the stereoselectivity of β-H elimination is usually disappointing, which makes this approach unsuitable for the highly stereoselective synthesis of 1,3-dienes.[8] In this paper, we wish to report the first highly regio- and stereoselective Pd(0)-catalyzed reaction of 3,4-alkadienoates with organic halides leading to 2(*E*),4-alkadienoates in high yields. Compared to the other reported protocols,[1] in which usually only disubstituted C═C bonds were formed, the current reaction forms the trisubstituted or even tetrasubstituted C═C bond highly stereoselectively.

Scheme 1. Regio- and Stereochemical Issues in the Pd-Catalyzed Synthesis of 1,3-Dienes from Allenes and Organic Halides



At the beginning, we tried the reaction of ethyl 3-butyl-3,4-pentadienoate **1a** with phenyl iodide under the conditions for the coupling cyclization of organic halides with 2,3-

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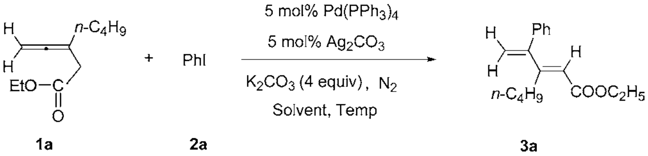
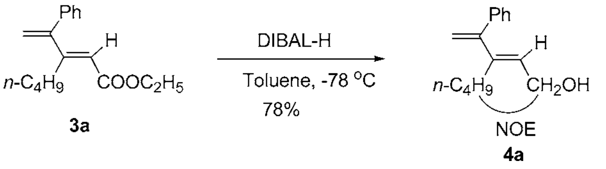
allenoic acids,[9] which afforded ethyl 4-phenyl-3-butyl-2(*E*),4-pentadienoate **3a** in 80% yield as the only product (entry 5, Table 1). The stereoselectivity is excellent, i.e., only the 2(*E*)-stereoisomer was formed, which is quite unique as compared to a similar nonstereoselective reaction with normal alkyl-substituted allenes.[8] The stereochemistry of **3a** was established via the combined NOE study of **3a** and **4a** (eq 1).

Table 1. Pd(0)/Ag^+-Catalyzed Carbopalladation and β-H Elimination Reaction of **1a** with PhI



entry	solvent	temp (°C)	time (h)	PhI (equiv)	yield of **3a** (%)^a
1	toluene	75	13	1.5	10
2	THF	75	14	1.5	45
3	dioxane	75	14	1.5	65
4	DMF	75	14	1.5	76
5	CH_3CN	75	13	1.5	80
6	CH_3CN	75^b	13	1.5	63
7	CH_3CN	60	13	1.5	16
8	CH_3CN	75	13	1.2	63
9	CH_3CN	75^c	13	1.5	71

^{a} Isolated yield. ^{b} Reaction was conducted in the absence of Ag_2CO_3. ^{c} Reaction was conducted in the presence of 2 equiv of K_2CO_3.



(1)

After the reaction was run in different solvents, it was observed that MeCN is the best solvent (entry 5, Table 1). Further study indicates the following: (1) The presence of Ag_2CO_3 is necessary since the reaction in the absence of 5 mol % Ag_2CO_3 only afforded **3a** in 63% yield (compare entry 5 with entry 6, Table 1). This may be explained by the interaction between the carbonyl group and Ag^+ to ensure a fast and regioselective β-H elimination. (2) The reaction temperature is also crucial since the reaction at 60 °C afforded **3a** in only 16% yield (entry 7, Table 1). (3) For a high-yielding reaction, 1.5 equiv of PhI and 4 equiv of K_2CO_3 are required (compare entry 5 with entries 8, 9, Table 1).

With these results in hand, we studied the scope of this transformation; some typical results are summarized in Table 2. From Table 2, it can be concluded that the reaction is general: R^2 can be H, alkyl, or aryl; both electron-withdrawing and electron-donating aryl halides can be used in this reaction (entries 7−12, Table 2). The reaction with thienyl bromide also proceeded smoothly, affording the corresponding 2(*E*),4-pentadienoate **3m** in 66% yield (entry 13, Table 2). No β-H elimination toward R^1 or R^2 was observed. However, under the conditions reported by Cheng et al.,[8] the reaction afforded a mixture of 1,3-dienes formed from the nonregioselective β-H elimination.

On the basis of the analysis of ^{1}H NMR spectra of the crude products, the extent of the formation of the 2(*Z*)-isomer

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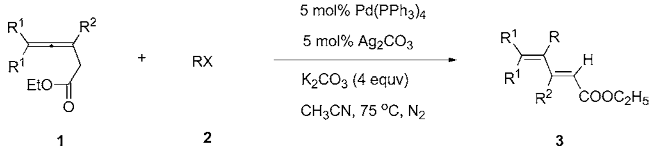
Table 2. Pd(0)/Ag$^+$-Catalyzed Reaction of 3,4-Alkadienoates with Organic Halides[a]

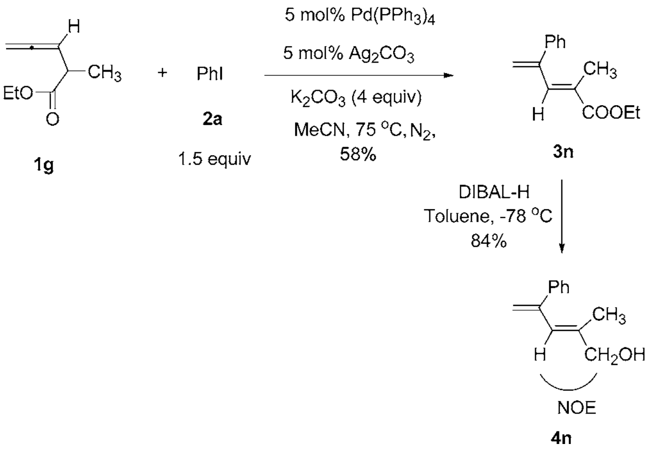


entry	R^1	R^2	RX	**2/1** (equiv)	time (h)	yield of **3** (%)[b]
1	H	n-C_4H_9 (**1a**)	PhI (**2a**)	1.5/1	13	80 (**3a**)
2	CH_3	H (**1b**)	PhI (**2a**)	1.5/1	23	82 (**3b**)
3	C_2H_5	H (**1c**)	PhI (**2a**)	1.5/1	19	77 (**3c**)
4	$(CH_2)_4$	H (**1d**)	PhI (**2a**)	1.5/1	11	85 (**3d**)
5	$(CH_2)_5$	H (**1e**)	PhI (**2a**)	1.5/1	19	77 (**3e**)
6	H	Ph (**1f**)	PhI (**2a**)	1.5/1	18	44 (**3f**)
7	H	n-C_4H_9 (**1a**)	p-$MeOC_6H_4I$ (**2b**)	1.2/1	11	65 (**3g**)
8	H	n-C_4H_9 (**1a**)	p-$CH_3C_6H_4I$ (**2c**)	1.5/1	11	65 (**3h**)
9	H	n-C_4H_9 (**1a**)	p-$Me_2NCOC_6H_4I$ (**2d**)	1/1.5	11	62 (**3i**)
10	H	n-C_4H_9 (**1a**)	p-$CH_3COC_6H_4I$ (**2e**)	1/1.2	46	75 (**3j**)
11	H	n-C_4H_9 (**1a**)	p-NCC_6H_4I (**2f**)	1/2	60	82 (**3k**)
12	H	n-C_4H_9 (**1a**)	p-$MeO_2CC_6H_4I$ (**2g**)	1/2	24	85 (**3l**)
13	H	n-C_4H_9 (**1a**)	2-thienyl bromide (**2h**)	1.5/1	21	66 (**3m**)

[a] Reaction was carried out using 0.3−0.5 mmol of 3,4-alkadienoates. [b] Isolated yield.

is <4%, if any. Even with ethyl 2-methyl-3,4-pentadienoate **1g**, the reaction afforded ethyl 2(*E*),4-pentadienoate **3n** highly stereoselectively, which was established by the NOE study of **3n** and **4n** (Scheme 2). The stereochemistry may be explained by the favorable *trans* orientation of the 3-vinyl group and the ester group referring to the α,*β*-C=C bond.

Scheme 2



In conclusion, we have established a highly regio- and stereoselective protocol for the synthesis of 2(*E*),4-alkadienoates. Due to the high stereoselectivity and easy availability of the starting allenes,[10] this method will be useful in organic synthesis. Further studies in the area are being pursued in our laboratory.

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Supporting Information Available: Analytical data for the compounds prepared, ^{1}H NMR and ^{13}C NMR spectra of those compounds (PDF). These material is available free of charge via the Internet at http://pubs.acs.org.

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