

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

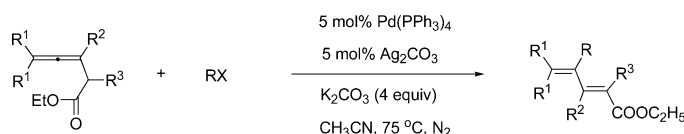
Chunling Fu[†] and Shengming Ma^{*,†,‡}

Laboratory of Molecular Recognition and Synthesis, Department of Chemistry, Zhejiang University, Hangzhou 310027, Zhejiang, P. R. China, and State Key Laboratory of Organometallic Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 354 Fenglin Lu, Shanghai 200032, P. R. China

masm@mail.sioc.ac.cn

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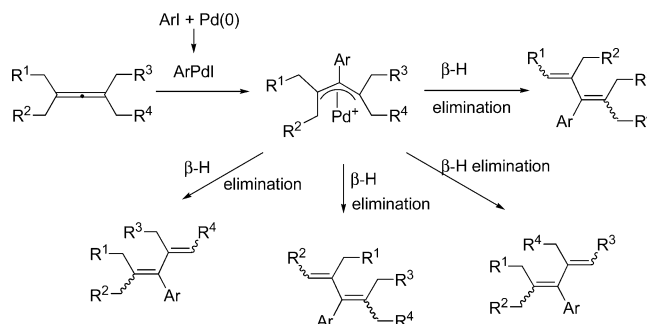
ABSTRACT



2(*E*),4-Alkadienoates were prepared highly stereoselectively via the Pd(0)/Ag₂CO₃-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 interest¹ 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

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



the trisubstituted or even tetrasubstituted C=C bond highly stereoselectively.

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-

* Fax: (+86) 21-64167510.

[†] Zhejiang University.

[‡] Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences.

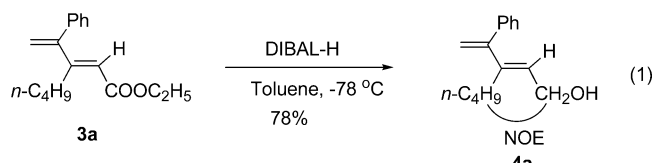
allenoic acids,⁹ which afforded ethyl 4-phenyl-3-butyl-2(*E*),4-pentadienoate **3a** in 80% yield as the only product (entry 5, Table 1). The stereoselectivity is excellent, i.e., only the 2(*E*)-

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 ₃ CN	75	13	1.5	80
6	CH ₃ CN	75 ^b	13	1.5	63
7	CH ₃ CN	60	13	1.5	16
8	CH ₃ CN	75	13	1.2	63
9	CH ₃ CN	75 ^c	13	1.5	71

^a Isolated yield. ^b Reaction was conducted in the absence of Ag₂CO₃. ^c Reaction was conducted in the presence of 2 equiv of K₂CO₃.

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).



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 Ag₂CO₃ is necessary since the reaction in the absence of 5 mol % Ag₂CO₃ 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 K₂CO₃ 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: R² 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 R¹ or R² 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 ¹H NMR spectra of the crude products, the extent of the formation of the 2(*Z*)-isomer

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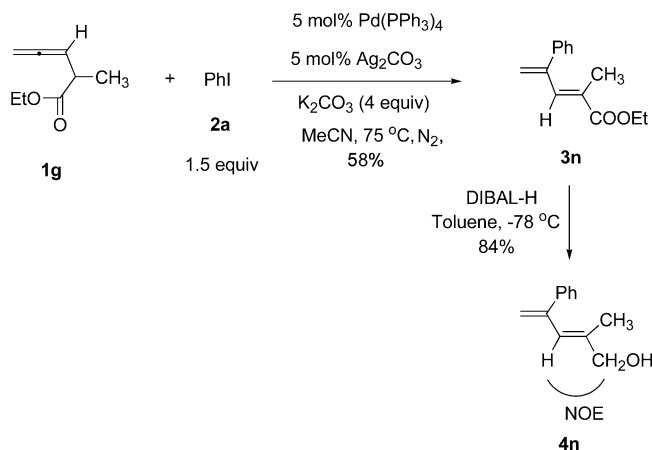
Table 2. Pd(0)/Ag⁺-Catalyzed Reaction of 3,4-Alkadienoates with Organic Halides^a

entry	R ¹	R ²	RX	2/1 (equiv)	time (h)	yield of 3 (%) ^b
1	H	<i>n</i> -C ₄ H 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 ₂ H 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	<i>n</i> -C ₄ H ₉ (1a)	<i>p</i> -MeOC ₆ H ₄ I (2b)	1.2/1	11	65 (3g)
8	H	<i>n</i> -C ₄ H ₉ (1a)	<i>p</i> -CH ₃ C ₆ H ₄ I (2c)	1.5/1	11	65 (3h)
9	H	<i>n</i> -C ₄ H ₉ (1a)	<i>p</i> -Me ₂ NCOC ₆ H ₄ I (2d)	1/1.5	11	62 (3i)
10	H	<i>n</i> -C ₄ H ₉ (1a)	<i>p</i> -CH ₃ COC ₆ H ₄ I (2e)	1/1.2	46	75 (3j)
11	H	<i>n</i> -C ₄ H ₉ (1a)	<i>p</i> -NCC ₆ H ₄ I (2f)	1/2	60	82 (3k)
12	H	<i>n</i> -C ₄ H ₉ (1a)	<i>p</i> -MeO ₂ CC ₆ H ₄ I (2g)	1/2	24	85 (3l)
13	H	<i>n</i> -C ₄ H 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

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.

Scheme 2

explained by the favorable *trans* orientation of the 3-vinyl group and the ester group referring to the α,β-C=C bond.

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Supporting Information Available: Analytical data for the compounds prepared, ¹H NMR and ¹³C 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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