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$Pd(OAc)_2$-Catalyzed Cyclization of 2,3-Allenoic Acids in the Presence of Terminal α,β-Unsaturated Alkynones: A One-Pot Highly Stereoselective Synthesis of 4-(3′-Oxo-1′(*E*)-alkenyl)-2(5*H*)-furanones

Guofei Chen,[†] Rong Zeng,[†] Zhenhua Gu,[‡] 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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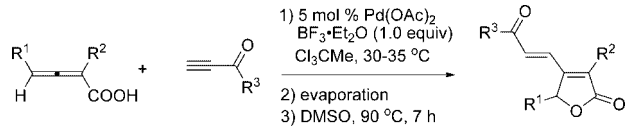
ABSTRACT



The $Pd(OAc)_2$-catalyzed cyclization reaction of 2,3-allenoic acids in the presence of terminal α,β-unsaturated alkynones afforded an *E*/*Z* mixture of 4-(3′-oxo-1′-alkenyl)-2(5*H*)-furanones. A subsequent complete isomerization of the *Z*-isomer to *E*-isomer was observed in DMSO at 90 °C, which led to a highly stereoselective synthesis of 4-(3′-oxo-1′(*E*)-alkenyl)-2(5*H*)-furanones. A possible mechanism is proposed.

Transition-metal-catalyzed reactions of allenes have received much attention from many synthetic organic chemists.[1,2] We and others have studied the cyclization of functionalized allenes in the presence of organic halides,[3] alkenes,[4] allenes,[5] and alkynes.[6] In our previous studies with alkynes, we have observed that the $Pd(OAc)_2$-catalyzed cyclization of 2,3-allenoic acids in the presence of methyl propiolate afforded the 2(5*H*)-furanones with the incorporation of two molecules of propynoate, which readily undergo double 1,7-hydrogen shifts to afford 3-(1′(*E*)-alkenyl)-4-(2′,4′-bis(alkoxycarbonyl)-1′(*E*)-alkenyl)-2(5*H*)-furanones as the final products.[6b] Herein, we wish to report the cyclization reaction of 2,3-allenoic

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† Zhejiang University.
‡ Chinese Academy of Sciences.

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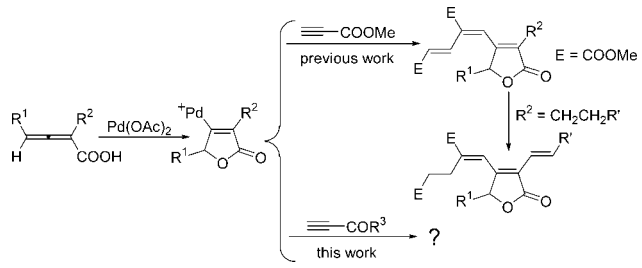
acids in the presence of terminal α,β-unsaturated alkynones (Scheme 1).

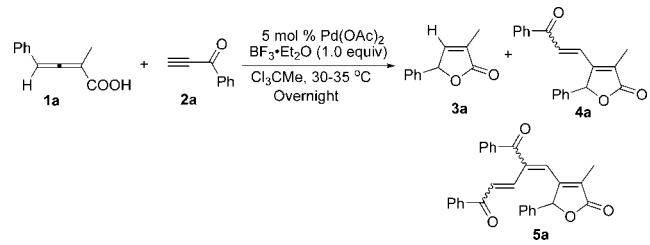
Scheme 1



Initially, we used 2-methyl-4-phenyl-2,3-butadienoic acid **1a** and 1-phenyl-2-propyn-1-one **2a** to try the reaction. To our surprise, different from the reaction of **1a** and methyl propiolate,[6b] no 1:2 product **5a** was afforded. Instead, a 1:1 adduct, i.e., an *E*/*Z* mixture of 4-(3′-oxo-1′-alkenyl)-2(5*H*)-furanone product **4a** referring to the noncyclic C═C bond, was formed together with the cycloisomerization product **3a** under the catalysis of 5 mol % $Pd(OAc)_2$ in the presence of BF_3•OEt_2, and $Sc(OTf)_3$ was not necessary. After screening different reaction conditions, no better *E*/*Z* ratio for **4a** was observed, and in most cases the *E*/*Z* isomeric ratio changed constantly, which indicated an *E*/*Z* isomerization. Some typical results are listed in Table 1, from which we concluded that Cl_3CMe is better than other solvents, such as DMSO, DMF, THF, dioxane, Et_2O, in terms of the yields of **4a** (compare entries 1−5 with entry 6, Table 1) and the influence of concentration of the substrates was negligible (compare entry 9 with entry 6, Table 1). Increasing the amount of alkynone **2a** or BF_3•Et_2O also failed to improve the yields (compare entries 7 and 8 with entry 6, Table 1).

With the observation that the *E*/*Z*-isomer of **4a** is interconvertable, a protocol for complete conversion of the *Z*-isomer to the thermodynamically more stable

Table 1. Optimization of Reaction Conditions of the Reaction of 2,3-Allenoic Acid **1a** and Alkynone **2a**[a]

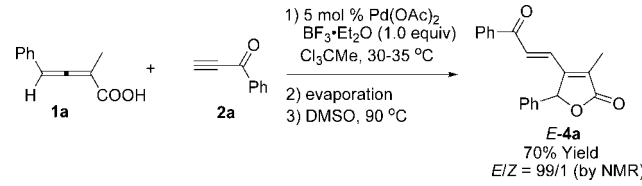


entry	**2a** (equiv)	solvent	yield of **3a**[b]	yield of **4a**[b,c]
1	1.1	DMSO	33	0
2	1.1	DMF	6	30
3	1.1	THF	19	59
4	1.1	dioxane	17	59
5	1.1	Et_2O	25	55
6	1.1	Cl_3CMe	12	71
7	1.5	Cl_3CMe	12	71
8	1.1	Cl_3CMe	11	70[d]
9	1.1	Cl_3CMe	14	67[e]

[a] The reaction was carried out using 0.25 mmol of **1a**, 1.1 equiv of **2a**, 5 mol % of $Pd(OAc)_2$, and 1.0 equiv of BF_3•Et_2O in 0.5 mL of solvent with stirring overnight at 35 °C, unless other noticed. [b] Yields were determined by ^1H NMR analysis with CH_2Br_2 or mesitylene as the internal standard. [c] The *E*/*Z* isomeric ratio of **4a** changed constantly. [d] 1.5 equiv of BF_3•Et_2O was used. [e] The concentration of **1a** was 0.125 M.

E-isomer was investigated. After some screening, we were happy to observe that after evaporation the addition of DMSO followed by heating at 90 °C for 7 h afforded *E*-**4a** (*E*/*Z* = 99/1) in 70% NMR yield (Scheme 2). The structure

Scheme 2



of *E*-**4a** was further confirmed by the X-ray diffraction study (Figure 1).[7]

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(7) **Crystal data for compound *E*-4a:** $C_{20}H_{16}O_3$, M_w = 304.33, monoclinic, space group *P*2(1)/*n*, Mo Kα, final *R* indices [$I > 2\sigma(I)$], R1 = 0.0349, wR2 = 0.0940, a = 11.5238 (3) Å, b = 8.6194 (2) Å, c = 16.6138 (5) Å, α = 90°, β = 102.1820 (10)°, γ = 90°, V = 1613.06 (7) Å^3, T = 296 (2) K, Z = 4, number of reflections collected/unique: 18026/2841 (R_{int} = 0.0205), number of observations: 2841 [$I > 2\sigma(I)$], parameters 209. CCDC 691718 contains the supplementary crystallographic data.

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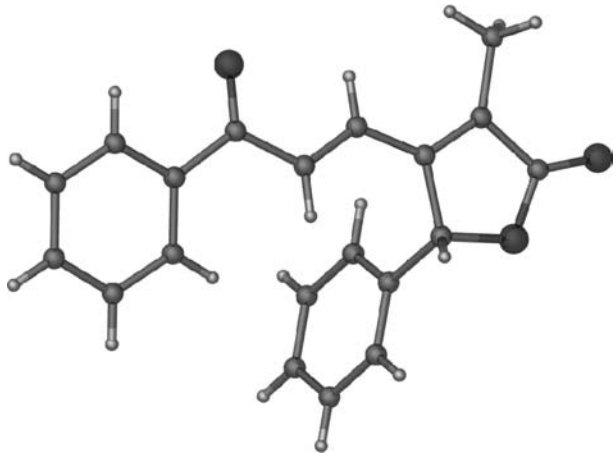
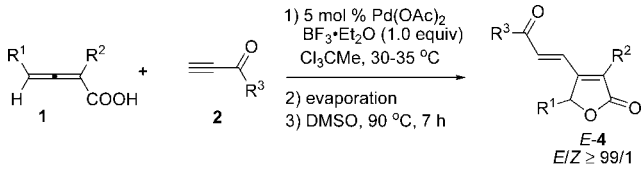


Figure 1. ORTEP representation of *E*-**4a**.

With the optimized reaction conditions in hand, the scope of the reaction was explored with some typical structures as summarized in Table 2. The substituent R^1 and R^3 can be an aryl or alkyl group; the substituent R^2 can be a normal alkyl group. The isolated yield is generally good averaging 60−72% for each step. However, when nonterminal α,β-unsaturated alkynone **2d** was applied, only cycloisomerization product **3c** was afforded with 87% NMR yield, which shows the steric effect of the alkynone on the reaction (Scheme 3).

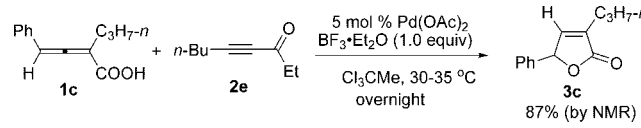
Table 2. $Pd(OAc)_2$-Catalyzed Cyclization of 2,3-Allenoic Acids and Terminal α,β-Unsaturated Alkynones and the Subsequent One-Way *Z* to *E* Isomerization[a]



entry	R^1	R^2	R^3	yield[b] of *E*-**4**
1	Ph	Me	Ph	70 (52) (**4a**)
2	Ph	Me	*p*-ClC_6H_4	54 (49) (**4b**)
3	Ph	Me	*p*-$MeOC_6H_4$	64 (48) (**4c**)
4	Ph	Et	Ph	57 (42) (**4d**)
5	Ph	Et	*p*-$MeOC_6H_4$	61 (46) (**4e**)
6	Ph	*n*-Pr	Ph	56 (48) (**4f**)
7	Ph	*n*-Pr	*p*-$MeOC_6H_4$	66 (59) (**4g**)
8	*p*-FC_6H_4	Me	*p*-$MeOC_6H_4$	62 (47) (**4h**)
9	*n*-C_4H_9	Me	*p*-$MeOC_6H_4$	49 (42) (**4i**)
10	*n*-C_6H_{13}	Me	Ph	51 (51) (**4j**)
11	*n*-C_6H_{13}	Me	*p*-$MeOC_6H_4$	53 (49) (**4k**)
12	*n*-C_7H_{15}	Me	Ph	51 (51) (**4l**)
13	*n*-C_7H_{15}	Me	*p*-$MeOC_6H_4$	57 (45) (**4m**)
14	Ph	Me	*n*-C_6H_{13}	42 (36) (**4n**)

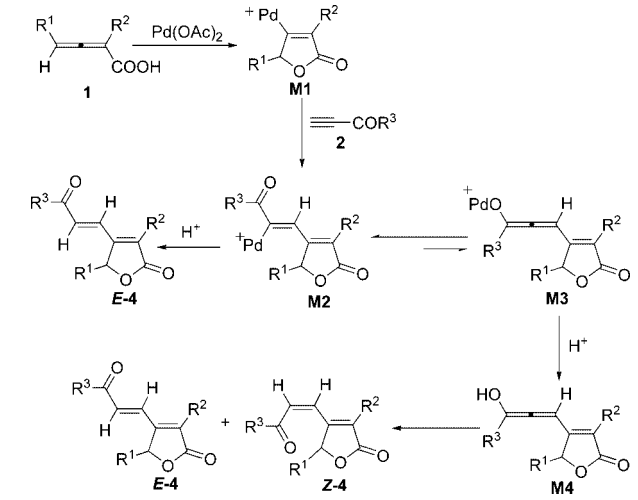
[a] The reaction was carried out using 0.25−0.5 mmol of **1**, 1.1 equiv of **2**, 5 mol % of $Pd(OAc)_2$, and 1.0 equiv of BF_3•Et_2O in 0.5−1 mL of Cl_3CMe with stirring overnight at 35 °C. After evaporation, 2−4 mL of DMSO was added, and the resulting mixture was heated at 90 °C with stirring for 7 h. [b] Yields were determined by ^1H NMR analysis with CH_2Br_2 or mesitylene as the internal standard; yields of the isolated products are given in parentheses.

Scheme 3



A rationale for this reaction is depicted in Scheme 4. The cyclic *anti*-oxypalladation of $Pd(OAc)_2$ with 2,3-allenoic acid **1** would form the furanonyl palladium intermediate **M1**. Subsequent stereoselective insertion of **M1** with the C≡C triple bond of alkynone **2** woud form the intermediate **M2**. Due to the presence of the ketonic carbonyl group, it may be converted to the enolate intermediate **M3**, which may explain the formation of *E*/*Z* isomeric mixture of **4** via protonolysis. As compared to the ester group,[6b] the ketonic carbonyl group may make the intermediates **M2** and **M3** to be more prone to protonolysis due to its stronger electron-withdrawing ability, and thus, no **5a**-type 1:2 adduct was formed.

Scheme 4



In conclusion, we have developed a $Pd(OAc)_2$-catalyzed cyclization reaction of 2,3-allenoic acids and terminal α,β-unsaturated alkynones in the presence of BF_3•Et_2O, which leads to one-pot synthesis of *E*/*Z* mixtures of 4-(3′-oxo-1′-alkenyl)-2(5*H*)-furanones. This *E*/*Z*-isomoric mixture may be highly stereoselectively converted to the thermodynamically more stable *E*-isomer exclusively after evaporation, adding DMSO, and heating the resulting reaction mixture at 90 °C for 7 h. As a result of the easy availability of starting materials[8] and the usefulness of the products,[9,10]

the reaction may have potential in organic synthesis. Further studies in this area are being pursued in our laboratory.

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Supporting Information Available: Typical experimental procedure and analytical data for all products not listed in the text as well as the $^{1}H/^{13}C$ NMR spectra of all the products. This material is available free of charge via the Internet at http://pubs.acs.org.

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