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Unexpected Regioselectivity Switch: Organophosphine-Triggered Reactions of Cyclopropene-1,1-dicarboxylates with Aldehydes

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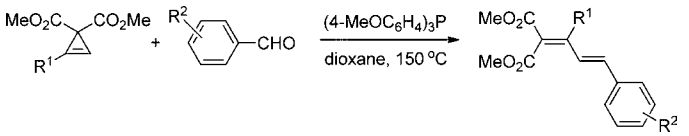
ABSTRACT



With tris(4-methoxyphenyl)phosphine as the nucleophilic reagent, the readily available cyclopropene-1,1-dicarboxylates undergo a ring-opening reaction to generate a Wittig-type intermediate, which would react with aromatic aldehydes to yield (*E*)-5-aryl-2-(methoxycarbonyl)-2,4-pentadienoates. It is interesting to observe that the regioselectivity of the ring-opening reaction is switched.

Cyclopropenes, highly strained yet readily accessible carbocyclic molecules, have been shown to possess useful reactivity in organic synthesis.[1] Over the past several years, more attention has been paid to the reactions of cyclopropenes: a variety of nucleophiles may add to the strained C=C bond[2] or open the strained three-membered ring.[3] In addition, a series of nonmetallic O-, S-, N-, P-based nucleophiles have been reacted with cyclopropenes.[4] In 2007, Gevorgyan and co-workers reported a phosphine-catalyzed sila-Morita–Baylis–Hillman reaction of cyclopropenes, in which no ring-opening reaction was

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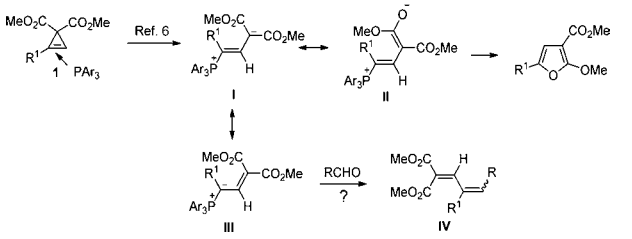
observed.[5] Recently, we have observed the formation of highly regioselective 2,3,5-trisubstituted furans via the intermediacy of intermediates **I** and **II** (Scheme 1).[6] In principle, intermediate **I** should be in resonance with Wittig-type intermediate **III**. Upon reacting with an aldehyde, 2,4-pentadienoates **IV** would be formed. Here, we wish to report an unexpected observation in this area.

Scheme 1. Possible Reaction Pathways



An initial attempt was conducted with the readily available cyclopropene **1a** and tricyclohexylphosphine. However, after careful analysis of all the data, the expected **IV**-type product **4aa** was not formed; instead, isomeric product (*E*)-3-butyl-2-(methoxycarbonyl)-5-phenyl-2,4-pentadienoic acid methyl ester *E*-**3aa** was formed (Table 1, entry 1). Electron-rich triarylphosphine derivatives such as tris(*p*-tolyl)phosphine and tri(3,4-dimethoxyphenyl)phosphine were more effective, and the yield was above 60% (Table 1, entries 2−4). But to our disappointment, no desired product was furnished when tri(2,4,6-trimethoxyphenyl)phosphine was used (Table 1, entry 5). Further screening led to the observation that tri(4-methoxyphenyl)phosphine was the best, affording the crude product **3aa** in 69% NMR yield (Table 1, entry 3). When 1.2 equiv of cyclopropene **1a** were used, a 71% NMR yield of **3aa** was obtained (Table 1, entry 11).

Then the solvent effect was examined: the yield was slightly lower with toluene as solvent (Table 1, entry 6); the reaction in DMF was complicated (Table 1, entry 7); a lower yield was observed in CH_3CN (Table 1, entry 8) and CH_2Cl_2 (Table 1, entry 9); no reaction was detected in THF (Table 1, entry 10); and dioxane was proved to be the best (Table 1, entry 3).

With the optimized conditions in hand (Table 1, entry 11), the scope of the reaction was explored. When R^1 is *n*-Bu and R^2 is H, the product **3aa** was obtained in 64% isolated yield (Table 2, entry 1). With R^2 being substituents such as 4-NC, 3-NC, 2-NC (Table 2, entries 2−5), 4-F_3C (Table 2, entry 6), 4-MeO_2C (Table 2, entry 7), 4-Cl, and 2,4-Cl (Table 2, entries 8 and 9) to the aryl ring, the reaction proceeded smoothly to afford the corresponding product in moderate to good yields. For substrates with R^2 being 4-Ph (Table 2, entry 10), 3-MeO (Table 2, entry 11), and 4-Br (Table 2,

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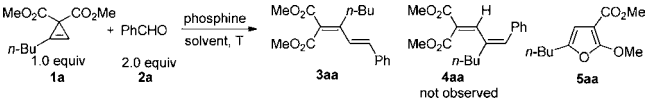
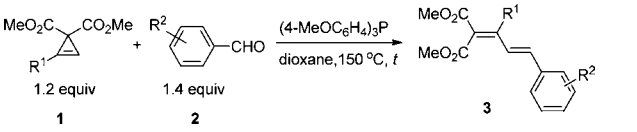
Table 1. Cascade Ring-Opening and Wittig-Type Reaction of **1a** with PhCHO under Different Reaction Conditions[a]



entry	phosphine	solvent	temp (°C)	*t* (h)	yield of **3aa** (%)[b]	recovery of **1a** (%)[b]
1	PCy_3	dioxane	150	34	12	27
2	$(4\text{-}MeC_6H_4)_3P$	dioxane	150	48	62	–
3	$(4\text{-}MeOC_6H_4)_3P$	dioxane	150	26	69	–
4	$(3,4\text{-}MeOC_6H_3)_3P$	dioxane	150	35	66	–
5	$(2,4,6\text{-}MeOC_6H_2)_3P$	dioxane	150	35	N/D	–
6	$(4\text{-}MeOC_6H_4)_3P$	toluene	150	28	65	–
7	$(4\text{-}MeOC_6H_4)_3P$	DMF	150	31	N/D	–
8	$(4\text{-}MeOC_6H_4)_3P$	CH_3CN	100	28	43	37
9	$(4\text{-}MeOC_6H_4)_3P$	CH_2Cl_2	70	45	14	55
10	$(4\text{-}MeOC_6H_4)_3P$	THF	80	48	n.r.	100
11[c]	$(4\text{-}MeOC_6H_4)_3P$	dioxane	150	26	71	–

[a] The reaction was conducted by using 0.4 mmol of **1a**, 0.8 mmol of PhCHO, and 0.4 mmol of phosphine in dioxane in a Schlenk tube with a screw cap. [b] The yield was determined by ^1H NMR spectroscopic analysis with CH_3NO_2 as the internal standard. [c] 0.34 mmol of $(4\text{-}MeOC_6H_4)_3P$ was used, with a 5% NMR yield of **5aa** formed.

Table 2. Scope of Cascade Ring-Opening and Wittig-Type Reaction of Cyclopropene-1,1-dicarboxylates with Aldehydes[a]



entry	R^1	R^2	*t* (h)	isolated yield of **3** (%)
1[b]	*n*-Bu (**1a**)	H (**2a**)	26	64 (**3aa**)
2	*n*-Bu (**1a**)	4-NC (**2b**)	30	68 (**3ab**)
3[c]	*n*-Bu (**1a**)	4-NC (**2b**)	30	67 (**3ab**)
4	*n*-Bu (**1a**)	3-NC (**2c**)	30	65 (**3ac**)
5	*n*-Bu (**1a**)	2-NC (**2d**)	30	66 (**3ad**)
6	*n*-Bu (**1a**)	4-F_3C (**2e**)	30	63 (**3ae**)
7	*n*-Bu (**1a**)	4-MeO_2C (**2f**)	30	64 (**3af**)
8	*n*-Bu (**1a**)	4-Cl (**2g**)	30	65 (**3ag**)
9	*n*-Bu (**1a**)	2,4-Cl (**2h**)	31	64 (**3ah**)
10	*n*-Bu (**1a**)	4-Ph (**2i**)	26	62 (**3ai**)
11	*n*-Bu (**1a**)	3-MeO (**2j**)	29	57 (**3aj**)
12	*n*-Bu (**1a**)	4-Br (**2k**)	29	65 (**3ak**)
13[b]	H (**1b**)	H (**2a**)	24	61 (**3ba**)
14[b]	*n*-Pr (**1c**)	H (**2a**)	30	63 (**3ca**)

[a] The reaction was conducted by using 0.4 mmol of **1**, 0.48 mmol of **2**, and 0.34 mmol of $(4\text{-}MeOC_6H_4)_3P$ in dioxane at 150 °C in a Schlenk tube with a screw cap; a 2−5% NMR yield of **5** was formed in all the reactions. [b] 0.8 mmol of **2** was used. [c] Conditions: 5.0 mmol of **1a** were used in this reaction.

entry 12), the reaction could also occur in moderate yields. As could be seen in Table 2, the position of CN on the phenyl ring had a limited effect on the yield (Table 2, entries 2–5). In addition, when R^2 is H, if R^1 is H or *n*-C_3H_7, the reaction is also working and the yield is 61% or 63%, respectively (Table 2, entries 13 and 14). To test the practicability, the reaction was carried out in gram scale (5.0 mmol) of **1a**, **2b** (6.0 mmol), and tri(4-methoxyphenyl)phosphine (4.3 mmol) to afford the desired product **3ab** in 67% yield (Table 2, entry 3).

The X-ray diffraction study of **3ai** clearly proves the configuration of C=C bond in the molecule and the regioselectivity of the ring-opening reaction (Figure 1).[7]

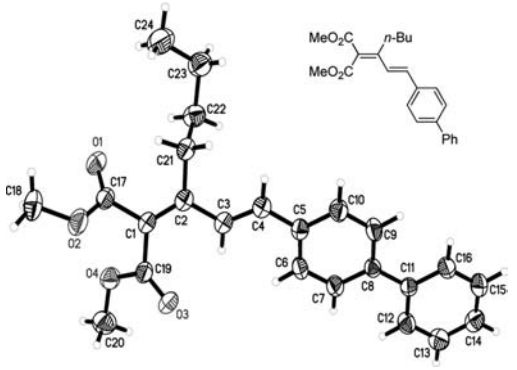
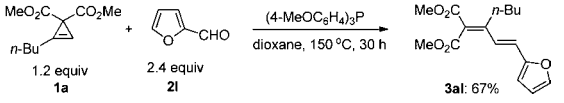


Figure 1. ORTEP structure of **3ai**.

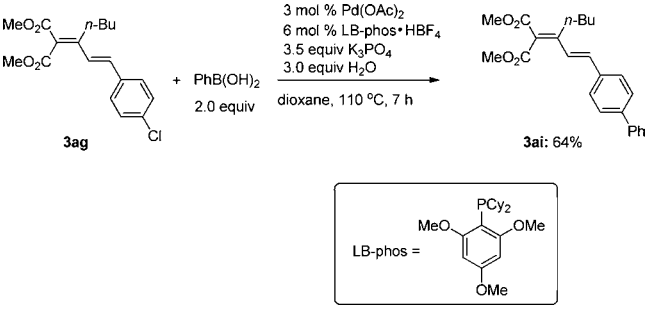
Heteroaromatic aldehydes could also be applied to this reaction. When 0.8 mmol of 2-furaldehye was used to react with 0.4 mmol of **1a** and 0.34 mmol of $(4\text{-MeOC}_6H_4)_3P$, 67% of **3al** could be isolated (Scheme 2). Citronellal and cyclohexanecarboxaldehyde proved to be ineffective in the reaction with **1a**, and no starting material was recovered.

Scheme 2



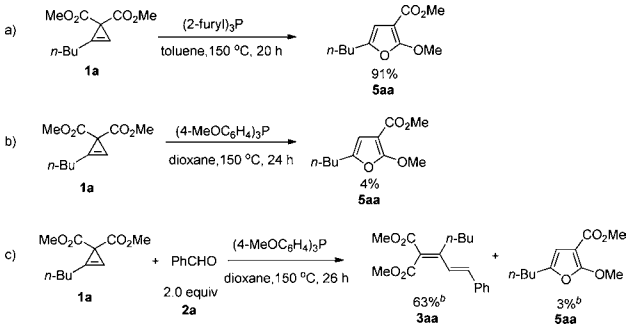
With LB-phos[8] as the ligand, a cross-coupling reaction could proceed smoothly between **3ag** and $PhB(OH)_2$ with 64% of the product **3ai** (Scheme 3).

Scheme 3



In an effort to shed further light on the mechanism, control experiments were conducted. Under the conditions used in our previous report,[6] **5aa** was obtained in 91% yield (eq a, Scheme 4); under the standard conditions in the absence of benzaldehyde **2a** in this study, we only observed 4% of **5aa** (eq b, Scheme 4) while the reaction of cyclopropene **1a** in the presence of aldehyde **2a** under the standard conditions afforded 63% of **3aa** together with 3% of **5aa** (eq c, Scheme 4).

Scheme 4. Control Experiments[a]



[a] 0.5 mmol of **1a** was used in all the reactions. [b] The yield was determined by ^1H NMR spectroscopic analysis with CH_3NO_2 as the internal standard.

A plausible mechanism for this transformation is depicted in Scheme 5. Initial attack of the tri(4-methoxyphenyl)phosphine at the less-substituted sp^2 carbon atom of cyclopropene **1** results in the formation of zwitterionic phosphonium adduct **V**. Due to the presence of the C=C bond, **V** is in resonance with Wittig-type intermediate **VI**. Based on the results shown in Scheme 4, we reasoned that the reversed selectivity for the first step may be caused by the much higher reactivity of intermediate **VI** toward aldehydes as compared to intermediate **III** due to the steric effect (Scheme 1). Thus, intermediate **VI** reacts with

(7) Crystal data for compound **3ai**: $C_{24}H_{26}O_4$, MW = 378.45, monoclinic, space group $P_2(1)$, final R indices [$I > 2\sigma(I)$], R_1 = 0.0472, wR_2 = 0.1223, R indices (all data), R_1 = 0.0593, wR_2 = 0.1310, a = 6.2434(5) Å, b = 8.0127(7) Å, c = 21.1301(18) Å, α = 90°, β = 90.262(2)°, γ = 90°, V = 1057.05(15) Å^3, T = 293 (2) K, Z = 2, reflections collected/unique: 6377/4106 [R(int) = 0.0195], number of observations [$>2\sigma(I)$] 3264; parameter: 256. Supplementary crystallographic data have been deposited at the Cambridge Crystallographic Data Center (CCDC 918034).

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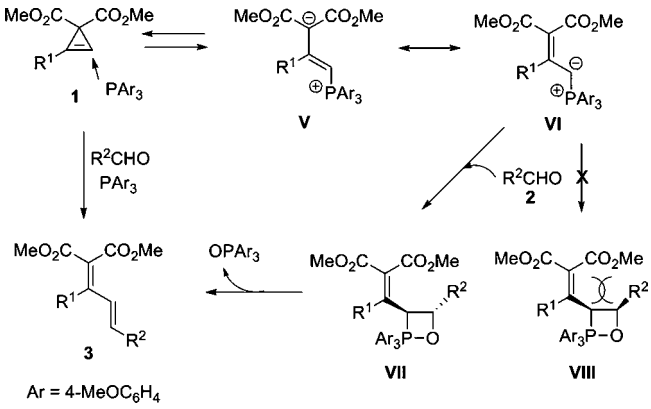
Scheme 5. A Plausible Mechanism



aldehyde **2** to generate the Wittig-type cyclic intermediate **VII**, which is preferred over **VIII** due to its steric hindrance. Finally, elimination of the Ar_3PO furnishes the (*E*)-2,4-pentadienoates **3**.

In conclusion, we have developed a new methodology to synthesize highly stereoselective (*E*)-5-aryl-2-(methoxycarbonyl)-2,4-pentadienoates from the nucleophilic ring-opening reaction of cyclopropene-1,1-dicarboxylates with aromatic aldehydes with a switch of the regioselectivity. Further studies of this reaction are being conducted in our laboratory.

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Supporting Information Available. General procedure and spectroscopic data. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.