Double α-Addition Reaction of *ortho*-Hydroxyacetophenones to Ethyl Propiolates Mediated by Ph_3P: Synthesis of Functionalized 1,4-Pentadienes

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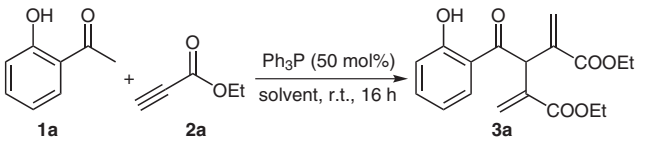
Abstract: A new way of synthesizing functionalized 1,4-pentadienes by double α-addition reaction of *ortho*-hydroxyacetophenones to ethyl propiolate mediated by Ph_3P in moderate yields is described. On the other hand, other *ortho*-hydroxyphenyl ketones resulted in the single α-addition products in moderate to good yields.

Key words: α-addition, functionalized 1,4-pentadienes, Ph_3P, *ortho*-acylphenols, ethyl propiolates

Functionalized 1,4-pentadienes are important intermediate in organic synthesis. They serve as key building blocks in the preparation of various interesting molecules.[1] Moreover, they are important structural units present in several biologically active molecules.[2] Consequently, some useful and new methodologies were developed for their synthesis.[3] The comparatively simple method to obtain a 1,4-diene framework is the Baylis–Hillman reaction, which was developed by Basavaiah.[4] However, the development of simple and mild methods for the synthesis of functionalized 1,4-pentadienes is strongly desirable.

The α-addition reaction is one of the most fundamental carbon–carbon bond-forming reactions in organic synthesis. In recent years, electron-deficient alkynes are often used as nucleophile precursors for the formation of carbon–carbon bonds and recent studies on the chemistry of organocatalysts via conjugate addition of N and P nucleophiles have uncovered a number of interesting reactions.[5] Trost, Taran, and our group have reported various phosphine-catalyzed α-addition reactions by using electron-deficient alkynes as substrates.[6,7] Most recently, we reported Ph_3P-catalyzed α-addition reactions of 1-(*o*-hydroxyaryl)-1,3-diketones to ethyl propiolates to give multifunctional vinylesters (Scheme 1).[8] In order to further develop new addition reactions, we investigated the α-addition reactions of *ortho*-acylphenols to terminal alkynoates in the presence of Ph_3P. Herein we reported that functionalized 1,4-pentadienes was formed via double α-addition reaction step when the *ortho*-acylphenols used were *ortho*-hydroxyacetophenones.

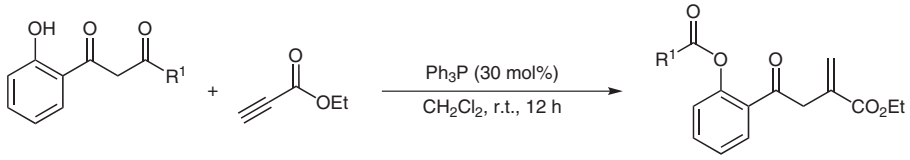
Table 1 Optimization of the Double α-Addition Reaction Conditions



1a 2a 3a

Entry	**1a** (mmol)	**2a** (mmol)	Solvent	Yield (%)[a]
1	0.3	0.6	CH_2Cl_2	21[b]
2	0.3	0.6	CH_2Cl_2	43
3	0.3	0.6	CH_2Cl_2	37[c]
4	0.3	0.6	CH_2Cl_2	23[d]
5	0.3	0.6	CH_2Cl_2	43[e]
6	0.3	0.9	CH_2Cl_2	45
7	0.6	0.6	CH_2Cl_2	53
8	0.6	0.6	$CHCl_3$	20
9	0.6	0.6	EtOAc	27
10	0.6	0.6	acetone	15
11	0.6	0.6	DMF	<10

[a] Isolated yields.
[b] 20 mol% Ph_3P was used.
[c] 100 mol% Ph_3P was used.
[d] At 0 °C.
[e] At reflux.



Scheme 1

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Our studies were initiated by addition of 0.5 equivalents of Ph_3P to a solution of 2-hydroxyacetophenone (**1a**) and 2.0 equivalents ethyl propiolate (**2a**) in CH_2Cl_2. A 43% yield of the functionalized 1,4-pentadiene product **3a** was formed from the double α-addition reaction of *ortho*-acylphenol to ethyl propiolate when the reaction was stirred at room temperature for 16 hours (entry 2, Table 1). Its structure was determined by NMR and HRMS spectra. The amount of Ph_3P has an obviously effect on this reaction. The desired product **3a** was obtained in only 21% yield when 20 mol% Ph_3P were used. The yield of the product was slightly decreased by further increasing the amount of Ph_3P. The yield of the double α-addition reaction could not be improved under reflux conditions and decreased when the reaction was stirred at 0 °C. The ratio of **1a** and **2a** also had an effect on the reaction, and the desired product **3a** was afforded in 53% yield when the amount of 2-hydroxyacetophenone was increased (entry 7, Table 1). Ph_3P as a catalyst was crucial for this reaction. A complex mixture was formed when tributylphosphine or tricyclohexylphosphine, in place of Ph_3P, was used. The use of other organic bases, such as 1,4-diazabicyclo-[2,2,2]-octane, 4-dimethylaminopyridine, Et_3N, and pyridine, did not give the desired products.

Table 2 Reaction of *ortho*-Acylphenols **1** with Terminal Alkynoates for the Synthesis of 1,4-Pentadienes

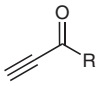
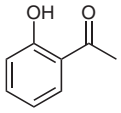
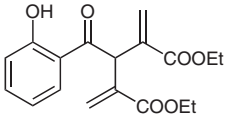
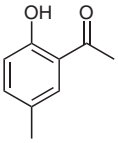
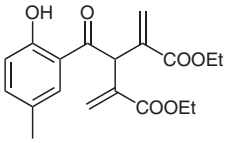
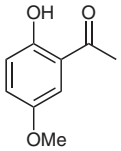
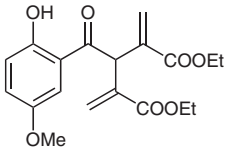
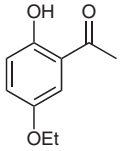
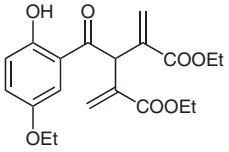
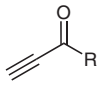
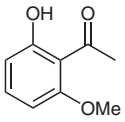
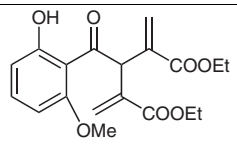
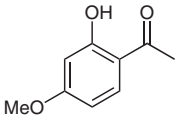
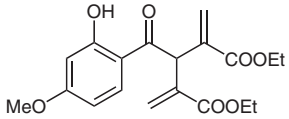
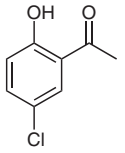
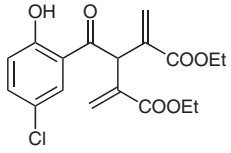
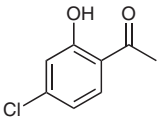
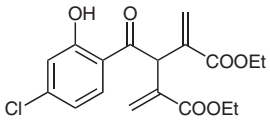
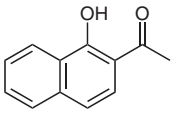
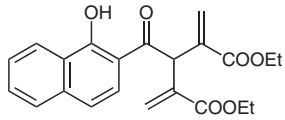
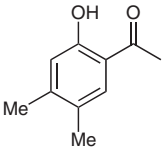
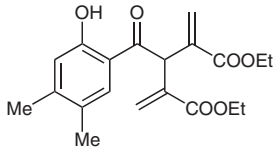
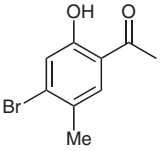
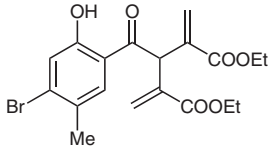
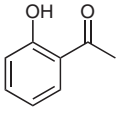
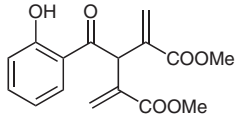
Entry	Substrate		Product, yield (%)[a]
1	 **1a**	EtO	 **3a** 53
2	 **1b**	EtO	 **3b** 47
3	 **1c**	EtO	 **3c** 54
4	 **1d**	EtO	 **3d** 40

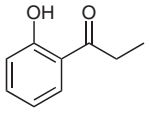
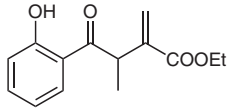
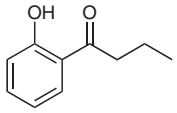
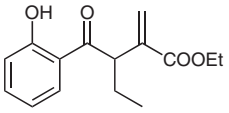
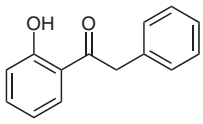
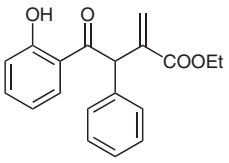
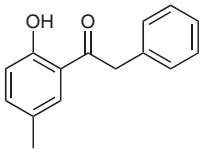
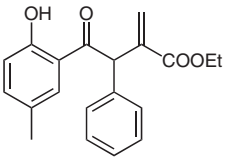
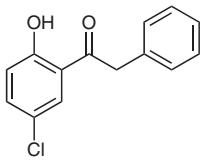
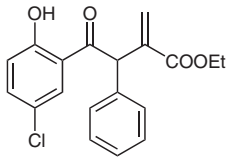
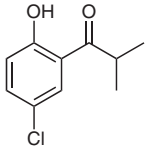
Table 2 Reaction of *ortho*-Acylphenols **1** with Terminal Alkynoates for the Synthesis of 1,4-Pentadienes (continued)

Entry	Substrate		Product, yield (%)[a]
5	 **1e**	EtO	 **3e** 56
6	 **1f**	EtO	 **3f** 45
7	 **1g**	EtO	 **3g** 48
8	 **1h**	EtO	 **3h** 50
9	 **1i**	EtO	 **3i** 40
10	 **1j**	EtO	 **3j** 45
11	 **1k**	EtO	 **3k** 51
12	 **1a**	MeO	 **3l** 46

[a] Isolated yields.

Further investigations conducted with various solvents were also performed. When shifting the solvent to $CHCl_3$ or ethyl acetate, the desired product **3a** was obtained in 20% and 27%, respectively. With acetone or DMF as solvents, the yield of reaction was even worse.

Table 3 Reaction of Ketones **4** with Ethyl Propiolates Mediated by Ph_3P (50 mol%)

Entry	Substrate	Product, yield (%)[a]
1	 **4a**	 **5a** 54
2	 **4b**	 **5b** 44
3	 **4c**	 **5c** 74
4	 **4d**	 **5d** 75
5	 **4e**	 **5e** 66
6	 **4f**	n.d.[b]

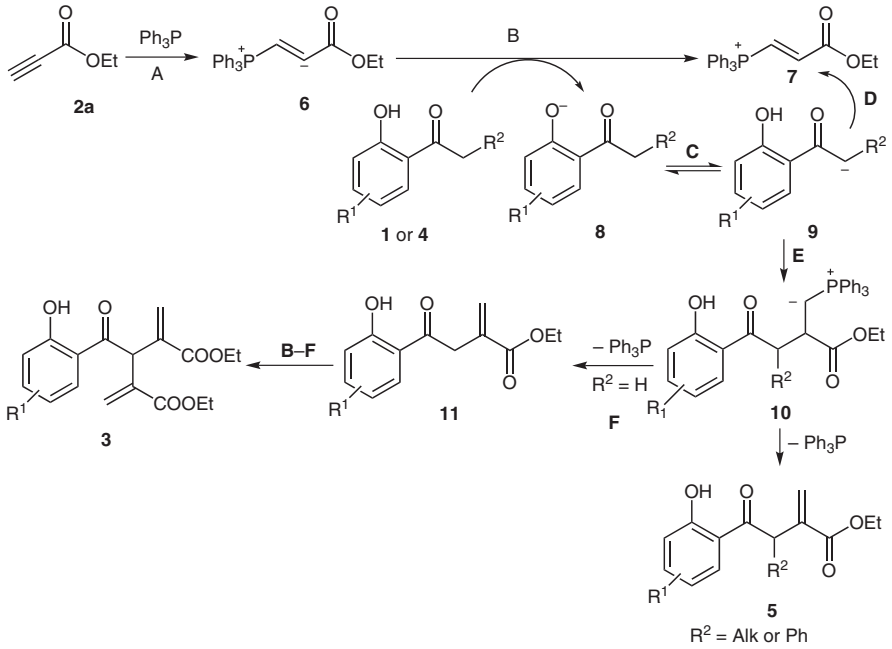
[a] Isolated yields.
[b] No desired product was detected.

Under these optimized conditions,[9] we next explored the scope of the double α-addition reaction, As shown in Table 2, a variety of *ortho*-hydroxyacetophenones **1** was employed as the reaction substrate and the corresponding functionalized 1,4-pentadienes were obtained in moderate yields. Clearly, substituents on the aromatic ring had no obviously effect on the yield of the double α-addition reactions. The naphthyl substrate **1i** also reacted smoothly with ethyl propiolate to give the desired product **3i** in 40% yield. Notably, when multisubstituted *ortho*-hydroxyacetophenones, such as 1-(2-hydroxy-4,5-dimethylphenyl)-ethanone (**1j**) and 1-(4-bromo-2-hydroxy-5-methylphenyl)ethanone (**1k**), could also be converted to the corresponding products in moderate yields. As expected, methyl propiolate could also be used as a substrate to react with **1a** to afford the desired product **3l** in 46% yield. However, acetylenic ketones, such as but-3-yn-2-one and 1-phenylprop-2-yn-1-one, failed to react under the same conditions. It was also noted that the yield of the double α-addition products were moderate (40–56%), this was due to the formation of other byproducts during the reaction.

To further evaluate the scope of this reaction, substituted ketones **4**, in which the methyl group were replaced by a longer alkyl group, were synthesized and tested under above standard conditions. The results are summarized in Table 3. In these occasions, the desired double α-addition products **3** were not formed, but single α-addition products were afforded in moderate to good yields, which might be due to steric hindrance of the substitutent. For example, exposure of substrate 1-(2-hydroxyphenyl)propan-1-one (**4a**) and 1-(2-hydroxy-phenyl)butan-1-one (**4b**) to **2a** in the presence of Ph_3P (50 mol%) at room temperature for 16 hours afforded the corresponding single α-addition products **5a** and **5b** in 54% and 44% yields, respectively. Furthermore, 1-(2-hydroxyphenyl)-2-phenylethanone (**4c**) substituted by phenyl group could be transformed into the corresponding product **5c** in 74% yield. Other substrates **4d**,**e** also gave good yields of the corresponding products. However, no desired product was detected when 1-(2-hydroxyphenyl)-2-methylpropan-1-one (**4f**) was submitted to this reaction, which might be due to steric hindrance of the isopropyl group.

On the basis of these results and previous investigations,[7,8] a mechanistic pathway for the unexpected α-addition reaction is proposed in Scheme 2. The first step of the reaction begins with conjugate addition of Ph_3P to ethyl propiolate to produce a zwitterion **6**, which then deprotonates the ketone **1** or **4** to generate **7** and **8**. The intermediate **8** could be converted to enolate **9** through proton transfer. The enolate **9** then undergoes α-C addition to the intermediate **7** to give **10**. When $R^2 = H$, the intermediate **10** would be followed by proton transfer and elimination of Ph_3P to generate **11**. The product **3** is formed through a second reaction process from steps **B** to **F**. On the other hand, when R^2 is an alkyl or phenyl group, the intermediate **10** will afford the single α-addition product **5** through proton transfer and elimination of Ph_3P. The compound **5** cannot be further converted into the double α-addition product due to the presence of alkyl or phenyl group, which prevents reacting with ethyl propiolate. Higher yield of product **5** was obtained when R^2 is a phenyl group, which might be ascribed to the carbanion of intermediate **9** well stabilized by phenyl ring. Our attempts to isolate **11** were not successful. The results imply that a second α-addition of **11** to ethyl propiolate proceeds faster than that of substrate **1**.

In order to elucidate the key effect of the hydroxyl group in the substrate, acetophenone and 2-acetylphenyl benzoate were subjected to the reaction with ethyl propiolate mediated by Ph_3P in CH_2Cl_2 at room temperature, but no reactions occurred. Furthermore, in the presence of phenol, acetophenone, and 2-acetylphenyl benzoate also provided no α-addition product under the typical conditions. The reaction of *para*-acylphenol, in place of *ortho*-



Scheme 2 Plausible mechanism for α-addition reactions

acylphenol, with ethyl propiolate only gave β-addition product ethyl 3-(4-acetylphenoxy)acrylate. These results show that hydroxyl group in *ortho*-acylphenol plays an important role in the α-addition reaction.

In conclusion, we have described an unexpected double α-addition reaction of *ortho*-hydroxyacetophenones to terminal alkynoates mediated by Ph_3P. The reaction afforded functional 1,4-pentadienes in moderate yields under mild conditions. Meanwhile, single α-addition reaction was occurred when substituted ketones **4**, in place of *ortho*-hydroxyacetophenones, were used as substrates. The hydroxyl group in substrate was important to form the α-addition products.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

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(9) **General Reaction Procedure**
To a solution of *ortho*-acylphenols (0.6 mmol) with terminal alkynoates (0.6 mmol) in dry CH_2Cl_2 (2 mL) was added Ph_3P (79 mg, 0.3 mmol), and the resulting mixture was stirred at r.t. for 16 h. The solvent was removed in vacuo, and the residue was purified by column chromatography on silica gel (PE–EtOAc = 20:1) to give the desired product.

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