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Phosphine-Mediated Olefination between Aldehydes and Allenes: An Efficient Synthesis of Trisubstituted 1,3-Dienes with High *E*-Selectivity

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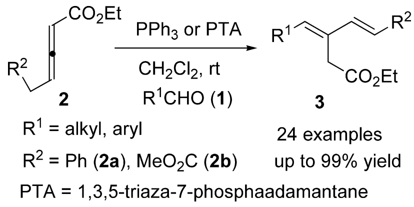
ABSTRACT



The phosphine-mediated olefination of aldehydes with electron-deficient allenes to afford trisubstituted conjugated dienes in fair to excellent yields with high *E*-selectivity is described. The reaction represents a new reactivity pattern of allenes with aldehydes and also provides a highly stereoselective synthetic method for preparing conjugated dienes. In the reaction, the phosphine acts as a nucleophilic promoter to generate in situ an active phosphorus ylide which mediates the intermolecular olefination.

Conjugated dienes represent one class of widely occurring and important organic compounds. Their importance stems largely from their versatility in organic transformations[1] and the widespread occurrence of the 1,3-diene substructure in a vast array of natural products of biological and medicinal interest.[2] The development of methods for the efficient, stereoselective, and practical synthesis of conjugated dienes has attracted much interest from synthetic organic chemists. Apart from the conventional P-, S-, and Si-based carbonyl olefination reactions[3] represented by P-based Wittig olefination[3a] and its variants, including the Horner−Wadsworth−Emmons[3b] and *Z*-selective Still−Gennari[3c]

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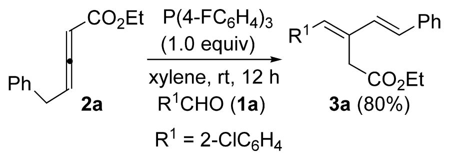
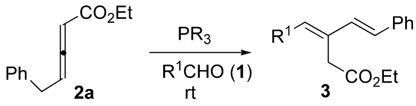
modifications, the S-based Julia olefination,[3d] and the Si-based Peterson olefination,[3] many powerful synthetic methods for dienes have been discovered,[2d,4] primarily involving transition-metal-catalyzed alkenyl−alkenyl cross-coupling reactions,[2b,4a] enyne cross-metathesis,[4b−d] and alkene−alkyne codimerization.[4e−h] Despite the effectiveness of these transformations, there remains significant room for the development of additional complementary processes. As a result, a number of new examples of the conjugated diene synthesis have been witnessed recently.[5]

Over the past decade, chemical transformations involving electron-deficient allenes have attracted much research interest, with a number of new allene-based reactions with high synthetic potentials having emerged.[6] For example, the phosphine- or amine-catalyzed annulations of allenoates with activated olefins, imines, and aldehydes provide attractive approaches for constructing carbocycles and heterocycles.[7] In our latest studies on the phosphine-catalyzed [3 + 2] annulation of γ-methyl allenoates with aldehydes,[8] we found that under the influence of $(4\text{-}FC_6H_4)_3P$ γ-benzyl allenoate (**2a**) underwent a stoichiometric olefination with *o*-chlorobenzaldehyde (**1a**), to give the (*E*,*E*)-diene **3a** exclusively in 80% isolated yield (eq 1). This reaction unveiled a new reactivity pattern of allenoates with aldehydes, while representing an efficient and stereoselective synthesis of trisubstituted (*E*,*E*)-dienes via the P-based olefination of an aldehyde. Herein we wish to report more preliminary results from further studies on this reaction.



(1)

Table 1. Optimization of Conditions for the Phosphine-Mediated Olefination of Aldehydes **1** with Allenoate **2a**[a]



entry	R^1	PR_3	solvent	time (h)	yield of **3** (%)[b,c]
1	$2\text{-}ClC_6H_4$	PPh_3	toluene	72	85
2	$2\text{-}ClC_6H_4$	PPh_3	CH_3CN	72	62
3	$2\text{-}ClC_6H_4$	PPh_3	THF	72	79
4	$2\text{-}ClC_6H_4$	PPh_3	DMF	72	62
5	$2\text{-}ClC_6H_4$	PPh_3	ethanol	72	64
6	$2\text{-}ClC_6H_4$	PPh_3	1,4-dioxane	72	82
7	$2\text{-}ClC_6H_4$	PPh_3	CH_2Cl_2	72	87
8	$2\text{-}ClC_6H_4$	PPh_3	CH_2Cl_2	40	80
9	$4\text{-}CH_3OC_6H_4$	PPh_3	CH_2Cl_2	24	<5[d]
10	C_6H_5	PPh_3	CH_2Cl_2	24	35[d]
11	C_6H_5	Ph_2PMe	CH_2Cl_2	17	99
12	C_6H_5	$PhPMe_2$	CH_2Cl_2	17	92
13	C_6H_5	PBu_3	CH_2Cl_2	24	81
14	C_6H_5	PTA	CH_2Cl_2	24	91

[a] Reaction conditions: for entries 1−7, both **2a** and the phosphine were used in 1.5 equiv; for entries 8−14, the two substrates used in 1.2 equiv. A typical procedure: a mixture comprising aldehyde **1** (0.5 mmol), allenoate **2a** (0.75 or 0.6 mmol), and phosphine (0.75 or 0.6 mmol) in the specified solvent (2 mL) was stirred at room temperature. [b] Isolated yield based on **1**. [c] *E*,*E*-isomer only. [d] The isomerization product **4** was isolated in 74% (based on **2a**, entry 9) and 62% (entry 10) yields, respectively.

Optimization of the reaction conditions for the olefination of aldehydes **1** with the allenoate **2a** was first carried out (Table 1). In place of $P(4\text{-}FC_6H_4)_3$, the convenient and cost-saving PPh_3 was used in the olefination of **2a**, giving comparable yields of the diene **3**. Using the PPh_3-mediated reaction of **2a** with **1a** as a probe, several common solvents were screened. Dichloromethane was found to afford the best yield of **3a**, although the other solvents gave comparable yields (Table 1, entries 1−7). When similar conditions were applied to the relatively electron-rich benzaldehyde (**1l**) and 4-methoxybenzaldehyde (**1n**), however, the corresponding olefination products **3l** and **3n** were only obtained in significantly reduced yields (35% and <5%, respectively) with the isomerization byproduct, ethyl (*E*,*E*)-5-phenyl-2,4-pentadienoate (**4**) from **2a**, being the major product (Table 1, entries 9 and 10). Employing the olefination reaction of **2a** with **1l** as a model, a few tertiary phosphines with relatively stronger nucleophilicity compared to PPh_3 were explored, generally furnishing the olefination product **3l** in good to excellent yields (Table 1, entries 11−14). 1,3,5-Triaza-7-phosphaadamantane (PTA) is a readily available, air-stable, and water-soluble phosphine with comparable nucleophilicity to trialkylphosphines (Figure 1).[9] Given the high yield of **3l** obtained with PTA (Table 1, entry 14) and its unique properties which benefit the handling and workup of the olefination reaction, PTA was chosen as the preferable phosphine for the less reactive aldehydes.

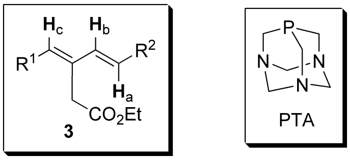


Figure 1. Structures of **3** and PTA.

With the optimized conditions in hand, a variety of aromatic and aliphatic aldehydes were explored in the

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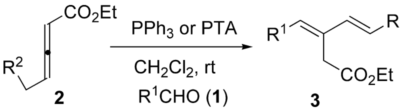
phosphine-mediated olefination with allenoate **2a**, giving rise to a series of trisubstituted dienes **3** in moderate to excellent yields (Table 2, entries 1−18). Aromatic aldehydes with electron-withdrawing groups were more reactive, furnishing the dienes **3** in high yield (Table 2, entries 2−6). Heteroaromatic aldehydes readily gave rise to the corresponding **3** in good yield following treatment with PPh_3 (Table 2, entries 7−11). For relatively electron-rich benzaldehydes and aliphatic aldehydes, the olefination with **2a** was best effected by the more nucleophilic PTA, affording the corresponding dienes **3** in moderate to excellent yield (Table 2, entries 12−15, 17, and 18). α,*β*-Unsaturated aldehydes like *trans*-cinnamaldehyde (**1p**) were the former also effective in the PPh_3-mediated olefination with **2a**, giving the (*E*,*E*,*E*)-triene **3p** in 30% yield (Table 2, entry 16).

Table 2. Synthesis of Dienes **3** from Aldehydes **1** and Allenoates **2**[a]



entry	R^1 in **1**	R^2 in **2**	phosphine	time (h)	yield of **3** (%)[b,c]
1	2-ClC_6H_4 (**1a**)	Ph	PPh_3	40	80 (**3a**)
2	2-$NO_2C_6H_4$ (**1b**)	Ph	PPh_3	32	99 (**3b**)
3	3-$NO_2C_6H_4$ (**1c**)	Ph	PPh_3	22	99 (**3c**)
4	4-$NO_2C_6H_4$ (**1d**)	Ph	PPh_3	28	92 (**3d**)
5	4-$CF_3C_6H_4$ (**1e**)	Ph	PPh_3	12	80 (**3e**)
6	2-CNC_6H_4 (**1f**)	Ph	PPh_3	13	99 (**3f**)
7	2-furyl (**1g**)	Ph	PPh_3	16	72 (**3g**)
8	2-pyridyl (**1h**)	Ph	PPh_3	20	70 (**3h**)
9	3-pyridyl (**1i**)	Ph	PPh_3	24	76 (**3i**)
10	4-pyridyl (**1j**)	Ph	PPh_3	36	76 (**3j**)
11	2-thiofuryl (**1k**)	Ph	PPh_3	40	71 (**3k**)
12	C_6H_5 (**1l**)	Ph	PTA	24	91 (**3l**)
13	4-$CH_3C_6H_4$ (**1m**)	Ph	PTA	46	51 (**3m**)
14	4-$CH_3OC_6H_4$ (**1n**)	Ph	PTA	12	50 (**3n**)
15	4-$Me_2NC_6H_4$ (**1o**)	Ph	PTA	46	43 (**3o**)
16	*E*-2-Ph vinyl (**1p**)	Ph	PPh_3	40	30 (**3p**)
17	C_2H_5 (**1q**)	Ph	PTA	52	44 (**3q**)
18	n-C_3H_7 (**1r**)	Ph	PTA	48	46 (**3r**)
19	2-ClC_6H_4 (**1a**)	CO_2Me	PTA	37	54 (**3s**)
20	3-$NO_2C_6H_4$ (**1c**)	CO_2Me	PTA	48	73 (**3t**)
21	4-$CF_3C_6H_4$ (**1e**)	CO_2Me	PTA	64	70 (**3u**)
22	C_6H_5 (**1l**)	CO_2Me	PTA	48	63 (**3v**)
23	4-$CH_3OC_6H_4$ (**1n**)	CO_2Me	PTA	65	33 (**3w**)
24	2-HOC_6H_4 (**1s**)	CO_2Me	PTA	48	71 (**3x**)

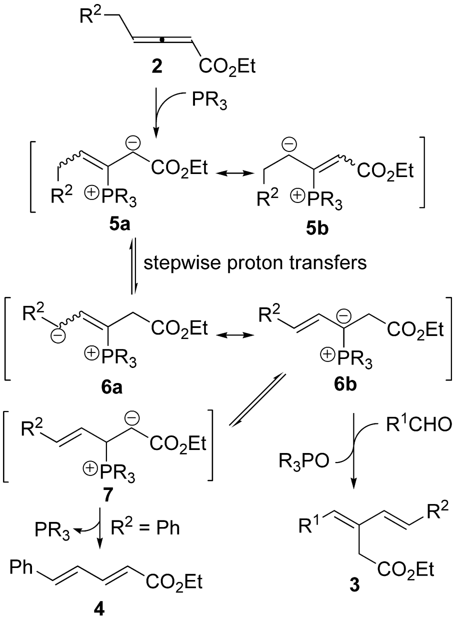
[a] See Supporting Information for experimental details. [b] Isolated yield based on **1**. [c] *E*,*E*-isomer only except **3r** and **3x** both obtained as an *E*,*E*- and *E*,*Z*-isomeric mixture with an *E*,*E*/*E*,*Z* ratio of 8:1 determined by ^1H NMR.

Given the prevalence and synthetic utility of conjugated diene−carbonyl compounds,[10] *γ*-(methoxycarbonyl)methyl allenoate (**2b**) was also studied. Under the mediation of PTA, a group of representative aromatic aldehydes bearing electron-withdrawing or electron-donating substituents readily undergo the expected olefination with **2b**, affording the corresponding dienoates **3** in moderate yields (Table 2, entries 19−24).

The structures of dienes **3** were identified by X-ray crystallography, in some cases, as well as ^1H and ^{13}C NMR spectroscopy, which included NOESY analyses for representative compounds (see Supporting Information). Most of the isolated dienes **3** were the (*E*,*E*)-isomers except for **3r** and **3x** which both were an (*E*,*E*)- and (*E*,*Z*)-isomeric mixture with a ratio of 8:1 according to their ^1H and ^{13}C NMR spectra. ^1H NMR data provided diagnostic evidence on the (*E*)-configurational assignment: the coupling constant magnitude (ca. 16 Hz) between the olefinic protons H_a and H_b clearly indicated (*E*)-geometry of disubstituted alkene substructure in **3** (Figure 1). For the trisubstituted alkene subunit in **3**, the cross peak between the olefinic protons H_b and H_c in the NOESY spectra confirmed the (*E*)-configurational assignment. Furthermore, X-ray crystallographic analyses[11] for **3c** and **3t** provide unambiguous evidence for the structure determination of **3**.

For the olefination reaction, a mechanism is proposed in which the phosphine fulfills two roles: a nucleophilic promoter and a mediator of the Wittig olefination (Scheme 1). The reaction is initiated by nucleophilic attack of the phosphine on the allenoate **2** to generate the phosphonium dienolate **5**, which stands in two resonance forms **5a** and

Scheme 1. Proposed Mechanism of Formation of **3** and **4**



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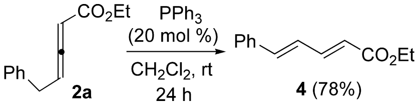
5b. Through a series of stepwise proton transfers under the aid of water,[12] **5** reversibly converts to the phosphorus ylide **6**, which also presumably exists in two resonance forms **6a** and **6b**. When R^2 is a conjugative group such as phenyl or methoxycarbonyl, it is believed that the more stable resonance form **6b** represents a common intermediate which is responsible for the formations of **3** and **4**. Thus, **6b** undergoes a set of proton transfers to generate the intermediate **7**, which eliminates the phosphine leading to the isomerization product **4**; in another scenario, while **6b** is intercepted by an aldehyde via a Wittig olefination, the diene **3** is formed.

Similar mechanisms[13] were also proposed for the phosphine-catalyzed isomerization of alkynoates into (*E*,*E*)-dienoates. An independent experiment confirmed that, under the catalysis of PPh$_3$ (20 mol %), the allenoate **2a** can be readily isomerized into its corresponding (*E*,*E*)-dienoate **4** in 78% isolated yield (eq 2). As the experimental results (Table 1, entries 9 and 10) show, isomerization and olefination take place competitively, presumably via the common intermediate **6b** (Scheme 1). Confirmation on the (*E*)-configuration of the disubstituted alkene subunits in **3** and **4** implies that the ylide **6b** has an (*E*)-geometry alkene subunit.



(2)

In summary, a highly stereoselective phosphine-mediated olefination of aldehydes with electron-deficient allenes, leading to an efficient synthesis of trisubstituted conjugated dienes, has been demonstrated. The reaction exemplifies a new reactivity pattern for allenoates with aldehydes. An in situ generated phosphorus ylide is believed to be the key intermediate involved in the olefination. Recently, in situ formed phosphorus ylides have gained renewed interest in the discovery of new organic transformations.[5d,f,g,14] Further efforts in our laboratory will be reported on the utility of this kind of in situ-generated phosphorus ylide in novel carbon–carbon bond forming reactions.

Acknowledgment. Financial support from the National Natural Science Foundation of China (Grant No. 20872063; 20672057) is gratefully acknowledged. The authors also thank the referees for their valuable comments about the olefination mechanism in this study.

Supporting Information Available: Experimental details and spectral data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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[11] The ORTEP presentations and CIF files of **3c** and **3t** are available in the Supporting Information.

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