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Stereoselective Synthesis of 1,2,3,4-Tetrasubstituted Dienes from Allenoates and Aldehydes: An Observation of Phosphine-Induced Chemoselectivity

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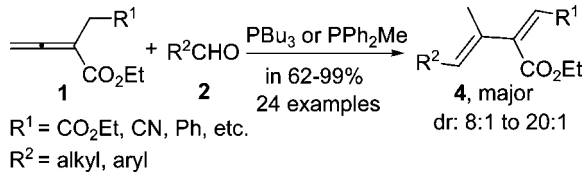
ABSTRACT



Phosphine-mediated olefination between α-substituted allenoates and aldehydes to form 1,2,3,4-tetrasubstituted 1,3-dienes is presented. High levels of chemo- and diastereoselectivity and yield are obtained for a wide scope of substrates with the choice of appropriate phosphines. This reaction evidences the capacity of phosphines in the control of reaction pathways and provides a highly efficient synthetic method for tetrasubstituted conjugated dienes.

Conjugated dienes are of great importance since they are present as substructures in a large number of naturally occurring and medicinally relevant substances[1] and also serve as versatile intermediates in many important organic transformations.[2] Classical procedures for the syntheses of 1,3-dienes mainly include the conventional elimination reactions from allyl bromide, allyl alcohol or dihalogenated compound,[3] the P-, S-, and Si-based carbonyl olefinations,[4] and the transition-metal-catalyzed diene formations.[5] Despite the effectiveness of the existing methods, the development of new strategies particularly aiming at the stereoselective synthesis of polysubstituted conjugated dienes remains challenging and highly desirable.[6] Recently, much effort has been devoted to this area.[7]

During the past decade, chemical transformations involving allenoates and a wide range of electron-poor C=C bonds

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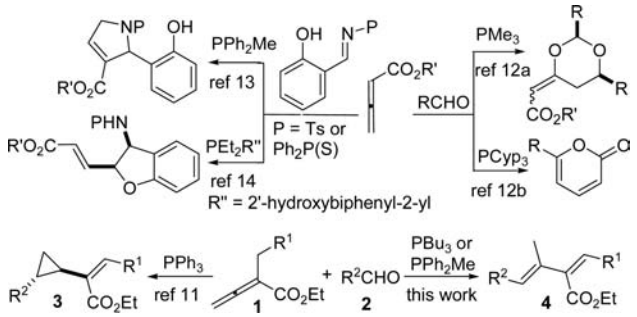
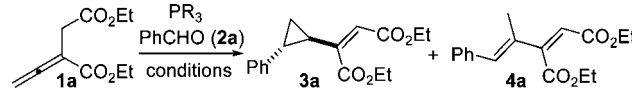
Scheme 1. Phosphine-Induced Chemoselectivity of Allenoates



or polarized C=X bonds (X = N, O) under the mediation of phosphines have been extensively studied.[8] A number of new reactions with high synthetic potentials have emerged, including many cycloaddition reactions,[9] olefination,[10] and cyclopropanation.[11] Relevant investigations have revealed that the electronic and steric properties of phosphines can exert significant influence on the reaction chemoselectivity. For example, Kwon et al.[12] reported that the use of small-size phosphine catalyst PMe_3 led to the formation of dioxane products, while bulky phosphines like $PCyp_3$ (Cyp = cyclopentyl) produced pyrones exclusively in the phosphine-catalyzed reactions of 2,3-butadienoates with aldehydes (Scheme 1, top right). Shi and co-workers[13] demonstrated that under the catalysis of PPh_2Me the reaction of 2,3-butadienoates with salicylic imines afforded the normal [3 + 2] cycloadducts, whereas Huang's investigations[14] unveiled that the difunctional catalyst (2′-hydroxybiphenyl-2-yl)-diethylphosphine was capable of tuning the reaction to a novel [4 + 1] annulation to form dihydrobenzofurans (Scheme 1, top left).

Recently, we reported a novel PPh_3-mediated reductive cyclopropanation between α-substituted allenoates **1** and aldehydes **2** to afford highly functionalized cyclopropanes **3**, in which PPh_3 acted as both a nucleophilic trigger and a deoxygenating agent (Scheme 1, bottom left).[11] Further survey on this reaction revealed that the choice of phosphines had a dramatic impact on the reaction chemoselectivity, leading to a new phosphine-mediated olefination reaction to form 1,2,3,4-tetrasubstituted 1,3-dienes **4** (Scheme 1, bottom right). Herein we wish to communicate the results from such a survey.

Table 1. Survey on Conditions for Formation of **4a**[a]



entry	PR_3	solvent	time (h)	**3a**: yield (%)[b]	**4a**: yield (%),[b] dr[c]
1	PBu_3	CH_2Cl_2	8	5	84, 20:1
2	$PPhMe_2$	CH_2Cl_2	48	trace	68, 20:1
3	PPh_2Me	CH_2Cl_2	48	trace	70, 6:1
4	PTA	CH_2Cl_2	54	8	66, 20:1
5	Ph_3P	CH_2Cl_2	48	48	/
6	$P(OMe)_3$	CH_2Cl_2	48	/	/
7	$P(NMe_2)_3$	CH_2Cl_2	48	/	/
8	PBu_3	CH_3CN	23	44	31, 20:1
9	PBu_3	1,4-dioxane	30	7	40, 20:1
10	PBu_3	DMSO	6	25	35, 20:1
11	PBu_3	DMF	27	55	25, 20:1
12	PBu_3	EtOH	33	/	14, 20:1
13	PBu_3	toluene	23	6	81, 20:1
14	PBu_3	xylene	30	17	64, 20:1
15	PBu_3	THF	23	15	84, 20:1
16	PBu_3	$CHCl_3$	24	3	87, 20:1
17	PBu_3	ethyl acetate	7	17	76, 20:1
18[d]	PBu_3	$CHCl_3$	24	10	57, 20:1
19[e]	PBu_3	$CHCl_3$	24	3	96, 20:1

[a] Typical conditions: under N_2 atmosphere and at room temperature, to a stirred solution of aldehyde **2a** (0.2 mmol) and allenoate **1a** (0.3 mmol) in solvent (2 mL) was added phosphorus reagent (0.3 mmol). [b] Isolated yield based on **2a**. [c] Based on the ^1H NMR assay of crude product with (*Z*,*E*)-**4a** being the major. [d] 1.0 equiv of water was added. [e] 5 mL of solvent was used.

Initial investigation showed that employing more nucleophilic PBu_3 instead of PPh_3 in the reaction of allenoate **1a** and benzaldehyde (**2a**) in CH_2Cl_2 at room temperature led to the formation of diene **4a** in 84% yield and excellent diastereoselectivity (dr 20:1), along with only a small amount of cyclopropane **3a** (5% yield) (Table 1, entry 1). Several other nucleophilic phosphorus reagents were also examined. Ph_2PMe, $PhPMe_2$, and 1,3,5-triaza-7-phosphaadamantane (PTA)[15] also readily produced the diene **4a**, but in lower yields or diastereoselectivity compared with PBu_3 (entries 2−4). PPh_3 only gave cyclopropane **3a** in 48% yield under similar conditions (entry 5), while $P(OMe)_3$ and $P(NMe_2)_3$ failed to mediate either cyclopropanation or olefination reaction (entries 6, 7). With the choice of PBu_3 as the

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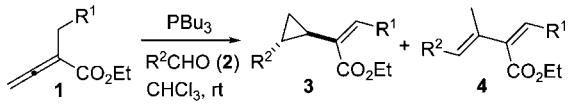
(15) An air-stable and water-soluble phosphine, often used as a nucleophilic trialkylphosphine. See ref 10 and references cited therein.

phosphine agent, further survey on conditions indicated such polar solvents as CH_3CN, 1,4-dioxane, DMSO, DMF, and ethanol were detrimental to the olefination reaction with regard to yield and chemoselectivity (entries 8−12). Among other tested solvents (entries 13−17), $CHCl_3$ emerged as the best, giving diene **4a** in 87% yield and excellent stereoselectivity (entry 16). Addition of water as a protic additive resulted in substantial decrease in both yield and chemoselectivity (entry 18). To our surprise, a relatively dilute reactant concentration was found to be good for the olefination, which gave **4a** in almost quantitative yield when run at 0.04 M concentration of **2a** (entry 19). Thus, the optimal conditions for the olefination were established.

Table 2. Synthesis of **4** from Allenoates **1** and Aldehydes **2**[a]



R^1: CO_2Et (**1a**), CN (**1b**), Ph (**1c**), *E*-styryl (**1d**)

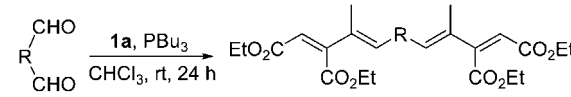
entry	**1**	R^2 in **2**	time (h)	**3** (%)[b]	**4** (%)[b], dr[c]
1	**1a**	C_6H_5	24	**3a**, 3	**4a**, 96, 20:1
2	**1a**	4-$CH_3C_6H_4$	24	**3b**, 3	**4b**, 85, 20:1
3	**1a**	4-$CH_3OC_6H_4$	24	\	**4c**, 87, 20:1
4	**1a**	2-$CH_3OC_6H_4$	23	**3c**, 99	\
5	**1a**	2-OHC_6H_4	1	\	**4d**, 72, 20:1
6	**1a**	3-Br-4-$CH_3OC_6H_3$	4	\	**4e**, 88, 20:1
7	**1a**	4-ClC_6H_4	24	**3d**, 9	**4f**, 90, 20:1
8	**1a**	3-ClC_6H_4	24	**3e**, 12	**4g**, 62, 9:1
9	**1a**	2-ClC_6H_4	24	**3f**, 83	\
10	**1a**	4-IC_6H_4	3	**3g**, 13	**4h**, 69, 12:1
11	**1a**	3-BrC_6H_4	1	**3h**, 14	**4i**, 72, 10:1
12	**1a**	4-FC_6H_4	2.5	**3i**, 8	**4j**, 84, 11:1
13[d]	**1a**	4-$NO_2C_6H_4$	1	**3j**, 2	**4k**, 63, 8:1
14[d]	**1a**	3-$NO_2C_6H_4$	1.2	\	**4l**, 79, 12:1
15[d]	**1a**	4-$CF_3C_6H_4$	6	**3k**, 4	**4m**, 95, 20:1
16[d]	**1a**	3-$CF_3C_6H_4$	6	\	**4n**, 96, 20:1
17[d]	**1a**	2-$CF_3C_6H_4$	4	**3l**, 51	\
18	**1a**	2-furyl	4	\	**4o**, 88, 20:1
19	**1a**	2-thiofuryl	1	\	**4p**, 85, 20:1
20	**1a**	*E*-styryl	24	\	**4q**, 80, 20:1
21	**1a**	C_2H_5	40	\	**4r**, 98, 20:1
22	**1a**	*n*-C_3H_7	24	\	**4s**, 99, 20:1
23	**1a**	*iso*-C_4H_9	24	\	**4t**, 97, 20:1
24	**1a**	*n*-C_5H_{11}	24	\	**4u**, 87, 20:1
25[d,e]	**1b**	C_6H_5	24	\	**4v**, 63, 12:1
26	**1c**	C_6H_5	24	\	**4w**, 91, 17:1
27	**1d**	C_6H_5	4	\	**4x**, 79, 20:1

[a] For details, see Supporting Information. [b] Isolated yield based on **2**. [c] Based on the ^1H NMR assay of crude product. [d] PPh_2Me was used instead of PBu_3. [e] 2.0 equiv of both **1b** and phosphine was used.

Under the optimized conditions, the substrate scope of this olefination was examined (Table 2). A variety of aldehydes **2** were explored with the allenoate **1a**. Except some *o*-substituted ones, aromatic aldehydes with electron-donating or -withdrawing groups readily gave dienes **4** in fair to excellent yields with good to high levels of diastereoselectivity (entries 1−17). *o*-Substituted benzaldehydes exclusively afforded cyclopropanation products **3** in 51−99% yields (entries 4, 9, 17) with an exception of salicylaldehyde, which underwent the olefination to give the corresponding diene **4d** in 72% yield (entry 5).[16] Relatively electron-rich benzaldehydes exhibited better chemoselectivity for the olefination, predominantly affording the dienes **4** in good to excellent yields (entries 1−3, 5−6). Halo-benzaldehydes produced the corresponding dienes **4** as the major associated with the cyclopropanation products as the minor (entries 7, 8, 10−12). For the more reactive benzaldehydes bearing electron-withdrawing substituents, their olefinations with the allenoate **1a** were better mediated with the less nucleophilic phosphine PPh_2Me, readily giving the dienes in fair to excellent yields (entries 13−16). Heteroaromatic aldehydes like furylaldehyde or thiofurylaldehyde also proved effective in the olefination with **1a**, giving the dienes **4o** and **4p** in good yields (entries 18, 19).

An α,*β*-unsaturated aldehyde such as (*E*)-cinnamaldehyde was also effective, giving (*Z*,*E*,*E*)-triene **4q** in 80% yield (Table 2, entry 20). Aliphatic aldehydes, in sharp contrast with their failure in the reported cyclopropanation,[11] worked well in the PBu_3-mediated olefination with allenoate **1a**, providing the corresponding dienes **4** in excellent yields with high chemo- and stereoselectivities (entries 21−24). Notably, dialdehydes like glutaraldehyde and terephthalic aldehyde readily incorporated with two molecules of the allenoate **1a**, forming tetraenes **5a** and **5b**, respectively, in moderate yield and high stereoselectivity (Scheme 2).

Scheme 2. Synthesis of Tetraenes **5** from Dialdehydes and **1a**



R = -$(CH_2)_3$-, 1,4-C_6H_4

5a (R= -$(CH_2)_3$-), 52%, dr > 20:1

5b (R =1,4-C_6H_4), 61%, dr > 20:1

Several structurally similar α-substituted allenoates **1** (R^1 = CN, **1b**; Ph, **1c**; *E*-styryl, **1d**; *n*-Pr, **1e**; H, **1f**) were also investigated in the olefination with benzaldehyde. The allenoates **1b**, **1c**, and **1d** all exhibited reactivity similar to that of **1a** and readily underwent the olefination under the mediation of PBu_3 or PPh_2Me, giving the corresponding dienes **4v** and **4w** or the triene **4x** in 63−91% yields and high stereoselectivity (Table 2, entries 25−27). However, α-butyl allenoate **1e** and α-methyl allenoate **1f** both failed to afford the corresponding olefination products.[17] This fact implies that an unsaturated conjugative group R^1 in **1** is required to effect the phosphine-mediated olefination.

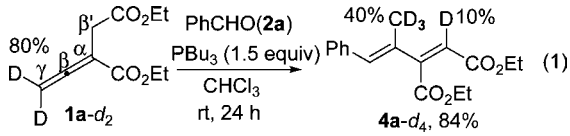
In all cases of the olefination listed in Table 2, the diastereoselectivity of the olefination products **4** remained on a modest to high level (8:1 to 20:1) with the illustrated isomer **4** as the major product. The structures and relative stereochemistry of the olefination products **4** and **5** were well

(16) The exceptional reactivity of *o*-substituted benzaldehydes, which presumably results from the increased steric hindrance, in the reactions with allenoates was also observed in ref 12a.

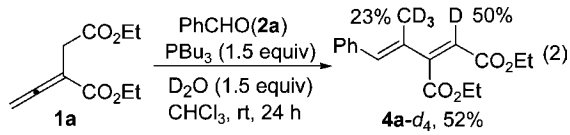
(17) A distinct Wittig olefination of α-methyl allenoate **1f** with salicylaldehydes or aromatic aldehydes to form *trisubstituted* dienes was observed: (a) He, Z.; Tang, X.; He, Z. *Phosphorus Sulfur Silicon Relat. Elem.* **2008**, *183*, 1518. (b) Khong, S. N.; Tran, Y. S.; Kwon, O. *Tetrahedron* **2010**, *66*, 4760.

identified by ^{1}H and ^{13}C NMR spectra and in some cases also by NOESY and X-ray crystallographic analyses (for characterization data, see Supporting Information).

The mechanism of the phosphine-mediated olefination was investigated through ^{31}P NMR tracking and deuterium-labeling experiments (for details, see Supporting Information). The reaction between the allenoate **1a** (0.075 mmol), *p*-chlorobenzaldehyde (0.05 mmol), and PBu_3 (0.075 mmol) in $CDCl_3$ (0.5 mL) was run in an NMR tube and monitored by ^{31}P NMR spectroscopy. An appreciable signal at δ 21.7 ppm appeared in the course of the reaction, along with two signals (δ 48.6 and −30.8 ppm) which corresponded to Bu_3PO and PBu_3, respectively. This signal could disappear in 5 min upon addition of more *p*-chlorobenzaldehyde (up to 0.025 mmol) into the sample. This result, in combination with the ^{31}P NMR chemical shift (δ 21.7 ppm), strongly implied that the emerging signal most likely came from a tetracoordinate phosphorus ylide intermediate.[18] In the deuterium-labeling experiments, a deuterated allenoate **1a**-d_2 (80% D) was subjected to the PBu_3-mediated olefination with benzaldehyde, resulting in a deuterated diene **4a**-d_4 in 84% yield with 40% and 10% deuterium at the γ- and β'-carbons, respectively (eq 1). In contrast with this result,



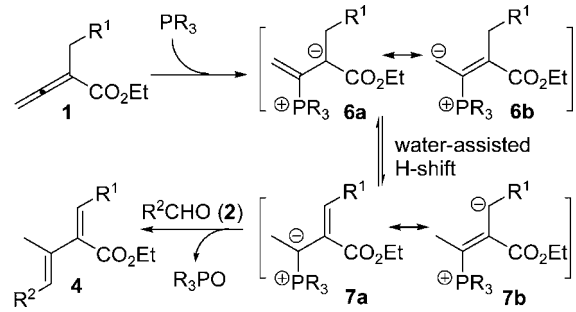
addition of D_2O (1.5 equiv) into the reaction of the nondeuterated allenoate **1a** with benzaldehyde also brought about partially deuterated product **4a**-d_4 in 52% yield with similar deuterium incorporations at the same carbons under otherwise identical conditions (eq 2). These results clearly indicated that a water-involved hydrogen shift occurred between the γ- and β'-hydrogens of the allenoate **1a**.



A plausible mechanism for the olefination is depicted in Scheme 3. Initially, nucleophilic attack of the phosphine at the allenoate **1** forms the resonance-stabilized zwitterionic intermediate **6**. Via a water-assisted hydrogen shift,[19] **6** reversibly converts into the allylic phosphorus ylide **7**, which also exists in two resonnance forms **7a** and **7b**. When R^1 in **7** is an unsaturated conjugative group such as CO_2Et, CN, Ph, or styryl, it is believed that the more stable form **7a** should be the major contributor to the phosphorus ylide **7** which is subsequently intercepted by an aldehyde **2** via a Wittig reaction yielding the olefination product **4**.

(18) Hudson, H. R.; Dillon, K. B.; Walker, B. J. ^{31}P NMR Data of Four Coordinate Phosphonium Salts and Betaines. In *Handbook of Phosphorus-31 Nuclear Magnetic Resonance Data*; Tebby, J. C., Ed.; CRC Press: Boca Raton, FL, 1991; pp 181−226.

Scheme 3. Proposed Mechanism for Formation of **4**



The high chemoselectivity in the olefination between allenoates **1** and aldehydes **2** may be ascribed to the increased reactivity of the in situ formed phosphorus ylide **7** for the Wittig reaction by employing electron-rich phosphines like PBu_3.[4b] Also, the high stereoselectivity of the olefination in this study could be well rationalized in terms of the Wittig reaction of the stabilized allylic phosphorus ylide **7** under neutral and salt-free conditions.[20]

In conclusion, a novel phosphine-mediated olefination of α-substituted allenoates with aldehydes has been successfully realized by choosing more nucleophilic phosphines. This olefination provides an efficient method for stereoselective synthesis of 1,2,3,4-tetrasubstituted 1,3-dienes from readily available starting materials. On the basis of the results in this work, the in situ generated phosphorus ylide **7** is believed to be the key intermediate which is responsible for the subsequent Wittig reaction with the aldehyde. Recently, in situ formed phosphorus ylides have proven to be powerful in construction of carbon carbon double bonds.[21] Future efforts on this olefination will be directed toward broadening its application in the synthesis of conjugated dienes and polyenes.

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Supporting Information Available: Experimental details, characterization data for new compounds, ^{1}H and ^{13}C NMR spectra for **3**, **4**, and **5**, as well as the X-ray crystallographical data (CIF files) for **4b** and **4k**. This material is available free of charge via the Internet at http://pubs.acs.org.

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