Olefination Reactions

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A Highly Regio- and Stereoselective Vinylogous Horner–Wadsworth–Emmons Route to Densely Substituted 1,3-Butadienes**

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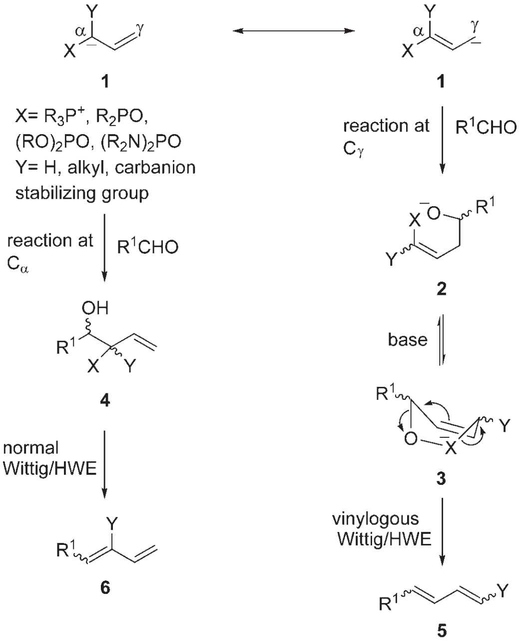
Since the landmark reports[1] by Wittig and co-workers in the early 1950s, the Wittig reaction has established itself as a gold standard for the olefination of carbonyl groups. Its efficacy was further elevated by employing phosphoryl-stabilized carbanions, in a modification known as the Horner–Wadsworth–Emmons (HWE)[2,3] reaction. In 1935, Fuson[4] formulated the principle of vinylogy to provide a better understanding of the "anomalous" reactivity of some unsaturated compounds. Since then, this concept has been applied in many important C–C bond-forming reactions[5] to extend the electrophilic or nucleophilic character of a functional group. Allylic phosphonium and phosphoryl ylides should in principle undergo a vinylogous Wittig/HWE reaction to give a new type of olefinic product that is regioisomerically different from that expected from the normal reaction course (Scheme 1).

Aldehydes and ketones usually react preferentially at the α position of allylic phosphorus ylides.[6] However, a few examples have been reported[7–9] in which, in spite of preferential reaction at the γ position, no vinylogous Wittig/HWE olefination products were formed. Corey and Erickson[10] reported a single example of a vinylogous Wittig reaction of (*E*)-3-methoxycarbonyl-2-methylallyltriphenylphosphonium bromide with hexanal under special conditions to give a stereoisomeric mixture of γ-condensed vinylogous products. It appears that the base used, the olefin geometry, and the substituents present were crucial to the success of this reaction. In contrast, the analogous *trans* phosphonate provided only the α-condensed HWE product.[10,11] Although there has been tremendous growth in the chemistry of allylic phosphorus ylides,[12] to our knowledge there has been no other report of a vinylogous Wittig or related reaction.

We speculated that for a vinylogous Wittig/HWE reaction to occur, three essential requirements should be fulfilled: 1) selective reaction of the ylide at the γ carbon atom, 2) selective isomerization of the vinyl phosphorus derivative **2** (Scheme 1) to the allyl phosphorus derivative **3**, and 3) the substituent Y should be able to modulate the reactivity of the phosphorus center and ensure rapid equilibration to facilitate the cycloelimination. A potential solution to these requirements might accrue from the application of our recently developed[13,14] sulfonium methylide[15] chemistry with suitably substituted vinyl phosphonates. Herein we present a highly regio- and stereoselective vinylogous HWE reaction[16] of aldehydes with allylic phosphonates generated in situ from α-cyano vinyl phosphonates.



Scheme 1. Two reaction pathways of an allylic phosphorus ylide and an aldehyde.

The vinyl phosphonates **7a–c** were prepared by a known method.[17] When **7a** was added to a mixture of sodium dimsylate and Me$_3$SI, and the intermediate was quenched with benzaldehyde, the 1,3-diene **5a** was formed along with a trace amount of the HWE product **6a** (method A). Diene **5a** must have been produced via the allylic ylide **1a** through a vinylogous HWE reaction (Scheme 2). The product was formed in moderate (ca. 45%) yield but with excellent regio- and stereoselectivity (**5a**/**6a** 94:6; purity of **5a**: >97%). The configurations of the double bonds in the products were determined by ^{1}H NMR spectroscopy: The *E* configuration of the disubstituted double bond in diene **5a** was ascertained from the ^{1}H NMR coupling constant (J = 16 Hz), whereas the *Z* configuration of the trisubstituted double bond was established from the NOE interactions of the olefinic hydrogen atoms. The *Z* configuration of the trisubstituted double bond in diene **6a** was assigned on the basis of the chemical-shift value of the hydrogen atom[18] attached to this double bond. For a quick assessment of the

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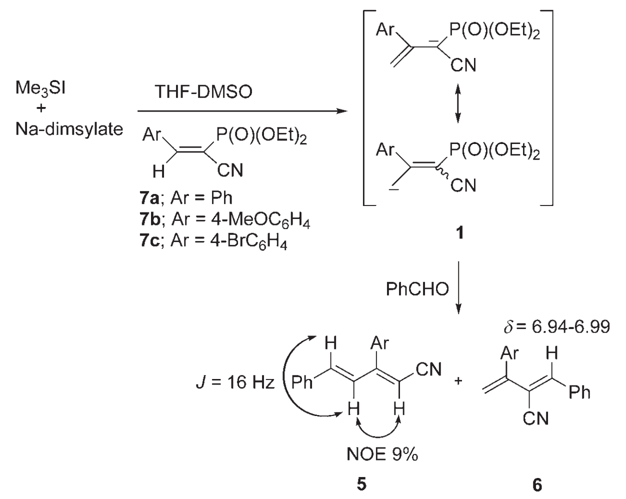
[**] The authors deeply appreciate the suggestion made by one referee concerning the mechanism of the reaction.

Supporting information for this article is available on the WWW under http://www.angewandte.org or from the author.



Ar	products	5/6	yield of 5 [%]
Ph	**5a**; **6a**	94:6	45
4-MeOC$_6$H$_4$	**5b**; **6b**	94:6	41
4-BrC$_6$H$_4$	**5c**; **6c**	94:6	44

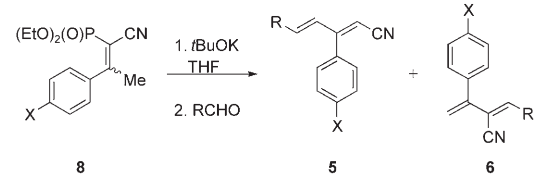
Scheme 2. Dimethylsulfonium methylide mediated olefination and vinylogous HWE reaction of vinyl phosphonates **7a–c**; dimsylate = methylsulfinyl carbanion (MeSOCH$_2^-$, DMSO = dimethylsulfoxide.

Table 1: Optimization of the reaction conditions for the vinylogous HWE reaction of vinyl phosphonate **8a** with benzaldehyde.[a]

Entry	Base	Solvent	**5a**/**6a**[b]	Yield of **5a** [%][c]
1	Li-dimsylate	DMSO/THF (7:3)	–[d]	–
2	Na-dimsylate	DMSO/THF (7:3)	94:6	82
3	K-dimsylate	DMSO/THF (7:3)	98:2	85
4	*t*BuOLi	THF	–[d]	–
5	*t*BuONa	THF	95:5	78
6	*t*BuOK	THF	98:2	89

[a] Reaction conditions as for method B in the Experimental Section, with the exception of the solvent and the base. [b] The ratio was determined by ^{1}H NMR spectroscopic analysis of the crude product. [c] Yield of the spectroscopically pure product isolated after chromatography on silica gel. [d] Formation of the product was not detected by NMR spectroscopy or TLC analysis.

Table 2: Regio- and stereoselective vinylogous HWE reaction of vinyl phosphonates **8a–c** with aldehydes.

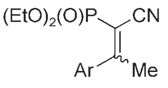


Entry	Substrate (X)	R	5/6[a]	Purity of 5 [%][a,b]	Product (yield [%])[c]
1	**8a** (H)	Ph	98.2:1.8	> 98	**5a** (89)
2	**8b** (OMe)	Ph	98.3:1.7	> 98	**5b** (87)
3	**8c** (Br)	Ph	98.0:2.0	> 83	**5c** (92)
4	**8a** (H)	4-MeOC$_6$H$_4$	96.5:3.5	> 97	**5d** (86)
5	**8a** (H)	3-MeOC$_6$H$_4$	99.1:0.9	> 97	**5e** (91)
6	**8a** (H)	2-MeOC$_6$H$_4$	99.1:0.9	> 96	**5f** (87)
7	**8a** (H)	4-BrC$_6$H$_4$	97.1:2.9	> 97	**5g** (91)
8	**8a** (H)	3-ClC$_6$H$_4$	97.4:2.6	> 89	**5h** (92)
9	**8a** (H)	4-CF$_3$C$_6$H$_4$	99.3:0.7	> 98	**5i** (93)
10	**8a** (H)	2-pyridyl	96.9:3.1	> 98	**5j** (92)
11	**8a** (H)	2-furyl	98.5:1.5	> 98	**5k** (85)
12	**8a** (H)	CH$_3$CH$_2$	35:65[d]	> 97[d]	**5l** (24)[e]
13	**8a** (H)	Me$_2$CH	78:22[d]	> 97[d]	**5m** (52)[f]
14	**8b** (OMe)	4-BrC$_6$H$_4$	96.2:3.8	> 96	**5n** (86)
15	**8c** (Br)	4-BrC$_6$H$_4$	96.7:2.3	> 87	**5o** (90)

[a] Determined by GC analysis of the crude product. [b] Refers to stereoisomeric and/or other inseparable impurities. [c] Yield of the spectroscopically pure product isolated after chromatography on silica gel. [d] Determined by ^{1}H NMR spectroscopy. [e] The product **6l** was isolated in 42% yield. [f] The product **6m** was isolated in 13% yield.

generality of this reaction, vinyl phosphonates **7b** and **7c** were also treated with Me$_3$SI and sodium dimsylate, followed by benzaldehyde. The vinylogous products **5b** and **5c** were formed, once again with very high regio- and stereoselectivities (Scheme 2). The poor yields probably resulted from side reactions, as we have reported previously.[13b]

We next aimed to improve the yield and the regioselectivity of this reaction. It was envisaged that the resonance-stabilized anion **1** could be formed directly from vinyl phosphonates **8a–c**[19] by treatment with a base. We established the optimal experimental conditions by screening different bases and solvents with **8a** and benzaldehyde.[20] The results of the studies, which showed that the base plays an important role in the reaction, are presented in Table 1. With the lithium bases (entries 1 and 4), the desired product was not formed, whereas with the sodium and potassium bases the vinylogous product **5a** was formed almost exclusively. The use of potassium bases (Table 1, entries 3 and 6) led to superior regioselectivity to that observed with the sodium bases. The best result was obtained with 1.2 equivalents of potassium *tert*-butoxide in THF (Table 1, entry 6); these conditions (method B) provided **5a** in 89% yield.



8a; Ar = Ph
8b; Ar = 4-MeOC$_6$H$_4$
8c; Ar = 4-BrC$_6$H$_4$

The scope of the stereoselective vinylogous HWE reaction was investigated under the optimized reaction conditions (Table 2). The treatment of a wide range of aldehydes bearing aryl, heteroaryl, and alkyl groups with vinyl phosphonates **8a–c** led to the vinylogous HWE products in all cases. The reactions of benzaldehyde derivatives with a variety of substituents and substitution patterns proceeded well. Propionaldehyde and isobutyraldehyde reacted to give the respective vinylogous products accompanied by a large amount of the normal HWE products (Table 2, entries 12 and 13). Except when the aliphatic aldehyde substrates were used, the products were formed in good to excellent yields with uniformly high regio- and stereoselectivities.

In conclusion, an unprecedented vinylogous HWE reaction of allylic phosphonates with aldehydes has been developed. This study has expanded the utility of the Wittig class of reactions to another dimension. Whereas traditional protocols based on Wittig and HWE reactions often give mixtures of *E* and *Z* isomers of di- and trisubstituted alkenes, the present modification provides stereochemically very pure 1,3-dienes[21] with a trisubstituted double bond.[22,23] The configurations of the two double bonds were controlled in a single step with very high selectivity.[24] The reactions can be performed on a scale of 1–5 mmol without affecting the yield or selectivity. In many cases, direct crystallization of the crude product gave the pure dienes **5**. The cyano group plays an important role: The reaction did not proceed in this fashion with allylic phosphorus ylides containing an α-alkoxy/silyloxy[8] or an anion-stabilizing carboxy ester functionality.[14] The compatibility of other functional groups in place of the cyano group and details of the course of the reaction are currently under active investigation.

Experimental Section

Method A: Solid Me_3SI (1.2 mmol) was added to a stirred solution of sodium dimsylate (2.5 mmol) in DMSO/THF (1:1, 6 mL) at −8°C. After 15 min, a solution of **7a** (1 mmol) in THF (4 mL) was added rapidly to the reaction mixture, which was slowly warmed to room temperature and stirred for 1 h. The reaction mixture was then cooled to 0°C, and benzaldehyde (1.2 mmol) was added. The resulting mixture was stirred at room temperature for 2 h, then diluted with water and extracted with hexane/EtOAc (1:1). The extract was concentrated, and the residue was purified by chromatography (SiO_2) to give the pure dienes **5a** (45%) and **6a** (1.3%).

Method B: A solution of **8a** (1 mmol) in THF (3 mL) was added to a stirred suspension of *t*BuOK (1.2 mmol) in THF (3 mL) at ≈10°C. The reaction mixture was allowed to warm to room temperature over 0.5 h. Freshly distilled benzaldehyde (1.2 mmol) was then added at 0°C, and the reaction mixture was stirred at room temperature for 2 h. The mixture was then diluted with water and extracted with hexane/EtOAc (1:1). The extract was concentrated, and the residue was purified by chromatography (SiO_2) to give the pure diene **5a** (89%).

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[24] A mechanistic rationale is provided in the Supporting Information.