

Communications

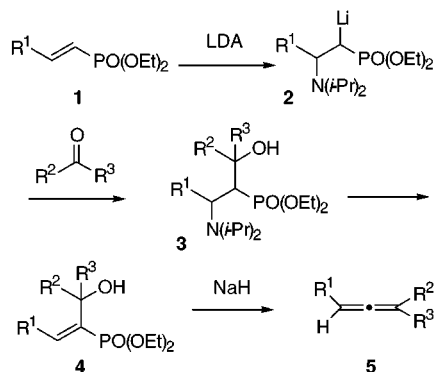
Baylis–Hillman-Type Carbon–Carbon Bond Formation of Alkenylphosphonates by the Action of Lithium Diisopropylamide

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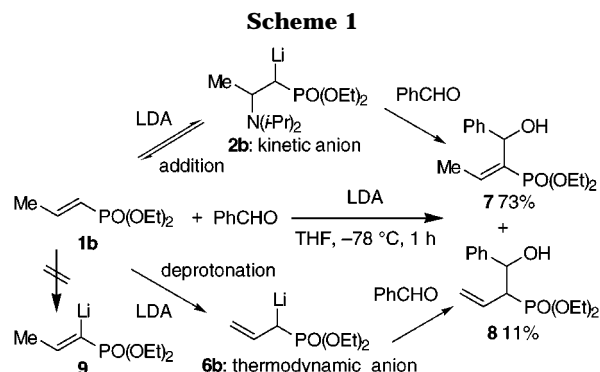
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Alkylphosphonates are versatile synthetic tools¹ as well as being potent biological components.² Conjugate addition of nucleophiles to alkenylphosphonates bearing a second electron-withdrawing group at the α -position has been established as a route to alkylphosphonates.³ Recently, the conjugate addition of organocoppers⁴ or enolates⁵ to alkenylphosphonates lacking an activating group has been reported.⁶ We have been involved in studies directed toward the development of enantioselective conjugate additions of organometallics to activated olefins.⁷ As part of our program related to the foregoing,⁸ we examined a sequence of reactions involving conjugate addition of lithium diisopropylamide (LDA) to alkenylphosphonates **1** and subsequent aldol-type reaction of the resultant lithiated phosphonates **2** with aldehydes or ketones, giving **3** or further elimination products **4**. It is important to note that **4** is readily converted to allenes **5**⁹ by treatment with a base under Horner–Wadsworth–Emmons conditions.



The conversion of **1** to **4** is equivalent to the Baylis–Hillman reaction.^{10,11} We describe herein that treatment of a mixture of **1** and carbonyl compounds with LDA afforded



4 in good to high yields. Furthermore, we provide mechanistic evidence for the intermediacy of **2**. This is contrary to the formation of the vinylic anion generated by deprotonation of the dimethyl ester corresponding to **1c** ($R^1 = \text{Ph}$) with LDA and found to undergo electrophilic trapping resulting in the synthesis of dimethyl ester of **4** ($R^1 = \text{Ph}$).¹²

We began our studies by examining the reaction of diethyl propenylphosphonate **1b** ($R^1 = \text{Me}$) with benzaldehyde with LDA as a nucleophilic Michael donor. At first, formation of anion **2b** was attempted by dropwise addition of **1b** to a cooled (-78°C) solution of LDA in THF. After being stirred 20 min, benzaldehyde was added dropwise to the solution and the reaction continued for 1 h at -78°C . This route failed to give the expected products **3** and **4** (**7**). The only isolable product was **8**, generated from **6b**, in 62% yield (Scheme 1).¹³ In another attempt, a mixture of **1b** and benzaldehyde in THF added to a solution of LDA in THF gave the desired product **7** along with **8** each in 21% yield.

These results imply that conjugate addition of LDA to **1b** enables the formation of the kinetic anion **2b**, which is not stable and is converted to the thermodynamic allylic anion **6b** as shown. This suggests that addition of LDA to **1b** in the presence of benzaldehyde would increase the yield of **7** because the initially formed anion **2b** may react rapidly with benzaldehyde before the establishment of the equilibrium with **6b**. Thus, addition of a solution of 1.1 equiv of LDA in THF to a mixture of **1b** and an equivalent of benzaldehyde in THF afforded, after 1 h at -78°C , the desired product **7** in acceptable 73% yield along with **8** in 11% yield.

The intermediacy of vinylic carbanion **9**¹² is ruled out by the fact that reaction of **1b** with 2 equiv of Davies' chiral

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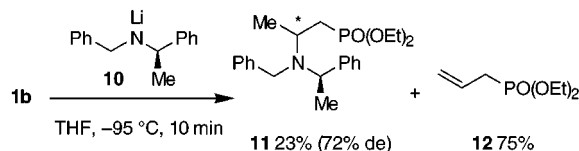
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lithium amide **10**¹⁴ in the absence of benzaldehyde at -95 °C for 10 min affords **11**¹⁵ and the isomerized olefin **12**, in 23 and 75% yields, respectively.¹⁶ Formation of **4** (**7**), instead of **3**, is probably due to the lower stability of the anionic form of **3** compared with that of **4** (**7**).¹⁷



Using the conditions established as above, reactions of alkenylphosphonates **1a–c** with aldehydes or ketones were examined. The results, including conversion of **4** to the allenes **5**, are summarized in Table 1.

Vinyl-, propenyl-, or phenylethenylphosphonates **1a–c** were converted to the corresponding Baylis–Hillman reaction-type products **4** in good to high yields. Ketones were also found to be good carbonyl substrates (entries 2, 3, 7, and 11). The *E* geometry of the product **4** was assigned on the basis of the observed phosphorus and the β -vinylic proton coupling constant of 25 Hz.¹⁸ We were very pleased to find that reactions with aldehydes and ketones bearing hydrogens at the α -position also proceeded smoothly to give the expected products **4** (entries 2, 3, 6, 7, 10, and 11). It is then apparent that conjugate addition of LDA to alkenylphosphonates is faster than deprotonation of the substrates.

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Table 1. Reaction of Alkenylphosphonate **1** with Aldehyde or Ketone with LDA Giving **4** and Conversion to **5**

entry	1	R ¹	R ²	R ³	4 ^a %	5 ^a %
1	a	H	<i>t</i> -Bu	H	87	
2	a	H	Et	Me	80	
3	a	H	4- <i>t</i> -butylcyclohexanone		80 ^b	
4	b	Me	<i>t</i> -Bu	H	80 ^c	
5	b	Me	Ph	H	73 ^c	
6	b	Me	PhCH ₂ CH ₂	H	78 ^c	58 ^d
7	b	Me	4- <i>t</i> -butylcyclohexanone		53 ^b	
8	c	Ph	<i>t</i> -Bu	H	90	72 ^e
9	c	Ph	Ph	H	50	60 ^e
10	c	Ph	PhCH ₂ CH ₂	H	66	58 ^f
11	c	Ph	Et	Me	78	52 ^g

^a Yields for products isolated by silica gel column chromatography. ^b Three equiv of LDA was used. ^c Allylphosphonates **8** were produced in 9–11% yields. ^d Harada, T.; Katsuhira, T.; Osada, A.; Iwazaki, K.; Maejima, K.; Oku, A. *J. Am. Chem. Soc.* **1996**, *118*, 11377–11390. ^e Elsevier, C. J.; Vermeer, P. *J. Org. Chem.* **1985**, *50*, 3042–3045. ^f Kim, S.; Cho, C. M.; Yoon, J. *J. Org. Chem.* **1996**, *61*, 6018–6020. ^g Keinan, E.; Bosch, E. *J. Org. Chem.* **1986**, *51*, 4006–4016.

Alcohols **4** were readily converted to the corresponding allenes **5** by NaH in THF under the conditions of the Horner–Wadsworth–Emmons reaction (Table 1).¹⁹

Extension of the present procedure to asymmetric versions is the subject of current study.²⁰

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Supporting Information Available: Experimental procedure and characterization of **4**, **5**, **8**, **11**, and **12** (9 pages).

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(20) Typical procedure (Table 1, run 8): A cooled (-78 °C) solution of LDA (0.55 mmol) in THF (5 mL) was added to a mixture of **1c** (0.5 mmol) and pivalaldehyde (0.5 mmol) in THF (5 mL) at -78 °C. After being stirred for 30 min at -78 °C, the reaction mixture was quenched with saturated NH₄Cl (10 mL) and extracted with EtOAc. Concentration and subsequent purification by silica gel column chromatography (EtOAc–hexane = 2:3) afforded **4** (R¹ = Ph, R² = *t*-Bu, R³ = H) in 90% yield.