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Stereoselective Synthesis of *E*,*Z*-1,3-Dienes via Tandem Nucleophile Addition to a Dienylphosphonium Salt Followed by Wittig Reaction

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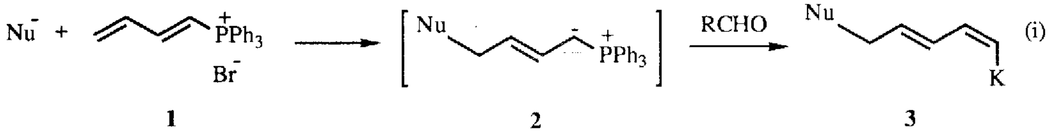
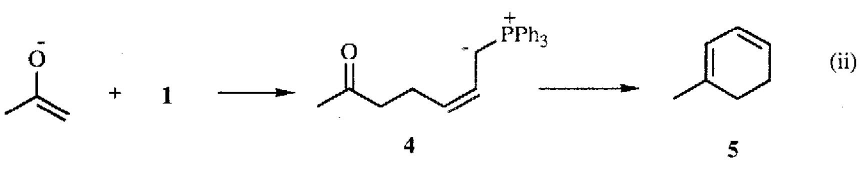
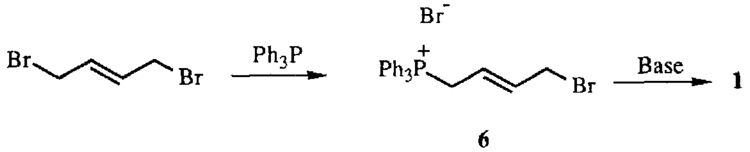
Abstract: *1,3-Dienes of E,Z configuration were synthesized by addition of nucleophilic anions to butadienyltriphenylphosphonium bromide followed by in situ Wittig reaction of the derived E allylic phosphorane to an aldehyde.*

The synthesis of 1,3-dienes of defined configuration continues to be an important objective,[1] especially since few methods exist for elaboration of this substructure in a complex milieu of functional groupings.[2] Our recent synthesis of latrunculin A[3] necessitated construction of a conjugated diene of *E,Z* configuration and, recognizing that a general solution to this problem would be of potentially broad utility, we initiated a comprehensive investigation into the synthesis of dienes of this class based on an extension of the Wittig olefination.[4] We now report that the tandem process expressed in equation (i) represents a practical, stereoselective diene synthesis in certain cases. The sequence relies on addition of a nucleophilic anion to the dienylphosphonium salt **1** to generate an *E* allylphosphorane **2**, which undergoes immediate Wittig reaction with an aldehyde. Under appropriate conditions (*vide infra*) an *E*,*Z*-1,3-diene **3** is produced with good stereoselection. A related process described by Fuchs[5] (equation ii), in which a carbonyl enolate was employed as nucleophile, led to cyclohexadiene **5**. This pathway presumably results from equilibration of phosphorane configuration followed by intramolecular Wittig reaction of the Z isomer **4**. Thus, the success of the proposed acyclic *E,Z* diene synthesis (i) depended on suppressing isomerization of the initially formed *E* phosphorane **2** while promoting a fast, kinetically controlled Wittig olefination.[6]

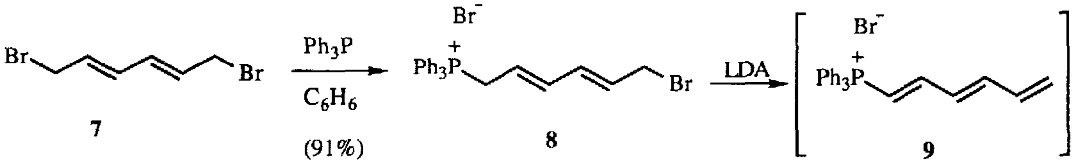






Butadienyltriphenylphosphonium bromide **1** is an unstable species[7] which is conveniently generated and used *in situ*. It is prepared by treatment of 1,4-dibromobut-2-ene (mixture of *E* and Z isomers) with one equivalent of triphenylphosphine,[8] followed by elimination of HBr from **6** (mp 187-188.5 °C) with a non-nucleophilic base at low temperature. The elimination step, which in some cases can be accomplished with the same base used to generate the anionic nucleophile, leads to a brown solution of **1**. Addition of the nucleophile to **1** causes a change of color to the orange-red characteristic of phosphoranylylides, which fades as Wittig reaction with the aldehyde ensues.[9]

The yield of 1,3-diene and the *E,Z*:*E,E* ratio for a variety of nucleophilic anions and aldehydes are shown in Table I. The products in all cases result from addition of the nucleophile in a 1,4 sense to **1**, with exclusive formation of an intermediate allylic phosphorane **2** of *E* configuration. Subsequent reaction of this ylide with aldehydes is highly Z selective in some cases but in others the stereoselectivity is poor. Stabilized anions such as that derived from malonate or the acetoacetate monoanion are too weakly nucleophilic to participate in the diene synthesis. They fail to add to **1** and instead condense directly with the aldehyde. By contrast, β-keto ester dianions,[10] particularly that derived from t-butyl acetoacetate (entries 1-3), and the dianion of 2,4-pentanedione (entry 4) result in 1,3-dienes with high *E,Z* stereoselectivity. In agreement with previous observations on the Wittig olefin synthesis,[4] α branched aldehydes give a higher proportion of the *E,Z* stereoisomer than straight chain aldehydes. Benzaldehyde shows poor stereoselectivity as expected, and α-sulfonyl anions (entry 5) exhibit either a low preference for the *E,Z* isomer or none at all. Dianions of sulfonyl compounds resulted in the destruction of **1** but, by comparison, dianions of carboxylic acids (entries 6 and 7) except acetic were effective partners in the diene synthesis. Lithium diisopropylamide proved to be superior to sodium hexamethyldisilazide as the base for generating both the anionic species and the dienylphosphonium salt **1**.



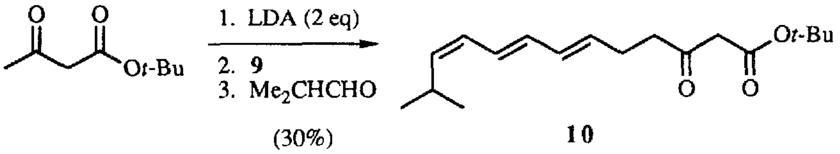
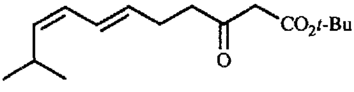
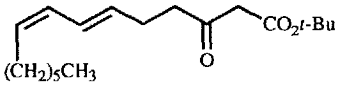
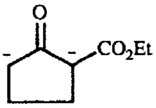
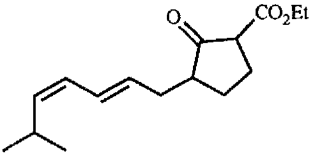
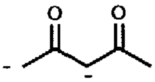
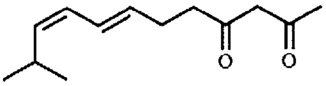
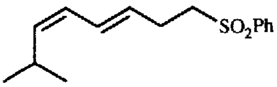
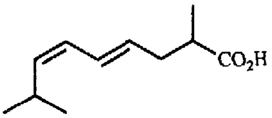
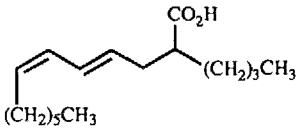


Table I. Synthesis of 1,3-Dienes

Entry	Nucleophile	Carbonyl Compound	Diene	Yield (%)	*E,Z:E,E* Ratio
1.	$\bar{C}H_2CO\bar{C}HCO_2t\text{-Bu}$	$(CH_3)_2CHCHO$		62	16:1
2.	$\bar{C}H_2CO\bar{C}HCO_2t\text{-Bu}$	$CH_3(CH_2)_5CHO$		62	6:1
3.		$(CH_3)_2CHCHO$		48	12:1
4.		$(CH_3)_2CHCHO$		43	>20:1
5.	$PhSO_2CH_2^-$	$(CH_3)_2CHCHO$		50	2:1
6.	$CH_3\bar{C}HCO_2^-$	$(CH_3)_2CHCHO$		55	8:1
7.	$CH_3(CH_2)_3\bar{C}HCO_2^-$	$CH_3(CH_2)_5CHO$		77	2.4:1

In an attempt to extend this three-component coupling to a synthesis of conjugated trienes, phosphonium salt **8** was prepared from *E,E*-1,6-dibromohexa-2,4-diene (7).[11] Elimination of HBr from **8** (mp 162-163 °C) produced a solution of the trienylphosphonium salt **9** which, upon addition of the dianion of t-butyl acetoacetate, turned to a vivid purple color indicative of the ylide. This faded upon Wittig reaction with isobutyraldehyde, which led to a modest yield of triene **10**.[12]

In summary, a sequence in which certain anions, butadienyltriphenylphosphonium bromide and an aldehyde are reacted in tandem is found to yield *E,Z*-1,3-dienes in a preparatively useful manner. The process, which inserts the butadiene unit stereoselectively between electrophilic and nucleophilic carbons, is a unique homologation that should find numerous synthetic applications.

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1. For a review see Normant, J.F.; Alexakis, A. In *Current Trends in Organic Synthesis*; Nozaki, H., Ed.; Pergamon Press: Oxford, 1983; pp 291-302.
2. For example, see Mori, K. In *The Total Synthesis of Natural Products*; ApSimon, J., Ed; Wiley: New York, 1981; Vol iv, pp 31-42.
3. White, J. D.; Kawasaki, M. *J. Am. Chem. Soc.* **1990**, *112*, 4991.
4. Ideses, R.; Shani, A. *Tetrahedron* **1989**, *45*, 3523.
5. Fuchs, P. L. *Tetrahedron Lett.* **1974**, *46*, 4055.
6. The conditions which promote stereoselectivity in the Wittig reaction have been summarized; Schlosser, M. *Top. Stereochem.* **1970**, *5*, 1.
7. Bromide **1** could not be isolated without decomposition. This is to be contrasted with ref. 5, footnote 2, in which mp 186-188.5 °C is attributed to **1**. The perchlorate corresponding to **1** is reported to be stable, mp 182-184 °C (Ford, Jr. J. A.; Wilson, C. V. *J. Org. Chem.* **1961**, *26*, 1433.)
8. Buchta, E.; Andree, F. *Justus Liebigs Ann. Chem.* **1961**, *640*, 29.
9. A typical procedure is as follows: To a stirred suspension of **6** (1 mmol) in dry THF (3 mL) at -78 °C is added a THF solution of LDA (1 mmol). The mixture is allowed to warm to -40 °C during which it changes to a brown color. To this solution is added a THF solution of the dilithio dianion of *t*-butyl acetoacetate (1 mmol, prepared with 2 equiv of LDA). The solution is allowed to warm to 0 °C and the aldehyde (0.3 mmol) is added to the reddish-brown mixture. After 10 min an ice-cold solution of 1% HCl is added and the product is extracted with ether and purified by flash chromatography.
10. Huckin, S. N.; Weiler, L. *J. Am. Chem. Soc.* **1974**, *96*, 1082.
11. Spangler, C. W.; McCoy, R. K.; Dembek, A. A.; Sapochak, L. S.; Gates, B. D. *J. Chem. Soc. Perkin Trans. 1* **1989**, 151.
12. Triene **10** is principally the *E,E,Z* isomer but minor amounts of isomeric trienes are present.

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