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Convergent synthesis of conjugated 1,2-disubstituted *E*-allylic alcohols from two aldehydes and methylenetriphenylphosphorane†

David M. Hodgson* and Rosanne S. D. Persaud

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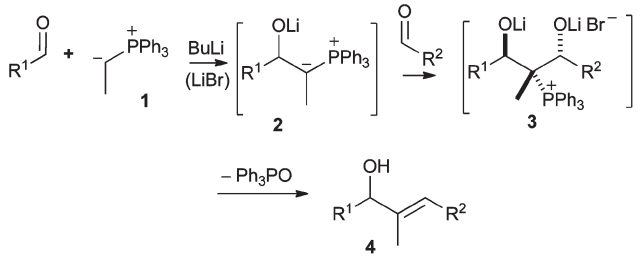
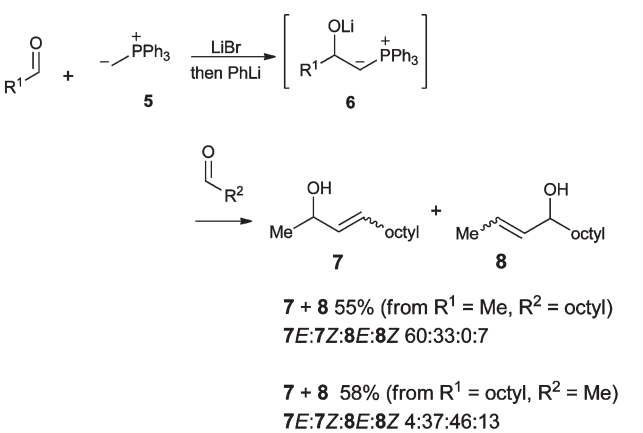
β-Lithiooxyphosphonium ylides, made *in situ* from an aldehyde and methylenetriphenylphosphorane, react with a second aldehyde to form *E*-allylic alcohols. α-Branching and α,β-unsaturation in the second aldehyde, together with the lack of further substitution on the phosphorane carbon play important roles in selectivity. A range of these aldehydes, in addition to aromatic aldehydes as the second aldehyde also provided synthetically useful access to *E*-allylic alcohols.

Allylic alcohols are widely used in organic synthesis, so experimentally straightforward methods of synthesising them under stereocontrol from readily available starting materials are of significance.[1] In 1970, Corey and Yamamoto reported a remarkable regio- and stereoselective synthesis of *E*-trisubstituted allylic alcohols **4** from ethylidenetriphenylphosphorane (**1**) and two aldehydes (Scheme 1).[2] A subsequent mechanistic study indicated that the origin of the positional selectivity and geometry of the double bond was due to stereocontrolled formation of a β-,β′-di(lithiooxy)phosphonium **3** arising from addition of β-lithiooxyphosphorane **2** to the second aldehyde, followed by preferential *syn*-elimination of Ph_3PO involving the oxygen from the second aldehyde; *syn*-elimination involving the oxygen from the first aldehyde would be a higher energy process leading to *Z*-stereochemistry.[3]



Scheme 1 Synthesis of *E*-trisubstituted allylic alcohols **4**.[2]

To the best of our knowledge, the above chemistry has not been studied with methylenephosphorane and two aldehydes (other than with one of the aldehydes being formaldehyde)[4,5] – despite the potential as an attractive route to *E*-1,2-disubstituted allylic alcohols (Scheme 2). The presumed intermediate β-lithiooxyphosphorane **6** has been generated on several occasions from double deprotonation of a β-hydroxy primary phosphonium salt, and has been shown to undergo the desired synthesis of 1,2-disubstituted allylic alcohols on reaction with aldehydes; however, these reactions require a stepwise synthesis of the phosphonium salt, appear very sensitive to experimental conditions, and yields are highly variable.[6] Also, α-lithiomethylenetriphenylphosphorane has been shown to react with 2 equivalents of (necessarily) the same aldehyde to give symmetrically substituted *E*-allylic alcohols (for example, **10c**).[7] In the present paper, we demonstrate that the coupling of two different aldehydes with methylenephosphorane is a synthetically useful regio- and stereocontrolled approach to *E*-1,2-disubstituted allylic alcohols, but only from certain classes of aldehydes (Scheme 2).



Scheme 2 Allylic alcohols using aliphatic aldehydes and methylenephosphorane **5**.

Department of Chemistry, Chemistry Research Laboratory, University of Oxford, 12 Mansfield Road, Oxford, OX1 3TA, UK.
E-mail: david.hodgson@chem.ox.ac.uk; Fax: +44 (0)1865 285002; Tel: +44 (0)1865 275697

†Electronic supplementary information (ESI) available: Experimental procedures and spectroscopic data along with ^1H and ^{13}C NMR spectra for all compounds synthesised. See DOI: 10.1039/c2ob26346g

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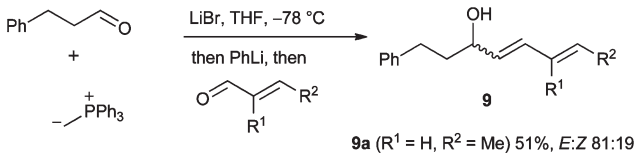
Preliminary experiments were not encouraging. Under previously established preferred conditions for generation of β-lithiooxyphosphoranes,[8,9] methylenetriphenylphosphorane (**5**), with acetaldehyde and nonanal as either the first or second aldehyde produced alcohols **7** and **8** as a mixture of chromatographically inseparable isomers in similar yield (Scheme 2).[10] Varying the concentration, the generation of β-lithiooxyphosphorane **6** by a warm–cool cycle,[8] the temperature at which the second aldehyde was added, the equivalents of LiBr or the second aldehyde, adding β-lithiooxyphosphorane **6** to the second aldehyde,[11] or adding *t*-BuOK[8] at the end of the reaction did not improve selectivity. In contrast, reaction of these aldehydes under the preferred conditions, but with ethylidenetriphenylphosphorane (**1**) gave exclusively *E*-trisubstituted allylic alcohols **4** (58% for R^1 = Me and R^2 = octyl; 63% for R^1 = octyl and R^2 = Me),[10] in complete accordance with Corey and Yamamoto's initial report. These results indicate a significant influence of phosphorane substitution in the reaction pathway from β-lithiooxyphosphorane to allylic alcohol.

Use of an α,β-unsaturated aldehyde as the second aldehyde component proved more promising (Scheme 3). In these cases, the newly formed double bond was always generated by elimination involving the oxygen from the second aldehyde, with the energy of the transition state for elimination likely being lowered due to developing conjugation. With α-branched α,β-unsaturated aldehydes, complete stereoselectivity for the *E*-isomer **9b–d** was observed.[12] This chemistry provides a convenient entry to dienols **9**, such as a functionalised isoprene unit **9d**, which are potentially useful in cycloadditions.[13]

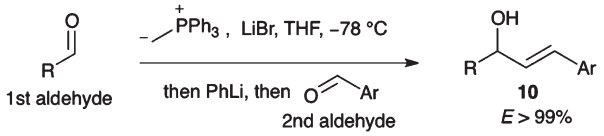


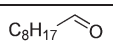
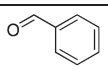
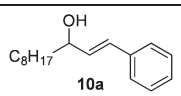
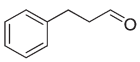
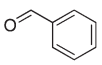
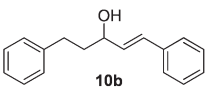
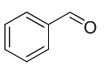
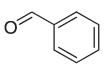
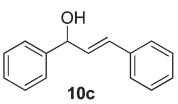
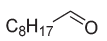
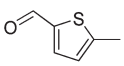
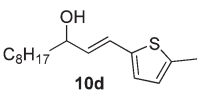
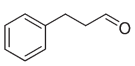
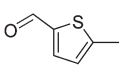
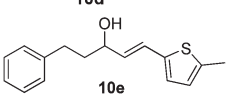
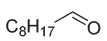
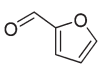
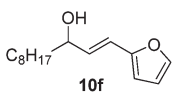
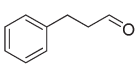
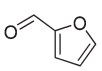
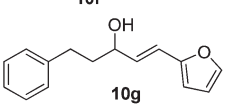
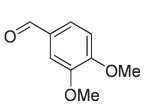
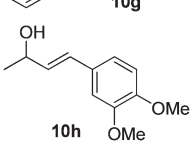
9a (R^1 = H, R^2 = Me) 51%, *E*:*Z* 81:19
9b (R^1, R^2 = $(CH_2)_4$) 44%, *E* > 99%
9c (R^1 = Me, R^2 = Ph) 39%, *E* > 99%
9d (R^1 = Me, R^2 = H) 63%, *E* > 99%

Scheme 3 Synthesis of dienols **9**.

Similarly, using aromatic aldehydes as the second aldehyde component led to single regio- and stereoisomeric aryl-substituted allylic alcohols **10** (Table 1).[14] Entry 8 illustrates the use of

Table 1 Formation of aryl-substituted allylic alcohols **10**



Entry	1st aldehyde	2nd aldehyde	Allylic alcohol	Yield (%)
1			 **10a**	46
2			 **10b**	41
3			 **10c**	67
4			 **10d**	59
5			 **10e**	60
6			 **10f**	49
7			 **10g**	56
8			 **10h**	65

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acetaldehyde and veratraldehyde in the direct synthesis of a simple natural product **10h**, originally isolated from the rhizomes of *Zingiber cassumunar*.[15]

The present work demonstrates the ability of methylenetriphenylphosphorane (**5**) to act as a methine trianion synthon,[7] connecting an aliphatic aldehyde with an α-branched α,β-unsaturated or aromatic aldehyde to give conjugated 1,2-disubstituted *E*-allylic alcohols.[16] We anticipate that this chemistry will find utility as a convenient method to access such allylic alcohols, due to the one-flask operation, commercial availability of all the reagents, together with the wide availability of aldehyde substrates.

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