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# Disubstituted *Z*-allylic esters by Wittig–Schlosser reaction using methylenetriphenylphosphorane†

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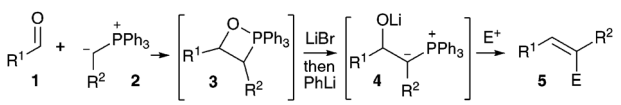
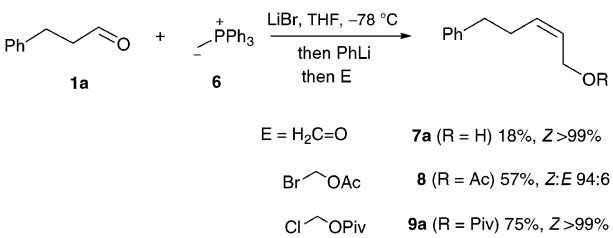
**β-Lithiooxyphosphonium ylides, generated *in situ* from aldehydes and methylenetriphenylphosphorane, react with halomethyl esters to form disubstituted allylic esters in good yields and with high *Z*-selectivity.**

Allylic alcohols and their derivatives are widely used in synthetic organic chemistry and, consequently, methods to access them from readily available starting materials and in an experimentally straightforward and, particularly, stereocontrolled manner are of value.[1] Two-carbon homologation of aldehydes to disubstituted *E*-allylic alcohols has been accomplished (for benzaldehyde) in low yield using the Wittig reagent from β-hydroxyethyl(triphenyl)phosphonium bromide,[2] and more efficiently by a Kocieński–Julia olefination approach.[3] Wittig–Schlosser methodology provides a direct way to make trisubstituted allylic alcohols **5** (E = $CH_2OH$, $R^2$ = alkyl, Scheme 1) and esters from aldehydes **1**.[4,5] It can be an efficient entry to such systems (particularly allylic esters),[5] and is highly *Z*-selective (typically >99 : 1). The process is believed to involve Li ion-promoted P–O cleavage in the first-formed oxaphosphetane **3**, followed by lithiation giving a β-lithiooxyphosphonium ylide **4**. This new ylide can be trapped at the ylidic carbon by a subsequently added electrophile (in this case formaldehyde, or an α-halomethyl ester), prior to elimination of $Ph_3PO$. Access to disubstituted allylic alcohols by this approach using methylenetriphenylphosphorane and formaldehyde was reported in the early 1970s by Schlosser and Coffinet as being inefficient (30–36%) and *E*-selective,[6] while the trapping with non-carbonyl-based electrophiles of the presumed intermediate β-lithiooxyphosphonium ylides which bear no further substitution at the ylidic carbon (**4**, $R^2$ = H) was considered to lack stereoselectivity.[4a,7] *Z*-Disubstituted allylic alcohols are typically prepared from aldehydes in 2 steps, by Still–Gennari or Ando olefination to give a *Z*-α,β-unsaturated ester[8] followed by 1,2-reduction, using DIBAL-H for example.[9] Despite the unencouraging early precedent using methylenetriphenylphosphorane, we believed that the combination of more recent advances in the generation of β-lithiooxyphosphonium ylides **4**, particularly using PhLi as the optimal base,[10] together with the use of a suitably reactive electrophile could lead to an efficient and stereoselective 2-carbon homologation of aldehydes using methylenetriphenylphosphorane to directly provide *Z*-disubstituted allylic esters and alcohols. Here we communicate our promising results on this theme.




**Scheme 1** Wittig–Schlosser reaction.

Initially, we carried out a Wittig–Schlosser reaction under optimal conditions[5,10,11] between hydrocinnamaldehyde (**1a**) and methylenetriphenylphosphorane (**6**), with PhLi-induced β-lithiooxyphosphonium ylide formation (−78 °C to room temperature), and trapping with monomeric[6a,12] formaldehyde at 0 °C (Scheme 2). In contrast to Schlosser and Coffinet's earlier studies,[6] this gave exclusively the corresponding *Z*-allylic alcohol **7a** (18% yield).[13] However, the *Z*-stereoselectivity is consistent with that seen in Wittig reactions using β-substituted-β-hydroxyethyl(triphenyl)phosphonium salts with aldehydes,[4b,c,14] and with that observed using methyl ketone substrates with methylenetriphenylphosphorane and formaldehyde.[15]




**Scheme 2** *Z*-Alkenes from aldehyde **1a** and methylenephosphorane **6**.

As noted earlier, we have recently reported that α-halomethyl esters are excellent electrophiles in the Wittig–Schlosser reaction, providing access to trisubstituted *Z*-allylic esters **5** (E = $CH_2O$acyl, $R^2$ = alkyl) from aldehydes **1**.[5] In the present chemistry, using bromomethyl acetate[16] (1.1 equiv.) instead of formaldehyde as the electrophile gave allylic acetate **8** in 57% yield and with high stereoselectivity (*Z* : *E* 94 : 6, Scheme 2).

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† 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/c0cc04429f

Improved yield and stereoselectivity was obtained when inexpensive chloromethyl pivalate was used, giving allylic pivalate **9a** (Piv = pivaloyl) in 75% yield, $Z > 99\%$.[17,18] The scope of the synthesis of disubstituted allylic pivalates **9** was then studied (Fig. 1).

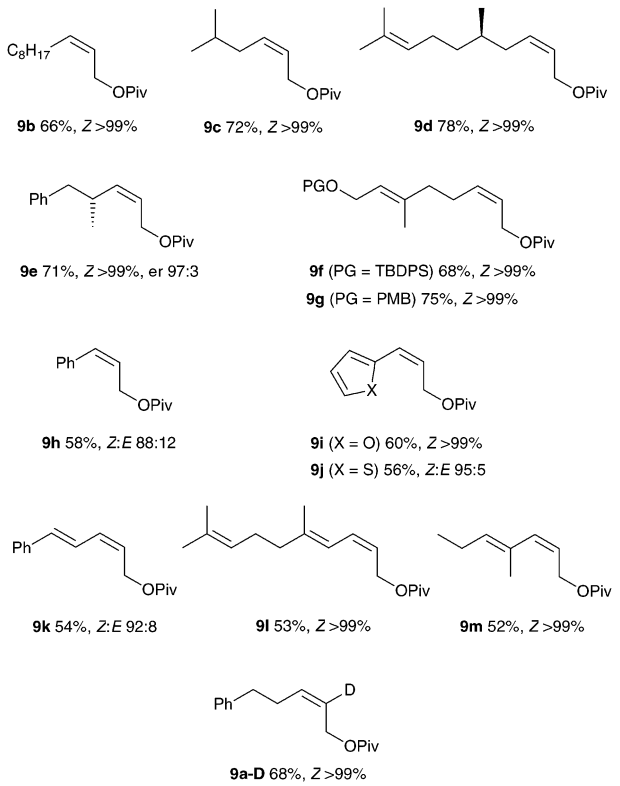
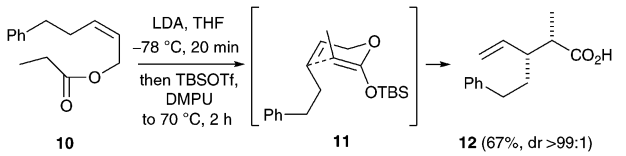



**Fig. 1** Other *Z*-allylic pivalates **9** synthesised.[13]

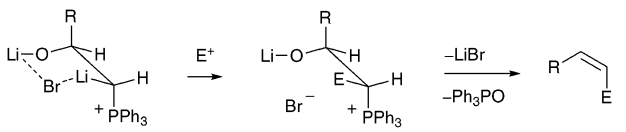
Aliphatic aldehydes gave uniformly excellent *Z*-selectivity (**9a–g**). The result for the α-branched system **9e**, indicates that a stereocentre α- to the aldehyde functionality can be tolerated without racemisation.[19] Silyl and MPM alcohol protection did not interfere with the homologation process (**9f,g**). Slight erosion of *Z*-selectivity was observed with certain aromatic aldehydes (**9h,j**). α,β-Unsaturated aldehydes possessing various substitution patterns proved to be viable substrates (**9k–m**), with a slight loss of *Z*-selectivity only being detected with extended aromatic conjugation (**9k**). Yields were slightly lower (by ~15%) for conjugated allylic pivalates (52–60% for **9h–m**), compared with those pivalates derived from aliphatic aldehydes (66–78% for **9a–g**). This may reflect more favourable direct elimination of $Ph_3PO$ from the first-formed oxaphosphetane **3** ($R^2$ = H), where the energy of the transition state for elimination is likely lowered due to developing conjugation. The methodology also provides a straightforward way to access a mono-deuterated *Z*-allylic pivalate such as **9a-D** (68% yield, $Z > 99\%$), by using the commercially available methyl-$D_3$-triphenylphosphonium iodide. While a disubstituted *Z*-allylic pivalate **9** might be required for a particular synthetic purpose,[20] if instead the corresponding allylic alcohol is desired then it can also be easily obtained: in an otherwise identical experiment to that for the synthesis of **9b**, the crude allylic pivalate **9b** was hydrolysed with KO*t*-Bu/$H_2O$ (2 : 1)[21] to give the corresponding *Z*-allylic alcohol **7b** (63% from nonanal) in a one-pot process.

The use of chloromethyl propionate[16] (1.1 equiv.) as the electrophile in the homologation procedure provided the enolisable allylic propionate **10** in 54% yield, $Z : E$ 99 : 1 (Scheme 3), which proved suitable for use in a completely diastereoselective Ireland–Claisen rearrangement.[22] The relative stereochemistry of the resulting γ,δ-unsaturated acid **12**, formed in 67% yield (dr >99%), was assigned on the basis of the intermediate *E*-silyl ketene acetal undergoing [3,3] sigmatropic rearrangement through a chair-like transition state **11**.




**Scheme 3** Ireland–Claisen rearrangement of allylic propionate **10**.

In conclusion, we have shown for the first time that simple methylenetriphenylphosphorane is capable of delivering good yields and high stereoselectivities in a three-component Wittig–Schlosser process. The origins of these favourable reaction characteristics may be a combination of efficient generation of a LiBr-complexed β-lithiooxyphosphonium ylide **13** (Scheme 4), bearing *anti*-disposed R and $Ph_3P$ groups, which also undergoes efficient electrophile trapping with retention of configuration (possibly aided by prior co-ordination of the electrophile to LiO). The resulting betaine **14** collapses with loss of LiBr and standard *syn*-elimination of $Ph_3PO$ to give the *Z*-alkene **15**. As all the reagents for this chemistry are commercially available (along with many aldehyde substrates)[23] and it is straightforward to carry out, we believe the methodology provides an attractive access to disubstituted *Z*-allylic esters and alcohols.




**Scheme 4** Possible origin of alkene stereochemistry.

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