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Dichotomous Reactivity in the Reaction of Triethyl- and Triphenylphosphane HBr Salts with Dimethyl Acetals: A Novel Entry to α-Alkoxy-Functionalized Ylides and General Synthesis of Vinyl Ethers and Alkoxy Dienes

Priyabrata Das[a] and James McNulty*[a]

Keywords: Alkenes / Wittig reactions / Enol ethers / Acetals

The discovery of dichotomous reactivity in the reaction of trialkyl- vs. triphenylphosphane HBr salts with acetals allows entry to functionalized α-methoxy phosphonium salts and a novel process for tertiary phosphane methylation. The new protocol opens a general entry to the synthesis of vinyl ethers and differentially substituted 1,3-dienes via Wittig reactions of the functionalized ylides derived from the α-methoxy phosphonium salts.

Enol ethers (**A**, Figure 1) and alkoxy-functionalized 1,3-dienes (**B** and **C**, Figure 1) play significant roles in synthetic organic chemistry as components in a variety of cycloaddition and other reactions.[1] In addition, enol ethers are occasionally found as constituent functional groups in bioactive natural products and analogs.[2] The classic approach to vinyl ether synthesis involved thermolysis and alcohol elimination from dialkyl ketals. Although of limited scope, a range of milder variants have been developed for this process.[3a–3e]

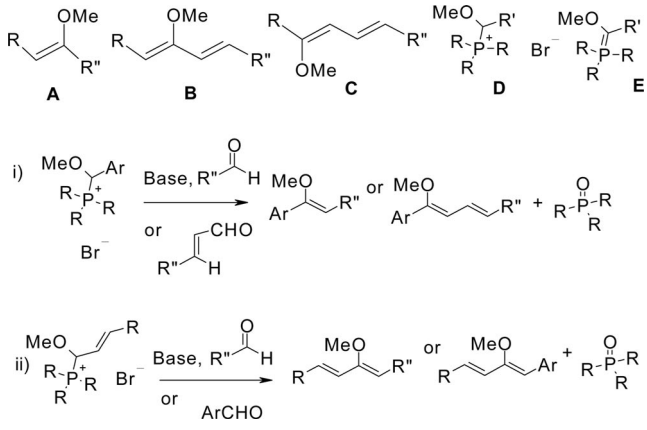

Figure 1. Synthesis and reactivity of α-alkoxy phosphonium salts.

Other general methods for vinyl ether synthesis include the Tebbe ester olefination reaction,[3f] metathesis reactions,[3g] Peterson olefination with α-alkoxysilanes,[3h] and the Greene method involving α-alkoxyphosphonate reduction.[3i] A direct Wittig-type entry toward the synthesis of functionalized vinyl ethers using simple α-alkoxy-functionalized ylides **E** derived from phosphonium salts **D** (R′ = alkyl, aryl) appears attractive, given the potential applications that can be envisioned (Figure 1, equations i and ii). Such a Wittig-type process has been realized in only limited cases. The use of ylides **E** derived from methoxymethyl phosphonium salts **E** (R′ = H), prepared from the reaction of a tertiary phosphane with chloromethyl methyl ether has been most often employed to prepare terminal methyl vinyl ethers and homologous aldehydes through their hydrolysis.[4]

The synthesis of α-alkoxy phosphonates and phosphonium salts has also been achieved from the reactions of α-halo ethers such as 2-chlorofuran and 2-chloropyran with a phosphite or triphenylphosphane respectively,[4d,4e] and also via strong acid promoted addition of triphenylphosphane to tetrahydropyran and ethyl vinyl ether.[4f,4g] A general preparation of α-alkoxy phosphonium salts of type **D** from the reaction of dimethyl acetals has not been reported. In this paper we report on the remarkable dichotomous reactivity of triphenylphosphane and triethylphosphane hydrobromide salts in their reactions with dimethyl acetals. Triphenylphosphane hydrobromide was found to react with dimethyl acetals, but the reaction proceeds to give the corresponding quaternary methyl(triphenyl) phosphonium salt (Figure 2). Remarkably, the reaction of triethylphosphane hydrobromide with dimethyl acetals was found to give the corresponding α-methoxy phosphonium salt. This new process is shown to be general allowing the synthesis of a range of α-methoxy functionalized phosphonium salts in high yield, under mild conditions. We also report the Wittig olefination of a range of examples with various aldehydes – see Figure 1, reactions i) and ii) – and the synthesis of structurally diverse enol ethers and alkoxy-substituted 1,3-dienes.

[a] Department of Chemistry and Chemical Biology, McMaster University,
1280 Main Street West, Hamilton, Ontario L8S 4M1, Canada
Fax: +1-905-522 2509
E-mail: jmcnult@mcmaster.ca

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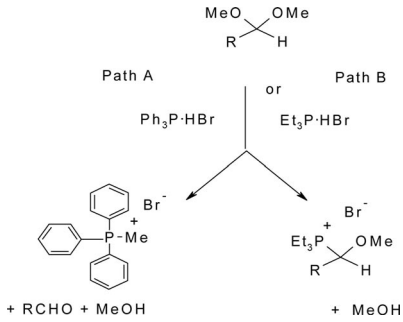
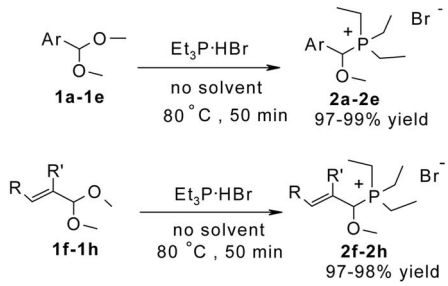


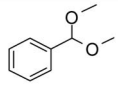
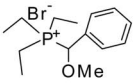
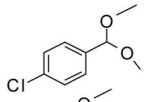
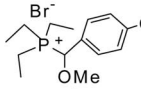
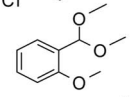
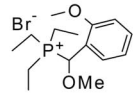
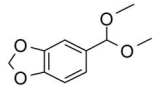
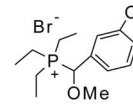
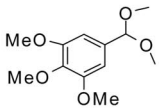
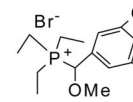
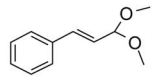
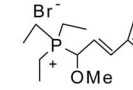
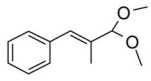
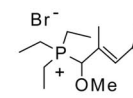
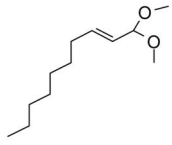
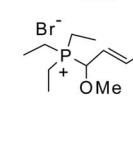
Figure 2. Dichotomous reactivity of dimethyl acetals with triphenyl- vs. triethylphosphane hydrobromide.

We have recently been exploring Wittig[5] reactions of tri*alkyl*phosphane-derived semi-stabilized ylides, prepared from allylic or benzylic alcohols or halides.[6] The reaction of a benzylic or allylic alcohol with anhydrous triethylphosphane hydrobromide was shown to proceed thermally to give the necessary phosphonium salt in high yields. In view of the problems and limitations described in the literature on the preparation and reactivity of α-alkoxy phosphonium salts,[4d,4e,4f,4g] we decided to explore a potential synthesis of α-alkoxy phosphonium salts from the reaction of triethylphosphane hydrobromide with a dimethyl acetal.

The reaction of benzaldehyde dimethyl acetal **1a** with triethylphosphane hydrobromide in a 1:1 ratio was found to proceed thermally, without solvent at 80 °C and was complete in under one hour. The product was determined to be the α-methoxy phosphonium salt **2a**. In contrast, the reaction of triphenylphosphane hydrobromide with **1a**, under identical conditions, yielded triphenyl(methyl)phosphonium bromide in essentially quantitative yield, a result we will return to momentarily. The successful synthesis of this initial α-methoxy phosphonium salt **2a** prompted us to explore the generality of the reaction of various dimethyl acetals with triethylphosphane hydrobromide. The reaction was found to proceed in identical fashion with all dimethyl acetals so far investigated providing access to the desired α-methoxy phosphonium salts in high yield. The synthesis of a selection of such salts, prepared from dimethyl acetals derived from aromatic aldehydes and α,β-unsaturated aldehydes, is summarized in Scheme 1. The reaction requires anhydrous conditions as both starting dimethyl acetals and resulting α-methoxy phosphonium salts are water-sensitive. The α-alkoxy phosphonium salts **2a**–**2h** were isolated without need of chromatographic purification through simply removing methanol under high vacuum. Tripropylphosphane and tributylphosphane hydrobromide salts reacted likewise with benzaldehyde dimethyl acetal producing the corresponding α-methoxyphosphonium salts.

We next investigated α-methoxy ylide formation and olefination of the range of substituted phosphonium salts **2a** to **2h** in reaction with one equivalent of the aromatic aldehyde anisaldehyde (Scheme 2). Dark red solutions of the ylides were generated in THF at 0 °C using lithium bistrimethylsilylazide (LHMDS, Scheme 2) and appeared to be

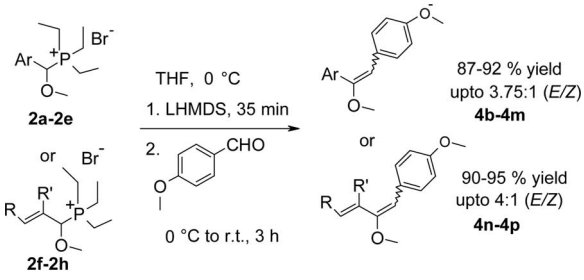


Entry	Acetal		Alkoxyphosphonium salt		% Yield
1		**1a**		**2a**	97
2		**1b**		**2b**	98
3		**1c**		**2c**	99
4		**1d**		**2d**	99
5		**1e**		**2e**	98
6		**1f**		**2f**	97
7		**1g**		**2g**	98
8		**1h**		**2h**	98

Scheme 1. Synthesis of α-methoxy phosphonium salts via direct thermolysis of dimethyl acetals with Et_3P·HBr.

relatively stable. Efficient olefination occurred in all cases upon addition of anisaldehyde and the corresponding vinyl ethers were purified by silica gel chromatography. The vinyl ethers **4** were isolated in 90–95% yields and with moderate to good (*E*)-configurational selectivity. Notably, this places the two aryl rings in a "*cis*" relationship as is found in the combretastatin series of anticancer stilbenes, a derivative of which is currently in human clinical trials.[7] The overall process described above (α-methoxyphosphonium salt synthesis, ylide formation and olefination) proceeded smoothly. The reactivity of α-alkoxy ylides prepared from vinyl ethers and equivalents has been reported to be problematic, with ylide decomposition and low yields of vinyl ethers obtained.[4d,4e,4f] These problems have usually been circumvented by switching to Horner phosphonate chemis-

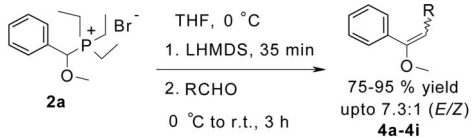
try.[4d–4g,8] Triethylphosphane HBr is only mildly acidic (pK_a = 8.69) and appears to provide the ideal chemoselectivity required for the success of this Wittig approach.



Entry	Methoxyphosphonium salt	Vinyl ether	% Yield	*E/Z*
1	**2a**	**4b**	90	3.75:1
2	**2b**	**4j**	92	2:1
3	**2c**	**4k**	87	1:1.5
4	**2d**	**4l**	90	2:1
5	**2e**	**4m**	92	2:1
6	**2f**	**4n**	90	3:1
7	**2g**	**4o**	95	4:1
8	**2h**	**4p**	93	4:1

Scheme 2. Olefination reactions of α-methoxy phosphonium salts with anisaldehyde.

We next investigated the scope of the Wittig reactions of the ylide derived from α-methoxyphenyl-triethyl phosphonium bromide **2a** with a range of aldehydes **3a** to **3i**, summarized in Scheme 3. In all cases, the methoxy vinyl ethers **4a** to **4i** were isolated by silica gel chromatography in yields of 75 to 95% with moderate to high (*E*)-stereocontrol. The reaction was successful with electron rich and electron deficient aromatic aldehydes, as well as an enolizable aliphatic aldehyde (entry 9). The success of the reaction with the α,β-unsaturated aldehyde (*E*)-cinnamaldehyde (Scheme 3, entry 4) allows entry to functionalized 1-methoxy-1,3-butadienes. In contrast, the use of the α-methoxy ylide derived from (*E*)-cinnamaldehyde in reaction with an aldehyde (Scheme 2, entries 6 and 7) provides access to the corresponding functionalized 2-methoxy-1,3-butadienes. Overall, the results shown in Schemes 2 and 3 indicate that all combinations of the general reactivity outlined in Figure 1 (see equations i and ii) are possible and the synthesis of a wide range of vinyl ethers and functionalized 1,3-butadienes can be contemplated using this method.



Entry	RCHO		Vinyl ether		% Yield	*E/Z*
1		**3a**		**4a**	90	3.75:1
2		**3b**		**4b**	91	3:1
3		**3c**		**4c**	95	7.3:1
4		**3d**		**4d**	89	1.8:1
5		**3e**		**4e**	94	1.1:1
6		**3f**		**4f**	93	2:1
7		**3g**		**4g**	90	2.1:1
8		**3h**		**4h**	91	5.25:1
9		**3i**		**4i**	75	0.9:1

Scheme 3. Olefination reactions of the ylide from α-methoxyphenyl phosphonium bromide with various aldehydes.

In returning to the unprecedented dichotomous chemoselectivity outlined in Figure 2, it was of interest to investigate the scope of this unusual process. Trialkyl(methyl)-phosphonium salts are frequently used as phase-transfer catalysts and are components of commercial ionic liquids.[9] In addition, they are employed in industrial processes such as the Monsanto acetic acid process and Eastman acetic anhydride process, both of which involve the carbonylation of methanol.[10] Their synthesis generally involves quaternization of a tertiary phosphane with toxic and reactive methylating agents such as iodomethane, methyl tosylate or dimethyl sulfate. We decided to investigate this dichotomy further and now report a remarkably simple green approach towards the methylation of tertiary phosphanes that employs only trimethyl orthoformate as the electrophilic meth-

ylating agent. Protonation and loss of methanol from the dimethyl acetal is expected to generate the oxonium cation shown (**i**), Figure 3.

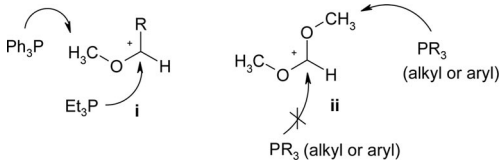
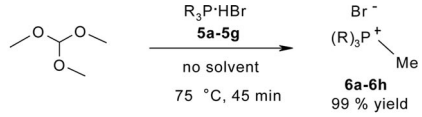
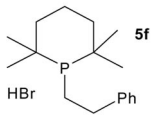
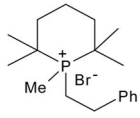


Figure 3. Dichotomous reactivity of Et_3P and Ph_3P with oxonium intermediates **i** and **ii**.

The dichotomy observed in the phosphane alkykylation is very clear cut. Triphenylphosphane attacks the methyl group rather than forming the α-alkoxy phosphonium salt, a result that can be ralionalized in view of both steric considerations and the soft nature of the nucleophile/electrophile. Conversely, the strongly nucleophilic triethylphosphane directly attacks the cationic site producing the alkoxy phosphonium salt. Triphenylphosphane hydrobromide was found to react with *any* dimethyl acetal, yielding the *P*-methyl phosphonium salt. These results prompted us to investigate the reaction with trimethyl orthoformate, which would be expected to generate the softer bis-methoxy-substituted oxonium ion shown (**ii**). Reaction with triphenylphosphane hydrobromide and triethylphosphane hydrobromide *both* now generated the corresponding *P*-methyl phosphonium salts, with no α-alkoxy salts being observed. It appears that either the reversibility of the α-alkoxy phosphonium salt formation with cation (**ii**) or decreased hard nature of the cation, in conjunction with steric effects, direct alkylation to the methyl termini rather than central cation. Interestingly, triphenylphosphane hydrobromide did not enter into reaction with triisopropyl orthoformate under the same conditions, indicating that the reaction is in fact subject to a considerable steric effect. The present *P*-methylation appears to be restricted to methoxy containing acetals. In view of the importance of trialkylmethyl and triarylmethyl phosphonium salts described above, we investigated the generality of this reaction and now report that any tertiary phosphane hydrobromide salt can be readily methylated in this fashion to yield the desired quaternary salt, summarized in Scheme 4. Increasing the steric demands around the tertiary phosphane had no impact on the course of the methylation (from **ii**) as even tri-*tert*-butylphosphane (entry 5) and the hindered cyclic phosphorinane (entry 6) HBr salts reacted to deliver the *P*-methyl quaternary salt in very high yield. This general method for *P*-methylation using inexpensive, readily available trimethyl orthoformate is a very attractive alternative to the use of toxic, methylating agents (CH_3I, DMS etc), alkylating agents that are the subject of strict regulations in many jurisdictions.

In conclusion, we have discovered the dichotomous reactivity of triethylphosphane hydrobromide in its reaction with dimethyl acetals as a general reaction leading to α-methoxy phosphonium salts. In contrast, triphenylphosphane hydrobromide is methylated under these conditions.



Entry	$(R)_3P{\cdot}HBr$		Methylated phosphonium salt		% Yield
1	$Et_3P{\cdot}HBr$	**5a**	$Et_3\overset{+}{P}Me\ Br^-$	**6a**	99
2	$nPr_3P{\cdot}HBr$	**5b**	$nPr_3\overset{+}{P}Me\ Br^-$	**6b**	99
3	$nBu_3P{\cdot}HBr$	**5c**	$nBu_3\overset{+}{P}Me\ Br^-$	**6c**	99
4	$iBu_3P{\cdot}HBr$	**5d**	$iBu_3\overset{+}{P}Me\ Br^-$	**6d**	99
5	$tBu_3P{\cdot}HBr$	**5e**	$tBu_3\overset{+}{P}Me\ Br^-$	**6e**	99
6		**5f**		**6f**	99
7	$Ph_3P{\cdot}HBr$	**5g**	$Ph_3\overset{+}{P}Me\ Br^-$	**6g**	99

Scheme 4. Quaternization reactions of tertiary phosphane hydrobromide salts using trimethyl orthoformate as electrophilic methylating agent.

Ylide formation/olefination reactions from the α-methoxy phosphonium salts so formed allowed for the synthesis of a wide range of vinyl ethers and variously functionalized 1,3-dienes. These studies led to the discovery of a novel, general *P*-methylation process for the production of useful quaternary phosphonium salts that avoids the use of toxic, regulated alkylating agents. Further investigations into the preparation and reactivity of these salts and applications of the vinyl ether products are under investigation in our laboratory.

Supporting Information (see also the footnote on the first page of this article): General experimental details, synthetic protocols for acetal formation, α-alkoxy phosphonium salt formation and Wittig reactions and characterization of the salts, enol ether and 1,3-diene products reported in the tables.

Acknowledgments

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