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[3,3]-Rearrangements of Phosphonium Ylides

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Ylides of phosphorus, sulfur, and nitrogen readily participate in olefination and ring-forming reactions.[1] Although sulfonium and ammonium ylides are also well-known to undergo synthetically useful thermal rearrangements, rearrangements of the corresponding phosphonium ylides have rarely been observed.[1c] We report here a unique reaction manifold for phosphonium ylides, a [3,3]-sigmatropic rearrangement by which a new C−C bond is generated. This process provides rapid access to phosphonates of diverse and complex structure. These products are valuable intermediates for the preparation of α-amino phosphonic acids[2] (amino acid mimics) and a variety of complex natural products.

The earliest characterized example of a phosphonium ylide rearrangement was reported by Baldwin and Armstrong who demonstrated that upon heating, ylide **1** underwent a [2,3]-rearrangement to provide a 7% yield of **2**, along with a number of additional products (Figure 1).[3] Little progress has since been reported, likely due to the apparent propensity of phosphonium ylides to undergo decomposition at the temperatures required for rearrangement.[1c,4] We hypothesized that structures such as **3** containing an allyloxy substituent would undergo a [3,3]-rearrangement in which the product **4** would be favored thermodynamically due to the formation of the P═O bond. In addition, incorporation of the oxygen should increase the leaving group ability of the phosphorus-containing moiety, thus lowering the energetic barrier of the rearrangement.[5]

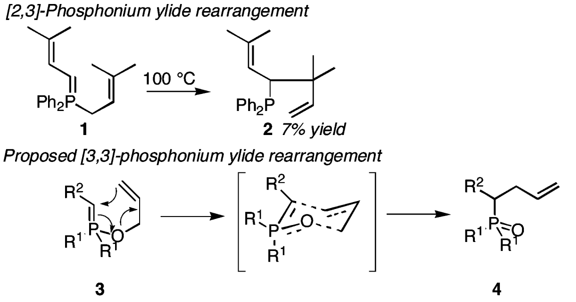
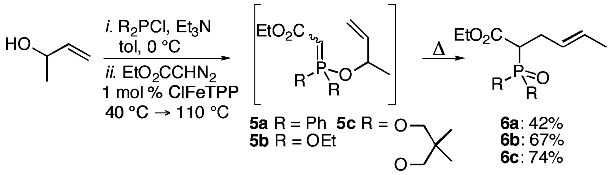


Figure 1. Phosphonium ylide rearrangements.

Investigation of our hypothesis required generation of the appropriate ylide intermediates, such as **3** (Figure 1), historically elusive due to the propensity with which they undergo dealkylation to produce phosphonates.[1] Recently, however, the reaction of phosphines and phosphites with transition-metal-generated carbenes has been shown to produce the desired ylides under mild conditions.[6] In our initial studies, generation of the ylide in situ was thus accomplished by first combining 3-buten-2-ol and an activated phosphorus(III) species followed by the addition of ethyl diazoacetate and 1 mol % of 5,10,15,20-tetraphenyl-21*H*,23*H*-porphine iron(III) chloride (ClFeTPP) to the reaction mixture (Scheme 1). Monitoring of reaction progress by ^{31}P NMR revealed that upon heating to 40 °C for 1 h, complete conversion to ylide **5** occurred.[7] Increasing the temperature of the reaction mixture then facilitated the [3,3]-rearrangement to provide the target product **6** in good overall yield. Similar to the related [3,3]-rearrangement of allylic phosphorimidates, the yield of the phosphonium ylide rearrangement is greater when the phosphorus bears alkoxy substituents (**6b**, 67%; **6c**, 74%) relative to carbon (**6a**, 42%).[8] Although heating the reaction mixture to 110 °C increases reaction efficiency, temperatures in excess of 140 °C lead to significantly lower yields. For example, the yield of **6c** was 54% at 140 °C, and products consistent with carbene dimerization were observed.

Scheme 1



The reaction conditions were applied to a variety of substrates and afforded a diverse group of phosphonates in good to excellent yields (Table 1). Substitution on the olefin is well tolerated, with monosubstituted (entries 1−3, 6) and 1,1-disubstituted (entries 4, 5) allylic ylides undergoing the rearrangement. 1,2-Substitution on the olefin also has no significant effect on reactivity, and compounds **13**−**15** are produced via the rearrangement in good yields. In addition, the carbene source is not limited to ethyl diazoacetate as (trimethylsilyl)diazomethane can also be employed in this capacity with excellent results (entries 1−10). Although significantly more sterically hindered than ethyldiazoacetate-derived ylides, the isolated yields of the TMS-containing phosphonates are generally higher. Since a broad range of carbene precursors can be generated from inexpensive starting materials,[9] the rearrangement will provide access to phosphonate products with a diversity of α-substituents.

With secondary allylic alcohols as the starting material (entries 2, 3, 6, 7), products with only *E*-olefin geometry are observed, suggestive of a chair-like, six-membered transition state for the rearrangement. Somewhat unexpectedly, incorporation of additional substitution on the olefin (entries 7−10) provides the desired products in good overall yield but as a mixture of diastereomers. Theoretical computations (DFT B3LYP/6-31G*) on a model ylide located a chair-like transition state 16.6 kcal/mol in energy above the starting ylide (see Supporting Information for details); however, there was little difference in energy between chair-like transition states with the ylide substituent in the axial versus equatorial positions. This is most likely due to a relatively long C−P bond (1.64 Å) that minimizes 1,3-diaxial interactions and interactions between the ylide and olefin substituents in the transition state. Fortuitously, diastereoselectivity in this context is a relatively unimportant consideration because, for most applications, the α-stereocenter will be destroyed or modified in subsequent transformations (vide infra). Among the disubstituted olefins investigated, cyclohexene-1-ol is also a good substrate for this reaction (entry 10), with phosphonate **15a** isolated in 62% yield; this is a

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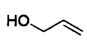
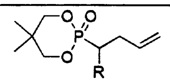
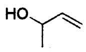
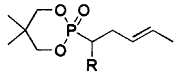
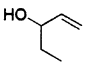
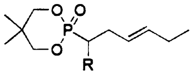
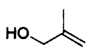
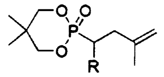
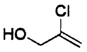
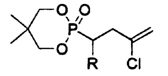
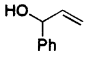
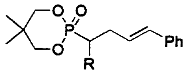
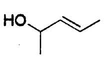
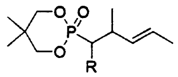
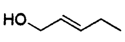
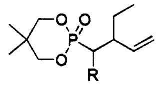
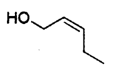
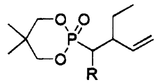
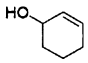
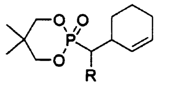
Table 1. Scope of the Rearrangement

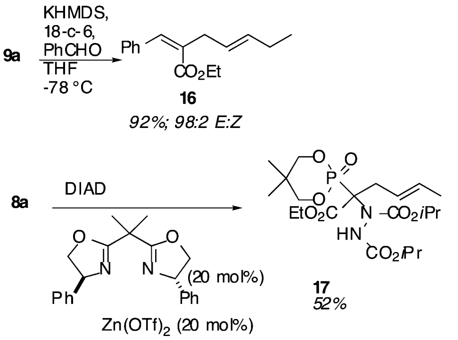
entry	substrate	product a: R = CO_2Et b: R = $SiMe_3$	yield[c]
1		 **7**	**7a** 86%[a] **7b** 90%[b]
2		 **8**	**8a** 79%[a] **8b** 88%[b]
3		 **9**	**9a** 84%[a] **9b** 83%[b]
4		 **10**	**10a** 71%[a] **10b** 82%[b]
5		 **11**	**11a** 73%[a] **11b** 77%[b]
6		 **12**	**12a** 79%[a] **12b** 78%[b]
7		 **13**	**13a** 76%[a] d.r. 1.3:1 **13b** 72%[b] d.r. 2:1
8		 **14**	**14a** 77%[a] d.r. 1.9:1 **14b** 78%[b] d.r. 3:1
9		 **14**	**14a** 68%[a] d.r. 1:1 **14b** 83%[b] d.r. 1:1
10		 **15**	**15a** 62%[a] d.r. 1:1 **15b** 73%[b] d.r. 2:1

[a] Conditions: (i) Allylic alcohol substrate (1 equiv), chlorophosphite (1 equiv), and Et_3N (1 equiv), tol, 0 °C, 1 h. (ii) Ethyl diazoacetate (1.2 equiv), 1 mol % of ClFeTPP, 40 °C, 1 h → 110 °C, 7 h. [b] Conditions: (i) Allylic alcohol substrate (1 equiv), chlorophosphite (1 equiv), and Et_3N (1 equiv), tol, 0 °C, 1 h. (ii) Trimethylsilyldiazoacetate (1.2 equiv), 1 mol % of ClFeTPP, 40 °C, 1 h → 110 °C, 7 h. [c] Isolated yields.

particularly notable case as phosphonates such as **15a** are excellent intermediates for the butyrolactone-containing family of natural products.[10]

The phosphonium ylide rearrangement affords entry into a range of desirable synthetic targets (Scheme 2). For example, employment of phosphonates such as **9a** in a Horner−Wadsworth−Emmons reaction produces nonsymmetrical, skipped dienes (**16**, for example) in excellent yields and high stereoselectivity (see Supporting Information for additional details). In addition, the phosphonates are excellent substrates for conversion into α-aminophosphonic esters via amination[2c] (**17**, for example). The tandem [3,3]-rearrangement−amination sequence should thus provide ready access to chiral, nonracemic aminophosphonic esters and acids. Such structures are in wide use as haptens for antibody generation, amino acid mimics, and as enzyme inhibitors.[11]

Scheme 2



In summary, we have reported a unique [3,3]-rearrangement of phosphonium ylides that provides access to phosphonates of complex structure and wide ranging synthetic utility. Current investigations are focused upon asymmetric variants of this reaction, and results will be reported in due course.

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Supporting Information Available: Experimental procedures and characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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