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# A Phosphorimidate Rearrangement for the Facile and Selective Preparation of Allylic Amines

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[3,3]-Sigmatropic rearrangements have long been a mainstay of synthetic organic chemistry due to the relative ease with which carbon−carbon bonds can be assembled with excellent regio- and stereocontrol to produce structurally complex targets.[1] In contrast, there are few such rearrangements available for selective carbon−nitrogen bond formation despite the enormous potential of such methods for the synthesis of molecules containing nitrogen-bearing stereocenters.[2] We describe here a phosphorimidate-to-phosphoramidate [3,3]-rearrangement for the controlled formation of carbon−nitrogen bonds, including quaternary centers. This novel transformation is readily carried out in one pot, starting from readily available allylic alcohols and thus provides rapid access to single isomers of allylic amines,[3,4] essential building blocks of structurally complex targets such as α- and β-amino acids, lactams, and alkaloid natural products.[3]

Simple phosphylimidates **1** are known to rearrange to phosphylamidates **2** either thermally or through electrophilic catalysis, with the formation of the phosphorus−oxygen double bond driving the process (Figure 1).[5] Under both conditions, reaction is believed to proceed in a bimolecular fashion through initial alkylation of the imidate nitrogen.[5] We reasoned that substitution of one of the ester groups of the phosphylimidate intermediates with an allyl substituent as in **3** would provide an *intra*molecular manifold by which the rearrangement could proceed with a 1,3-transposition of functionality to provide a protected allylic amine (**4**).[6]

The substrates for this rearrangement are readily prepared in situ by the Staudinger reaction between azides and phosphines or phosphites (Table 1)[7,8] The phosphorus substituents as well as the solvent polarity play central roles in the reaction pathway. For example, with phenyl substituents on the phosphorus (entries 1 and 2), the major isolated product was the undesired regioisomer **7a**, most likely obtained via the intermolecular reaction pathway. In polar solvents such as acetonitrile (entry 1), **7a** was the only phosphoramidate product isolated. Increasing the reaction temperature and decreasing solvent polarity had the combined effect of increasing overall conversion and produced a 2:3 mixture of the desired allylic amine **6a** to the undesired **7a**.

The introduction of ethoxy substituents on the phosphorus resulted in a substantial yield increase of **6b** (55%) with no **7b** observed in the crude reaction mixture (Table 1, entry 3). Increasing the steric bulk around the phosphorus by replacing the ethyl groups with a 2,2-dimethylpropyl group provided a further boost in yield (88%). Similar to the results obtained with **5a**, the reaction pathway from **5c** was strongly dependent upon solvent polarity as changing the solvent to acetonitrile from xylenes provided only a low yield (14%) of the undesired primary allylic amine **7c**. The temperature at which the reaction is run also plays an important role; the use of benzene or toluene, while providing only the desired product, gave low yields. Preliminary data suggest that the need for the greater reaction temperatures stems in part from the attenuated reactivity of the phosphite in the Staudinger reaction step.[8]

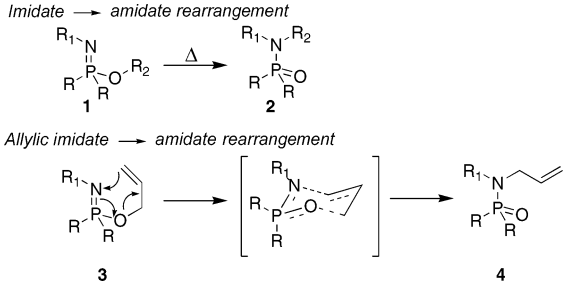
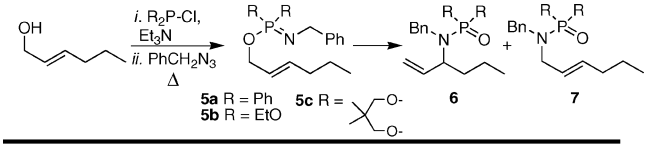



***Figure 1.*** Allylic imidate-to-amidate rearrangement.

***Table 1.*** Optimization of the Rearrangement




| Entry[a] | R | Solvent | Temp. | Yield of **6**[b] | Yield of **7**[b] |
|---|---|---|---|---|---|
| 1 | Ph | $CH_3CN$ | 80 °C | --- | 30% |
| 2 | Ph | Xylenes | 140 °C | 17% | 23% |
| 3 | EtO | Xylenes | 140 °C | 55% | ---- |
| 4 |  | Xylenes | 140 °C | 88% | ---- |

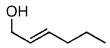
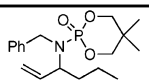
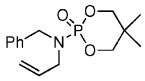
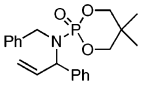
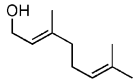
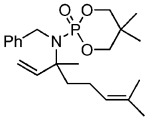
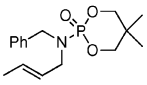
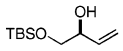
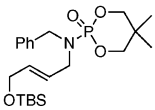
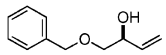
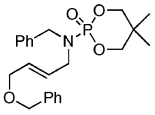
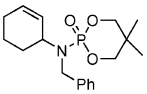
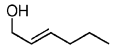
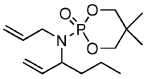
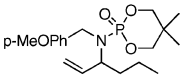
[a] Conditions: *i*. *E*-2-hexen-1-ol (1.25 equiv), 1.25 equiv of the diphenylchlorophosphine (entries 1 and 2) or chlorophosphite (entries 3 and 4) and 1.25 equiv of $Et_3N$ in $Et_2O$; 0 °C, 20 min. *ii*. Benzyl azide (1 equiv), reflux, 4 h. [b] Isolated yields. Identity of **6** and **7** confirmed by conversion to the benzyl-protected amine and comparison with an authentic sample.

This new [3,3]-rearrangement is tolerant of substitution on the allyloxy moiety, providing good to excellent yields of allylic phosphoramidates with a variety of substituents (Table 2). Both *E*- and *Z*-olefins are effective substrates in the reaction, as *E*-2-hexen-1-ol and *Z*-2-hexen-1-ol each produce allylic phosphoramidate **6c** in comparable yields (entries 1 and 2). Remarkably, quaternary stereocenters may also be formed in this reaction, as demonstrated by the rearrangement of a geraniol-derived phosphorimidate to provide **10** (entry 5). Consistent with a sigmatropic process, the phosphorimidate derived from 3-buten-2-ol (entry 6) undergoes rearrangement to **11** with >20:1 selectivity for the *E*-olefin-containing product. Furthermore, other C1 substituents are also well tolerated (entries 7 and 8). Despite reduced conformational flexibility, cyclic allylic alcohols also undergo rearrangement upon conversion to phosphorimidates to provide useful amines such as **14** (entry 9).

An attractive feature of the phosphorimidate rearrangement is that the product contains a fully protected amine amenable to subsequent reaction sequences. One of the protecting groups is derived from the azide precursor and can thus be easily varied. Benzyl azide, *p*-methoxybenzyl azide, and allyl azide each serve as effective azide sources in the reaction and provide several choices


10.1021/ja0490469 CCC: $27.50 

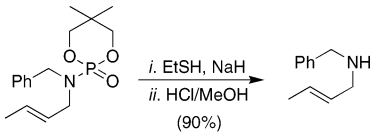
***Table 2.*** Scope of the Rearrangement[a]

| Entry | Allylic alcohol | Azide | Product | Yield[c] |
|---|---|---|---|---|
| 1 |  | Bn-$N_3$ |  **6c** | 88% |
| 2 |  | | **6c** | 75% |
| 3 |  | |  **8** | 80% |
| 4 |  | |  **9** | 70% |
| 5 |  | |  **10** | 60% |
| 6 |  | |  **11** | 70%[d] |
| 7 |  | |  **12** | 55%[d] |
| 8 |  | |  **13** | 65%[d] |
| 9 |  | |  **14** | 65% |
| 10[b] |  | allyl-$N_3$ |  **15** | 60% |
| 11 | | PMB-$N_3$ |  **16** | 80% |

[a] Conditions as described in Table 1. Additional details are available in the Supporting Information. [b] Due to the volatility of allyl azide, an excess (3 equiv) was used. [c] Isolated yield after purification. [d] The *E*-olefin isomer was produced with >20:1 selectivity as determined by $^1$H NMR analysis of the crude reaction mixture.

for the final protecting group (Table 2, entries 10 and 11). The amine is also protected as a phosphoramidate, an excellent protecting group imparting stability under a variety of reaction conditions.[9] It can readily be removed, however, by treatment with a nucleophilic thiol[10] followed by acid hydrolysis.[11] In the case of phosphoramidate **11**, for example, treatment with ethanethiolate followed by HCl/MeOH provided the benzyl-protected amine product in excellent (90%) yield.

In summary, we have disclosed a unique [3,3]-rearrangement of allylic phosphorimidates to phosphoramidates as a facile and




**11**

selective approach to allylic amines. This reaction is tolerant of a range of substitution patterns, and by choosing appropriate combinations of reactants (allylic alcohol and azide source), the preparation of a wide range of allylic amine products can readily be envisioned. It thus serves as a valuable and versatile addition to the current approaches for the preparation of these valuable synthetic intermediates.

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**Note Added in Proof.** A related transformation catalyzed by palladium was recently communicated by Batey and Lee. See *Angew. Chem., Int. Ed.* **2004**, *43*, 1865−1868.

**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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