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Thermal and Catalyzed [3,3]-Phosphorimidate Rearrangements

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Abstract: [3,3]-Sigmatropic rearrangements have been widely utilized for the synthesis of structurally complex organic molecules because of the ease with which carbon−carbon bonds are formed in a regio- and stereocontrolled manner. However, there are far fewer [3,3]-rearrangements available for the selective formation of carbon−nitrogen bonds despite the enormous potential of such reactions for the preparation of stereodefined allylic amines. We describe here the scope and mechanism of a [3,3]-rearrangement of allylic phosphorimidates that provides access to stereodefined allylic amines of diverse structure. The reactive intermediate in the reaction, an allylic phosphorimidate, is produced in situ through the combination of readily available starting materials (allylic alcohols, chlorophosphites, and organic azides), rendering the reaction an efficient three-component process. Analogous to other [3,3]-rearrangements, the stereochemistry in an allylic alcohol starting material is transferred with fidelity to the allylic amine product and, further, allylic amines are produced as single olefin isomers. In addition, a crossover experiment indicates that the rearrangement is an intramolecular process. Finally, activation of the allylic moiety either through incorporation of electron-deficient functional groups or through the use of a transition-metal catalyst significantly facilitates the reaction and consequently the preparation of a wider range of substitution patterns.

Introduction

Since the first report of the Claisen rearrangement, numerous [3,3]-sigmatropic rearrangements leading to the selective formation of carbon−carbon bonds have been developed.[1−3] Because of their exquisite regio- and stereocontrol, these reactions have been widely employed for the synthesis of complex organic molecules.[1−3] In contrast, the development of [3,3]-sigmatropic rearrangements for the formation of carbon−nitrogen bonds has been considerably slower, despite the enormous potential of such reactions for the synthesis of molecules containing nitrogen-bearing stereocenters. The prototype for this reaction class is the Overman thermal rearrangement of allylic trichloracetimidates, a reaction that provides allylic amines protected as acetamides with excellent regio- and stereocontrol.[4,5] Stereodefined allylic amines are essential building blocks of important targets such as α- and β-amino acids, lactams, and alkaloid natural products.[6] The development of novel reaction manifolds that employ readily generated precursors and provide access to a wide range of substitution patterns thus remain highly desirable.[7]

Toward that end, we recently reported a thermally driven [3,3]-sigmatropic rearrangement of allylic phosphorimidates for the synthesis of protected allylic amines of varying structure.[8] The concept of this reaction arose from the rearrangement of phosphorimidates to phosphoramidates that occurs readily under thermal conditions (Figure 1).[9] As demonstrated by Challis and co-workers, this is an intermolecular reaction with one imidate undergoing nucleophilic attack by the nitrogen of a second imidate molecule.[10] We reasoned that replacement of one of the phosphorimidate ester groups with an allyl substituent would provide an *intra*molecular manifold by which the reaction could proceed. The intramolecular reaction would thus lead to a 1,3-transposition of functionality to provide a protected allylic

(1) Wipf, P. In *Comprehensive organic synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, 1991; Vol. 5, p 827.
(2) Ziegler, F. E. *Chem. Rev.* **1988**, *88*, 1423−1452.
(3) Bennett, G. B. *Synthesis* **1977**, 589−606. Bartlett, P. A. *Tetrahedron* **1980**, *36*, 3−72. Lutz, R. P. *Chem. Rev.* **1984**, *84*, 205−247. Nubbemeyer, U. *Synthesis* **2003**, 961−1008. Castro, A. M. M. *Chem. Rev.* **2004**, *104*, 2939−3002. Ito, H.; Taguchi, T. *Chem. Soc. Rev.* **1999**, *28*, 43−50.
(4) Overman, L. E. *J. Am. Chem. Soc.* **1974**, *96*, 597−599. Overman, L. E. *Acc. Chem. Res.* **1980**, *13*, 218−224.
(5) Overman, L. E. *J. Am. Chem. Soc.* **1976**, *98*, 2901−2910.
(6) For example see: Johannsen, M.; Jorgensen, K. A. *Chem. Rev.* **1998**, *98*, 1689−1708. Cativiela, C.; Diaz-de-Villegas, M. D. *Tetrahedron: Asymmetry* **1998**, *9*, 3517−3599. Petranyi, G.; Ryder, N. S.; Stutz, A. *Science* **1984**, *224*, 1239−1241. Burgess, K.; Ohlmeyer, M. J. *J. Org. Chem.* **1991**, *56*, 1027−1036. Vedejs, E.; Gingras, M. *J. Am. Chem. Soc.* **1994**, *116*, 579−588. Johnson, T. A.; Curtis, M. D.; Beak, P. *J. Am. Chem. Soc.* **2001**, *123*, 1004−1005.
(7) For recent examples see: Wipf, P.; Kendall, C.; Stephenson, C. R. J. *J. Am. Chem. Soc.* **2003**, *125*, 761−768. Patel, S. J.; Jamison, T. F. *Angew. Chem., Int. Ed.* **2003**, *42*, 1364−1367. Pawlas, J.; Nakao, Y.; Kawatsura, M.; Hartwig, J. F. *J. Am. Chem. Soc.* **2002**, *124*, 3669−3679. Matsushima, Y.; Onitsuka, K.; Kondo, T.; Mitsudo, T.; Takahashi, S. *J. Am. Chem. Soc.* **2001**, *123*, 10405−10406. Evans, P. A.; Robinson, J. E.; Nelson, J. D. *J. Am. Chem. Soc.* **1999**, *121*, 6761−6762. Petasis, N. A.; Zavialov, I. A. *J. Am. Chem. Soc.* **1998**, *120*, 11798−11799. Denmark, S. E.; Nakajima, N.; Nicaise, O. J. C. *J. Am. Chem. Soc.* **1994**, *116*, 8797−8798. Grossman, R. B.; Davis, W. M.; Buchwald, S. L. *J. Am. Chem. Soc.* **1991**, *113*, 2321−2322. Buchwald, S. L.; Watson, B. T.; Wannamaker, M. W.; Dewan, J. C. *J. Am. Chem. Soc.* **1989**, *111*, 4486−4494. Hayashi, T.; Yamamoto, A.; Ito, Y.; Nishioka, E.; Miura, H.; Yanagi, K. *J. Am. Chem. Soc.* **1989**, *111*, 6301−6311 and references therein.
(8) Chen, B.; Mapp, A. K. *J. Am. Chem. Soc.* **2004**, *126*, 5364−5365.
(9) Challis, B. C.; Frenkel, A. D. *J. Chem. Soc., Chem. Commun.* **1972**, 303−308.
(10) Challis, B. C.; Challis, J. A.; Iley, J. N. *J. Chem. Soc., Perkin Trans. 2* **1978**, 813−818.

10.1021/ja050759g CCC: $30.25

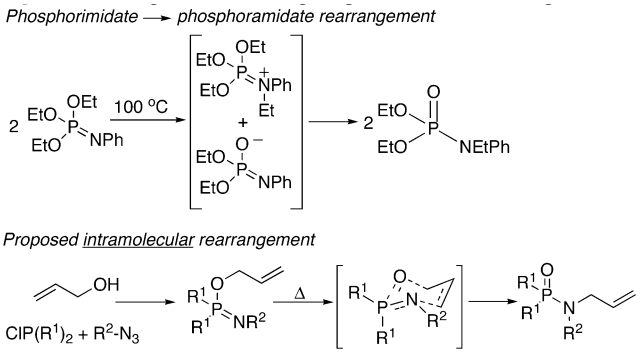


Figure 1. Phosphorimidate to phosphoramidate rearrangement.

amine. The advantage of this approach is that the key intermediate, a phosphorimidate, can be readily prepared in situ by the combination of an allylic alcohol, a chlorophosphite, and an azide, making this reaction an efficient three-component entry into a variety of allylic amines. Concurrent with our report, Batey and co-workers reported a similar reaction in which a thermally inert phosphylimidate derivative is first isolated and then treated with a Pd(II) catalyst to initiate a 1,3-transposition of functionality; presumably, this occurs through a stepwise mechanism analogous to the metal-catalyzed variant of the allylic acetimidate rearrangement.[11]

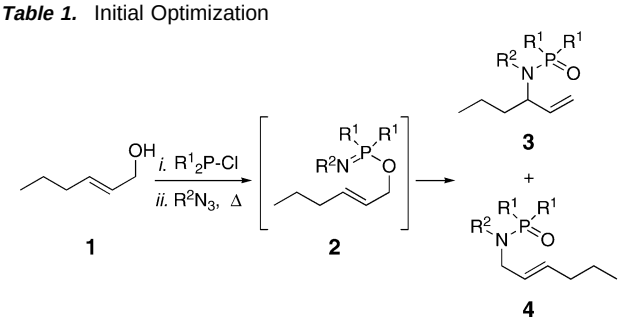
Here, we provide a more complete description of the scope and mechanism of the allylic phosphorimidate → phosphoramidate rearrangement. Because of its substrate tolerance and the ready availability of the reactants (allylic alcohol, chlorophosphite, and azide), the rearrangement is applicable to a wide range of allylic amines. This includes typically challenging synthetic targets such as those containing nitrogen-bearing quaternary stereocenters as well as precursors to β-amino acids. Enhancing its general utility, the allylic amines are produced as single olefin isomers, and efficient stereochemical transfer from an allylic alcohol starting material to the product allylic amine is observed; in addition, we provide experimental and computational evidence consistent with a concerted, intramolecular mechanistic pathway for the reaction. Further, we find that the thermal accessibility of the rearrangement is strongly influenced by the substituents on the imidate nitrogen, with electron-deficient phosphorimidates requiring activation of the allylic moiety. This can be accomplished either through appropriate substitution of the double bond or through the inclusion of a catalytic amount of a Pd(II) salt in the reaction solution. These studies provide a framework by which a wider range of nitrogen substitution patterns can be readily accessed and, further, paves the way for the future development of catalytic, asymmetric variants of the reaction.

Results and Discussion

Initial Studies of the Thermal Rearrangement. The goal at the outset of the investigation was the identification of the appropriate phosphorus substituents and reaction conditions that would promote the [3,3]-rearrangement rather than the intermolecular reaction. The key intermediate in the reaction, a phosphorimidate, is prepared in situ by the Staudinger reaction[12] between azides and a phosphite or phosphine containing an allyl substituent, enabling a range of modifications to be explored.

(11) Lee, E. E.; Batey, R. A. *Angew. Chem., Int. Ed.* **2004**, *43*, 1865−1868.
(12) Gololobov, Y. G.; Kasukhin, L. F. *Tetrahedron* **1992**, *48*, 1353−1406.

Table 1. Initial Optimization



Entry	2[a]	R^1	R^2	Solvent	Yield of 3[b]	Yield of 4[b]
1	**2a**	Ph	Bn	CH_3CN	---	30%
2	**2a**	Ph	Bn	xylenes	17%	23%
3	**2b**		Bn	xylenes	20%	---
4	**2c**		Bn	xylenes	55%	---
5	**2d**		Bn	xylenes	80%(0.1M) 88%(0.5M) 85%(2.0M)	---
6	**2d**		Bn	benzene	30%	---
7	**2d**		Bn	benzene	50%	---

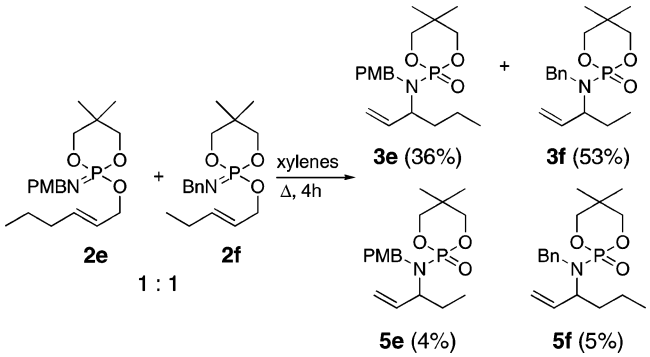
[a] Conditions: (i) 1.25 equiv *E*-2-hexen-1-ol, 1.25 equiv diphenylchlorophosphine (entries 1 and 2) or chlorophosphite (entries 3−7), and 1.25 equiv of Et_3N in Et_2O at 0 °C, 20−30 min. (ii) 1.0 equiv benzyl azide added in the indicated solvent and the mixture was heated at reflux for 4 h. [b] Isolated yields. Identity of **3** and **4** confirmed by conversion to the benzyl-protected amine and comparison of spectral data with an authentic sample.

The allylic alcohol chosen for the initial study was (*E*)-2-hexen-1-ol (**1**), and it was readily converted to the corresponding phosphorimidate by treatment with a chlorophosphine or chlorophosphite reagent followed by the addition of benzyl azide. The formation of the P═N bond and the progress of the subsequent transformations were monitored by the characteristic ^{31}P resonances of the various P(III) and P(V) species, and this greatly facilitated optimization of the reaction.

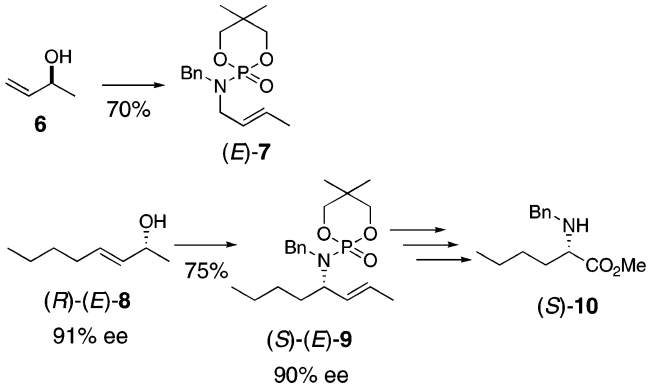
As illustrated in Table 1, the reaction pathway is strongly dependent upon solvent polarity and reaction temperature. Reactions carried out in polar solvents such as acetonitrile lead only to products derived from the intermolecular pathway. An example of this is entry 1 in which the rearrangement of **2a** produced only phosphoramidate **4a** in 30% yield; analogous results were obtained with other substrates. Decreasing the solvent polarity increases the yield of the desired [3,3]-rearrangement product (entries 2−7), with xylenes providing the optimal combination of polarity and temperature. Reactions carried out in benzene and toluene contained only the desired product, but the reaction rate was significantly slower. The observed solvent dependence reflects the probable mechanistic differences between the inter- and intramolecular processes. The intermolecular reaction proceeds in a stepwise fashion in which one or more intermediates are charged[10] (Figure 1) while the intramolecular pathway is likely a concerted process (vide infra).

Allylic phosphites proved to be superior substrates for the [3,3]-rearrangement (entries 3−7). For example, replacement of the phenyl substituents of **2a** with a dioxyethyl group (**2b**) leads to the exclusive production of the desired product **3b** (entry

Scheme 1



Scheme 2



3). These results are consistent with the general trends observed with [3,3]-rearrangements such as the Claisen in which electron-donating groups at the analogous position produce both rate acceleration and increased yields of the desired rearrangement products.[1,2,13] In the case of **2b**, the remainder of the material observed in the product mixture arose from nucleophilic ring opening of the cyclic phosphite. Thus, increasing the size of the phosphite substituents first to ethyl (entry 4) and then to 2,2-dimethylpropyl (entry 5) provided further yield improvements (55% and 88%, respectively); the increased steric bulk of **2d** relative to **2b** and **2c** (entries 3 and 4) evidently further facilitates the targeted reaction pathway. Other sterically bulky phosphite substituents are also likely to be effective in the reaction, and incorporating chirality at this position may prove to be an excellent avenue for introducing diastereocontrol in future investigations.

Mechanistic Investigation. The broad utility of [3,3]-rearrangements arises in large part from the predictable transfer of stereochemical information from starting material to product. In the Claisen rearrangement, for example, the stereochemistry of the newly formed allylic center is dictated by the olefin geometry and allylic alcohol stereochemistry of the starting material and is predictable on the basis of an intramolecular, chairlike six-membered transition state.[2] Several lines of evidence indicate that the thermal allylic phosphorimidate rearrangement exhibits similar properties (Schemes 1 and 2). A crossover experiment was first employed to probe the intramolecular nature of the reaction (Scheme 1). In this

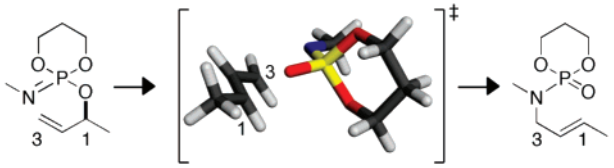


Figure 2. Bonding changes in the transition state.

experiment, two phosphorimidates with minor structural differences were prepared using standard conditions and isolated in crude form. Phosphorimidate **2e** has a *p*-methoxybenzyl group on the nitrogen and a propyl chain on the olefin wherease **2f** contains a benzyl protecting group at nitrogen and a shorter alkyl chain on the double bond moiety. The crude phosphorimidates were combined in a 1:1 ratio and subjected to standard thermal rearrangement conditions (xylenes, reflux, 4 h). From this reaction, the two products of the intramolecular [3,3]-rearrangement were isolated as the major components (**3e** and **3f**). Much smaller quantities of the formally crossed products (**5e** and **5f**) were observed and can be attributed to imine exchange that occurs at high temperatures.[14] Thus, in contrast to the formal 1,3-rearrangement of phosphorimidates originally described by Challis,[10] the allylic phosphorimidate rearrangement can be formulated as an intramolecular process.

The [3,3]-transposition of functionality provides allylic amines as single olefin isomers (Scheme 2). For example, allylic alcohol **6** rearranges readily to provide the protected allylic amine product **7** as a single *E*-olefin isomer (see also entries 11−14, 16, and 17 in Table 2). Further, enantiomerically enriched allylic alcohol (*R*)-**8** undergoes clean conversion to (*S*)-**9** with no erosion of stereochemical purity. The absolute stereochemistry of the product allylic amine was verified by the conversion of protected amine **9** to amino ester **10** through standard manipulations and comparison of the optical rotation with literature values (see Supporting Information for details).[15] Thus, the reaction can be visualized as proceeding through a chairlike six-membered transition state, enabling facile prediction of product structure. This notion is consistent with theoretical computations. DFT B3LYP/631G* calculations on a simplified model structure (Figure 2) located a chairlike transition state 23.9 kcals in energy above the starting phosphorimidate. Consistent with studies on the Claisen rearrangement,[16] bond breaking is advanced in the transition state with the breaking C1−O bond elongated to 1.887 Å versus 1.464 Å. In addition, the forming C3−N bond is 2.222 Å in length in the transition state and 1.646 Å in the product. The transition state thus resembles two interacting allyl fragments in a chairlike arrangement.

Reaction Scope. Allyloxy Substitution. The thermal [3,3]-rearrangement is tolerant of a range of substitution patterns on the allyloxy group of the phosphorimidate (Table 2). Allylic alcohols bearing hydrogen, alkyl, aryl, and halogen at either C2 or C3 of the double bond moiety are all effective substrates for the reaction. Phosphorimidates derived from simple allyl alcohol rearrange to the protected amine (entry 1). The reaction

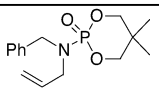
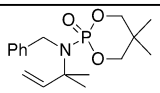
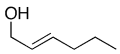
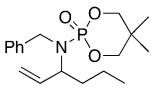
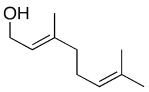
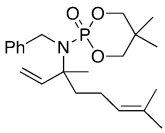
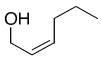
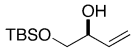
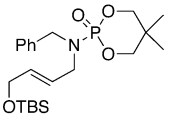
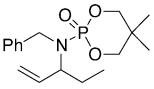
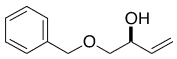
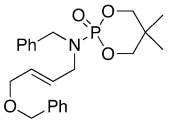
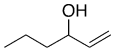
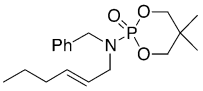
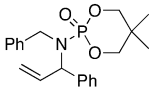
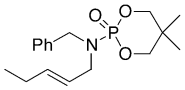
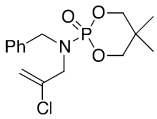
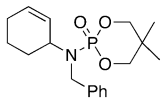
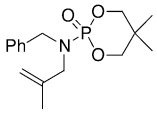
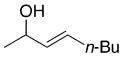
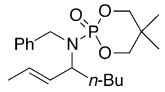
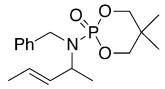
(13) Felix, D.; Gschwend-Steeen, K.; Wick, A. E.; Eschenmoser, A. *Helv. Chim. Acta* **1969**, *52*, 1030−1033. Ireland, R. E.; Mueller, R. H. *J. Am. Chem. Soc.* **1972**, *94*, 5897−5898. Johnson, W. S.; Werthemann, L.; Bartlett, W. R.; Brocksom, T. J.; Li, T. T.; Faulkner, D. J.; Petersen, M. R. *J. Am. Chem. Soc.* **1970**, *92*, 741−743.

(14) Johnson, A. W. *Ylides and imines of phosphorus*; John Wiley & Sons: 1993. Rivard, E.; Huynh, K.; Lough, A. J.; Manners, I. *J. Am. Chem. Soc.* **2004**, *126*, 2286−2287.

(15) Marshall, J. A.; Garofalo, A. W. *J. Org. Chem.* **1993**, *58*, 3675−3680. Caddick, S.; Afonso, C. A. M.; Candeias, S. X.; Hitchcock, P. B.; Jenkins, K.; Murtagh, L.; Pardoe, D.; Santos, A. G.; Treweeke, N. R.; Weaving, R. *Tetrahedron* **2001**, *57*, 6589−6605.

(16) Aviyente, V.; Houk, K. N. *J. Phys. Chem. A* **2001**, *105*, 383−391.

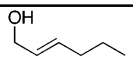
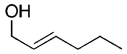
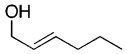
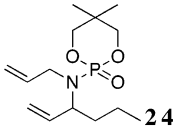
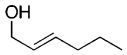
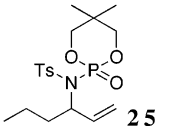
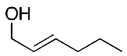
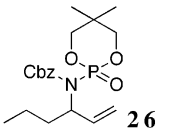
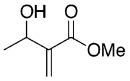
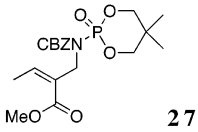
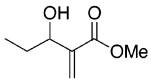
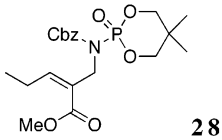
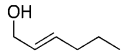
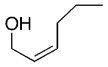
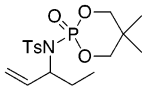
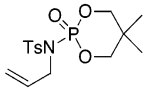
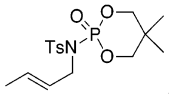
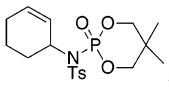
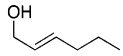
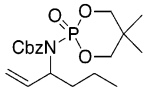
Table 2. Scope of the Rearrangement: Allyloxy Substituents

Entry	Allylic alcohol	Product	Yield (3-step)	Entry	Allylic alcohol	Product	Yield (3-step)
1		 **11**	80%	9		 **15**	70%
2		 **3d**	88%	10		 **16**	65%
3		**3d**	82%	11		 **17**	55%
4		 **3f**	85%	12		 **18**	65%
5		**3f**	81%	13		 **19**	60%
6		 **12**	80%	14		 **20**	50%
7		 **13**	75%	15		 **21**	65%
8		 **14**	60%	16		 **22**	75%
				17		 **23**	80%

is largely unaffected by olefin geometry (entries 2−5); for example, allylic phosphorimidates derived from either *E*-2-pentenol or *Z*-2-pentenol provide phosphoramidate **3f** in nearly identical yields (85% and 81%, respectively). Substitution at C2 of the allyloxy group with methyl or chloride is also well tolerated (entries 7 and 8). Notably, nitrogen-bearing quaternary centers are also readily formed in this reaction by using C3-disubstituted allylic alcohols. Both dimethylallyl alcohol (entry 9) and geraniol (entry 10) served as precursors to the rearrangement and were converted to the corresponding protected allylic amines in good yields. Because quaternary C−N stereocenters remain a significant challenge for the synthesis of alkaloid natural products and other biologically active molecules, the latter two results highlight the potential utility of the allylic phosphorimidate rearrangement.

As briefly addressed in the previous section, incorporation of a C1 substituent into the allylic alcohol substrate provides a means to prepare *E*-allylic amines with excellent stereochemical fidelity (entries 11−14, 16−17). In all cases, >20:1 selectivity for the *E*-isomer was observed, consistent with a sigmatropic process.[2] Consistent with other [3,3]-sigmatropic rearrangements,[2,5] substitution at C1 accelerates the reaction, with the rearrangement proceeding to completion in less than 1 h compared to the approximately 4-h reaction times required for entries 1−10. Substrates with substitution at both C1 and C3 of the allyloxy moiety are also excellent substrates in the reaction (entries 15−17). This includes the phosphorimidate derived from cyclohexenol that also provides the desired allylic amine product (entry 15).

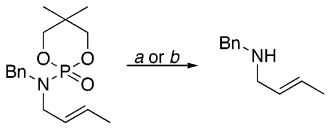
Table 3. Scope of the Rearrangement: Nitrogen Substituents

Entry[a]	Allylic alcohol	R^2	Reaction conditions[a]	Product	Yield[b] (3 steps)
1		Bn	A	**3d**	88%
2		PMB	A	**3e**	80%
3		Allyl	A	 **24**	60%
4		Ts	A	 **25**	25%
5		Cbz	A	 **26**	15%
6		Cbz	B	 **27**	65%
7		Cbz	B	 **28**	60%
8		Ts	C	**25**	95%
9		Ts	C	**25**	90%
10		Ts	C	 **29**	90%
11		Ts	C	 **30**	95%
12		Ts	C	 **31**	82%
13		Ts	C	 **32**	55%
14		Cbz	C	 **26**	90%

[a] Conditions: A: (i) 1.25 equiv allylic alcohol, 1.25 equiv chlorophosphite, 1.25 equiv Et_3N, Et_2O, 0 °C, 20−30 min. (ii) 1 equiv azide, xylenes, rt→reflux, 4 h. B: (i) 1.25 equiv allylic alcohol, 1.25 equiv chlorophosphite, 1.25 equiv Et_3N, Et_2O, 0 °C, 20−30 min. (ii) 1 equiv azide, xylenes rt→40 °C, 4 h. C: (i) 1 equiv allylic alcohol, 1 equiv chlorophosphite, 1 equiv Et_3N, Et_2O, 0 °C, 20−30 min. (ii) 1.5 equiv azide, CH_2Cl_2, 0.5−1 h followed by 10 mol % $PdCl_2(CH_3CN)_2$. [b] Isolated yield.

Nitrogen Substitution: Thermal and Pd(II)-Catalyzed Reactions. One advantage of the allylic phosphorimidate rearrangement is that the product is a fully protected allylic amine. One of the protecting groups is the phosphoramidate, a group that confers stability under a wide range of reaction conditions to the allylic amine.[17] This group can readily be removed, however, either by treatment with TMS-I or by the addition of nucleophilic thiol[18] followed by HCl/MeOH. In the

case of **7**, for example, either method provided the corresponding benzyl-protected amine product in excellent yield (91% and 90%, respectively).



7 **Conditions:**
a: *i.*TMSI, DMF; *ii.* HCl/MeOH; 91% yield
b: *i.* EtSH, NaH; *ii.*HCl/MeOH; 90% yield

The second protecting group arises from the azide used in the reaction and can thus easily be varied. As shown in Table 3, benzyl azide, *p*-methoxybenzyl azide, and allyl azide each serve as effective nitrogen sources in the reaction and provide several choices for the amine protecting group in the final product (entries 1−3). In contrast, both Ts azide and Cbz azide gave the undesired regioisomer as the major product with the targeted [3,3]-rearrangement product isolated in 25% and 15% yield, respectively (entries 4 and 5). This change in the reaction pathway preference is presumably due to the improved leaving group ability of the phosphorimidate. These results mirror the recent observation of Batey and co-workers that stereoelectronically similar substrates do not undergo thermal [3,3]-rearrangement reactions.[11] We reasoned that increasing the electrophilicity of the allyloxy moiety through substitution of an electron-withdrawing group might alter the reaction preference and provide entry into an additional class of structurally complex allylic amines. Indeed, incorporation of an ester into the allyloxy moiety significantly altered the reactivity profile (entries 6 and 7). The addition of this electron-withdrawing group at C2 activates the double bond and the rearrangement occurs at lower temperatures with Cbz azide as the nitrogen source (40 °C). The products of the reaction (**27** and **28**) are suitably protected precursors to β-amino acids, requiring only a reduction of the double bond. Because the allylic alcohol starting materials for these transformations are easily accessible by the Bayliss−Hillman reaction, this combination provides a facile entry into an important class of compounds. In addition, the rearrangement products are a class of allylic alcohols that are difficult to access as single olefin isomers but, via the [3,3]-allylic phosphorimidate rearrangement, are isolated as stereochemically pure *E*-olefin isomers.

An alternative approach for increasing the electrophilicity of double bonds employs metal catalysts that form transient complexes with the substrate. This strategy was elegantly utilized by Overman and co-workers who found that, for example, Pd(II) salts effectively catalyze the rearrangement of allylic trichloracetimidates, enabling the reaction to occur at room temperature.[19] A two-step mechanism involving the attack of the imidate nitrogen onto a Pd-complexed alkene and subsequent deoxypalladation is proposed for the rate acceleration. More recently, Lee and Batey disclosed a $PdCl_2(CH_3CN)_2$-catalyzed [3,3]-rearrangement of (allyloxy)iminodiazaphopholidines, and a similar two-step mechanism was invoked for this reaction.[11,20] These results prompted us to examine Pd(II)-catalysis in our system (Table 3, method C).

Phosphorimidates that are good substrates for the thermal reaction do not provide the desired products under metal-catalyzed conditions. In the case of a phosphorimidate derived from (*E*)-2-hexen-1-ol and benzyl azide, for example, the protected allylic amine produced upon treatment with $PdCl_2(CH_3CN)_2$ arose from the undesired reaction pathway (**4d**). Similar results were obtained with other commonly employed soluble palladium catalysts. However, decreasing the nucleophilicity/basicity of the nitrogen by incorporation of an electron-withdrawing group sufficiently altered the reactivity of the intermediate phosphorimidates for the desired reaction to occur (entries 8−14). Both the tosyl group (entries 8−13) and Cbz (entry 14) were effective in this capacity, with excellent yields of the [3,3]-rearrangement products isolated in all cases. Typically, the intermediate phosphorimidate was prepared in situ using conditions analogous to the thermal reaction. This was then treated with 10 mol % of the Pd(II) salt in CH_2Cl_2 and all reactions were complete after 30 min at room temperature. Comparable yields were observed at catalyst loadings as low as 2 mol %, although the reaction time increased (2−12 h).

As with the thermal reaction, the Pd(II)-catalyzed [3,3]-rearrangement is tolerant of significant substrate structural variation (Table 3). Both *E*-2-hexen-1-ol and *Z*-2-hexen-1-ol underwent the rearrangement to provide the desired phosphorimidate **25** in excellent yield (95% and 90%, respectively). In addition, high diastereoselectivity ($E/Z > 20:1$) and good yield were obtained with a secondary allylic alcohol (entry 12). The rearrangement of the conformationally restricted 2-cyclohexen-1-ol was more sluggish, giving the corresponding phosphoramidate **32** in moderate yield (entry 13). Cbz azide also proved to be an effective azide source, affording **26**, for example, in excellent yield (entry 14).

Conclusions

In summary, we have described the development, scope, and mechanism of a unique [3,3]-sigmatropic rearrangement of allylic phosphorimidates. As a three-component process utilizing readily available starting materials (allylic alcohols, azides, and a chlorophosphite), this reaction provides an efficient entry into allylic amines of diverse substitution and complexity. Substitution in the allyl moiety is well tolerated in both the thermal and catalyzed versions of the reaction. Our study of the effect of nitrogen substitution on the rearrangement revealed that access to a variety of nitrogen substitution patterns is possible by choice of azide reagent combined with proper selection of reaction conditions. The preparation of allylic amine products containing electron-withdrawing protecting groups such as Cbz is facilitated by activation of the double bond with a Pd(II) catalysts whereas Bn or PMB protection can be accomplished under standard thermal conditions. Given the widespread use of allylic amines as entry points to alkaloid natural products, α- and β-amino acids, and other biologically active structures, this method is a valuable addition to the synthetic arsenal. Future

(17) Ramage, R.; Hopton, D.; Parrott, M. J.; Kenner, G. W.; Moore, G. A. *J. Chem. Soc., Perkin Trans. 1* **1984**, 1357−1370.
(18) Dahl, B. H.; Bjergarde, K.; Henriksen, L.; Dahl, O. *Acta Chem. Scand.* **1990**, *44*, 639−641.
(19) Anderson, C. E.; Overman, L. E. *J. Am. Chem. Soc.* **2003**, *125*, 12412−12413.
(20) Lee and Batey have demonstrated that the transfer of stereochemical information for enantiomerically enriched *E*-olefin-containing substrates proceeds with high fidelity in the presence of $PdCl_2(CH_3CN)_2$ while *Z*-olefin-containing substrates provide products with slightly reduced enantiomeric excesses. See ref 11 for details.

studies will focus on the development of asymmetric variants of this [3,3]-rearrangement through the employment of chiral phosphorus reagents, chiral azides, and chiral Pd(II) catalysts.

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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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