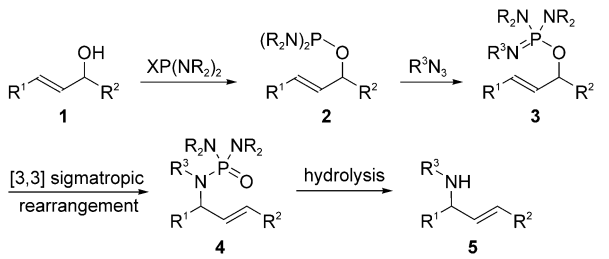
Sigmatropic Rearrangement

Palladium-Catalyzed [3,3] Sigmatropic Rearrangement of (Allyloxy)iminodiazaphospholidines: Allylic Transposition of C–O and C–N Functionality**

*Ernest E. Lee and Robert A. Batey**

The principle of driving reactions thermodynamically through the conversion of P^{III} reagents into P^{V}=O products is well established, as exemplified by the Wittig and Mitsunobu reactions, and the [2,3] sigmatropic rearrangement of allyl phosphites into allyl phosphonates.[1] Herein we describe a novel [3,3] sigmatropic rearrangement in which allylic transposition is driven by a P^{V}=N to P^{V}=O interconversion (Scheme 1). We envisaged a process whereby conversion of



Scheme 1. Proposed route to allylic amines based on the [3,3] sigmatropic rearrangement of phospholidines **3**.

an allylic alcohol **1** into a phosphoramidite **2**, followed by a Staudinger reaction[2] would generate a phospholidine **3**. A [3,3] sigmatropic 3-aza-2-phospha-1-oxa-Cope[3] rearrangement of **3** would then generate a phosphoramide **4**, which on deprotection would lead to the transposed allylic amine **5**.[4] The overall process is analogous to the aza variants of the Cope [3,3] sigmatropic rearrangement,[5] the most important example of which is the well-known Overman rearrangement of allylic imidates into allylic amides.[6] The estimated thermodynamic driving force for a phospholidine–phosphoramide interconversion,[7] such as would occur in a sigmatropic rearrangement, is approximately 25 kcal mol^{-1}.[8]

The feasibility of this approach was tested by using (allyloxy)iminodiazaphospholidines **6** and **7** as substrates.

[*] E. E. Lee, Prof. R. A. Batey
Department of Chemistry, University of Toronto
80 St. George Street, Toronto, Ontario, M5S 3H6 (Canada)
Fax: (+1) 416-978-5059
E-mail: rbatey@chem.utoronto.ca

[**] The Natural Science and Engineering Research Council (NSERC) of Canada funded this research. E.E.L. thanks the Ontario Ministry of Training for funding in the form of an Ontario Graduate Scholarship. R.A.B. gratefully acknowledges receipt of a Premier's Research Excellence Award. We also thank Dr. Alex Young for mass spectral analysis and Dr. Tim Burrow for NMR assistance.

Supporting information for this article is available on the WWW under http://www.angewandte.org or from the author.

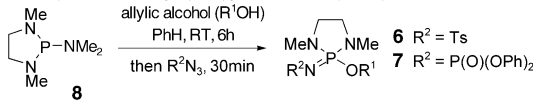
 DOI: 10.1002/anie.200353284

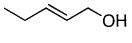
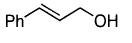
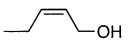
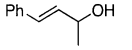
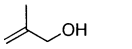
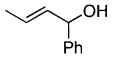
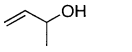
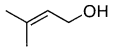
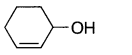
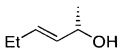
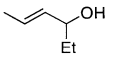
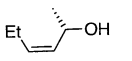
These compounds were cleanly prepared in a one-pot process by the sequential treatment of the corresponding allylic alcohols with the phospholidine **8**,[9] as described by Alexakis et al.,[10] followed by tosyl azide and diphenylphosphoryl azide (DPPA),[11] respectively (Table 1).[12] The reaction was monitored by ^{31}P NMR spectroscopy to ensure complete conversion of the intermediate phosphoramidite ($\delta \approx 130$ ppm for **2**, whereas $\delta \approx 24$ ppm for **6** and $\delta \approx 24$ and -10 ppm for **7**). The iminodiazaphospholidines were then purified by chromatography on silica gel, with Et_3N as an additive to prevent acid-promoted decomposition.

Initial attempts at the thermal rearrangement of compounds **6** were unsatisfactory and led to products arising from pathways of both the desired [3,3] and formal [1,3] sigmatropic rearrangement. As Pd^{II} and Hg^{II} catalysts are known to catalyze the [3,3] sigmatropic rearrangement of allylic imidates,[6] a variety of Pd^{II} catalysts were screened for the rearrangement of **6a** into **9a**, but only $[PdCl_2(MeCN)_2]$ was found to be an active catalyst.[13] In the presence of $[PdCl_2(MeCN)_2]$ (5 mol%), the rearrangement of both **6** and **7** proceeded smoothly at room temperature to yield only the products of [3,3] rearrangement **9** and **10**, respectively (Table 2). In the reactions of the DPPA-derived substrates **7**, the addition of 4-Å molecular sieves was required to ensure complete conversion into **10**. The rearrangements were conveniently monitored by ^{31}P NMR spectroscopy ($\delta \approx 20$ ppm for **9**, and $\delta \approx 20$ and -4 ppm for **10**). The phosphoramides **9** and **10** were cleaved under acidic conditions to yield the allylic tosylamines **11** and free allylic amines **12**, respectively.[14] As mild, acidic conditions are used for the final hydrolysis, this overall process complements the Overman rearrangement of allylic imidates. Strongly basic conditions (3–5 M NaOH) are employed for the hydrolysis of the intermediate trichloroacetamides in the Overman protocol.

A variety of substitution patterns are tolerated on the allylic substrates **6** and **7**, including substitution in the allylic group α, β, and γ to the oxygen atom. Notably, the reaction worked well for substrates substituted at the β position (**6c** and **7c**), as previous attempts at metal-catalyzed rearrangements of the corresponding allylic imidates have had mixed success.[15] Substrates **6f** and **7f** both underwent rearrangement in good yield to afford only the *E* isomers **9f** and **10f**. The reaction of the substrates **6d** and **7d**, derived from a simple secondary allylic alcohol, to give

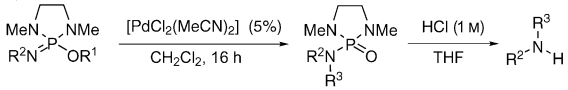
Table 1: Preparation of (allyloxy)iminodiazaphospholidines.



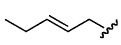
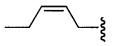
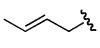
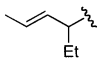
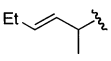
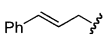
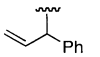
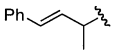
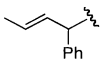
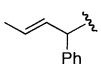
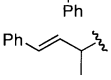
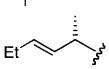
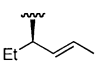
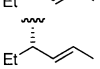
R^1OH		Yield [%][a]	R^1OH		Yield [%][a]
	**6a**	92		**6g**	94
	7a	87		**7g**	91
	**6b**	93		**6h**	92
	7b	90		**7h**	84
	**6c**	95		**6i**	–[b,c]
	7c	92		**7i**	–[b,c]
	**6d**	91		**6j**	92
	7d	89		**7j**	87
	**6e**	89		**6k**	86
	7e	89		**7k**	78
	**6f**	93		**6l**	87
	7f	86		**7l**	80

[a] Yield of isolated product, 0.6-mmol scale. [b] These compounds could not be purified by column chromatography on silica gel and were used crude in subsequent transformations. [c] Reaction conducted in $[D_6]$benzene. Ts = *p*-toluenesulfonyl.

Table 2: Pd-catalyzed [3,3] sigmatropic rearrangement of (allyloxy)iminodiazaphospholidines and subsequent hydrolysis.



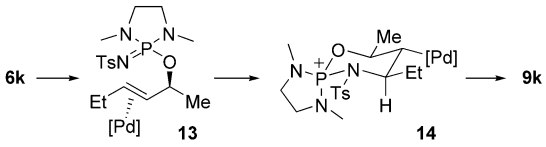
6 R^2 = Ts, **7** R^2 = P(O)(OPh)$_2$ → **9** R^2 = Ts, **10** R^2 = P(O)(OPh)$_2$ → **11** R^2 = Ts, **12** R^2 = H•HCl

	R^1	R^3		Yield [%][a]		Yield [%][a]
6a			**9a**	95	**11a**	88
7a			**10a**[b]	90	**12a**[f]	81
6b			**9a**	93	**11a**	88
7b			**10a**[b]	89	**12a**[f]	81
6c			**9c**	95	**11c**	97
7c			**10c**[b]	91	**12c**[f]	87
6d			**9d**	91	**11d**	93
7d			**10d**[b]	86	**12d**[f]	85
6e			**9e**[c,d]	88	**11e**	90
7e			**10e**[b]	trace	**12e**[f]	–
6f			**9f**[c]	90	**11f**	83
7f			**10f**[b]	93	**12f**[f]	79
6g			**9g**[c,d]	75	**11g**	85
7g			**10g**[b]	n.r.[e]	**12g**[f]	–
6h			**9h**[c,d]	76	**11h**	80
7h			**10h**[b]	n.r.[e]	**12h**[f]	–
6i			**9i**[c]	80	**11i**	78
7i			**10i**[b]	n.r.[e]	**12i**[f]	–
6j			**9j**	n.r.[e]	–	–
7j			**10j**[b]	n.r.[e]	–	–
6k			**9k**	90	**11k**	82
7k			**10k**[b]	84	**12k**[f]	78
6l			**9l**	88	**11l**	90
7l			**10l**[b]	83	**12l**[f]	79

[a] Yield of isolated product, 0.6-mmol scale. [b] Reaction conducted in the presence of 4-Å molecular sieves. [c] Reaction conducted in toluene. [d] Reaction conducted at 45 °C. [e] Only starting material was observed by ^{31}P NMR spectroscopy. [f] Reaction conducted with HCl (1 M) in MeOH.

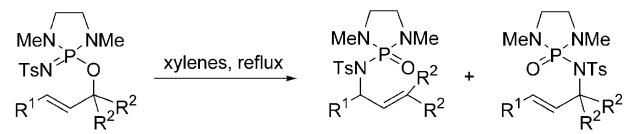
the corresponding primary allylic phosphoramides occurred in excellent yields at room temperature. However, reactions of the 2-cyclohexenyl substrates were far more sluggish, with **6e** requiring heating at 45 °C and **7e** yielding only trace amounts of products after 48 h at 80 °C. A similar trend was observed with substrates **6g–i** and **7g–i**. It is apparent that substrates with sterically demanding substituents react more slowly in the case of tosyl-derived, and are unreactive in the case of DPPA-derived substrates. The steric limitations of this reaction are further emphasized by the lack of reactivity of the substrates **6j** and **7j**, which are derived from a γ,γ-disubstituted allylic alcohol.

The transposition of the enantioenriched *E* substrates **6k** and **7k** produced only the *E* phosphoramides **9k** and **10k** with clean transfer of chirality. The *Z* substrates **6l** and **7l** underwent rearrangement to the *E* products **9l** and **10l**, albeit with diminished enantiomeric excess.[16] The [3,3] sigmatropic rearrangement presumably proceeds through intramolecular attack on the palladium-coordinated double bond by the lone pair of electrons on the nitrogen atom of P^{V}=N, followed by rearrangement of the resulting phosphonium intermediate. For example, in the case of **6k** the reaction proceeds via the π complex **13** and phosphonium ion **14** in a fashion analogous to that proposed for the rearrangement of allylic imidates (Scheme 2).[6a,d] The absolute configuration[17] and olefin geometry of the products in both cases are consistent with this mechanism.



Scheme 2. Proposed mechanism for the Pd-catalyzed reaction, as exemplified by the conversion of **6k** into **9k**.

Comparison of the results of the Pd^{II}-catalyzed [3,3] sigmatropic rearrangement at ambient temperatures with the thermal rearrangement of substrates **6** clearly demonstrates the advantages of metal catalysis to facilitate clean rearrangements. For example, the thermal rearrangement of the diazaphospholidine **6a** at 130 °C led to the [3,3] product **9a** and [1,3] product **15a** in a ratio of 3.5:1 (Scheme 3). Furthermore, the thermal rearrangement of **6g** only yielded the [1,3] product **15g**, whereas that of **6m** only yielded the [3,3] product **9m**. In the last two examples, only the thermodynamically more stable allylic phosphoramide was formed. These results suggest that ionization and subsequent recombination is competitive with the [3,3] sigmatropic rearrangement under thermal conditions.



Scheme 3. Thermal rearrangements of phospholidines **6**.

In conclusion, a novel palladium(II)-catalyzed rearrangement of (allyloxy)iminodiazaphospholidines has been developed for the synthesis of allylic amines and tosylamines. Investigations into diastereo- and enantioselective variants are currently underway in our laboratory.

Received: November 10, 2003 [Z53284]

Keywords: allylic amines · azides · homogeneous catalysis · palladium · sigmatropic rearrangement

[1] T. Janecki, R. Bodalski, *Synthesis* **1990**, 799–801, and references therein.
[2] Y. G. Gololobov, L. F. Kasukhin, *Tetrahedron* **1992**, *48*, 1353–1406.
[3] Classification based on the allylic imidate rearrangement described in: F. Vögtle, E. Goldschmitt, *Chem. Ber.* **1976**, *109*, 1–40.
[4] Allylic amines are important synthetic intermediates as well as targets. For a review of their synthesis, see: M. Johannsen, K. A. Jørgensen, *Chem. Rev.* **1998**, *98*, 1689–1708.
[5] a) K. Ritter in *Houben-Weyl. Stereoselective Synthesis*, *Vol. E 21e* (Eds.: G. Helmchen, R. W. Hoffmann, J. Mulzer, E. Schaumann), Thieme, Stuttgart, **1996**, pp. 5677–5699; b) R. P. Lutz, *Chem. Rev.* **1984**, *84*, 206–247.
[6] a) L. E. Overman, *J. Am. Chem. Soc.* **1976**, *98*, 2901–2910; b) L. E. Overman, *Acc. Chem. Res.* **1980**, *13*, 218–224; c) L. E. Overman, *Angew. Chem.* **1984**, *96*, 565–573; *Angew. Chem. Int. Ed. Engl.* **1984**, *23*, 579–586; d) T. G. Schenck, B. Bosnich, *J. Am. Chem. Soc.* **1985**, *107*, 2058–2066; e) M. Calter, T. K. Hollis, L. E. Overman, J. Ziller, G. G. Zipp, *J. Org. Chem.* **1997**, *62*, 1449–1456; f) T. Nishikawa, M. Asai, N. Ohyabu, M. Isobe, *J. Org. Chem.* **1998**, *63*, 188–192; g) Y. Uozumi, K. Kazuhiko, T. Hayashi, *Tetrahedron: Asymmetry* **1998**, *9*, 1065–1072; h) I. Savage, E. J. Thomas, P. D. Wilson, *J. Chem. Soc. Perkin Trans. 1* **1999**, 3291–3303; i) T. Donde, L. E. Overman, *J. Am. Chem. Soc.* **1999**, *121*, 2933–2934; j) L. E. Overman, C. E. Owen, M. M. Pavan, C. J. Richards, *Org. Lett.* **2003**, *5*, 1809–1812; k) C. E. Anderson, L. E. Overman, *J. Am. Chem. Soc.* **2003**, *125*, 12412–12413.
[7] For the use of phospholidine–phosphoramide interconversion as a thermodynamic driving force in other rearrangements, see: a) T. A. Mastryukova, N. V. Mashchenko, I. L. Odinets, P. V. Petrovskii, M. I. Kabachnik, *Russ. J. Gen. Chem.* **1988**, *58*, 1756–1761; b) E. J. Cabrita, C. A. M. Afonso, A. Gil de Oliveira Santos, *Chem. Eur. J.* **2001**, *7*, 1455–1467.
[8] The thermodynamic driving force for the [3,3] sigmatropic rearrangement of **3** into **4** was estimated by comparison with the analogous conversion of $(NH_2)_2(MeO)P{=}NH$ into $(NH_2)_2(MeNH)P{=}O$, a formal [1,3] sigmatropic rearrangement which involves the same overall bonding reorganization. Geometry optimizations, single-point energies, and vibrational analysis were calculated at the B3LYP/6-311G* level. For comparison, the driving force of a C=NH to C=O transposition can be estimated by the energy difference between the imidate Me(MeO)C=NH and the amide Me(MeNH)C=O, the latter calculated to be 18.6 kcal mol^{-1} lower in energy at the B3LYP/6-311G*level. (Calculations were performed on a Dual 2-GHz Power PC G5 by using Spartan'02, Version 1.0.4e, Wavefunction Inc., Irvine, CA).
[9] The phospholidine **8** was prepared as described in: S. Hanessian, Y. L. Bennani, Y. Leblanc, *Heterocycles* **1993**, *35*, 1411–1424.
[10] A. Alexakis, S. Mutti, P. Mangeney, *J. Org. Chem.* **1992**, *57*, 1224–1237.

[11] Although we have experienced no problems with either of these azides, appropriate safety measures should be taken.
[12] a) J. Bellan, M. Sanchez, M. R. Marre-Mazières, A. M. Beltran, *Bull. Soc. Chim. Fr.* **1985**, *3*, 491–495; b) M. R. Marre, M. Sanchez, J. F. Brazier, R. Wolf, J. Bellan, *Can. J. Chem.* **1982**, *60*, 456–468.
[13] The use of the following catalysts resulted in complete recovery of **6a**: $PdCl_2$, $[PdCl_2(PPh_3)_2]$, $[PdCl_2(PCHX_3)_2]$, $[Pd_2Cl_2(allyl)_2]$, $[PdCl_2(cod)]$. cod = 1,5-cyclooctadienone.
[14] V. Mizrahi, T. A. Modro, *J. Org. Chem.* **1983**, *48*, 3030–3037.
[15] Depending on the allylic imidate used, either prolonged reaction time was required or no reaction was observed: P. Metz, C. Mues, A. Schoop, *Tetrahedron* **1992**, *48*, 1071–1080, and references therein.
[16] Compounds **6k** and **7k** (95% *ee*) underwent rearrangement to give **9k** and **10k** with 91% *ee*, whereas the rearrangement of **6l** and **7l** (95% *ee*) gave **9l** and **10l** with 70% *ee* (determined by HPLC on a chiral phase).
[17] The optical rotation of the methyl ester prepared by the ozonolysis of **11k** was compared to that of a previously reported authentic sample; see Supporting Information for details.

