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Palladium-Catalyzed Allylic Transposition of (Allyloxy) Iminodiazaphospholidines: A Formal [3,3]-Aza-phospha-oxa-Cope Sigmatropic Rearrangement for the Stereoselective Synthesis of Allylic Amines

Ernest E. Lee and Robert A. Batey*

Contribution from the Department of Chemistry, University of Toronto, Toronto, Ontario, Canada

Received June 23, 2005; E-mail: rbatey@chem.utoronto.ca

Abstract: The synthesis of *N*-protected allylic amines has been achieved utilizing a palladium(II)-catalyzed, [3,3]-rearrangement of (allyloxy) iminodiazaphospholidines. This [3,3]-aza-phospha-oxa-Cope sigmatropic rearrangement reaction is thermodynamically driven by a P═N to P═O interconversion and is an alternative to the Overman rearrangement. The overall process involves the nucleophilic displacement of an allylic alcohol onto a P(III) precursor, followed by a Staudinger reaction to generate the (allyloxy) iminodiazaphospholidine precursors. Pd(II)-catalyzed [3,3]-aza-phospha-oxa-Cope rearrangement then gives a phosphoramide, which is readily hydrolyzed under acidic conditions to yield allylic amine derivatives. Pd(II) catalysis is believed to occur in a fashion analogous to that of the rearrangement of allylic imidates. The scope of racemic, diastereoselective, and enantioselective variants of this rearrangement is described. The use of chiral diamine auxiliaries in diastereoselective rearrangements is reported. Rearrangement of chiral *N*,*N*′-dimethyl cyclohexanediamine derived diazaphospholidines gives rise to phosphoramides with moderate diastereoselectivities (up to 3.5:1 dr). The same major diastereomeric product in these rearrangements was prepared irrespective of the starting allylic alcohol geometry. An enantioselective variant of the reaction was demonstrated for the rearrangement of cis-(allyloxy) iminodiazaphospholidines with cobalt oxazoline palladacycle (COP−X) catalysts (5 mol %) in high yield and enantioselectivity (up to 96% ee).

Introduction

Efficient methods for the formation of allylic amines are useful for the preparation of many nitrogen-containing compounds, such as amino acids, amino sugars, alkaloids, and other complex natural products.[1] One general approach to their synthesis utilizes aza-analogues of the Cope [3,3]-sigmatropic rearrangement, including aza-, aza-oxa-, aza-thia, and diaza-Cope rearrangements.[2] Undoubtedly the most important member of this family is the aza-oxa-Cope rearrangement of allylic imidates **1** into allylic amides **2**, originally developed by Overman (Figure 1).[3] The aza-oxa-Cope or Overman rearrangement is a widely utilized reaction, and on hydrolysis of the resultant amide **2** provides a convenient route to the synthesis of allylic amines. It has been utilized in a number of syntheses,[4] with the rearrangement usually occurring with excellent regiochemical control, geometrical-control, and transfer of stereochemistry when starting with stereodefined allylic imidates.

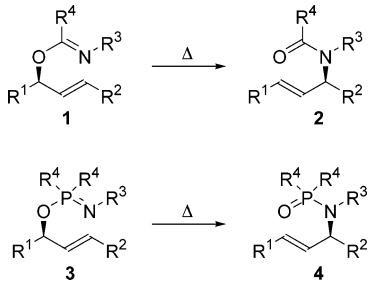
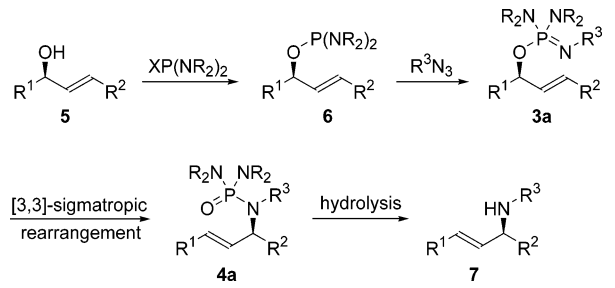


Figure 1. Aza-oxa-Cope and aza-phospa-oxa-Cope rearrangements.

We envisaged an analogous [3,3]-sigmatropic rearrangement of **3** into **4**, in which allylic transposition is driven by a P(V)═N to P(V)═O interconversion (Figure 1). Our initial communication outlined the conversion of iminodiazaphospholidines **3** into phosphoramides **4** ($R^4 = NR_2$),[5] under Pd(II)-catalyzed conditions. This conversion was the first example of an aza-phospha-oxa-Cope rearrangement. Almost simultaneous with our initial study on the Pd(II)-catalyzed variant of this reaction, Mapp and Chen reported a similar thermal rearrangement of

(1) Johannsen, M.; Jørgensen, K. A. *Chem. Rev.* **1998**, *98*, 1689−1708.
(2) (a) Ritter, K. In *Houben-Weyl. Stereoselective Synthesis*, E 21e; Helmchen, G., Hoffmann, R. W., Mulzer, J., Schaumann, E., Eds.; Thieme: Stuttgart, 1996; pp 5677−5699. (b) Lutz, R. P. *Chem. Rev.* **1984**, *84*, 205−247.
(3) (a) Overman, L. E. *J. Am. Chem. Soc.* **1976**, *98*, 2901−2910. (b) Overman, L. E. *Acc. Chem. Res.* **1980**, *13*, 218−224. (c) Overman, L. E. *Angew. Chem.* **1984**, *96*, 565−573; *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 579−586. (d) Schenck, T. G.; Bosnich, B. *J. Am. Chem. Soc.* **1985**, *107*, 2058−2066. (e) Nishikawa, T.; Asai, M.; Ohyabu, N.; Isobe, M. *J. Org. Chem.* **1998**, *63*, 188−192. (f) Savage, I.; Thomas, E. J.; Wilson, P. D. *J. Chem. Soc., Perkin Trans. 1* **1999**, 3291−3303.
(4) Overman reports that over 180 publications utilize allylic imidate rearrangement for allylic amine synthesis (see ref 14c).
(5) Lee, E. E.; Batey, R. A. *Angew. Chem.* **2004**, *116*, 1901−1904; *Angew. Chem., Int. Ed.* **2004**, *43*, 1865−1868.

Scheme 1



phosphorimidates **3** (R^4 = OR).[6] Our investigations were inspired by the knowledge that reactions in which products containing P(V)═O bonds are formed are often thermodynamically favorable. There are many examples of reactions employing the conversion of P(III) to P(V)═O species, such as the Wittig and Mitsunobu reactions. Similarly, the [2,3]-sigmatropic rearrangement of allyl phosphites is a valuable approach to the synthesis of allylphosphonates.[7] Furthermore, thermal rearrangements of phosphorimidates to phosphoramides in which formal [1,3]-alkyl migration from oxygen to nitrogen concomitant with P(V)═N to P(V)═O interconversion have also been described.[8] The thermodynamic driving force of the phospholidine−phosphoramide interconversion of **3** into **4** can be estimated by considering the model system of (allyl-O)-$(NH_2)_2$P═NH, which on [3,3]-sigmatropic rearrangement is converted into (allyl-NH)$(NH_2)_2$P═O.[9] The energy change for this transformation is estimated at −24.4 kcal mol^{-1}, calculated at the B3LYP/6-31G* level. By comparison, the thermodynamic driving force for the rearrangement of **1** into **2**, as for the transformation of the imidate (allyl-O)CH═NH into the amide (allyl-NH)CH═O, is estimated at −17.1 kcal mol^{-1}.

We now report a full study on the development of a metal-catalyzed aza-phospha-oxa-Cope rearrangement of **3** into **4**, detailing the scope of the reaction, auxiliary-based diastereoselective rearrangement, and the use of chiral catalysts to accomplish enantioselective rearrangement. The overall strategy employs allylic alcohols **5** as substrates, compounds that are commonly used as synthetic precursors, and for which there are numerous methods developed for their synthesis.[10] Nucleophilic substitution of **5** on an appropriate P(III) reagent then gives phosphoramidite **6** (Scheme 1). The electron-rich phosphoramidite can then readily undergo a room-temperature Staudinger reaction[11] with electron-deficient azides to generate a phospholidine **3a**. Metal-catalyzed [3,3]-sigmatropic 3-aza-2-phospha-1-oxa-Cope[12] rearrangement of **3a** then generates phosphoramide **4a**, which can be deprotected under mild, acidic conditions to give the transposed allylic amine **7**. In contrast to allylic imidates, this system contains two variable substituents on phosphorus that could be used to control the reactivity and selectivity of the rearrangement. In addition, the use of azides in the Staudinger reaction allows the introduction of a range of different nitrogen substituents.

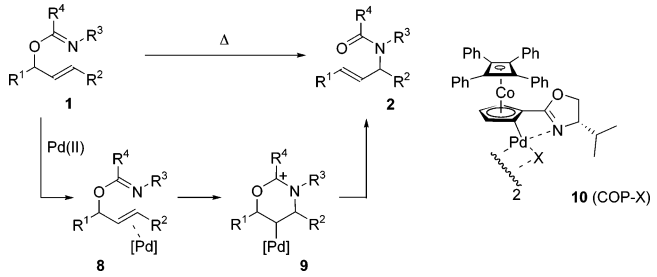


Figure 2. Palladium-catalyzed cyclization-induced rearrangement of allylic imidates.[13,14]

We were particularly interested in the development of a metal-catalyzed variant of the aza-phospha-oxa-Cope rearrangement. Metal catalysts including Pd(II) and Hg(II) have been demonstrated by Overman to catalyze the [3,3]-sigmatropic rearrangement of allylic imidates.[3] Metal-catalyzed reaction of **1** is believed to occur in a stepwise fashion, with Pd(II) first activating the alkene to nucleophilic attack by the *N*-atom of the imidate in a 6-*endo*-trig fashion, leading to a metal intermediate **9** that then undergoes rapid breakdown to yield **2** (Figure 2). An analogous metal-catalyzed process for the rearrangement of **3** into **4** would allow the use of lower reaction temperatures and permit the use of more sensitive substrates. Moreover, the use of a chiral metal catalyst would, in principle, allow the development of an asymmetric variant of the reaction. Indeed, at the outset of our investigations, there had been increasing interest in the use of chiral Pd(II) catalysts for enantioselective allylic imidate Overman rearrangements.[13] Early catalysts, although high yielding and highly selective, were plagued by limitations of the substrates to *N*-aryl imidates. The enantioselective rearrangement of substrates containing readily deprotected *N*-functionality has only recently been accomplished with various chiral cobalt oxazoline palladacycles (COP−X) **10**, a culmination of several generations of axially chiral

(6) (a) Chen, B.; Mapp, A. K. *J. Am. Chem. Soc.* **2004**, *126*, 5364−5365. (b) Chen, B.; Mapp, A. K. *J. Am. Chem. Soc.* **2005**, *127*, 6712−6718.
(7) Janecki, T.; Bodalski, B. *Synthesis* **1990**, 799−801.
(8) (a) Challis, B. C.; Frenkel, A. D. *J. Chem. Soc., Chem. Commun.* **1972**, 303−308. (b) Challis, B. C.; Challis, J. A.; Iley, J. N. *J. Chem. Soc., Perkin Trans. 2* **1978**, 813−818. (c) Mastryukova, T. A.; Mashchenko, N. V.; Odinets, I. L.; Petrovskii, P. V.; Kabachnik, M. I. *Russ. J. Gen. Chem.* **1988**, *58*, 1756−1761. (d) Cabrita, E. J.; Afonso, C. A. M.; Gil de Oliveira Santos, A. *Chem.-Eur. J.* **2001**, *7*, 1455−1467.
(9) Geometry optimizations, single-point energies, and vibrational analysis were calculated at the B3LYP/6-31G* level. Calculations were performed using Spartan'04 Version 1.0, Wave function Inc., Irvine, CA.
(10) There are numerous synthetic methods for the formation of enantioenriched allylic alcohols. Resolution of allylic alcohols: (a) Drauz, K.; Waldmann, H. *Enzyme Catalysis in Organic Synthesis: A Comprehensive Handbook*, 2nd ed.; Wiley-VCH: Weinheim, Germany, 2002; Vols. I−III. (b) Pàmies, O.; Bäckvall, J.-E. *Chem. Rev.* **2003**, *103*, 3247−3261. (c) Carlier, P. R.; Mungall, W. S.; Schröder, G.; Sharpless, K. B. *J. Am. Chem. Soc.* **1988**, *110*, 2978−2979. (d) Choi, J. H.; Choi, Y. K.; Park, E. S.; Kim, E. J.; Kim, M.-J. *J. Org. Chem.* **2004**, *69*, 1972−1977. Asymmetric reduction of enones and ynones: (e) Noyori, R. *Angew. Chem., Int. Ed.* **2002**, *41*, 2008−2022. (f) Itsuno, S. *Org. React.* **1998**, 395−576. Synthesis of enantioenriched propargylic alcohols and subsequent reduction: (g) Anand, N. K.; Carreira, E. M. *J. Am. Chem. Soc.* **2001**, *123*, 9687−9688. (h) McKew, J. C.; Kurth, M. J. *Org. Proc. Proc. Int.* **1993**, *25*, 125−130. Asymmetric addition to unsaturated aldehydes: (i) Soai, K.; Niwa, S. *Chem. Rev.* **1992**, *92*, 833−856.
(11) Gololobov, Y. G.; Kasukhin, L. F. *Tetrahedron* **1992**, *48*, 1353−1406.
(12) Classification based on the allylic imidate rearrangement described in: Vögtle, F.; Goldschmitt, E. *Chem. Ber.* **1976**, *109*, 1−40.
(13) (a) Calter, M.; Hollis, T. K.; Overman, L. E.; Ziller, J.; Zipp, G. G. *J. Org. Chem.* **1997**, *62*, 1449−1456. (b) Hollis, T. K.; Overman, L. E. *Tetrahedron Lett.* **1997**, *38*, 8837−8840. (c) Uozumi, Y.; Kazuhiko, K.; Hayashi, T. *Tetrahedron: Asymmetry* **1998**, *9*, 1065−1072. (d) Cohen, F.; Overman, L. E. *Tetrahedron: Asymmetry* **1998**, *9*, 3213−3222. (e) Jiang, Y.; Longmire, J. M.; Zhang, X. *Tetrahedron Lett.* **1999**, *40*, 1449−1450. (f) Donde, T.; Overman, L. E. *J. Am. Chem. Soc.* **1999**, *121*, 2933−2934. (g) Leung, P.-H.; Ng, K.-H.; Li, Y.; White, A. J. P.; Williams, D. J. *Chem. Commun.* **1999**, 2435−2436. (h) Kang, J.; Yew, K. H.; Kim, T. H.; Choi, D. H. *Tetrahedron Lett.* **2002**, *43*, 9509−9512. (i) Kang, J.; Kim, T. H.; Yew, K. H.; Lee, W. K. *Tetrahedron: Asymmetry* **2003**, *14*, 415−418. (j) Anderson, C. E.; Donde, Y.; Douglas, C. J.; Overman, L. E. *J. Org. Chem.* **2005**, *70*, 648−657.

palladacycle catalysts described by Overman and co-workers.[14] This COP−X class of palladacycles has also proven to be the most effective catalyst for the (allyloxy) iminodiazaphospholidine rearrangement, with high enantioselectivities (up to 96%) and yields obtained.[15]

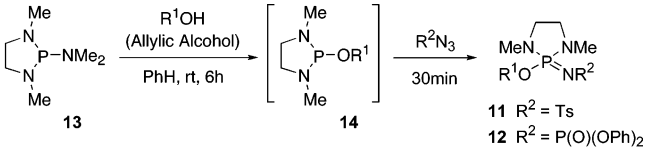
Results and Discussion

The feasibility of the (allyloxy) iminodiazaphospholidine rearrangement was demonstrated using **11** and **12** as substrates. These compounds were cleanly prepared in a one-pot process by the sequential treatment of allylic alcohols with phospholidine **13**,[16] as described by Alexakis and co-workers,[17] followed by reaction with tosyl azide and diphenylphosphoryl azide (DPPA),[18] respectively (Table 1).[19] The reaction was monitored by ^{31}P NMR to ensure complete conversion of the intermediate phosphoramidite **14** ($\delta \approx 130$ for **14**, whereas $\delta \approx 24$ for **11** and $\delta \approx 24$ and 10 ppm for **12**) (Figure 3). The iminodiazaphospholidines were then purified by silica gel chromatography, using Et_3N as an additive to prevent acid promoted decomposition.

Alternatively, the substrates could be prepared by treatment of PCl_3 sequentially with the diamine and allylic alcohol in the presence of Et_3N to generate the phosphorus(III) intermediate **15** (Scheme 2). Reaction of **15** with an azide then gives the desired substrates **11** and **12**. Although this route gives comparable yields, the procedure is less convenient because of the need for lower temperatures and filtration of the Et_3N·HCl salts generated.

Initial attempts at the thermal rearrangement of **11** were unsatisfactory, leading to products arising from both the desired [3,3] and the formal [1,3]-sigmatropic rearrangement pathways. For example, thermal rearrangement of diazaphospholidine **11c** at 130 °C in xylenes led to the [3,3]-product **16c** and [1,3] product **17c** in a 3.5:1 ratio (Scheme 3). Furthermore, thermal rearrangement of **11m** only yielded the [1,3]-product **17m**, whereas reaction of **11s** only yielded the [3,3]-product **16s**. The thermal rearrangements of **11m** and **11s** give the thermodynamically more stable allylic phosphoramides, suggesting that ionization of the diazaphospholidine substrates **11** and subsequent recombination is competitive under thermal conditions, particularly for those substrates that lead to more stable allylic carbocation intermediates.[20] Interestingly, the thermal aza-phospha-oxa-Cope rearrangements of phosphorimidates (in refluxing xylenes), reported by Mapp and Chen, give the [3,3]-products more cleanly.

Table 1. Preparation of (Allyloxy) Iminodiazaphospholidines



R^{1}OH (Allylic Alcohol)	Yield[a] (%)		Allylic Alcohol	Yield[a] (%)	
*n*Pr, OH	**11a**	91	OH	**11j**	91
	12a	-[d]		**12j**	89
*n*Pr, OH	**11b**	85	OH	**11k**	89
	12b	-[d]		**12k**	89
Et, OH	**11c**	92	OH, Et	**11l**	93
	12c	87		**12l**	86
Et, OH	**11d**	93	Ph, OH	**11m**	94
	12d	90		**12m**	91
TBSO, OH	**11e**	88	Ph, OH	**11n**	91
	12e	-[d]		**12n**	84
TBSO, OH	**11f**	91	OH, Ph	**11o**	–[b,c]
	12f	-[d]		**12o**	–[b,c]
Me, OH	**11g**	84	OH	**11p**	92
	12g	-[d]		**12p**	87
Me, OH	**11h**	86	Et, OH	**11q**	86
	12h	87		**12q**	78
OH	**11i**	95	Et, OH	**11r**	87
	12i	92		**12r**	80

[a] Isolated yields, 0.6 mmol scale. [b] These compounds could not be purified by silica gel column chromatography and were used crude in subsequent transformations. [c] Reaction conducted in benzene-d_6. [d] Substrates not prepared.

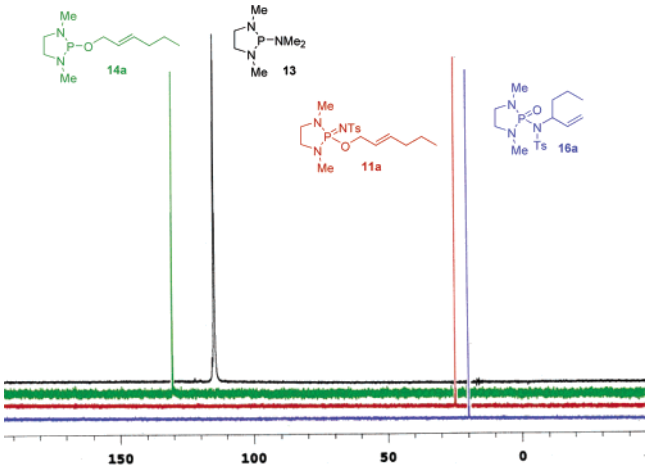


Figure 3. ^{31}P NMR of intermediates involved in the stepwise conversion of allylic alcohols into allylic amines via an aza-phospha-oxa-Cope rearrangement.

The lack of selectivity observed in the thermal rearrangements of the diazaphospholidines **11** can be overcome through the use of Pd(II) catalysis. A variety of Pd(II) catalysts were screened for the rearrangement of **11c** into **16c**, but only $PdCl_2(MeCN)_2$ was found to be an active catalyst.[21] In the presence of 5 mol

(14) (a) Overman, L. E.; Owen, C. E.; Pavan, M. M.; Richards, C. J. *Org. Lett.* **2003**, *5*, 1809−1812. (b) Anderson, C. E.; Overman, L. E. *J. Am. Chem. Soc.* **2003**, *125*, 12412−12413. (c) Kirsh, S. F.; Overman, L. E.; Watson, M. P. *J. Org. Chem.* **2004**, *69*, 8101−8104. (d) Kirsh, S. F.; Overman, L. E. *J. Org. Chem.* **2005**, *70*, 2859−2861.

(15) Lee, E. E.; Batey, R. A. 229th ACS National Meeting, San Diego, 2005, abstract 637.

(16) Prepared as described in: Hanessian, S.; Bennani, Y. L.; Leblanc, Y. *Heterocycles* **1993**, *35*, 1411−1424.

(17) Alexakis, A.; Mutti, S.; Mangeney, P. *J. Org. Chem.* **1992**, *57*, 1224−1237.

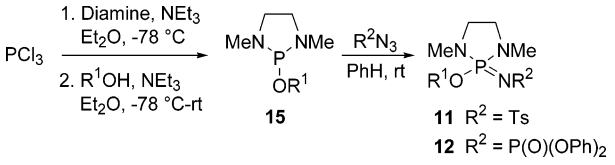
(18) Although we have experienced no problems with either of these azides, appropriate safety measures should be taken. For discussion on the hazards associated with azides, see: *Prudent Practices in the Laboratory: Handling and Disposal of Chemicals*; National Academy Press: Washington, DC, 1995.

(19) (a) Bellan, J.; Sanchez, M.; Marre-Mazières, M. R.; Beltran, A. M. *Bull. Chim. Soc. Fr.* **1985**, *3*, 491−495. (b) Marre, M. R.; Sanchez, M.; Brazier, J. F.; Wolf, R.; Bellan, J. *Can. J. Chem.* **1982**, *60*, 456−468.

(20) Mapp and Chen (ref 6a) have also reported mixtures of [3,3]-rearranged and formal [1,3]-rearranged products being formed under thermal conditions for phenyl substituted phosphorimidates.

(21) The following catalysts resulted in no reaction with complete recovery of **11c**: $PdCl_2$, $PdCl_2(PPh_3)_2$, $PdCl_2(PCy_3)_2$, $Pd_2Cl_2(allyl)_2$, $PdCl_2(COD)$.

Scheme 2



Scheme 3

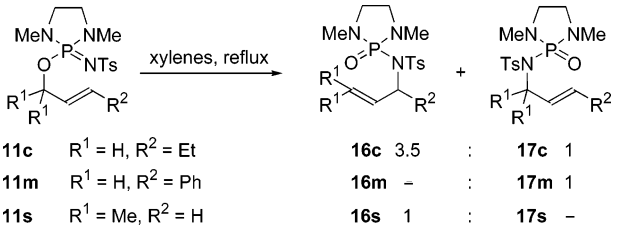
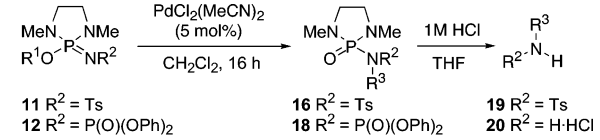
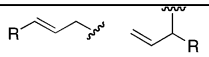
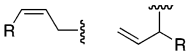
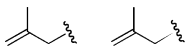


Table 2. Pd-Catalyzed [3,3]-Sigmatropic Rearrangement of (Allyloxy) Iminodiazaphospholidines and Their Subsequent Hydrolysis



Sub	R^1	R^3	Yield[a] (%)		Yield[a] (%)	
						
11a	R = *n*Pr		**16a**	91	**19a**	90
11c	R = Et		**16c**	95	**19c**	88
12c	R = Et		**18c**[b]	90	**20c**	81[c]
11e	R=CH_2OTBS		**16e**	88	**19e**	-
11g	R = Me		**16g**	88	**19g**	82
						
11b	R = *n*Pr		**16a**	85	**19a**	86
11d	R = Et		**16c**	93	**19c**	88
12d	R = Et		**18c**	89	**20c**	81[c]
11f	R=CH_2OTBS		**16e**	91	**19e**	-
11h	R = Me		**16g**	86	**19g**	80
11i			**16i**	95	**19i**	97
12i			**18i**[b]	91	**20i**	87[c]

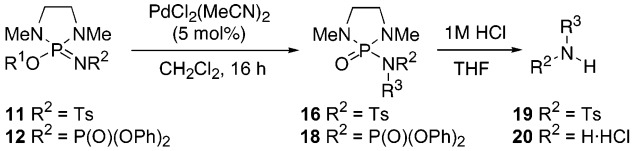
[a] Isolated yields, 0.6 mmol scale. [b] Conducted in the presence of 4 Å molecular sieves. [c] 1 M HCl in MeOH.

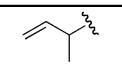
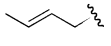
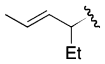
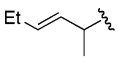
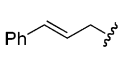
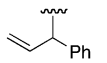
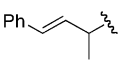
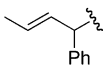
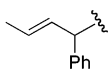
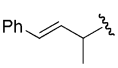
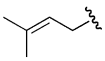
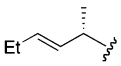
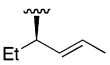
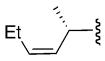
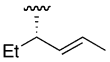
% $PdCl_2(MeCN)_2$, the rearrangement of both **11** and **12** proceeded smoothly at room temperature yielding only the [3,3]-products **16** and **18**, respectively (Table 2). In the reactions of the DPPA derived substrates **12**, the addition of 4 Å molecular sieves was required to ensure complete conversion into **18**. The rearrangements were conveniently monitored using ^{31}P NMR ($\delta \approx 20$ for **16** and $\delta \approx 20$ and -4 ppm for **18**) (Figure 3). The phosphoramides **16** and **18** were deprotected under acidic conditions, yielding allylic tosylamides **19** and the HCl salts of allylic amines **20**, respectively.[22]

A variety of substitution patterns are tolerated on the allylic substrates **11** and **12**, including substitution at the α-, β-, and

(22) Mizrahi, V.; Modro, T. A. *J. Org. Chem.* **1983**, *48*, 3030−3037.

Table 3. Pd-Catalyzed [3,3]-Sigmatropic Rearrangement of More Highly Substituted (Allyloxy) Iminodiazaphospholidines and Their Subsequent Hydrolysis



Sub	R^1	R^3	Yield[a] (%)		Yield[a] (%)	
11j			**16j**	91	**19j**	93
12j			**18j**[b]	86	**20j**	85[e]
11k			**16k**	88[c]	**19k**	90
12k			**18k**[b]	trace	-	-
11l			**16i**	90[c]	**19l**	83
12l			**18l**[b]	93	**20l**	79[e]
11m			**16m**	75[c]	**19m**	85
12m			**18m**[b]	n.r.[d]	-	-
11n			**16n**	76[c]	**19n**	80
12n			**18n**[b]	n.r.[d]	-	-
11o			**16o**	80[c]	**19o**	78
12o			**18o**[b]	n.r.[d]	-	-
11p			**16p**	n.r.[d]	-	-
12p			**18p**[b]	n.r.[d]	-	-
11q			**16q**	90	**19q**	82
12q			**18q**[b]	84	**20q**	78[e]
11r			**16r**	88	**19r**	90
12r			**18r**[b]	83	**20r**	78[e]

[a] Isolated yields, 0.6 mmol scale. [b] Conducted in the presence of 4 Å molecular sieves. [c] Conducted at 45 °C in toluene. [d] Only starting material was observed by ^{31}P NMR. [e] 1 M HCl in MeOH.

γ-positions of the allylic group. Notably, the reaction worked well for substrates substituted at the β position (**11i** and **12i**), as previous reports of metal-catalyzed allylic imidate rearrangements for these substrates have had mixed success.[23] Substrates derived from secondary alcohols, **11j**, **12j**, **11l**, and **12l**, all rearranged in good yields to afford only their respective *E*-isomers **16j**, **18j**, **16l**, and **18l**. Reactions of the 2-cyclohexenyl substrates were far more sluggish, with **11k** requiring heating at 45 °C and **12k** yielding only trace amounts of products after 48 h at 80 °C. A similar trend was observed with substrates **11m**−**o** and **12m**−**o**. It is apparent that the rearrangement works very well when unhindered substrates **11a**−**h** (Table 2) are used, while the more sterically demanding substrates **11m**−**o** (Table 3) react far more slowly. The steric limitations of this reaction are further emphasized by the lack of reactivity in the γ,γ-disubstituted substrates **11p** and **12p** and by the trend of lower reactivity for the bulky DPPA derived substrates.

Transposition of the enantioenriched *E*-substrates **11q** and **12q** produced only the *E*-phosphoramides **16q** and **18q** with clean transfer of chirality. The *Z*-substrates **11r** and **12r**

(23) Depending on the allylic imidate used, either prolonged reaction time was required or no reaction was observed: Metz, P.; Mues, C.; Schoop, A. *Tetrahedron* **1992**, *48*, 1071−1080 and references cited.

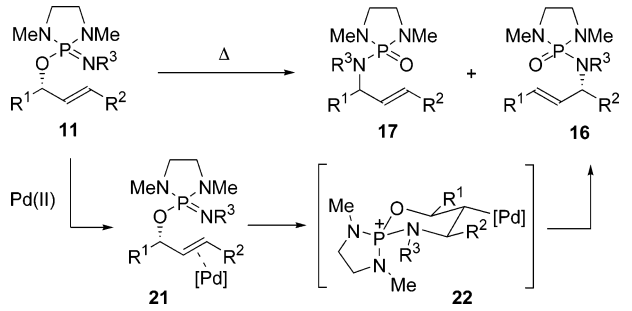


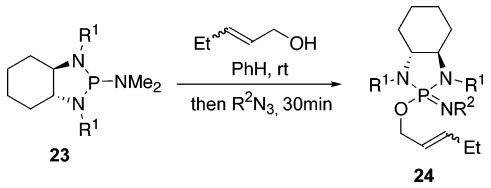
Figure 4. Proposed mechanism for palladium-catalyzed aza-phospha-oxa-Cope rearrangement.

rearranged to the *E*-products **16r** and **18r**, albeit, with slightly lower enantioenrichment.[24] The [3,3]-sigmatropic rearrangement presumably proceeds via intramolecular attack of the nitrogen lone pair on a palladium coordinated olefin **21**, followed by rearrangement of the resulting phosphonium intermediate **22** (Figure 4). The intermediacy of a π-complex **21** (R^1 = Me and R^2 = Et) and phosphonium ion **22** is analogous to the mechanism proposed for the rearrangement of allylic imidates (Figure 2).[3a,c,d] The absolute stereochemistry and olefin geometry of the products in both cases are consistent with this mechanism. Comparison of the ambient temperature Pd(II)-catalyzed reactions with the thermal rearrangement of **11** demonstrates the advantages of metal catalysis to achieve efficient [3,3]-sigmatropic rearrangement with these diazaphospholidine systems.

Diastereoselective Rearrangements. Inherent in the design and synthesis of the (allyloxy) diazaphospholidine structure was the potential to readily incorporate chiral auxiliaries in place of the diamine subunit. To prevent the potential complication of diastereomeric mixtures at the phosphorus center, our investigation was restricted to C_2 symmetric auxiliaries. The synthesis of tartrate derived substrates was unsuccessful as the azide Staudinger reaction required heating, resulting in a complex mixture of products. Utilizing *N*,*N*′-dialkyl cyclohexanediamine auxiliaries was more successful as the preparation and purification of phospholidine **24** could be accomplished in a fashion similar to that of the *N*,*N*′-dimethylethylenediamine derived substrates **11** and **12**. The use of chiral cyclohexanediamines is also convenient as the resolution[25] and substitution of trans cyclohexanediamine[26] has been well developed. Preparation of the phospholidine **23** was accomplished by heating the appropriate diamine with hexamethylphosphorus triamide[17] at 100 °C. The one-pot reaction of **23** with allylic alcohols and then azides yielded the desired chiral (allyloxy) diazaphospholidines **24** in good yields (Table 4).

Stirring the trans and cis substrates **24a** and **24c** at room temperature in the presence of 5 mol % $PdCl_2(MeCN)_2$ led to clean conversion to the desired products **25a** in 83% and 81% yield, respectively (Table 5). Interestingly, the same major diastereomer was formed in a ratio of 3.5:1 for both substrates. The analogous DPPA derived substrates **24b** and **24d** afforded the products in decreased yields and diastereoselectivities (1.7:1

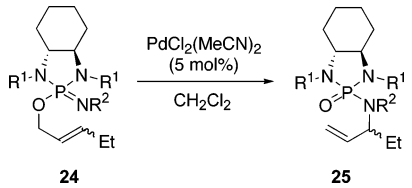
Table 4. Preparation of (Allyloxy) Iminodiazaphospholidines Incorporating a *N*,*N*′-Dialkyl Cyclohexanediamine Auxiliary



R^1	R^2	geometry	product	yield[a] (%)
Me	Ts	trans	**24a**	85
Me	$OP(OPh)_2$	trans	**24b**	73
Me	Ts	cis	**24c**	75
Me	$OP(OPh)_2$	cis	**24d**	81
*i*Pr	Ts	trans	**24e**	80
*i*Pr	$OP(OPh)_2$	trans	**24f**	78
Bn	Ts	trans	**24g**	85
Bn	$OP(OPh)_2$	trans	**24h**	82

[a] Isolated yields, 0.6 mmol scale.

Table 5. Diastereoselective Rearrangements of (Allyloxy) Iminodiazaphospholidines Incorporating an *N*,*N*′-Dialkyl Cyclohexanediamine Auxiliary



precursor	R^1	R^2	geometry	dr[b]	yield (%) **25**
24a	Me	Ts	trans	3.5:1	83[c]
24b	Me	$OP(OPh)_2$	trans	1.7:1	27[d]
24c	Me	Ts	cis	3.5:1	81[c]
24d	Me	$OP(OPh)_2$	cis	1.5:1	35[d]
24e	*i*Pr	Ts	trans	2.5:1	80
24f	*i*Pr	$OP(OPh)_2$	trans	1.5:1	77
24g	Bn	Ts	trans	1:1	73
24h	Bn	$OP(OPh)_2$	trans	1:1	85

[a] Isolated yields, 0.6 mmol scale. [b] Determined by ^1H and ^{31}P NMR integration. [c] Hydrolysis formed **19c** (56% ee in favor of the *S* enantiomer as determined by chiral HPLC; see Experimental Section in Supporting Information for absolute configuration assignment). [d] Formal [1,3]-rearrangement was the major side reaction.

and 1.5:1 dr, respectively). Deprotection of the chiral auxiliary with 1 M HCl yielded the allylic tosylamide **19c** in 56% ee in favor of the *S* enantiomer. A decrease in diastereoselectivity was observed for the *N*-isopropyl substrates substrates **24e** and **24f** (2.5:1 and 1.5:1 dr, respectively). Reaction of the *N*-benzyl substituted substrates **24g** and **24h** afforded the products as a 1:1 mixture of diastereoisomers.

We believe that the *R*,*R*-cyclohexanediamine adopts a conformation **26** similar to that described by Hanessian and coworkers in models explaining their asymmetric conjugate additions and cyclopropanations of crotyl and allyl phosphoramides.[27] Palladium(II) coordination to the two faces of the olefin[3d] and subsequent cyclization would produce the chairlike, cationic intermediates **27** or **28** (Scheme 4). The chairlike intermediate **27** leading to the minor diastereomer in this model is disfavored because of the steric interaction between the

(24) **11q** and **12q** (95% ee) were rearranged to give **16q** and **18q** with 91% ee, whereas **11r** and **12r** (95% ee) were rearranged to give **16r** and **18r** with 70% ee (determined by chiral HPLC).

(25) Resolution on 160 g scale: Larrow, J. F.; Jacobsen, E. N. *J. Org. Chem.* **1994**, *59*, 1939−1942.

(26) (a) Bennani, Y. L.; Hanessian, S. *Chem. Rev.* **1997**, *97*, 3161−3195. (b) Denmark, S. E.; Su, X.; Nishigaichi, Y.; Coe, D. M.; Wong, K.-T.; Winter, S. B. D.; Choi, J. Y. *J. Org. Chem.* **1999**, *64*, 1958−1967.

(27) (a) Hanessian, S.; Gomstyan, A. *J. Org. Chem.* **1993**, *58*, 5024−5032. (b) Hanessian, S.; Andreotti, D.; Gomtsyan, A. *J. Am. Chem. Soc.* **1995**, *117*, 10393−10394.

Scheme 4

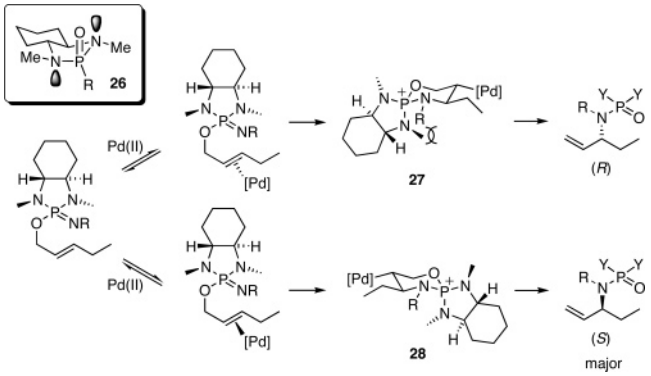
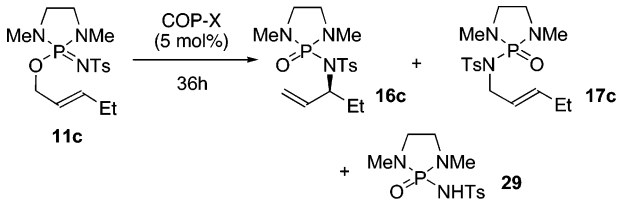


Table 6. Enantioselective Rearrangement Using COP−X Catalysts



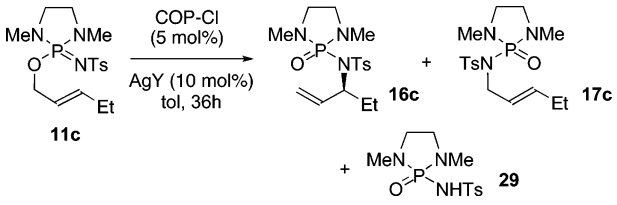
entry	X	solvent	*T*	**16c**[a] (%)/(ee)	**17c**[a] (%)	**11c**[a] (%)
1	OAc	CH_2Cl_2	room temp			100
2	OAc	Tol	90	trace		99
3	Cl	CH_2Cl_2	room temp	trace		99
4	Cl/4 Å MS	CH_2Cl_2	room temp		13	87
5	Cl	Tol	50	27		73
6	Cl/4 Å MS	Tol	50		78	22
7	Cl	Tol	100	33/(70)	7[b]	49
10	Cl/4 Å MS	Tol	100	24	61	15
11	Cl	Tol	120	47/(69)	8[c]	25
12	Cl	Tol	140[d]	30/(57)	8	62

[a] Ratio determined by ^{31}P NMR integration. [b] 11% of the ionized product **29** was observed. [c] 20% of the ionized product **29** was observed. [d] Heated for 1.5 h in a microwave reactor.

nitrogen substituent R (tosyl or phosphoryl) and the *pseudo*-axial methyl substituted nitrogen of the chiral diamine. The cis substrate presumably reacts through a boatlike intermediate to alleviate 1,3-diaxial interactions in the cyclic intermediate, thus giving rise to the same diastereomer.

Enantioselective Rearrangements. Initial attempts at the enantioselective rearrangement of substrates **11c** and **11d** proved disappointing, with most palladium(II) catalyst/ligand combinations resulting in no reaction. Not surprisingly, as reported for the allylic imidate rearrangement,[13a] phosphine-containing ligands such as (*R*)-BINAP, or (*R*,*S*)-Josiphos resulted in no reaction, and only recovery of starting material. Early generation ligands successful in allylic imidate rearrangements such as the oxazolidinyl-phosphine, bis-oxazoline, or diamine-based ligands also showed negligible reactivity. Most surprisingly was the lack of reactivity when utilizing the chiral cobalt oxazoline palladacycles (COP−X) successfully utilized in the enantioselective rearrangement of allylic imidates.[14] Reaction of substrate **11c** in the presence of 5 mol % COP−OAc in CH_2Cl_2 at room temperature or at 90 °C in toluene showed only starting material when monitored by ^{31}P NMR (Table 6, entries 1 and 2). For reaction of **11c** using the chloride analogue COP−Cl, no reaction was observed at room temperature, while a 27% conversion to product **16c** could be effected at 50 °C (Table 6, entries 3 and 5). Interestingly, reaction of **11c** in the presence of powdered 4 Å molecular sieves and COP−Cl at room temperature led to the formation of the formal [1,3]-product **17c** in 13% yield. Under the same conditions at 50 °C in toluene, 78% conversion to **17c** was observed. Heating the reaction of **11c** with COP−Cl at 100 °C in toluene for 36 h resulted in low conversion (33%) to the desired product **16c** in 70% ee. Under the same conditions, the deleterious effect of 4 Å molecular sieves is again clearly evident, as the conversion to product **16c** is lowered to 24% and the conversion to the formal [1,3]-product **17c** is increased to 61%. Heating the reaction at 120 °C, or at 140 °C under microwave irradiation, led to a decrease in the observed enantioselectivity of **16c**, presumably as a result of competing thermal rearrangement, as well as ionization of the substrate to the byproduct **29**.

Table 7. Counterion Effect on COP−Cl-Catalyzed Rearrangements



entry	*T*	AgY	**16c**[a] (%)/(ee)	**17c**[a] (%)	**29**[a] (%)	**11c**[a] (%)
1	90	Ag_3PO_4	9	5	0	86
2	90	AgF	16	9	7	68
3	90	$AgSbF_6$	12	28	30	30
4	90	AgOTf	16	40	34	10
5	50	AgOTs	31/(81)	7	12	50
6	50	$AgNO_3$	31/(82)	4		65
7	90	AgTFA	35/(79)	tr		64

[a] Ratio determined by ^{31}P NMR integration.

As the nature of the catalyst counterion has been demonstrated to greatly affect the reactivity of palladium catalysts used in the asymmetric allylic imidate rearrangements, we modified the COP−Cl catalyst by addition of a variety of silver(I) salts. Interestingly, the counterion of the silver salt plays a significant role in the formation of the two undesired products **17c** and **29**. The addition of Ag_3PO_4 or AgF to the reaction was the most detrimental as only small quantities of any products were observed (Table 7, entries 1 and 2). The addition of $AgSbF_6$ and AgOTf increased the conversion of starting material mostly to the undesired formal [1,3]-product **17c** and ionized product **29** (Table 6, entries 3 and 4). Greater success was realized with the use of AgOTs and $AgNO_3$ as additives. At 50 °C in both cases, minimal side products were formed, and the desired rearrangements were achieved in 31% yield with 81% and 82% ee, respectively. The best result was obtained with AgTFA at 90 °C, giving the desired product **16c** in 35% yield with 79% ee, and with only a trace amount of the formal [1,3]-product **17c** observed.

Increasing the substrate concentration to 0.8 M and stirring at 70 °C for 40 h increased the yield of **16c** to 60% and the enantiomeric excess to 82% (Table 8). At a concentration of 0.8 M, lowering the temperature to 50 °C and room temperature resulted in an increase in enantioselectivity to 84% and 86% ee, respectively. Unfortunately, the increase in selectivity achieved at lower temperatures was accompanied by a drastic decrease in the yield of **16c** to 43% and 16% respectively. To

Table 8. Enantioselective Rearrangements with COP−Cl and AgTFA

sub	R	*T* (°C)	[**11**] (M)	*t* (h)	yield[a]		ee[b,c] (%)
11c	*trans*-Et	70	0.8	40	**16c**	60	82/*S*
11c	*trans*-Et	50	0.8	40	**16c**	43	84/*S*
11c	*trans*-Et	rt	0.8	40	**16c**	16	86/*S*
11d	*cis*-Et	50	0.8	40	**16c**	97	92/*R*
11a	*trans*-*n*Pr	45	2.0	60	**16a**	55	86/*S*
11b	*cis*-*n*Pr	45	0.8	40	**16a**	90	96/*R*
11c	*trans*-Et	45	2.0	60	**16c**	60[d]	84/*S*
11d	*cis*-Et	45	0.8	10	**16c**	92[d]	93/*R*
11d	*cis*-Et	rt	0.8	40	**16c**	88	94/*R*
11e	(*E*)-CH_2OTBS	45	2.0	60	**16e**	44	86/*S*
11f	(*Z*)-CH_2OTBS	45	2.0	60	**16e**	82	92/*R*
11g	*trans*-Me	45	2.0	60	**16g**	45	86/*S*
11h	*cis*-Me	45	2.0	40	**16g**	86	91/*R*

[a] Isolated yields. [b] Determined by deprotection to **16** and chiral HPLC analysis. [c] Refer to Supporting Information for absolute configuration assignment. [d] Similar results are obtained when the reaction is carried out in CH_2Cl_2 in a sealed tube.

our surprise, a significantly improved result was obtained for the cis substrate **11d**. The cis substrate **11d** was cleanly rearranged in 97% yield and 92% ee, when stirred for 40 h at 50 °C. The improved reactivity of cis substrates over trans substrates was observed for a series of alkyl substituents on the olefin. The highest enantioselectivity of 96% was observed for reaction of *cis*-*n*Pr substrate **11b**, formed in 90% yield. The *cis*-CH_2OTBS **11f** and *cis*-Me **11h** substrates were also obtained in good yields (82% and 86%) and with high enantioselectivities of 92% and 91%, respectively.

In comparison to the corresponding cis analogues, reaction of the *trans*-substrates (**11a**, **11c**, **11e**, **11f**) occurred in slightly lower enantioselectivities (82−86% ee), but in significantly lower yields, even at an increased reaction concentration of 2.0 M. Intriguingly, Overman has reported an opposite trend for the COP−Cl promoted rearrangements of *cis*-allylic imidates, which rearrange in lower yields and enantioselectivities than their trans analogues.[28] In all cases, only unreacted starting material **11** was observed as monitored by ^{31}P NMR of the crude reaction mixtures. When the cis and trans substrates **11d** and **11c** were periodically monitored by ^{31}P NMR over a 100 h span, it was clear that the rate of reaction of the cis substrate **11d** is faster than the trans substrate **11c** at 45 °C, as nearly complete conversion of **11d** is accomplished in 10 h. In contrast, the trans substrate **11c** reaches only 45% conversion in the same amount of time. The difference in initial reaction rates of the two substrates **11d** and **11c** was estimated to be 14 times faster for the reaction of the *cis*-substrates **11d**.

(28) For rearrangement of the imidate derived from *trans*-2-hexenol and trichloroacetonitrile, 99% yield and 95% ee was obtained. For the *cis*-2-hexenol derived imidate, 17% yield and 71% ee was obtained (see ref 14b).

Conclusion

In conclusion, a novel palladium(II)-catalyzed rearrangement of (allyloxy) iminodiazaphospholidines has been developed for the synthesis of allylic amines and tosylamides. The overall process involves displacement on phospholidine **13** with an allylic alcohol to give a phosphoramidite followed by Staudinger reaction and Pd(II)-catalyzed aza-phospha-oxa-Cope rearrangement. Diastereoselective rearrangements of **24** were carried out in good yields with diastereoselectivities as high as 3.5:1. Interestingly, in these rearrangements, the same major diastereomer was formed from both the trans and the cis starting substrates. The first enantioselective rearrangements of iminodiazaphospholidines were also achieved by the use of the cobalt oxazoline palladacycles (COP−X) class of catalysts. There is a very dramatic dependence on the catalyst counterion and olefin geometry for the COP−Cl catalyst system. With reasonably low catalyst loading at 45 °C, cis substrates of **11** underwent rearrangement in high yields (up to 97%) and enantioselectivities (up to 96% ee). These results demonstrate the synthetic utility of the COP−X family of catalysts for enantioselective [3,3]-sigmatropic rearrangements other than the Overman rearrangement.

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Supporting Information Available: Experimental procedures for substrate preparation, substrate rearrangement, characterization, spectra (^{1}H, ^{13}C NMR), and HPLC traces used to determine enantiopurity for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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