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[2,3]-Sigmatropic Rearrangements of 2-Phosphineborane 2-Propen-1-ols: Rapid Access to Enantioenriched Diphosphine Monoxide Derivatives

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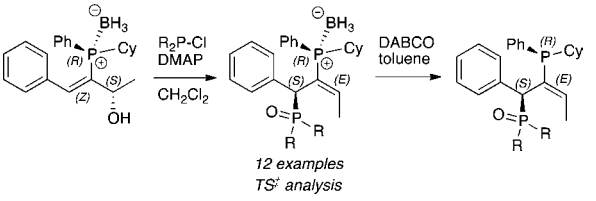
ABSTRACT



Hydrophosphination of secondary propargylic alcohols generates phosphine-containing allylic alcohols that undergo facile [2,3]-sigmatropic rearrangements with chlorophosphines, furnishing highly enantioenriched, crystalline diphosphine monoxides. The configuration at the newly formed stereocenter is opposite to that expected based on prior studies, and an ab initio computational evaluation of the possible transition states was performed to help explain the stereochemical course of the reaction.

Allylic alcohols and their derivatives demonstrate a large number of useful transformations with both nucleophiles and electrophiles.[11] We have recently developed the first uncatalyzed hydrophosphination of propargylic alcohols and amines with phosphine boranes.[2,3] These facile reactions proceed at or below ambient temperature and utilize bench-stable phosphine boranes rather than pyrophoric-free phosphines.[4] The phosphine-containing products derived from propargylic alcohols possess an allylic alcohol moiety that can be utilized to introduce additional carbon–heteroatom bonds onto the carbon chain. Previous studies by Knochel[5] on [2,3]-sigmatropic rearrangements of allylic alcohols (lacking any phosphine substitution) with chlorophosphines inspired us to examine the reactivity

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(1) For reviews, see: (a) Emer, E.; Sinisi, S.; Capdevila, M. G.; Petruzziello, D.; De Vincentiis, F.; Cozzi, P. G. *Eur. J. Org. Chem.* **2011**, 647–666. (b) Lu, Z.; Ma, S. *Angew. Chem.* **2008**, *120*, 264–303. *Angew. Chem., Int. Ed.* **2008**, *47*, 258–297. (c) Pfaltz, A.; Lautens, M. Allylic Substitution Reactions. In *Comprehensive Asymmetric Catalysis I–III*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer-Verlag: Berlin, 1999; pp 833–884. (d) Trost, B. M.; Zhang, T.; Sieber, J. D. *Chem. Sci.* **2010**, *1*, 427–440.

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(3) See also: Mimeau, D.; Gaumont, A.-C. *J. Org. Chem.* **2003**, *68*, 7016–7022.

(4) Staubitz, A.; Robertson, A. P. M.; Sloan, M. E.; Manners, I. *Chem. Rev.* **2010**, *110*, 4023–4078.

(5) (a) Liron, F.; Knochel, P. *Chem. Commun.* **2004**, 304–305. (b) Dermay, S.; Harms, K.; Knochel, P. *Tetrahedron Lett.* **1999**, *40*, 4981–4984.

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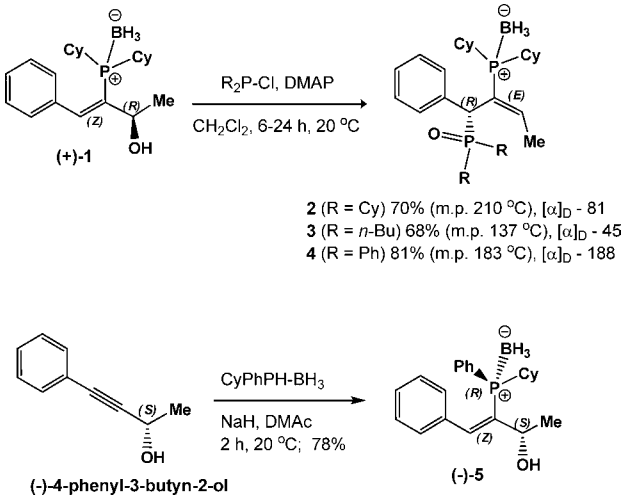
of the new hydrophosphination adducts toward phosphorus electrophiles. As shown in Scheme 1, treatment of (*R*)-(+)-**1** with three different chlorophosphines R_2P-Cl generated the rearrangement products (*E*)-**2**, -**3**, and -**4** in good overall yields as single enantiomers. The configuration at the new stereocenter was anticipated to be (*S*) on the basis of the suprafacial nature of the rearrangement[6] and earlier precedent,[5] yet a VCD analysis of **4** (Figure 1) showed that the new stereogenic carbon had in fact the (*R*)-configuration.

Scheme 1. Rearrangements of Allylic Alcohol (+)-**1**



Next, 12 different aryl- and alkylchlorophosphines[5] were examined in the rearrangement of *P*-chiral alcohol (S,R_P)-(−)-**5**, as shown in Table 1. Alcohol (−)-**5** was obtained from the base-mediated, uncatalyzed hydrophosphination of enantioenriched (−)-phenylbutynol, as previously reported (Scheme 1).[2] The rearrangement products of (−)-**5** were generally formed as single diastereomers with *E*-geometries, and each of the bis-phosphineborane derivatives **6a**–**l** was isolated in good yield as a crystalline solid. X-ray structures of two products, **6d** and **6l**, derived from aryl and alkyl chlorophosphines, respectively, show that the isolated products also possess the unexpected (*S*)-configuration at the newly formed stereogenic carbon (Figure 2), in agreement with the stereochemical course of the reaction observed for (+)-**1**.

The [2,3]-sigmatropic rearrangement allowed access to a broad variety of allylic phosphine oxides. *Ortho*-substituents on the phenyl rings of **6a** were well tolerated, as were electron-donating groups such as the methoxide functions in **6c** and **6d**. The conversion was also high with naphthyl (**6e**) and furan (**6i**) groups on the phosphine oxide. Finally,

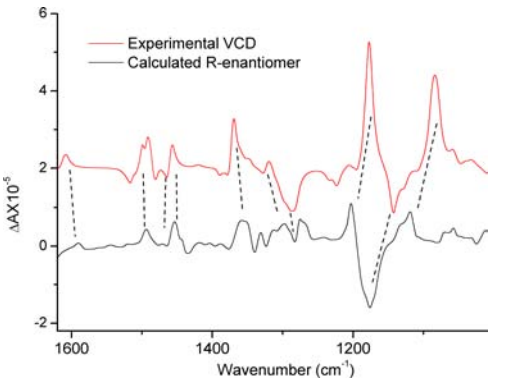


Figure 1. Calculated and experimental VCD spectra of phosphine oxide **4**.

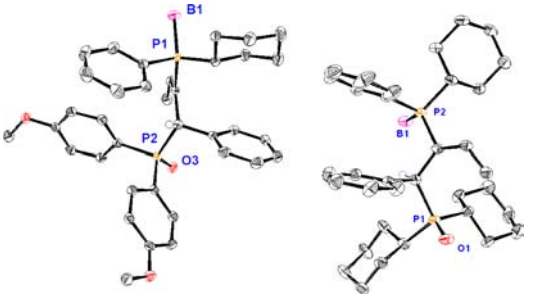


Figure 2. Crystal structures of **6d** (left) and **6l** (right).

straight alkyl chains, such as in **6k** and **6j**, as well as branched chains, such as the cyclohexyl substituents in **6l**, did not interfere with the process.

In all cases, a uniform stereochemical course was observed, and the *P*-chirality had no apparent effect on the rearrangement.[7]

The unexpected stereochemical outcome of the reaction was further explored through an ab initio analysis of the transition state of the [2,3]-rearrangement leading to **6l** (Figure 3). Models for the conversion of **5** to the (*R*,*Z*)-isomer **6l*** and the (*S*,*E*)-isomer **6l** were minimized using molecular mechanics calculations in Spartan'10,[8] and the resulting geometries were subjected to a transition-state calculation at the HF-6311+G** level of theory. TS_A leading to **6l*** was found to be 5.0 kcal/mol higher in energy than the transition state TS_B leading to the (*S*,*E*)-isomer **6l**. This difference in energy is mainly due to a significant $A^{1,2}$-interaction between the methyl substituent and the phosphine−borane group in TS_A, which provides a more severe steric clash than the $A^{1,3}$-strain between the methyl group and the allylic substituents in TS_B. Accordingly, the presence of the bulky phosphine−borane substituent at the 2-position of the alkene redirects the stereochemical

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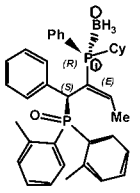
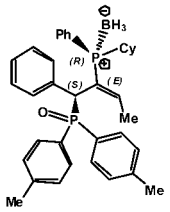
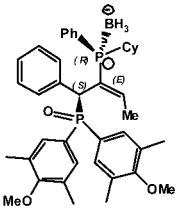
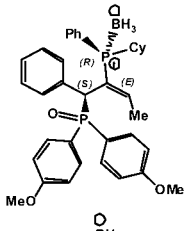
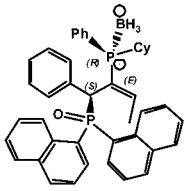
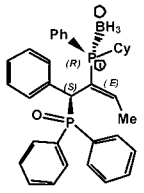
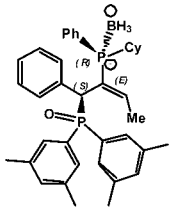
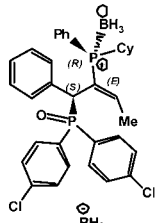
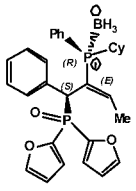
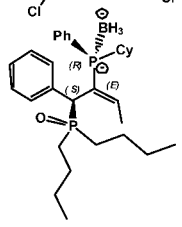
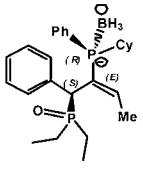
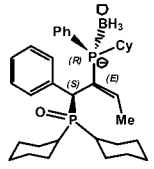
(7) (a) Legrand, O.; Brunel, J. M.; Buono, G. *Tetrahedron* **2000**, *56*, 595–603. (b) Velder, J.; Robert, T.; Weidner, I.; Neudoerfl, J.-M.; Lex, J.; Schmalz, H.-G. *Adv. Synth. Catal.* **2008**, *350*, 1309–1315. (c) Tayama, E.; Otoyama, S.; Tanaka, H. *Tetrahedron: Asymmetry* **2009**, *20*, 2600–2608. (d) Miyata, O.; Hashimoto, J.; Iba, R.; Naito, T. *Tetrahedron Lett.* **2005**, *46*, 4015–4018. (e) Denmark, S. E.; Marlin, J. E.; Rajendra, G. *J. Org. Chem.* **2013**, *78*, 66–82.

(8) Wavefunction, Inc., Irvine, CA.

Table 1. Rearrangement Products

product	time (h)	yield[a] (%)	structure	product	time (h)	yield[a] (%)	structure
6a	24	76		**6b**	18	65	
6c	36	70		**6d**	36	77	
6e	2	80		**6f**	24	69	
6g	24	66		**6h**	36	74	
6i	24	72[b]		**6j**	24	78	
6k	2	78		**6l**	2	75	

course of the sigmatropic rearrangement opposite to the results previously obtained by Knochel et al.[5]

Amine-mediated deprotection of BH_3-protected diphosphine monoxides provides the corresponding diphosphines in high yield. Treatment of **6l**, for example, with DABCO in toluene at 70 °C led to the deboronated **7** in 87% yield (Scheme 2).[9] The structure of this diphosphine was confirmed by X-ray analysis (Figure 4). The conformation of **7** is very similar to that of **6l** in the solid state; the

(9) (a) Imamoto, T.; Oshiki, T.; Onozawa, T.; Kusumoto, T.; Sato, K. *J. Am. Chem. Soc.* **1990**, *112*, 5244–5252. (b) Imamoto, T.; Watanabe, J.; Wada, Y.; Masuda, H.; Yamada, H.; Tsuruta, H.; Matsukawa, S.; Yamaguchi, K. *J. Am. Chem. Soc.* **1998**, *120*, 1635–1636.

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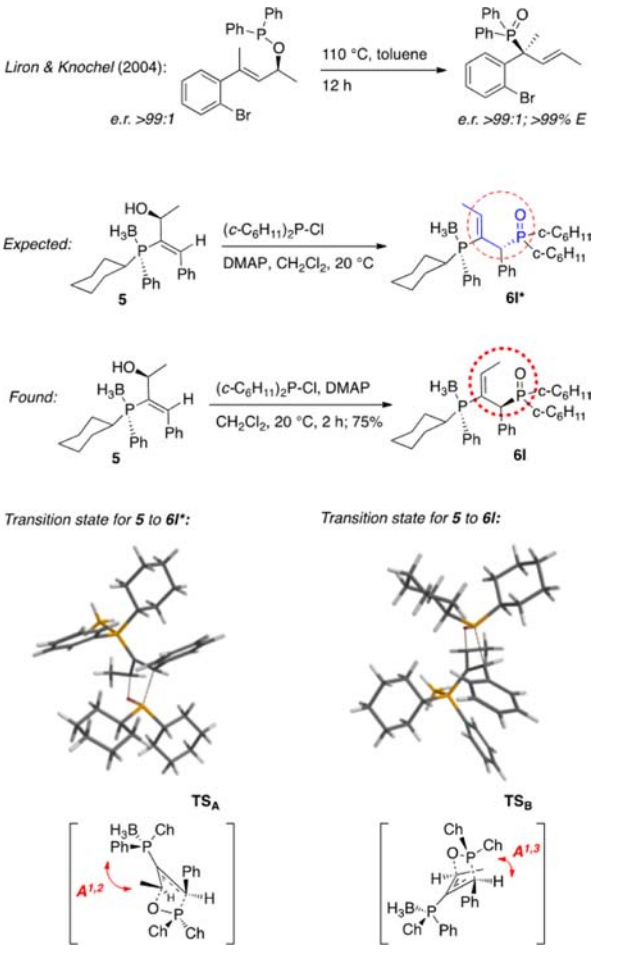
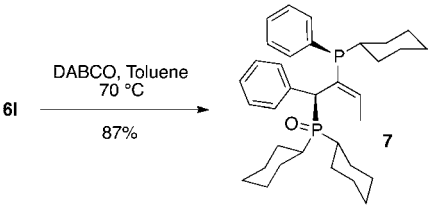


Figure 3. Ab initio transition-state analysis of the [2,3]-rearrangement of (S,R_P)-(−)-**5**.

only major difference is the rotation of P2 to minimize the allylic strain.

In conclusion, we have developed a new, straighforward synthesis of BH_3-protected diphosphine monoxides. Mild hydrophosphination of enantioenriched propargylic alcohols provides 2-phosphineborane 2-propen-1-ols, which

Scheme 2. Deprotection of Diphosphine **6l**



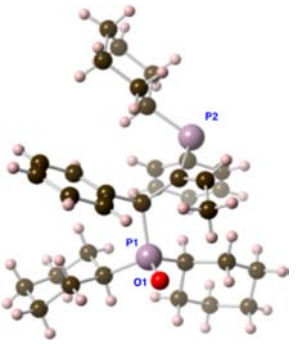


Figure 4. Crystal structure of **7**.

can be subjected to a stereospecific [2,3]-sigmatropic rearrangement with chlorophosphines to give diversely substituted diphosphine monoxides in high overall yields. After removal of the borane protective group, these novel P−P species with stereogenic phosphorus and carbon atoms can serve as chiral ligands in catalytic asymmetric transformations,[9,10] and we are currently investigating pertinent applications.

Supporting Information Available. Experimental procedures, compound characterization, and chiral HPLC analyses. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.