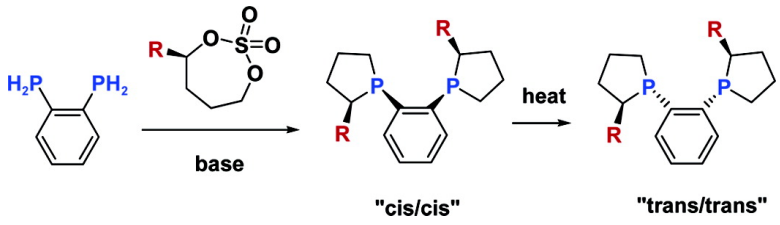
Communication

Stereoselective Cyclization and Pyramidal Inversion Strategies for P-Chirogenic Phospholane Synthesis

Garrett Hoge

J. Am. Chem. Soc., **2004**, 126 (32), 9920-9921• DOI: 10.1021/ja048079l • Publication Date (Web): 23 July 2004



More About This Article

Additional resources and features associated with this article are available within the HTML version:

- Supporting Information
- Links to the 2 articles that cite this article, as of the time of this article download
- Access to high resolution figures
- Links to articles and content related to this article
- Copyright permission to reproduce figures and/or text from this article

View the Full Text HTML

J|A|C|S
COMMUNICATIONS

Published on Web 07/23/2004

Stereoselective Cyclization and Pyramidal Inversion Strategies for P-Chirogenic Phospholane Synthesis

Garrett Hoge*

Pfizer Global Research and Development, 2800 Plymouth Road, Ann Arbor, Michigan 48105

Received April 2, 2004; E-mail: garrett.hoge@pfizer.com

Many contemporary bisphosphine ligands for asymmetric hydrogenation applications are P-chirogenic.[1] However, despite the current popularity of this motif, direct methodologies for producing single enantiomer P-chirogenic compounds remain scarce. Our recent efforts in this area were dedicated to the synthesis of P-chirogenic ligand **1** (Figure 1) and its application to the highly enantioselective rhodium-catalyzed asymmetric hydrogenation of a substrate precursor to the pharmaceutical candidate, pregabalin.[2] Desiring to diversify our ligand library, ligands such as 1,2-bisphospholanobenzene **2** were enticing targets. However, ligand **1** was synthesized via $CuCl_2$-promoted oxidative coupling of the *s*-BuLi generated methyllithium anion of **3**. It was apparent that a nonparallel synthetic approach would be required for the synthesis of P-chirogenic bisphospholanobenzenes.

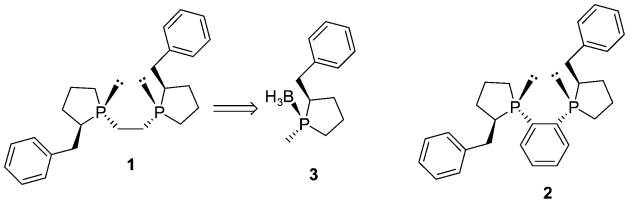
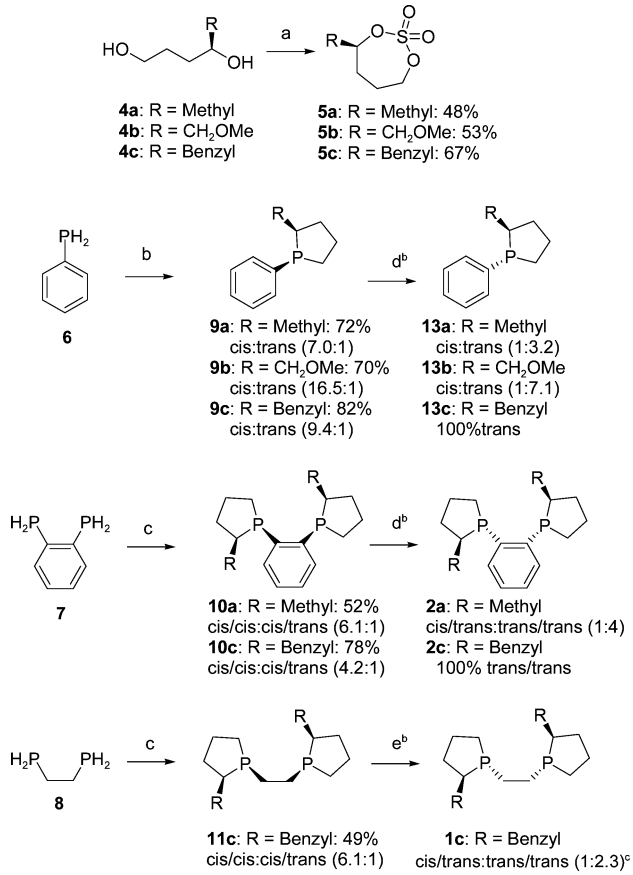


Figure 1. Retrosynthetic analysis of 1,2-bisphospholanoethane, **1**, and structure of 1,2-bisphospholanobenzene, **2**.

A classic approach to the synthesis of phospholane ring systems employs the reaction of lithium phosphide anions (derived from deprotonation of primary phosphines) with symmetrical cyclic sulfates (derived from chiral 1,4-diols).[3] Vedejs has reported the utilization of this approach to synthesize P-chirogenic monophospholanes from unsymmetrical cyclic sulfates.[4] Desiring to apply this methodology to a broader range of mono- and bisphospholanes, unsymmetrical cyclic sulfates **5a**−**5c** were synthesized from chiral 1,4-diols **4a**−**4c**. The diols **4a**,**4b** were accessible on 50-g scale from L-glutamic acid via literature methods,[5] while **4c** was synthesized as previously described from (*S*)-2,3-epoxypropylbenzene (Scheme 1).[2] Under similar conditions to those reported by Vedejs,[4] we found that reaction of the lithium phosphide anions of **6**−**8** with cyclic sulfates **5a**−**5c** produced phospholanes **9**−**11** (Scheme 1). Interestingly, the cyclizations provided good selectivity for cis monophospholanes and cis/cis bisphospholanes in all cases (Scheme 1).[6,7] No trans/trans isomer was observed from cyclization in any of the bisphospholane cases. Despite the opposite configuration of **10c** (cis/cis) with respect to that of target ligand **2** (trans/trans) this cyclization method offers a unique foray into a synthetically challenging P-chirogenic compound class.

Having uncovered an acceptable method for producing the P-chirogenic five-membered ring phospholane scaffold, it was speculated that thermodynamically driven pyramidal inversion might promote the conversion of predominantly cis or cis/cis adducts to trans or trans/trans products. Pyramidal inversion is a well-known phenomenon for phosphines[8] as well as for other

Scheme 1. Stereoselective Cyclization and Epimerization[a]



[a] Reagents and conditions: (a) (1) $SOCl_2$, CH_2Cl_2, 0 °C; (2) $RuCl_3$, $NaIO_4$, $CH_2Cl_2/CH_3CN/H_2O$, 0 °C → 25 °C. (b) (1) 1 equiv *n*-BuLi, THF, 0 °C; (2) **5**; (3) 1 equiv *n*-BuLi. (c) (1) 2 equiv *n*-BuLi, THF, 0 °C, (2) **5** (3) 2 equiv *n*-BuLi; (d) 190 °C, 8 h; (e) 205 °C, 20 h. [b] One-pot sequential cyclization and epimerization. Epimerization yields were essentially equal to cyclization yields. [c] 4% of the cis/cis isomer remained unepimerized.

atoms.[9] However, this subtle transformation has been under-utilized in practical synthesis of P-chirogenic phosphines. Epimerization via pyramidal inversion is an ideal reaction in terms of atom efficiency and workup. Reagents and solvent are not necessary to promote the transformation. Heating is the only requirement.[10] Provided that decomposition of the epimerization substrate or product does not occur at reaction temperature (or, in the case of phosphorus epimerization, that oxygen is not present to promote phosphine oxide formation), epimerization yields can easily approach 100%.

When epimerized products were desired, it was convenient to cyclize and then epimerize via a one-pot procedure (Scheme 1). Solvent from cyclization reactions was merely removed in vacuo, and then the resulting residue (a mixture of predominantly cis or

10.1021/ja048079l CCC: $27.50

cis/cis phospholanes and sulfate salts) was heated to the appropriate temperature without solvent in an oil bath under a nitrogen atmosphere. While **2c** and **13c** were isolated as completely epimerized products, the methyl- and methoxymethyl-substituted compounds, **2a** and **13a,13b** showed incomplete epimerization under the same conditions.[11] Phospholane **1c** was even more difficult to epimerize despite a higher applied temperature (205 vs 190 °C).

The mechanism for pyramidal inversion-induced epimerization likely involves a transition state featuring an sp^2 phosphorus atom that is in equilibrium with each form of the phospholane, **9** (cis) and **13** (trans), as shown in Figure 2. The reaction is driven toward the more thermodynamically stable trans phospholane, **13**. That **9a** and **10a** provide relatively lower conversions to cis and cis/cis phospholanes **13a** and **2a** may be a function of similar energies of cis vs trans isomers as a result of lessened steric effects from the small methyl substituents of each compound.

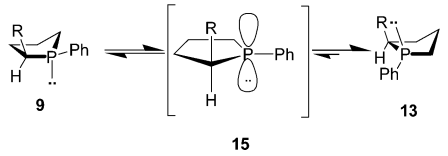
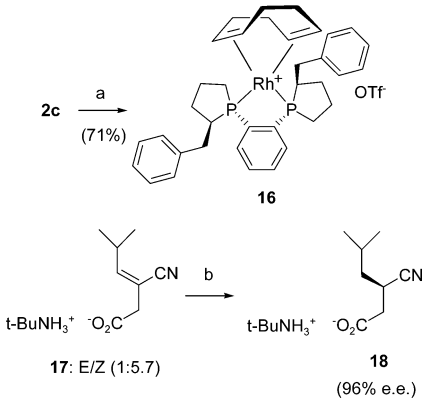


Figure 2. Pyramidal inversion mechanism.

To highlight the potential utility of the trans/trans bisphospholanes reported in this communication, ligand **2c** was converted to cationic rhodium complex **16** (Scheme 2). Rhodium complex **16** was then used as a catalyst for the asymmetric hydrogenation of **17** to form **18**. Product **18** was the sole hydrogenation product with 96% enantiomeric excess. The (*S*) isomer of **18** is a precursor to pharmaceutical candidate pregabalin.[2,12]

Scheme 2. Asymmetric Hydrogenation of a Pregabalin Precursor[a]



[a] Reagents and conditions: (a) 1. $[Rh(COD)_2]^+$ OTf^-, MeOH; 2. recrystallization from THF. (b) 1 mol % **16**, MeOH, 30 psi H_2, 25 °C, 2 h.

In conclusion, stereoselective cyclization and epimerization via pyramidal inversion have been demonstrated as viable routes for the synthesis of a variety of P-chirogenic phospholanes. Given the generality of the two approaches we speculate that these methodologies may find applicability to the synthesis of as yet undiscovered P-chirogenic ligands as well as new synthetic routes to those that are known already. Furthermore, the use of **2c** in the highly enantioselective rhodium-catalyzed asymmetric hydrogenation of **17** bodes well for broader application of the ligands presented in this communication.

Acknowledgment. I thank Brian Samas for assistance with X-ray crystallography of phospholanes. Pfizer, Inc. is acknowledged for continuing support of this research.

Supporting Information Available: Synthetic procedures, proof of relative and absolute phospholane stereochemistry, spectral data, representative determinations of the ratio of phospholane diastereomers, and methods for converting to and purifying their borane and sulfide adducts. This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) (a) Imamoto, T.; Watanabe, J.; Wada, Y.; Masuda, H.; Yamada, H.; Tsuruta, H.; Matsukawa, S.; Yamaguchi, K. *J. Am. Chem. Soc.* **1998**, *120*, 1635−1636. (b) Yamanoi, Y.; Imamoto, T. *J. Org. Chem.* **1999**, *64*, 2988−2989. (c) Tsuruta, H.; Imamoto, T. *Tetrahedron: Asymmetry* **1999**, *10*, 877−882. (d) Miura, T.; Imamoto, T. *Tetrahedron Lett.* **1999**, *40*, 4833−4836. (e) Ohashi, A.; Imamoto, T. *Org. Lett.* **2001**, *3*, 373−375. (f) Oohara, N.; Katagiri, K.; Imamoto, T. *Tetrahedron: Asymmetry* **2003**, *14*, 2171−2175. (g) Tang, W.; Zhang, X. *Angew. Chem., Int. Ed.* **2002**, *41*, 1612−1614. (h) Tang, W.; Wang, W.; Chi, Y.; Zhang, X. *Angew. Chem., Int. Ed.* **2003**, *42*, 3509−3511. (i) Hoge, G.; Wu, H.-P.; Kissel, W. S.; Pflum, D. A.; Greene, D. J.; Bao, J. *J. Am. Chem. Soc.* **2004**, *126*, 5966−5967.

(2) Hoge, G. *J. Am. Chem. Soc.* **2003**, *125*, 10219−10227.

(3) Burk, M. J. *J. Am. Chem. Soc.* **1991**, *113*, 8518−8519.

(4) (a) Vedejs, E.; Daugulis, O. *J. Am. Chem. Soc.* **1999**, *121*, 5813−5814. (b) Vedejs, E.; Daugulis, O. *J. Am. Chem. Soc.* **2003**, *125*, 4166−4173.

(5) (a) Herdeis, C. *Synthesis* **1986**, 232−233. (b) Brunner, H.; Lautenschlager, H.-J. *Synthesis* **1989**, 706−709. (c) Mori, K. *Tetrahedron* **1975**, *31*, 3011−3012. (d) Ravid, U.; Silverstein, R. M.; Smith, L. R. *Tetrahedron* **1978**, *34*, 1449−1452. (e) Nemoto, H.; Nagai, M.; Fukumoto, K. *J. Org. Chem.* **1985**, *50*, 2764−2766. (f) Cai, X.; Chorghade, M. S.; Fura, A.; Grewal, G. S.; Jauregui, K. A.; Lounsbury, H. A.; Scannell, R. T.; Yeh, C. G.; Young, M. A.; Yu, S. *Org. Process Res. Dev.* **1999**, *3*, 73−76.

(6) The terms "cis" and "trans" refer to the arrangement of substituents around the monophospholane rings to prevent confusion with the arrangement of the lone pair. The terms "cis/cis", "cis/trans", and "trans/trans" refer to the arrangement of each phospholane ring within one molecule of a bisphospholane.

(7) In most cases cis and cis/cis diastereomers could be isolated from cis:trans and cis/cis:cis/trans mixtures via either crystallization or column chromatography of borane or sulfide adducts of the phosphines as described in the Supporting Information.

(8) (a) Hommer, H.; Gordillo, B. *Phosphorous, Sulfur Silicon* **2002**, *177*, 465−470. (b) Egan, W.; Tang, R.; Zon, G.; Mislow, K. *J. Am. Chem. Soc.* **1970**, *92*, 1442−1444. (c) Cremer, S. E.; Chorvat, R. J.; Chang, C. H.; Davis, D. W. *Tetrahedron Lett.* **1968**, *55*, 5799−5802.

(9) Reviews: (a) Lambert, J. B. *Top. Stereochem.* **1971**, *6*, 19−104. (b) Rauk, A.; Allen, L. C.; Mislow, K. *Angew. Chem., Int. Ed. Engl.* **1970**, *9*, 400−414.

(10) While heating is a requirement for the epimerizations involved in the current discussion, it is not a requirement for all pyramidal inversions to occur.

(11) In the cases of incomplete epimerization, most trans and trans/trans diastereomers could be isolated from cis:trans and cis/trans:trans/trans mixtures via either recrystallization or column chromatography of borane or sulfide adducts of the phosphines as described in the Supporting Information.

(12) Burk, M. J.; de Konig, P. D.; Grote, T. M.; Hoekstra, M. S.; Hoge, G.; Jennings, R. A.; Kissel, W. S.; Le, T. V.; Lennon, I. C.; Mulhern, T. A.; Ramsden, J. A.; Wade, R. A. *J. Org. Chem.* **2003**, *68*, 5731−5734.

JA048079L