A Journal of the Gesellschaft Deutscher Chemiker

Angewandte International Edition Chemie

GDCh

www.angewandte.org

Accepted Article

Title: Inversion of Configuration at the Phosphorus Nucleophile in Diastereoselective and Enantioselective Synthesis of P-Stereogenic syn-Phosphiranes from Chiral Epoxides

Authors: Jake Muldoon, Balazs Varga, Meaghan Deegan, Timothy Chapp, Adam Eordogh, Russell Hughes, David S. Glueck, Curtis Moore, and Arnold Rheingold

To be cited as: *Angew. Chem. Int. Ed.* 10.1002/anie.201801427
Angew. Chem. 10.1002/ange.201801427

Link to VoR: http://dx.doi.org/10.1002/anie.201801427
http://dx.doi.org/10.1002/ange.201801427

WILEY-VCH

10.1002/anie.201801427

WILEY-VCH

COMMUNICATION

Inversion of Configuration at the Phosphorus Nucleophile in Diastereoselective and Enantioselective Synthesis of P-Stereogenic *syn*-Phosphiranes from Chiral Epoxides

Jake A. Muldoon,[a] Balázs R. Varga,[a] Meaghan M. Deegan,[a] Timothy W. Chapp,[a] Ádám M. Eördögh,[a] Russell P. Hughes,*[a] David S. Glueck,*[a] Curtis E. Moore,[b] and Arnold L. Rheingold [b]

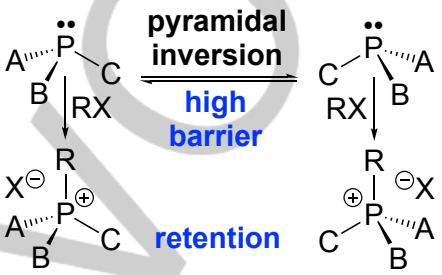
Abstract: Nucleophilic substitution results in inversion of configuration at the electrophilic carbon (S_N2) or racemization (S_N1). Stereochemistry at the nucleophile is rarely considered, but phosphines, which have a high barrier to pyramidal inversion, attack electrophiles with retention of configuration at P. Surprisingly, cyclization of bifunctional secondary phosphine alkyl tosylates proceeded under mild conditions with inversion of configuration at the nucleophile to yield P-stereogenic *syn*-phosphiranes. DFT studies suggested that the novel stereochemistry results from acid-promoted tosylate dissociation to yield an intermediate phosphenium-bridged cation, which undergoes *syn*-selective cyclization.

The stereochemistry of nucleophilic substitution provides valuable mechanistic information (inversion: S_N2; racemization: S_N1). [1] Textbooks do not mention the stereochemistry at the nucleophile, which is usually achiral. However, P-stereogenic phosphines, which have high barriers to pyramidal inversion,[2] undergo nucleophilic reactions, such as quaternization with alkyl halides, with retention of configuration at phosphorus (Scheme 1).[3] We report here the first reversal of this paradigm, in which intramolecular nucleophilic substitution proceeds at room temperature with *inversion* of configuration at phosphorus, as the key step in controlling the diastereo- and enantioselective synthesis of P-stereogenic *syn*-phosphiranes.

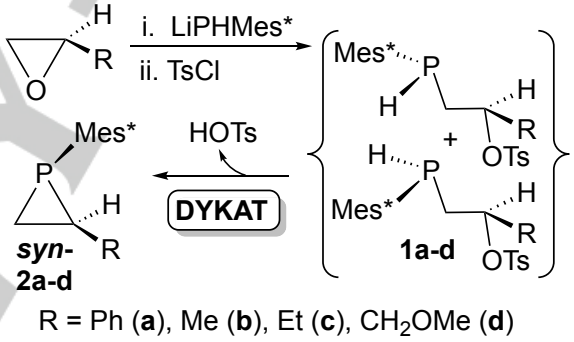
Treatment of chiral epoxides with LiPHMes* (Mes* = 2,4,6-(t-Bu)$_3$C$_6$H$_2$), followed by tosyl chloride, yielded a ca. 1:1 mixture of diastereomeric tosylates **1** via highly regioselective ring opening at the less substituted carbon.[4,5] As generated, tosylates **1** cyclized at 25 °C to selectively form *syn*-phosphiranes **2** in a dynamic kinetic asymmetric transformation (DYKAT, Scheme 2, Table 1). [6] The *syn*-stereochemistry and inversion of configuration at the epoxide carbon were established by X-ray crystal structures of *syn*-**2a** and -**2c** and of *anti*-**2a**,[7] which were consistent with NMR data.[8]

[a] J. A. Muldoon, Dr. B. R. Varga, M. M. Deegan, Dr. T. W. Chapp, A. M. Eördögh, Prof. R. P. Hughes, Prof. D. S. Glueck
Department of Chemistry, Dartmouth College, 6128 Burke Laboratory, Hanover, New Hampshire 03755, United States
E-mail: rph@dartmouth.edu, glueck@dartmouth.edu
[b] Dr. C. E. Moore, Prof. A. L. Rheingold
Department of Chemistry, University of California, San Diego, 9500 Gilman Drive, La Jolla, California, 92093, United States

Supporting information for this article is given via a link at the end of the document.



Scheme 1. Phosphines Undergo Nucleophilic Reactions with Retention of Configuration at Phosphorus



Scheme 2. Generation and Cyclization of Diastereomeric Tosylates **1**. Both Intermediates Formed the Same Phosphirane Products *syn*-**2** [9]

Table 1. Synthesis of *syn*-Phosphiranes **2a-d**[a]

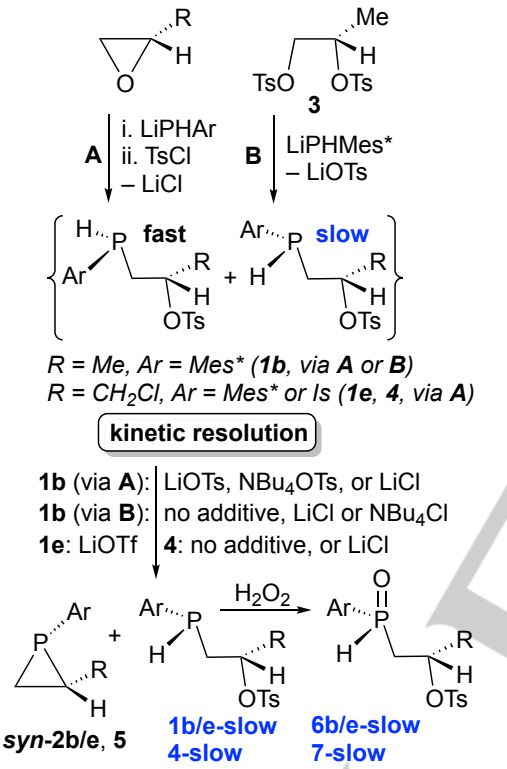
No.	R	time (h)	yield (%)	dr	er
2a	Ph	14	71	>99:1	99:1
2b	Me	24	74	>99:1	>99:1
2c	Et	38	70	>99:1	>99:1
2d	CH_2OMe	110	63	>95:5	>99:1

[a] In THF at ambient temperature, isolated yields; see the Supporting Information for details

Changes in reaction conditions or epoxide and phosphine substituents switched this DYKAT to a kinetic resolution (KR), in which one diastereomer (**1-fast**) formed *syn*-**2**, leaving unreacted **1-slow** (Scheme 3). The reactivity of **1b** was particularly sensitive to conditions, including its method of generation and the presence of added chloride- or tosylate-containing salts. When **1b** was formed, along with LiCl, from propylene oxide (Scheme 3, route **A**), DYKAT occurred as in

10.1002/anie.201801427

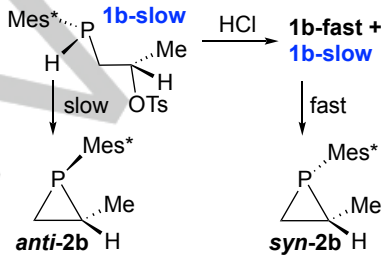
Scheme 2. However, **1b** underwent a slower KR when it was generated, along with LiOTs, from chiral ditosylate **3** (Scheme 3, route **B**). Adding LiOTs, NBu_4OTs, or LiCl to the epoxide-derived reaction mixtures (route **A**) caused KR, while DYKAT proceeded normally in the presence of NBu_4PF_6. Adding LiCl or NBu_4Cl to the **1b**/LiOTs mixture (route **B**) promoted KR, which with LiCl now occurred in 1 d instead of 3 d. When propylene oxide was replaced with epichlorohydrin (**1e**, R = CH_2Cl, route **A**), very slow DYKAT (50% conversion, 17 d) changed to KR on addition of 0.1 equiv of LiOTf and heating to 60 °C for 24 h. Finally, epichlorohydrin and the less bulky nucleophile LiPHIs (Is = 2,4,6-(*i*-Pr)$_3$C$_6$H$_2$) formed secondary phosphine diastereomers **4**, whose KR gave *syn*-phosphirane **5** and **4-slow**; this cyclization was also faster with added LiCl.



Scheme 3. Kinetic Resolution of Diastereomeric Tosylates **1b/e** and **4**.[9] (R = Me, Ar = Mes* (**1b/2b/6b**); R = CH_2Cl, Ar = Mes* (**1e/2e/6e**) or Ar = Is (**4/5/7**))

Although the origin of these effects of reaction conditions and substrate substituents on DYKAT vs KR are not clear, these observations enabled determination of the stereochemistry of cyclization by correlating the absolute configurations of the tosylate intermediates and phosphirane products. After KR processes resulted in complete consumption of **1b/e-fast** or **4-fast**, the slow diastereomers were separated from phosphiranes **2b/e** or **5** and isolated directly (**1b-slow**), or after oxidation (H_2O_2) with retention of P-configuration (**6b/e-slow** or **7**, Scheme 3).[3a] The crystal structures of the secondary phosphine oxides **6e-slow** and **7-slow•H_2O**,[7a] along with NOESY studies of these oxides and of **1b-slow**, established their absolute configurations and, by extension, those of the fast diastereomers, which have the opposite P-configuration, as shown in Scheme 3.

Cyclization with the usual retention at P, as evident from arrow-pushing for nucleophilic attack of the P lone pair at the tosylate-bearing carbon, would yield *anti*-**2** from **1-fast** and *syn*-**2** from **1-slow**, contradicting the experimental observations. Therefore, cyclization occurred *with inversion of configuration at the P-nucleophile*. Consistent with this conclusion, isolated **1b-slow** very slowly formed *anti*-phosphirane **2b**, but added HCl caused epimerization to an equilibrium mixture of **1b-fast** and **1b-slow**, which quickly formed ***syn*-2b** (Scheme 4). These observations suggest Curtin-Hammett behavior in the DYKAT of Scheme 2,[10] where acid-mediated interconversion of the P-epimeric secondary phosphine diastereomers **1-fast** and **1-slow** is faster than their cyclization,[11] and *syn*-**2** forms more quickly than *anti*-**2** (Scheme 5).

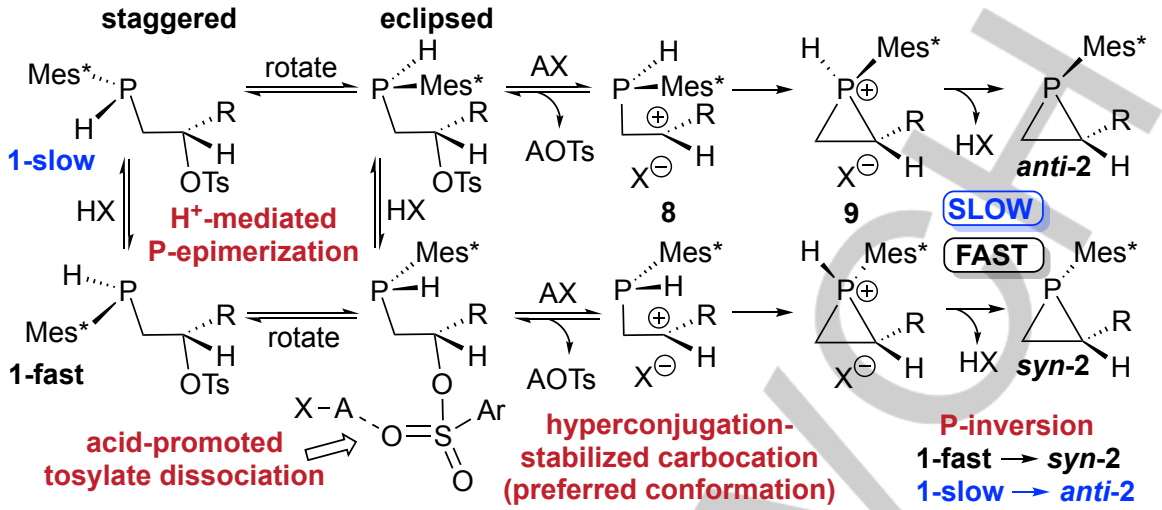


Scheme 4. Reactions of **1b-slow**.[9]

We used DFT studies (B3LYP-D3/6-311G**++/THF) and literature precedent to propose a mechanism of cyclization consistent with the experimental stereochemistry (Scheme 5). The P-inversion requires cyclization from eclipsed conformers of **1**, which are accessible; the energies of eclipsed and staggered structures for both fast and slow diastereomers of **1b** were the same within the expected error of the calculations, 1 kcal/mol. Direct S_N2 displacement of tosylate from **1b** with retention or inversion at P was ruled out by locating the transition states, with activation energies of ca. 25 kcal/mol, inconsistent with the observed room-temperature reactivity. Instead, S_N1-like dissociation of tosylate from **1**, promoted by steric crowding and Lewis or Brønsted acids, could give cation **8**.[12] Previously, loss of X^- from hypothetical $H_2PCH_2CHMe(X)$ was predicted to yield a related carbocation stabilized (23 kcal/mol) by hyperconjugation with the P–C σ-bond; because the eclipsed rotamer was preferred over the staggered one by 15 kcal/mol,[13] Scheme 5 also shows the eclipsed geometry for **8**. Cyclization of **8** followed by deprotonation of cation **9** would yield phosphirane **2**. Overall inversion at P would occur by staggered-to-eclipsed rotation of the PHMes* unit around the P-CH_2 bond in **1**, followed by attack at C in **8** by the rear lobe of the P lone pair.

To probe the proposed formation and cyclization of the key intermediate, cation **8**, we computed the effects of tosylate O-protonation in **1b** (Figure 1).[14] At equilibrium, the protonated diastereomer **1b(H^+)-fast** is preferred over the slow one by 3.7 kcal/mol. Rotation about the P-C bond to give the eclipsed conformer results in essentially barrierless formation of an intermediate cation **8b** in which HOTs is dissociated and PHMes* semi-bridges the two carbon atoms; a transition state for HOTs dissociation could not be located. As in the O-

protonated precursors, the cation **8b** formed from **1b-fast** is more stable than the slow one.



Scheme 5. Proposed Mechanism and Stereochemistry of *syn*-Phosphirane Formation (AX = Brønsted/Lewis acid, such as HOTs or LiCl)[9]

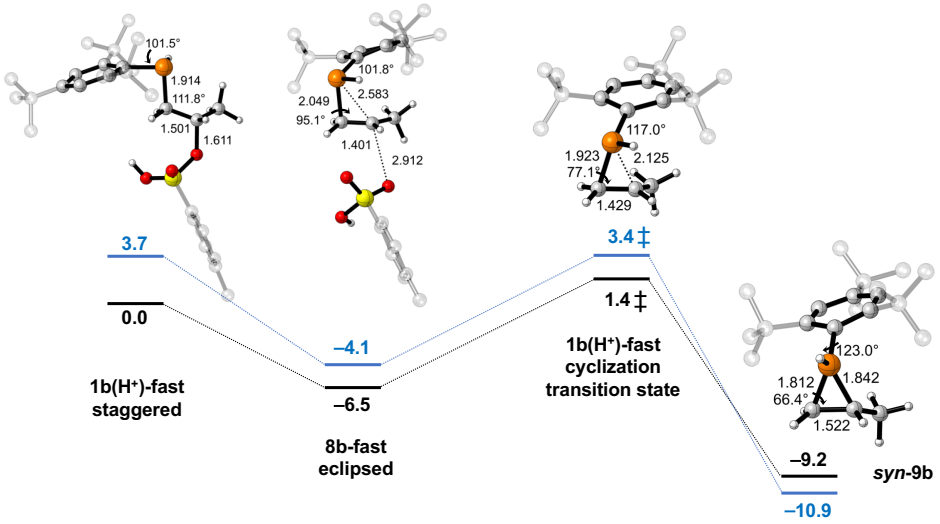


Figure 1. Structures (for the fast diastereomers) and energies for staggered and eclipsed conformers of **1b(H⁺)-fast** (black) and **1b(H⁺)-slow** (blue) and transition states for their conversion via cations **8b** to *syn*-**9b** (black) and *anti*-**9b** (blue) with inversion at P. Mes* C-H atoms are omitted.

NBO studies revealed details of the bonding in staggered and eclipsed cations **8b**. The Natural Localized Molecular Orbitals (NLMOs)[15] for the P lone pair (P_{lp}) showed small delocalization from the NBO reference Lewis structure (Figure 2) into the nominally vacant C_β(p)-orbital (row A), and significant hyperconjugative delocalization from P-C_α(σ) into C_β(p) (row B), consistent with NBO orbital occupancies and Wiberg Bond Indices (WBI: row C). Comparison of NBO occupancies and WBIs for intermediate conformers reveals less electron depletion of P_{lp} and the P-C_α(σ) bond with correspondingly lower population of C_β(p) in staggered **8b** (row D) than in eclipsed **8b** (row C). In addition, small delocalizations from P-H and P-Mes* σ-bonds contribute to the greater stability of the eclipsed conformer.

Both eclipsed cations **8b-fast** and **8b-slow** undergo low energy ring closure to give the protonated phosphirane **9b** via the transition states shown in Figures 1-2. The transition state formed from **8b-fast** involves contraction of the C_α-C_β-P angle (95.1°→77.1°), and opening of the Mes*-P-H angle (101.8°→117.0°), consistent with evolution of the P lone pair into the nascent P-C_β σ-bond with inversion at P. Loss of HOTs from phosphiranium cation **9b** to give *syn*-**2b** is downhill by 7.5 kcal/mol, consistent with experiment, where protonated phosphiranes **9** were not observed. Finally, the proposed kinetic origin of *syn*-selectivity agrees with the computed energies of the products; both *anti*-**2b** and protonated [*anti*-**9b**][OTs] are more stable than the *syn*- isomers, by 1.3 and 1.7 kcal/mol respectively. The thermodynamic preference for **1b(H⁺)-fast** in the Curtin-Hammett equilibrium (Figure 1), coupled with a lower energy pathway for its cyclization via the energetically preferred cation **8b-fast**, provides a rationale for

10.1002/anie.201801427

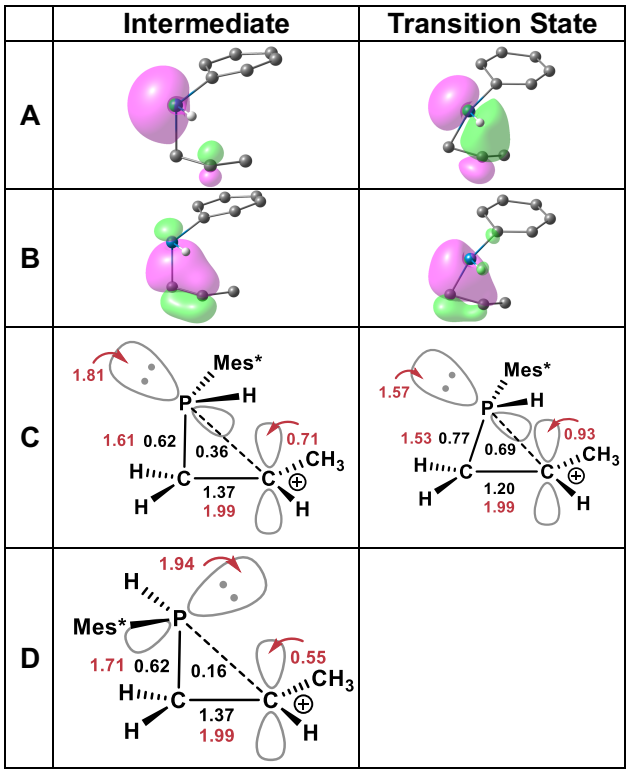


Figure 2. Intermediate cations (**8b**) and cyclization transition state arising from **1b(H⁺)-fast**. Rows A, B: NLMOs for the P_{lp} and P-$C_{\alpha}(\sigma)$, with *t*-Bu groups and all C-H omitted. Rows C (eclipsed) and D (staggered); NBO orbital occupancies (red) and WBI values (black).

the observed *syn*-selectivity, which might also be promoted by dispersive attractions with the Mes* group.[16]

In conclusion, we have reported stereochemical behavior new for phosphines, with inversion of configuration at phosphorus in nucleophilic substitution. The difference from textbook examples showing retention of configuration at the nucleophile is the formation of a small ring, for which the normal linear S_N2 transition state is inaccessible, as in the proposed inversion of configuration at a nitrogen nucleophile via an unobserved azetidinium intermediate.[17] While inversion at nitrogen is facile, the high barrier in phosphines makes our observations remarkable. Figures 1 and 2 show how inversion can be promoted. Cation **8b** is hyperconjugatively stabilized by PHMes* semi-bridging both carbons, preserving stereochemical information from the chiral epoxide precursor, which would otherwise be lost in a conventional S_N1 intermediate. The preferred conformation of this cation dictates evolution of the rear lobe of the P lone pair into the new P–C bond in the transition state, thereby providing energetic compensation to circumvent the normally high barrier to inversion at P.

Besides its fundamental importance, the unusual stereochemistry of P–C bond formation controls selectivity in formation of P-stereogenic chiral phosphiranes.[18] Although phosphiranes have unique stereoelectronic properties, with smaller cone angles and higher P-inversion barriers than their acyclic analogs, and are thought to be poorer σ-donors and better π-acceptors,[19] their use as ligands[20] in metal-catalyzed reactions is rare.[21] Chiral phosphiranes are especially unusual,[22] so our convenient new one-pot synthesis is potentially useful[23] for expanding their currently limited applications in asymmetric catalysis.[24,25] We are now investigating this possibility, as well as the intriguing role of Li^+ and other Lewis acids in mediating phosphirane formation.

Acknowledgements

We thank the US National Science Foundation for funding (CHE-126578, -1562037, and -1011887) and the US Department of Education (GAANN, TWC and JAM), Dartmouth College (MMD), and the Rosztoczy Foundation (AME) for fellowship support.

Keywords: nucleophilic substitution • stereochemistry • mechanism • phosphirane • P-stereogenic

[1] a) J. McMurry, *Organic Chemistry,* 9th ed., Cengage Learning, Boston, **2016**. b) K. P. C. Vollhardt, N. E. Schore, *Organic Chemistry. Structure and Function*, 6th ed., W. H. Freeman, New York, **2011**.

[2] a) Typical experimental values: 29-36 kcal/mol (R. D. Baechler, K. Mislow, *J. Am. Chem. Soc.* **1970**, *92*, 3090-3093). b) Computation yielded other barriers, such as 43.2 kcal/mol for PMe_3: L. Goerigk, R. Sharma, *Can. J. Chem.* **2016**, *94*, 1133-1143.

[3] a) L. D. Quin, *A Guide to Organophosphorus Chemistry*, Wiley-Interscience, New York, **2000**, pp 299-303. b) Retention of configuration at P was also observed in the Arbuzov reaction, coordination to boranes and transition metals, and other reactions of phosphine nucleophiles: K. M. Pietrusiewicz, M. Zablocka, *Chem. Rev.* **1994**, *94*, 1375-1411.

[4] a) T. Koch, S. Blaurock, F. Somoza, Jr., E. Hey-Hawkins, *Eur. J. Inorg. Chem.* **2000**, 2167-2172. b) K. Issleib, H.-R. Roloff, *Chem. Ber.* **1965**, *98*, 2091-2098. c) J. Heinicke, I. Kovacs, L. Nyulaszi, *Chem. Ber.* **1991**, *124*, 493-496. d) K. L. Marsi, M. E. Co-Sarno, *J. Org. Chem.* **1977**, *42*, 778-781. e) C. H. Schuster, B. Li, J. P. Morken, *Angew. Chem. Int. Ed.* **2011**, *50*, 7906-7909.

[5] Quenching with NH_4Cl instead of TsCl yielded the alcohols Mes*$HPCH_2CH(R)(OH)$ (**10**). Styrene oxide gave a second minor set of regioisomeric tosylates and alcohols (for similar results with $LiPPh_2$, see: G. Muller, D. Sainz, *J. Organomet. Chem.* **1995**, *495*, 103-111.)

[6] a) J. Steinreiber, K. Faber, H. Griengl, *Chem. Eur. J.* **2008**, *14*, 8060-8072. b) Diastereoselectivity of formation of *syn*-phosphiranes **2** depended on the R group and the conditions; small amounts (<10%) of the *anti*-phosphiranes were observed in some reaction mixtures. c) Racemic phosphirane **2b** (R = Me) was prepared earlier as a *syn-anti* mixture: T. Oshikawa, H. Yamashita, *Synthesis* **1985**, 290-291.

[7] a) CCDC 1571673-1571677 (b) Repeating the synthesis of racemic *anti*-**2a** (M. Yoshifuji, K. Toyota, N. Inamoto, *Chem. Lett.* **1985**, *14*, 441-442) with (*R*)-epoxide gave enantiomerically enriched *anti*-**2a**.

[8] a) S. Chan, H. Goldwhite, H. Keyzer, D. G. Rowsell, R. Tang, *Tetrahedron* **1969**, *25*, 1097-1103. b) W. J. Richter, *Chem. Ber.* **1983**, *116*, 3293-3300. c) X. Li, K. D. Robinson, P. P. Gaspar, *J. Org. Chem.* **1996**, *61*, 7702-7710.

[9] For convenience, epoxides, phosphiranes **2**, and intermediates are drawn with the same absolute configuration. See the Supporting Information (SI) for details of the absolute configurations of specific epoxides, intermediates and products.

[10] J. R. Seeman, *Chem. Rev.* **1983**, *83*, 83-134.

[11] a) J. Albert, J. Magali Cadena, J. Granell, G. Muller, D. Panyella, C. Sañudo, *Eur. J. Inorg. Chem.* **2000**, 1183-1186. b) A. Bader, T. Nullmeyers, M. Pabel, G. Salem, A. C. Willis, S. B. Wild, *Inorg. Chem.* **1995**, *34*, 384-389. c) Y. Huang, Y. Li, P.-H. Leung, T. Hayashi, *J. Am. Chem. Soc.* **2014**, *136*, 4865–4868. d) Slow P-epimerization

would result in the observed KR. With the high sensitivity of this process to reaction conditions, we have not attempted to model the origin of KR and instead focus here on the mechanism and stereochemistry of the key cyclization step.

[12] E. N. Peters, H. C. Brown, *J. Am. Chem. Soc.* **1974**, *96*, 263-265.

[13] J. B. Lambert, Y. Zhao, *J. Am. Chem. Soc.* **1996**, *118*, 3156-3167.

[14] We also computed protonation at P with HOTs (unfavorable by 7.1 kcal/mol) or with HCl (favorable by 1.3 kcal/mol (SI)). If protonation, or Lewis acid binding, at O or at P was reversible, but cyclization was irreversible, an equilibrium mixture of O- and P-protonated cations (or Lewis acid-base adducts) could evolve to yield the observed products.

[15] A. E. Reed, F. Weinhold, *J. Chem. Phys.* **1985**, *83*, 1736-1740.

[16] J. P. Wagner, P. R. Schreiner, *Angew. Chem. Int. Ed.* **2015**, *54*, 12274-12296.

[17] a) C. H. Heathcock, T. W. Von Geldern, C. B. Lebrilla, W. F. Maier, *J. Org. Chem.* **1985**, *50*, 968-972. b) P. Kocovsky, J. Srogl, M. Pour, A. Gogoll, *J. Am. Chem. Soc.* **1994**, *116*, 186-197.

[18] The very bulky Mes*PH_2 was not required, as seen in the formation of **4** and IsPCH_2CHMe (19:1 *syn*/*anti*) from IsPH_2. For more information on the scope of the phosphirane synthesis, see the SI.

[19] a) F. Mathey, *Chem. Rev.* **1990**, *90*, 997-1025. b) J. Liedtke, S. Loss, C. Widauer, H. Grutzmacher, *Tetrahedron* **2000**, *56*, 143-156.

[20] K. D. Cooney, T. R. Cundari, N. W. Hoffman, K. A. Pittard, M. D. Temple, Y. Zhao, *J. Am. Chem. Soc.* **2003**, *125*, 4318–4324.

[21] J. C. Slootweg, K. Lammertsma, In *Phosphorus(III) Ligands in Homogeneous Catalysis: Design and Synthesis*; P. C. J. Kamer, P. W. N. M. van Leeuwen, Eds.; John Wiley & Sons: Chichester (UK), 2012, pp. 309-320.

[22] a) A. Marinetti, In *Phosphorus Ligands in Asymmetric Catalysis. Synthesis and Applications,* A. Börner, Ed.; Wiley-VCH: Weinheim, 2008; Vol. 1, pp. 114-135. b) F. Lang, H. Grutzmacher, *Chimia* **2003**, *57*, 187-190.

[23] Treatment of **3** with LiPHMes (Mes = 2,4,6-$Me_3C_6H_2$), followed by *n*-BuLi, gave a 1.3:1 mixture of *anti*- and *syn*-phosphiranes, which were not separated (ref 8c).

[24] a) A. Marinetti, F. Mathey, L. Ricard, *Organometallics* **1993**, *12*, 1207-1212. b) A. Marinetti, L. Ricard, F. Mathey, *Synthesis* **1992**, 157-162.

[25] a) A. Ficks, I. Martinez-Botella, B. Stewart, R. W. Harrington, W. Clegg, L. J. Higham, *Chem. Commun.* **2011**, 8274-8276. b) A. Ficks, W. Clegg, R. W. Harrington, L. J. Higham, *Organometallics* **2014**, *33*, 6319–6329. c) A. F. Abdel-Magied, M. H. Majeed, M. F. Abelairas-Edesa, A. Ficks, R. M. Ashour, A. Rahaman, W. Clegg, M. Haukka, L. J. Higham, E. Nordlander, *J. Organomet. Chem.* **2017**, *849–850*, 71–79.

10.1002/anie.201801427

WILEY-VCH

Entry for the Table of Contents (Please choose one layout)

Layout 1:

COMMUNICATION

Text for Table of Contents

((Insert TOC Graphic here))

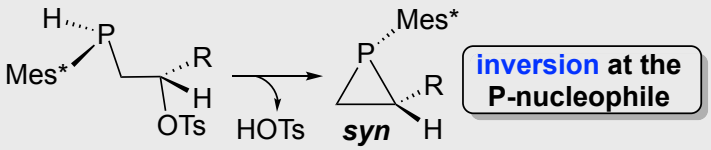
*Author(s), Corresponding Author(s)**

Page No. – Page No.

Title

Layout 2:

COMMUNICATION



Nucleophilic substitution results in inversion (S_N2) or racemization (S_N1) at the electrophile, but what about the nucleophile? P-stereogenic phosphines act as nucleophiles with retention of P-configuration. In the first reversal of this paradigm, we report intramolecular nucleophilic substitution with *inversion* at phosphorus as the key step in controlling the diastereo- and enantioselective synthesis of P-stereogenic *syn*-phosphiranes.

Jake A. Muldoon, Balázs R. Varga, Meaghan M. Deegan, Timothy W. Chapp, Ádám M. Eördögh, Russell P. Hughes, David S. Glueck,* Curtis E. Moore, and Arnold L. Rheingold*

Page No. – Page No.

Inversion of Configuration at the Phosphorus Nucleophile in Diastereoselective and Enantioselective Synthesis of P-Stereogenic *syn*-Phosphiranes from Chiral Epoxides