

**Synthesis of *P*-stereogenic phosphonothioic acids
and phosphonothioates
via an axis-to-center chirality transfer
and their properties**

(キラリティー転写を経由する P-キラルチオホスホン酸と
チオホスホン酸エステルの合成とその性質の解明)

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Chapter 1

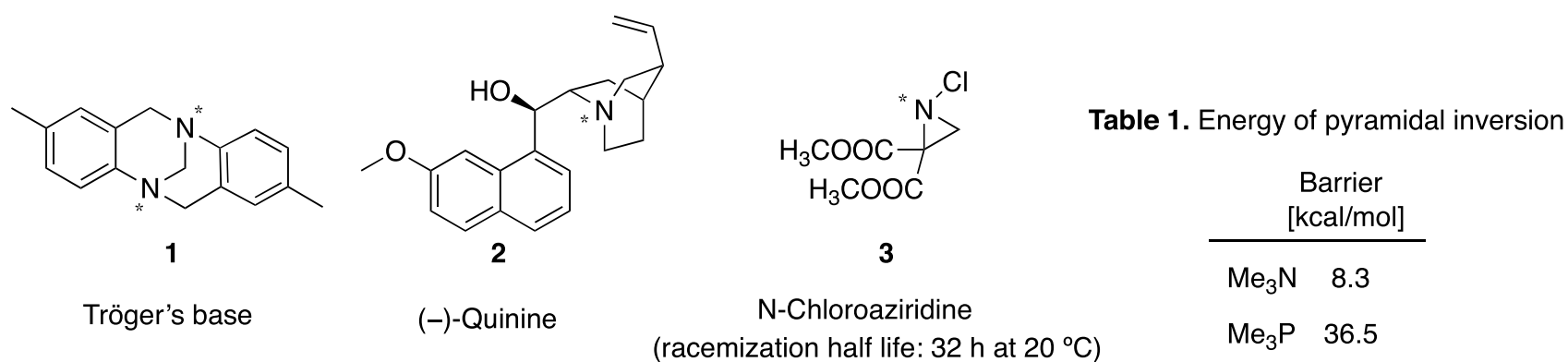
General Introduction

1.1. Introduction

The importance of chirality has increased not only in the fields of chemistry but also in the fields of physics, biology, and pharmacy since Louis Pasteur resolved enantiomer of tartaric acid for the first time in the 19th century. Chirality is defined that the objects cannot be superposed onto their mirror images. For example, the carbon atom is chiral when it has four different substituents. Heteroatoms such as nitrogen, oxygen, phosphorus and sulfur atoms can also be chiral if three different substituents attach to these heteroatoms.

1.2. Chirality at N and P (III) Atom

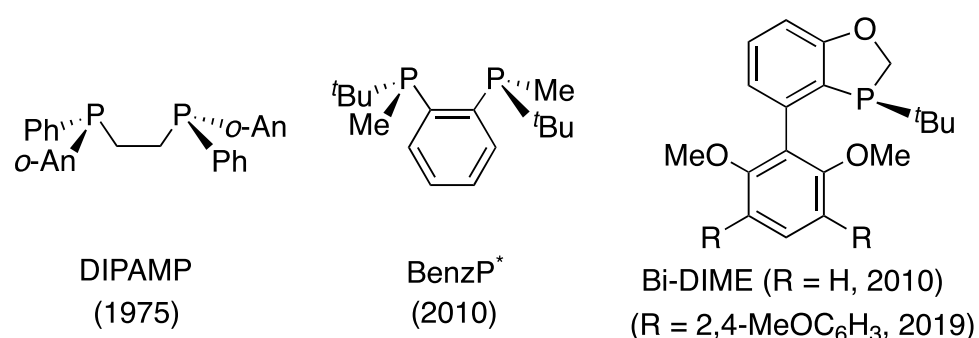
The enantiomer with a chiral center at the nitrogen atom readily racemizes via pyramidal inversion with exception of several cyclic amines having conformational strains such as Tröger's base **1**, (–)-quinine **2**, *N*-chloroaziridine **3** and so on (Scheme 1).¹ In contrast, each enantiomer of *P*-stereogenic tricoordinate trivalent phosphorus (P(III)) compounds can be easily isolated because the inversion energy at the



Scheme 1. Chiral amines with chirality at the nitrogen atom

phosphorus atom is higher when it is compared with that at the nitrogen atom (Table 1).²

Due to the stabilities of chirality at the phosphorus atom, trivalent *P*-stereogenic phosphines have attracted attentions as chiral ligands in asymmetric reactions since Knowles prepared DIPAMP and achieved catalytic asymmetric hydrogenation in 1975 (Scheme 2).³



Scheme 2. Examples of *P*-Stereogenic phosphines

On the other hand, phosphoniumyl radical cations **5** which is generated from the corresponding phosphines **4** by oxidation easily racemize (Figure 1).⁴

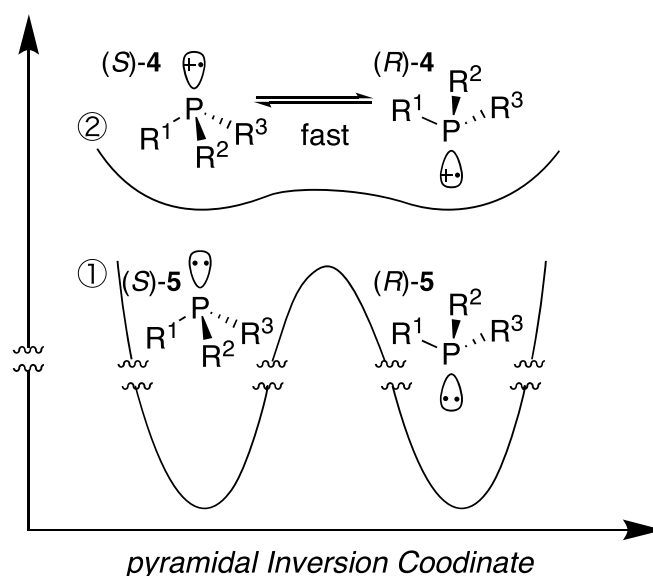
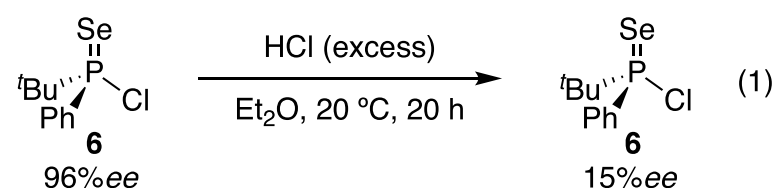


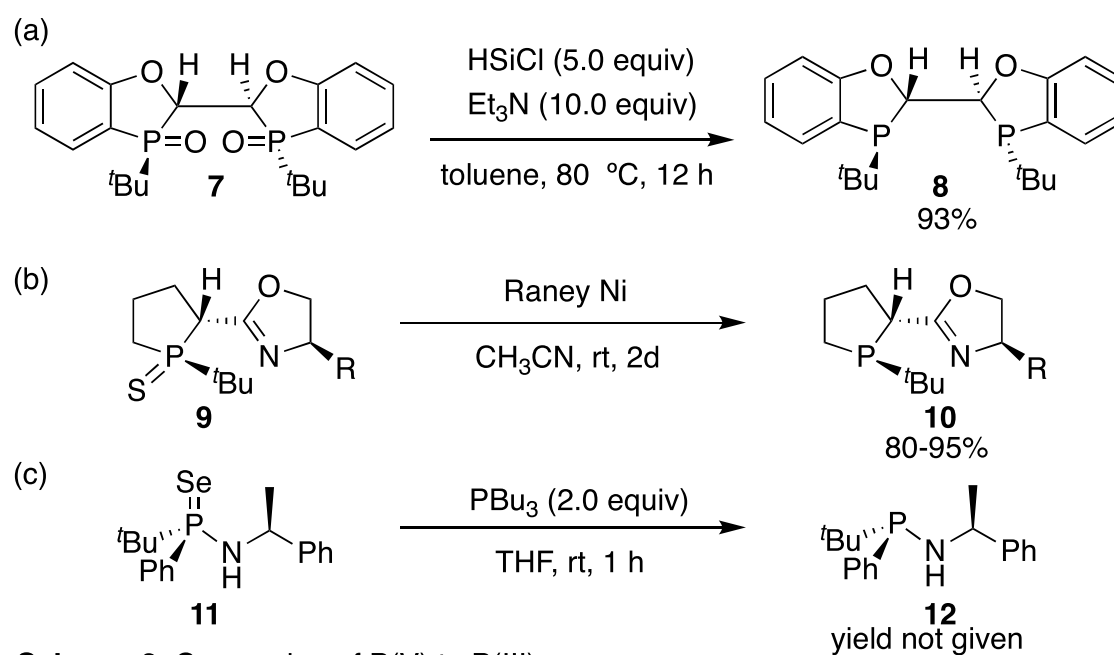
Figure 1. Energy coordinate diagram for pyramidal inversion of neutral phosphine **4** (1) and phosphoniumyl radical cation **5** (2).

1.3. Chirality at P (V) Atom

The chirality at tetracoordinate pentavalent phosphorus (P(V)) atom is stable because pyramidal inversion does not occur. However, exchange reaction at the phosphorus atom such as chlorine exchange causes racemization (Eq. (1)).⁵



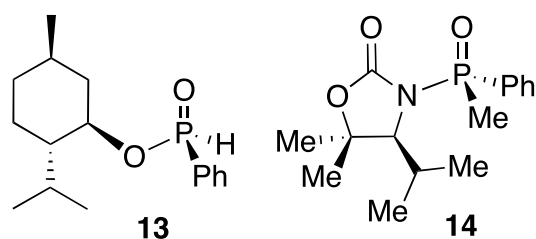
The *P*-stereogenic P(V) compounds have synthetic utilities as precursors to P(III) compounds. The oxygen, sulfur and selenium atom on the phosphorus atoms can be removed by reducing agents to give the corresponding P(III) compounds **8-10** (Scheme 3).^{3c,6}



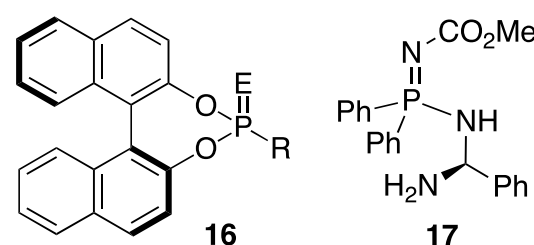
Scheme 3. Conversion of P(V) to P(III)

Considerable efforts have been made on stereospecific synthesis of *P*-stereogenic P(V) compounds. The synthesis of *P*-stereogenic P(V) compounds classically rely on the use of chiral auxiliaries. Menthyl H-phenylphosphinate **13** was firstly reported by Emmick in 1968, and isolated as a diastereomerically enriched isomer by Mislow in 1970. The compound **13** has been widely used as *P*-stereogenic building blocks to lead various *P*-stereogenic P(V) compounds by the reaction with nucleophiles, olefins and coupling partners until today.⁷ The precursors having oxazolidine **14** and amino alcohol **15** as chiral auxiliaries can be classified as similar precursors of **13** which has a chiral phosphorus atom with a chiral auxiliary (Scheme 4, Class A).⁸ The precursors which have an achiral phosphorus atoms with a chiral auxiliary such as the compounds **16** and **17** do not require separation of diastereomers in the preparation step (Scheme 4, Class B).⁹ The precursors without a chiral auxiliary such as **18-23** can be converted to the corresponding *P*-stereogenic compounds with a small amount of chiral source (Scheme 4, Class C).¹⁰ In general, precursors of Class A and B are converted *via* nucleophilic substitution reaction at the phosphorus atom accompanied with elimination of the chiral auxiliaries. On the other hand, the reaction of precursors of Class C takes place at the substituents attached to the phosphorus atom with the combination of transition metal catalysis and chiral ligands.

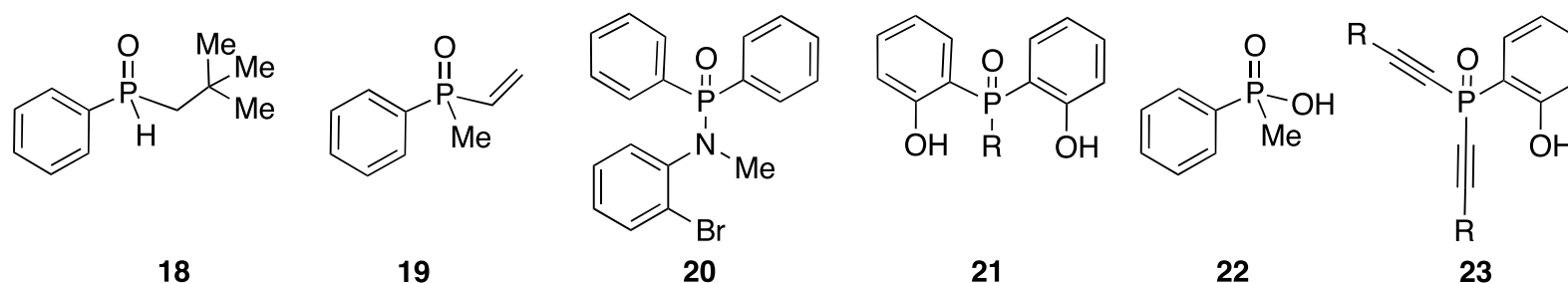
Class A: *P*-Stereogenic center with a chiral auxiliary



Class B: *P*-Prochiral center with a chiral auxiliary



Class C: Without chiral auxiliary



Scheme 4. Precursors leading *P*-stereogenic compounds

In addition to the synthetic utilities, P(V) compounds have attracted attentions because of their biological properties for more than several decades.¹¹ Several P(V) compounds are toxic to insects and mammals. Their toxicities are attributed to their ability to inhibit acetylcholinesterase (AChE).¹² They had been developed for two applications, one is nerve agent such as Sarin and VX, and the other one is pesticide. Importantly, the bioactivities of these *P*-stereogenic P(V) compounds depend on their chirality at phosphorus atom (Scheme 5).¹³ This is because their biological targets are chiral and discriminate the enantiomers.

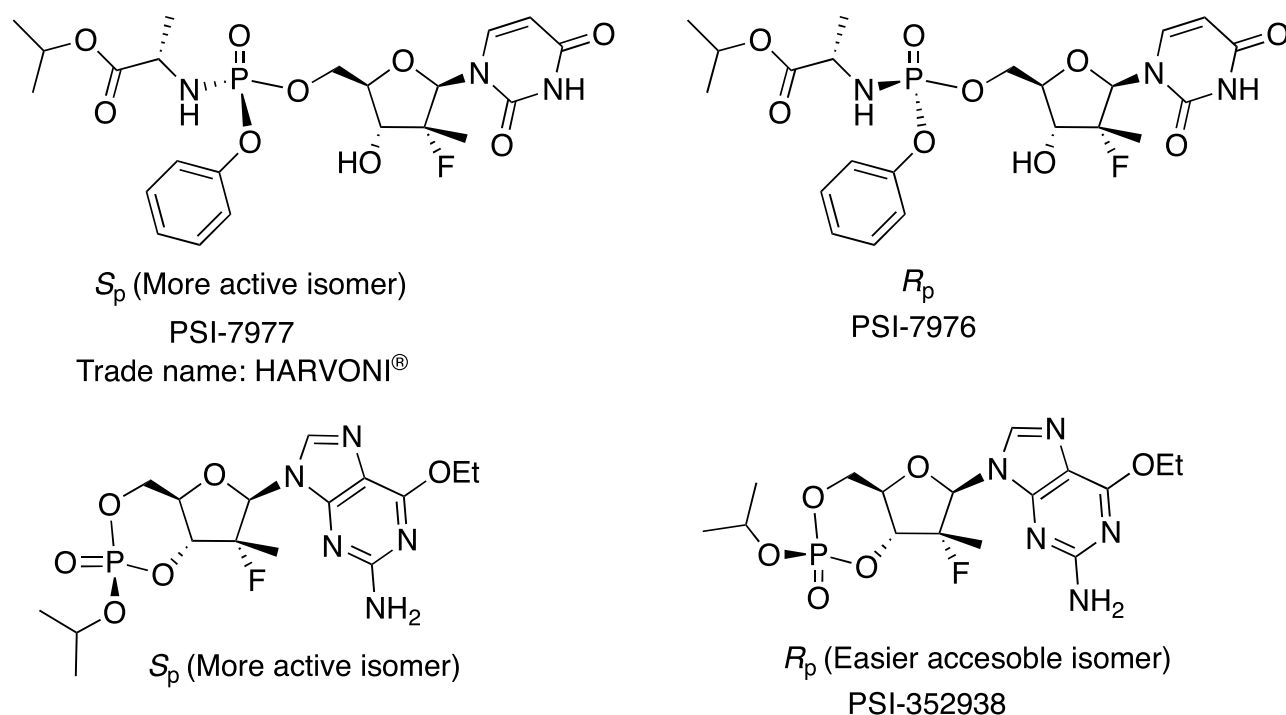
	(+)-Sarin	(+)-VX	(-)-Sarin	(-)-VX
Less toxic	→			More toxic
Rate constant for AChE inhibition at 25 °C (/M/min)	$<3 \times 10^3$ ^a	2×10^6	1×10^7	4×10^8
LD ₅₀ mouse (μg/kg)	–	165 ^b	41 ^b	13 ^b

^aEstimated from an experiment with optically enriched (+)-sarin (64%*ee*).

^bIntravenous administration.

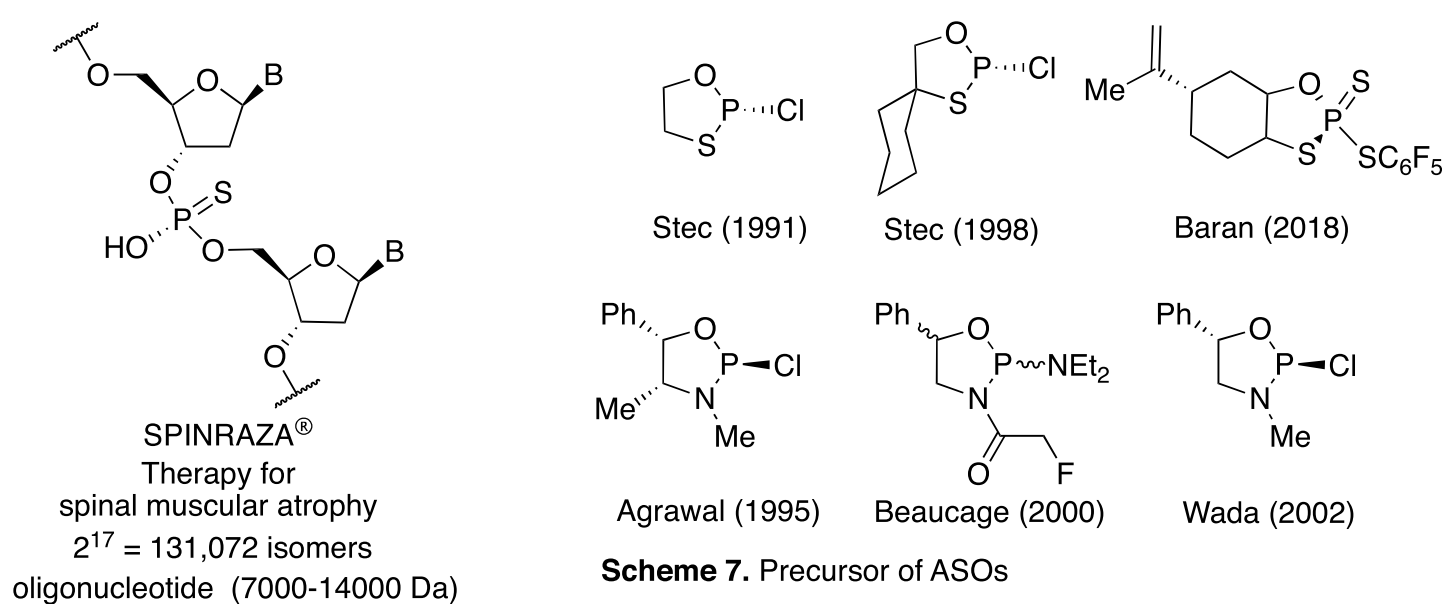
Scheme 5. The effect of nerve agent stereochemistry on anticholinesterase activity and acute lethality of nerve agent stereochemistry

P(V) compounds work not only as a toxic agent but also as drugs. Since the stereochemistry of the phosphorus atom directly affects the activity of drugs, both isomers have been synthesized and their activity has been carefully evaluated (Scheme 6).¹⁴



Scheme 6. Nucleotide prodrugs (HCV NS5B polymerase inhibitors)

Recently, in addition to the small molecule drugs, the development of antisense oligonucleotides (ASOs) which consist of ten to several tens of nucleic acids is active area to provide drugs designed to treat a variety of intractable disease.¹⁵ The control of the stereochemistry on the phosphorus atoms of ASOs is more challenging issues. For example, SPINRAZA[®] which is used as therapy for spinal muscular atrophy, consists of 18 nucleosides in which each nucleoside is linked with *P*-stereogenic phosphorothioate moiety. As a result, SPINRAZA[®] involves 17 *P*-stereogenic phosphorothioate moieties. Even if one of the phosphorus atoms possesses different stereochemistry, it affects physicochemical properties and biological activities. Because of the difficulty to control the stereochemistry of each phosphorus atom independently, SPINRAZA[®] is synthesized as mixtures of 131,072 isomers and all of isomers are administered to patients.¹⁶ Therefore, much effort has been made toward stereospecific synthesis of ASOs. Chiral auxiliaries such as hydroxyethanthiols, amino alcohols were introduced to the phosphorus atom to control the following substitution reaction with nucleosides.^{16a,17}



1.4. Phosphonothioic Acids

Phosphonothioic acids RO(R')P(S)OH are the sulfur analogues of phosphonic acids. The phosphorus atom of phosphonic acid racemizes by tautomerization even if three different substituents attached to the phosphorus atom. On the other hand, in the case of phosphonothioic acids, no racemization occurs at the phosphorus atom, and they are present as a mixture of thiono ($\text{P}=\text{S}$) and thiolo ($\text{P}-\text{S}$) tautomers in equilibrium. The pK_a values of phosphonothioic acids depend on the electronic character of the substituents

(R¹ or R²) (Figure 2).¹⁸ Longer alkyl chain generally raises the pK_a of the P-OH/P-SH group due to the increasing of electron-donating effect of the alkyl group.

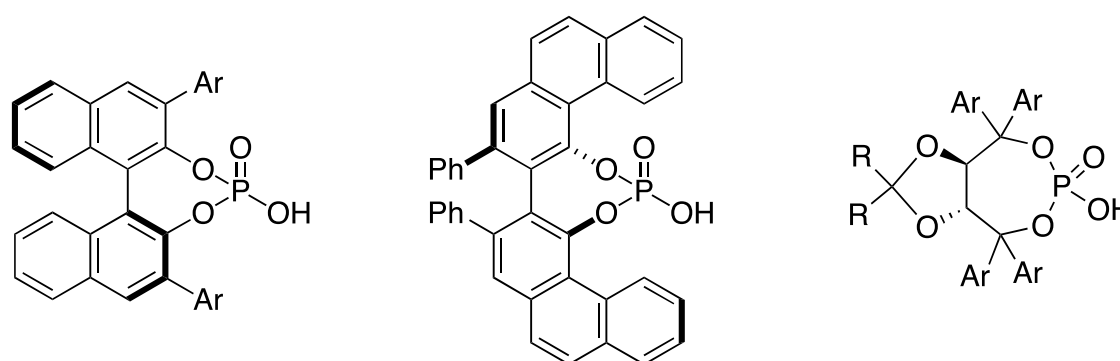
Thiono **A** Thiolo **B** phosphonic acids

R ¹	R ²	pK _a ^a	% A	% B	pK _a ^b	% A	% B
Et	Me	1.82	81	19	3.51	98	2
<i>n</i> -Pr	Me	1.87	85	15	3.78	99	1
<i>n</i> -Bu	Me	1.95	88	12	3.77	99	1
Et	Et	1.88	86	14	3.72	99	1
Et	<i>n</i> -Pr	2.00	88	12	3.81	99	1
Et	<i>n</i> -Bu	2.11	90	10	3.95	99	1

^a pK_a in 93% H₂O and 7% EtOH. ^b pK_a in 80% EtOH and 20% H₂O.

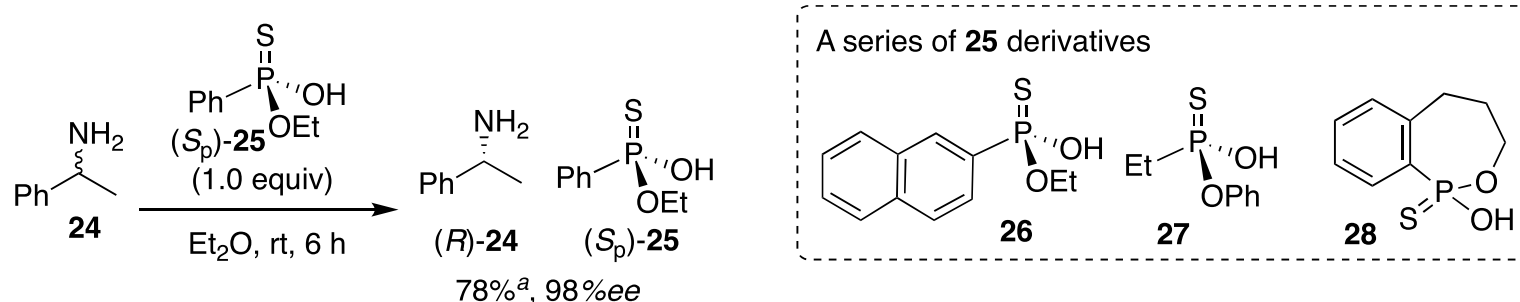
Figure 2. pK_a data for phosphonothioic acids

Recently, chiral phosphoric acid derivatives have been developed as organocatalysts.¹⁹ In general, they have a chiral backbone on the phosphorus atom, and the acidic functional group is attached to the achiral phosphorus atom (Scheme 8).²⁰ On the other hand, the phosphorus atom in phosphonothioic acids is not only an acidic functional group but also a chiral center. Therefore, the structural features of phosphonothioic acids could be expected to rigorously discriminate the stereochemistry between enantiomers and control stereochemistry of the reaction.



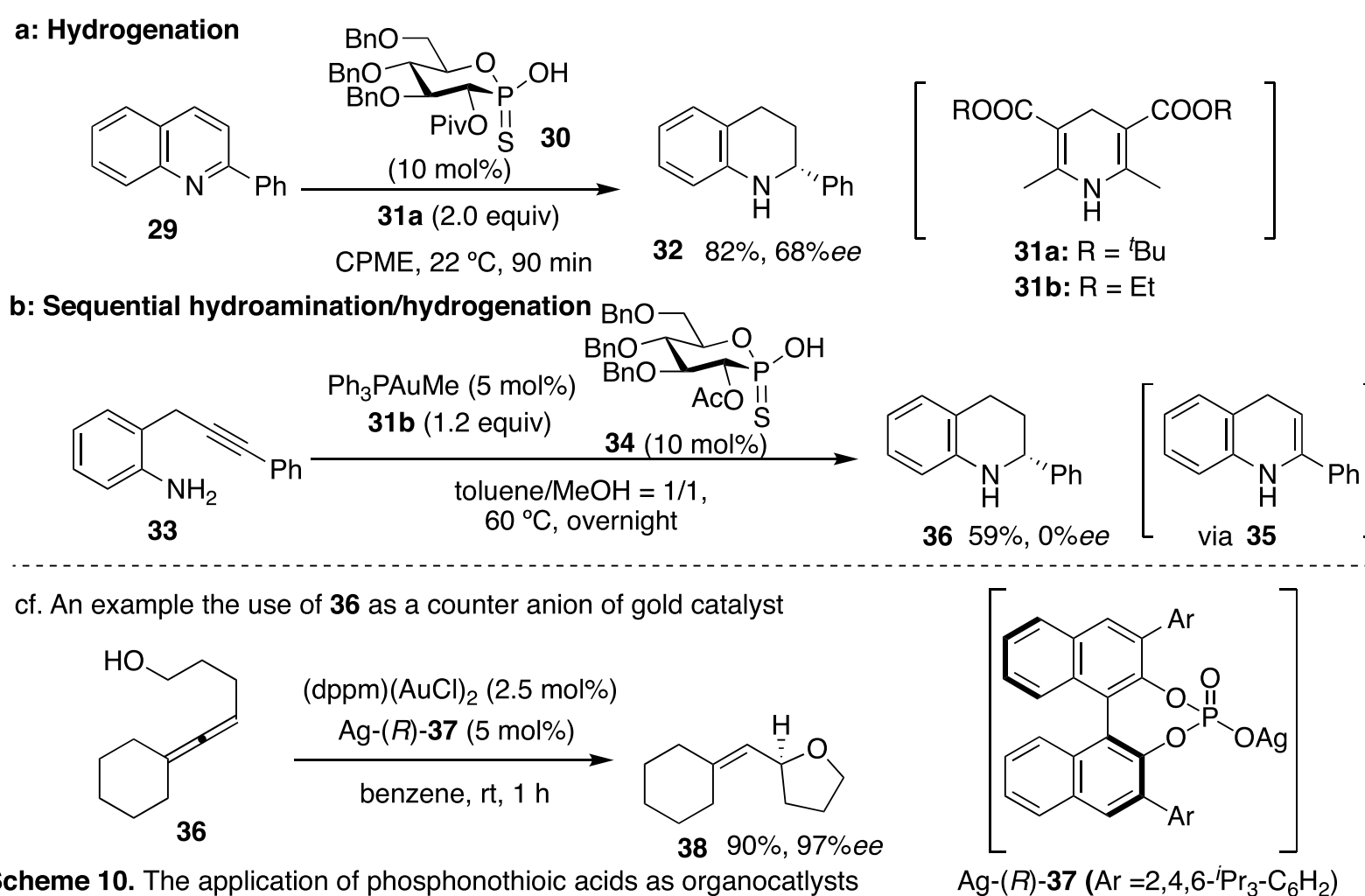
Scheme 8. Chiral phosphoric acid derivatives

However, applications of *P*-stereogenic phosphonothioic acids are still limiting. Saigo demonstrated the abilities of a series of phosphonothioic acids **25-28** as resolving agents of chiral amines (Scheme 9).²¹ X-Ray crystal structure analyses of the ammonium salts generated by phenylethylamine **24** with phosphonothioic acids suggested that the inter/intramolecular CH/ π interactions are important factors of the chiral recognition ability in addition to hydrogen-bonding network.



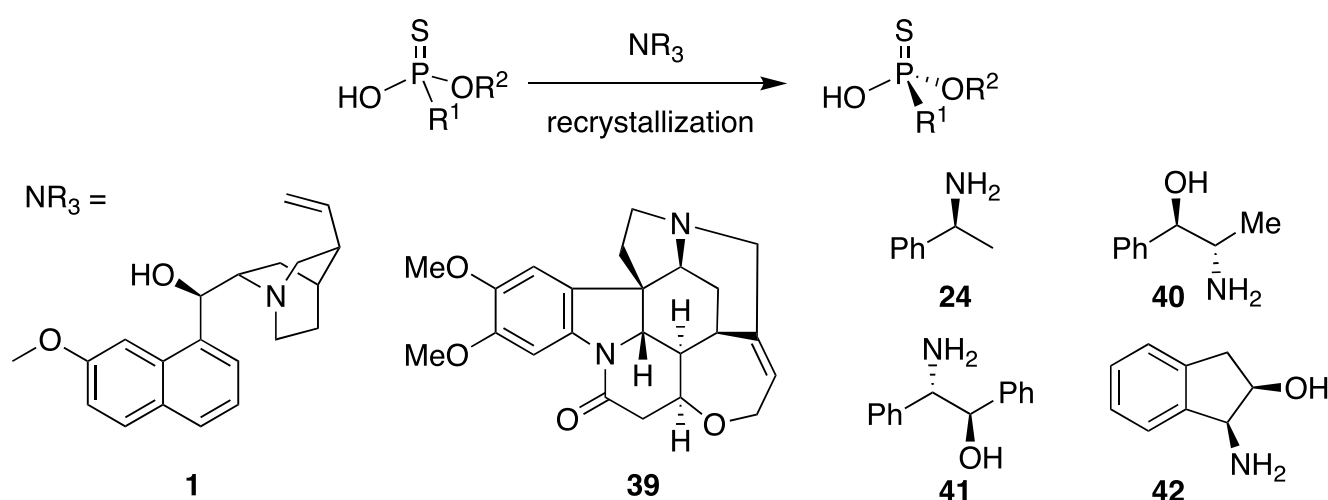
Scheme 9. The application of phosphonothioic acids as resolving agents for chiral amines

Guinchard and Voituriez have shown the utilities of phosphonothioic acid **30** as organocatalysts in the reduction of quinoline **29** with Hantzsch ester **31a** to give hydrogenated product **32** with moderate enantioselectivity (Scheme 10a).²² In contrast, attempts of the sequential reaction involving intramolecular hydroamination of **33** and reduction of the intermediate **35** with **31b** in toluene catalyzed by a gold complex and phosphonothioic acid **34** resulted in the recovery of the starting material **33**. The use of methanol promoted the reaction but the reaction did not show any enantio differentiation. (Scheme 10b).²³ This result is in contrast to an example in which the phosphoric acid **37** was used as the counter anion of a gold catalyst (Scheme 10, cf.).²⁴ It may be due to the higher affinity of the sulfur atom to the gold atom, and it may cause the decrease of the catalytic activity of gold atom.



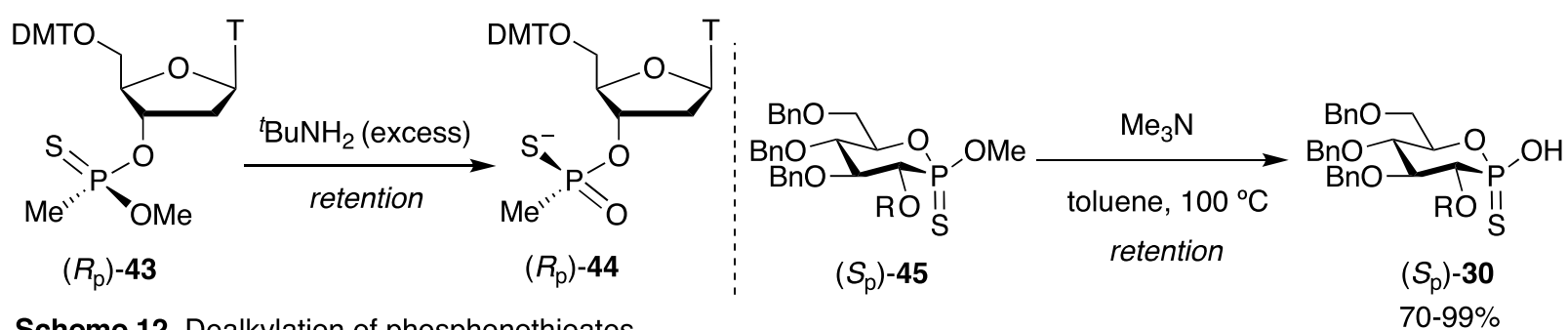
Scheme 10. The application of phosphonothioic acids as organocatalysts

Synthesis of *P*-stereogenic phosphonothioic acids classically relies on optical resolutions by using chiral amines since the first resolution of enantiomeric phosphonothioic acid by Aaron from the epimeric quinine salts in 1958 (Scheme 11).²⁵ The efficiency of the resolutions was improved by using appropriate amines as shown in Scheme 9, but individual optimization of recrystallization conditions was necessary.^{21,26}

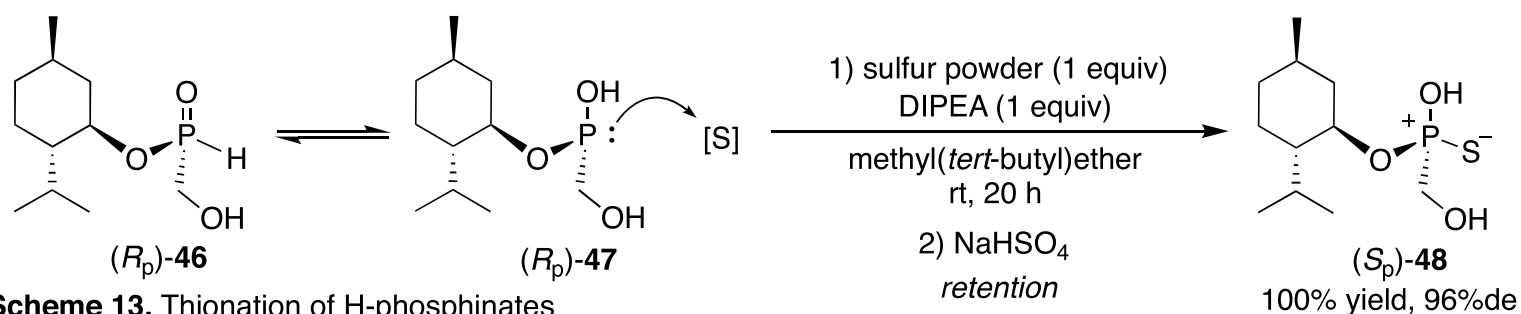


Scheme 11. Resolution of *P*-stereogenic phosphonothioic acids with chiral amines

Alternatively, dealkylation of phosphonothioates (*R_p*)-**43** and (*S_p*)-**45** with alkyl amines afforded *P*-stereogenic phosphonothioic acids (*R_p*)-**44** and (*S_p*)-**30** without the loss of diastereomeric purity of the starting materials and the reactions proceeded with *retention* of the configuration at the phosphorus atoms (Scheme 12).^{22,27} H-phosphinates (*R_p*)-**46** provided an access to *P*-stereogenic phosphonothioic acids (*S_p*)-**48**. H-phosphinate (*R_p*)-**46** is present in equilibrium with its phosphinous acid (*R_p*)-**47** which then reacts with the latter reacted with an elemental sulfur in a stereospecific manner to give (*S_p*)-**48** (Scheme 13).²⁸



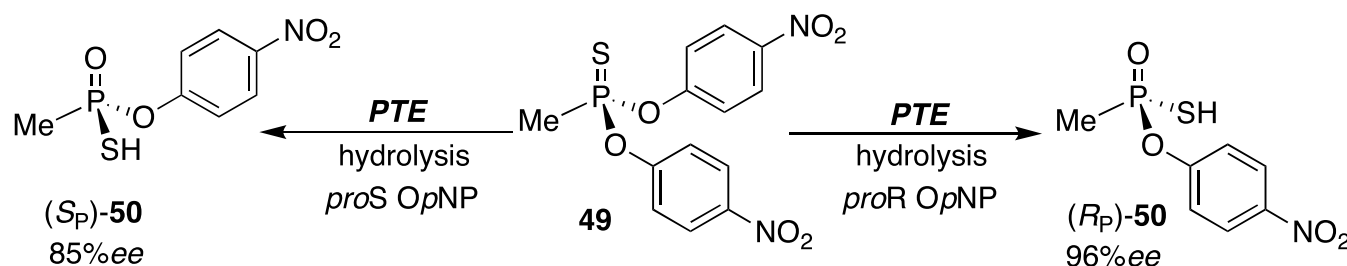
Scheme 12. Dealkylation of phosphonothioates



Scheme 13. Thionation of H-phosphinates

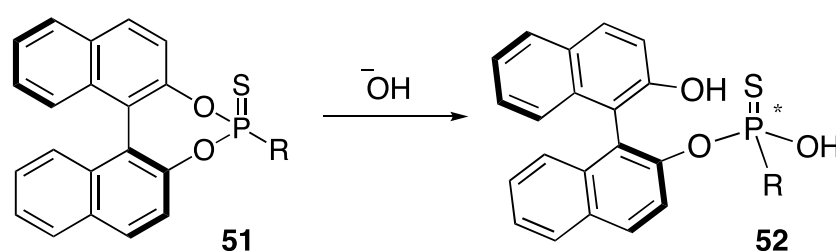
However, these methods inevitably involve diastereomeric resolution in the

preparation stage of starting materials. In my best knowledge, the reaction using *P*-achiral starting materials is only limited to the desymmetrization of phosphonothioates **49** with enzyme reported by Raushel (Scheme 14).²⁹



Scheme 14. Desymmetrization of phosphonothioates **49**

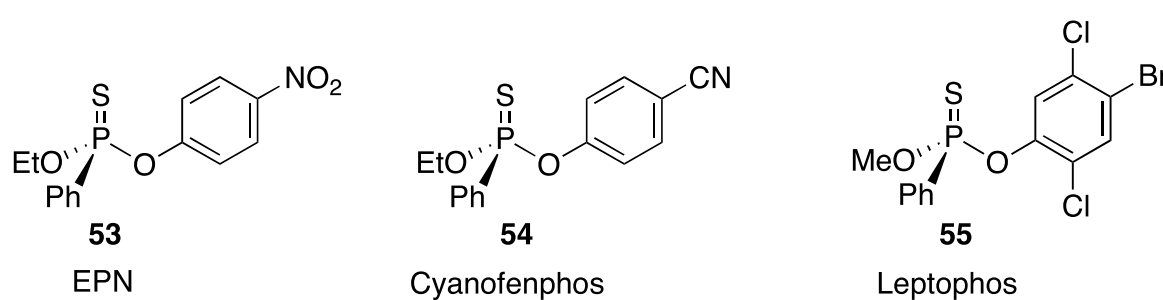
In chapter 2 of the present thesis is described the hydrolysis of phosphonothioates **51** having an optically active binaphthyl group (Scheme 15). The reaction proceeded via the transfer of axial chirality of the binaphthyl group to the central chirality of the phosphorus atom to give *P*-stereogenic phosphonothioic acids **52** with high diastereoselectivities. The utilities of the resulting products as chiral ligands and chiral discriminating agents are also shown.



Scheme 15. Hydrolysis of phosphonothioates having a binaphthyl group

1.5. Phosphonothioates

P-Stereogenic phosphonothioates have been developed as insecticides due to their ability to inhibit AChE. EPN **53**, Cyanophos **54** and Leptophos **55** were synthesized as enantiopure form to reveal the biological activities depend on their stereochemistry at the phosphorus atom (Scheme 16).^{25, 30}

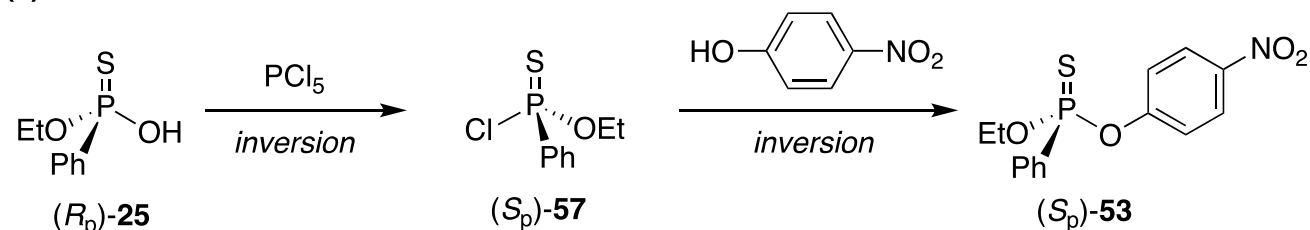


Scheme 16. Insecticides of *P*-stereogenic phosphonothioate

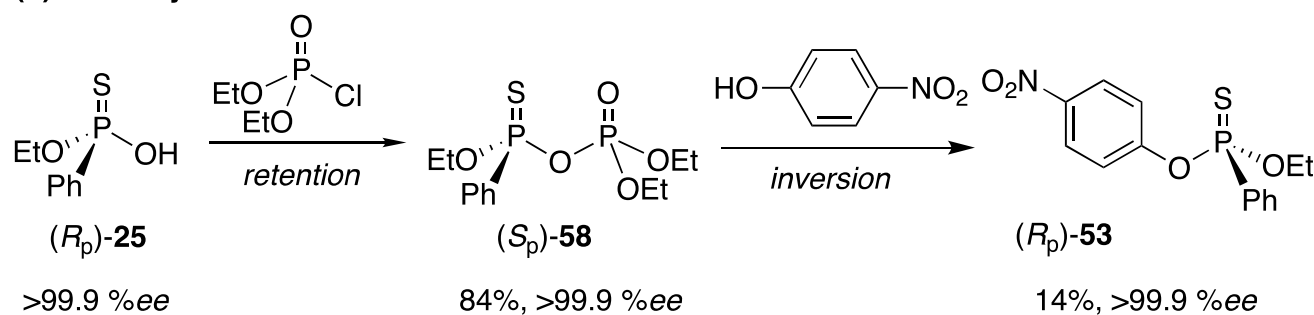
Typically, they were synthesized via alcoholysis of chloride **57** obtained from the

corresponding phosphonothioic acid **25** (Scheme 17a).³⁰ Chlorination of (*R*_p)-**25** and alcoholysis of (*S*_p)-**57** proceeded with *inversion* of configuration at the phosphorus atom respectively to give (*S*_p)-**53** from (*R*_p)-**25**. On the other hand, (*R*_p)-**53** was obtained from (*R*_p)-**25** via the once formed anhydride (*S*_p)-**58** because the phosphorylation of (*R*_p)-**53** occurred with *retention* of the configuration (Scheme 17b).³¹

(a) *via Chloride*

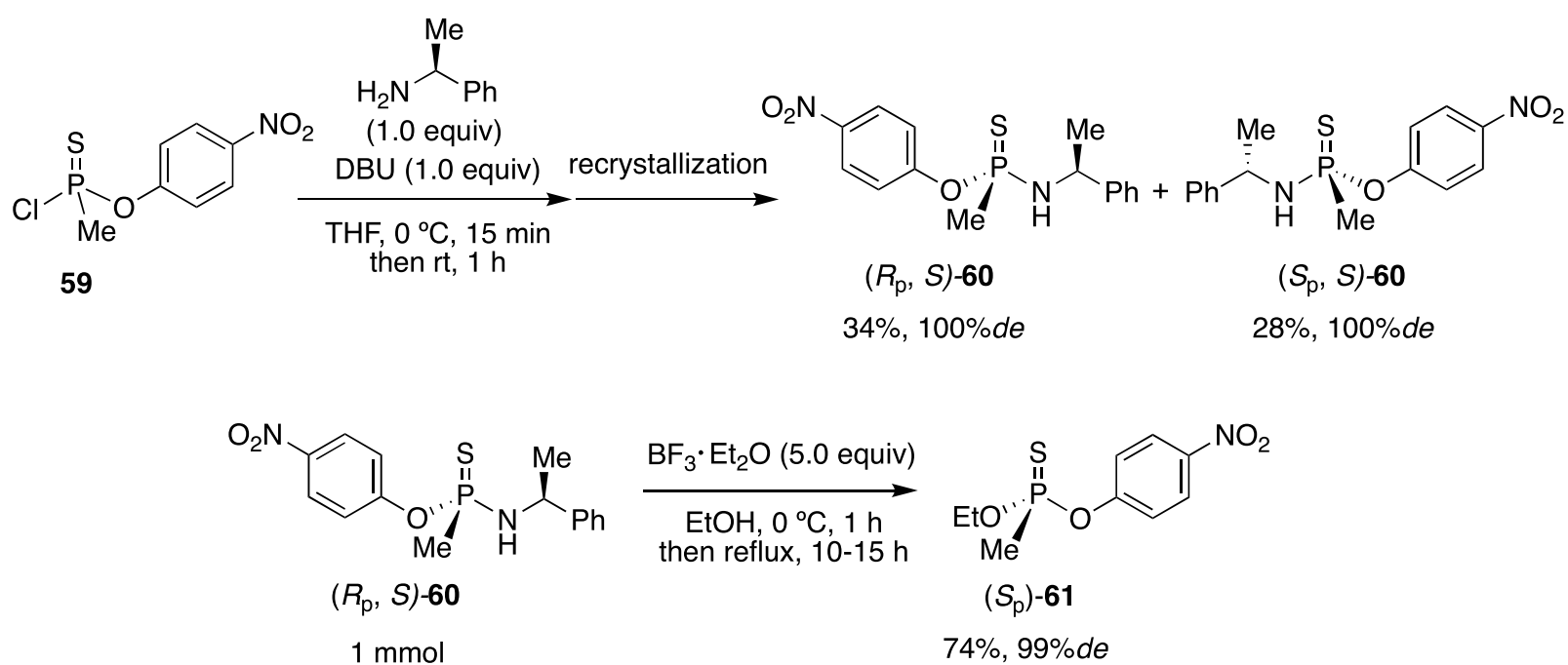


(b) *via Anhydride*



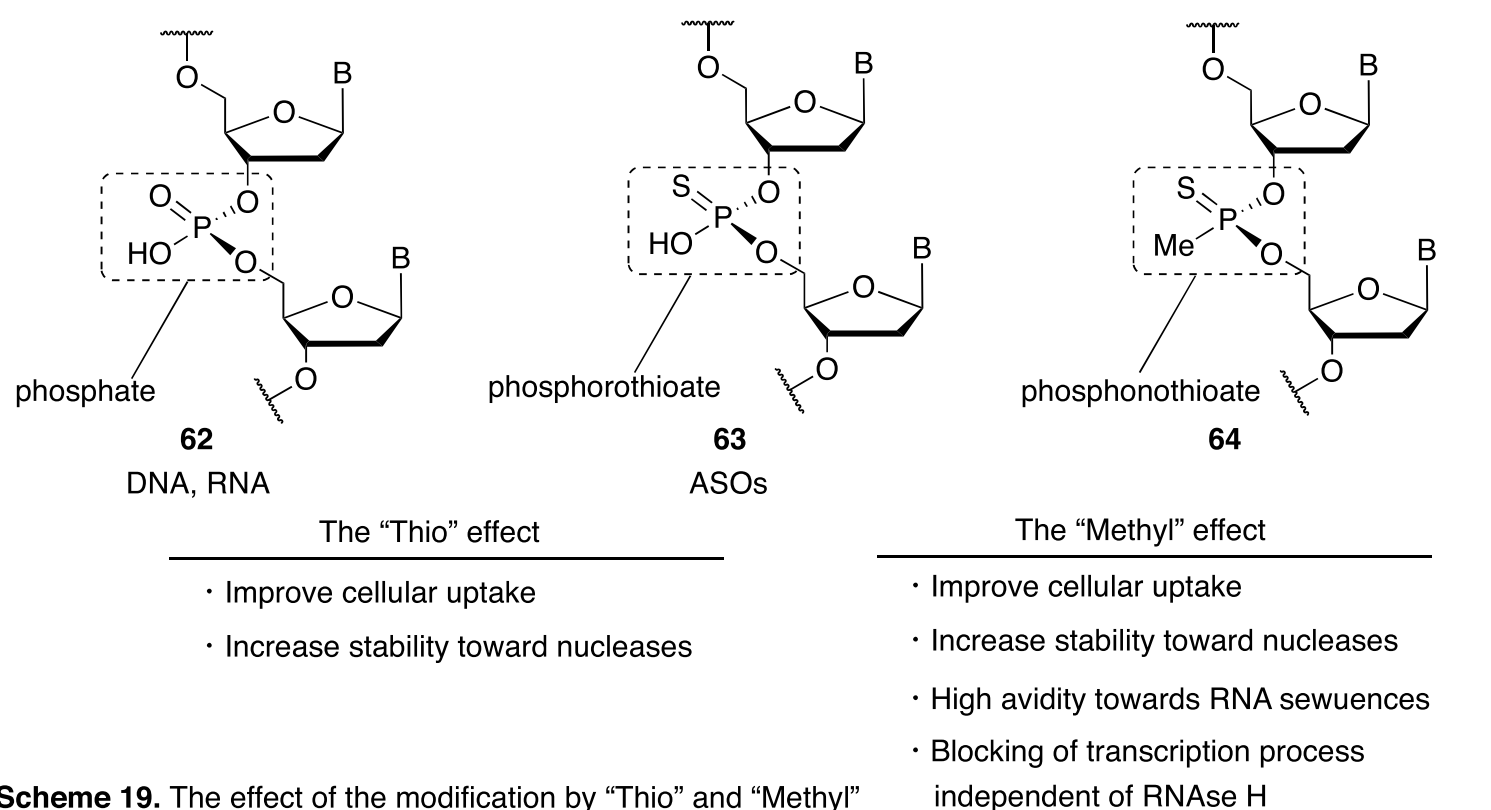
Scheme 17. Synthesis of *P*-stereogenic phosphonothioates from phosphonothioic acids

In addition to the method using *P*-stereogenic phosphonothioic acids resolved by chiral amines as shown in Scheme 9, the precursor **60** in which the chiral amine was attached to the phosphorus atom, also gave the corresponding phosphonothioate **61** with a stereoselective manner (Scheme 18).³²

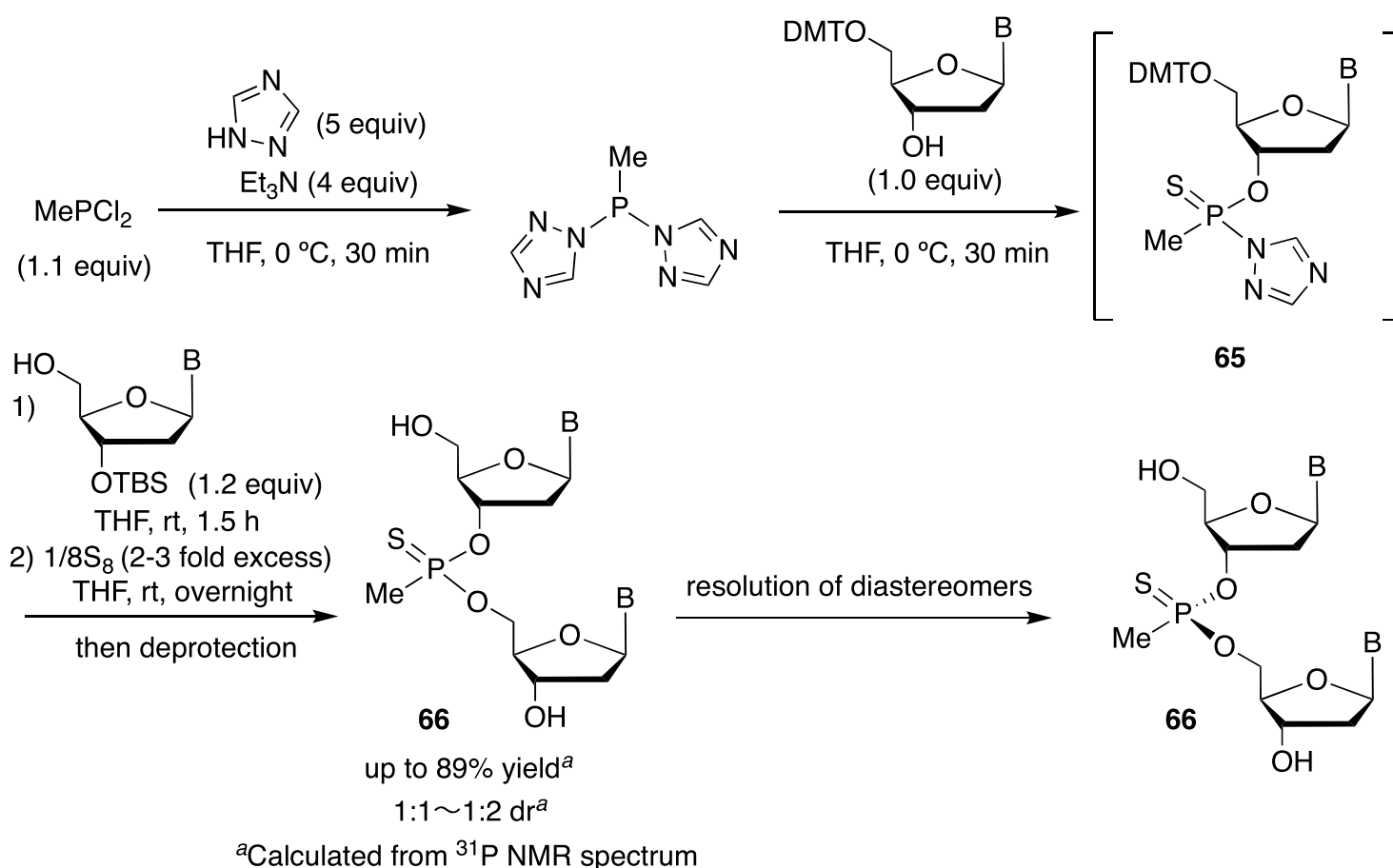


Scheme 18. The methods by using precursor **60**

P-Stereogenic phosphonothioates have also attracted attentions as oligonucleotide therapeutics. Nucleotides **62** are consisting of a nucleoside and a phosphate group, and are basic building blocks of DNA and RNA. Modification of the P=O bond of the phosphate **62** to the P=S bond improves cellular uptake and increases stability toward nucleases (Scheme 19).³³ Further modification of P-OH bond to the P-Me bond not only enhances cellular uptake and stability toward nucleases but also shows high activity toward RNA sequence and blocking of transcription process independent of RNNase H.³⁴ Wozniak synthesized phosphonothioates **66** as diastereomeric mixtures and resolved the diastereomers by silica gel column chromatography (Scheme 20).^{35,36}

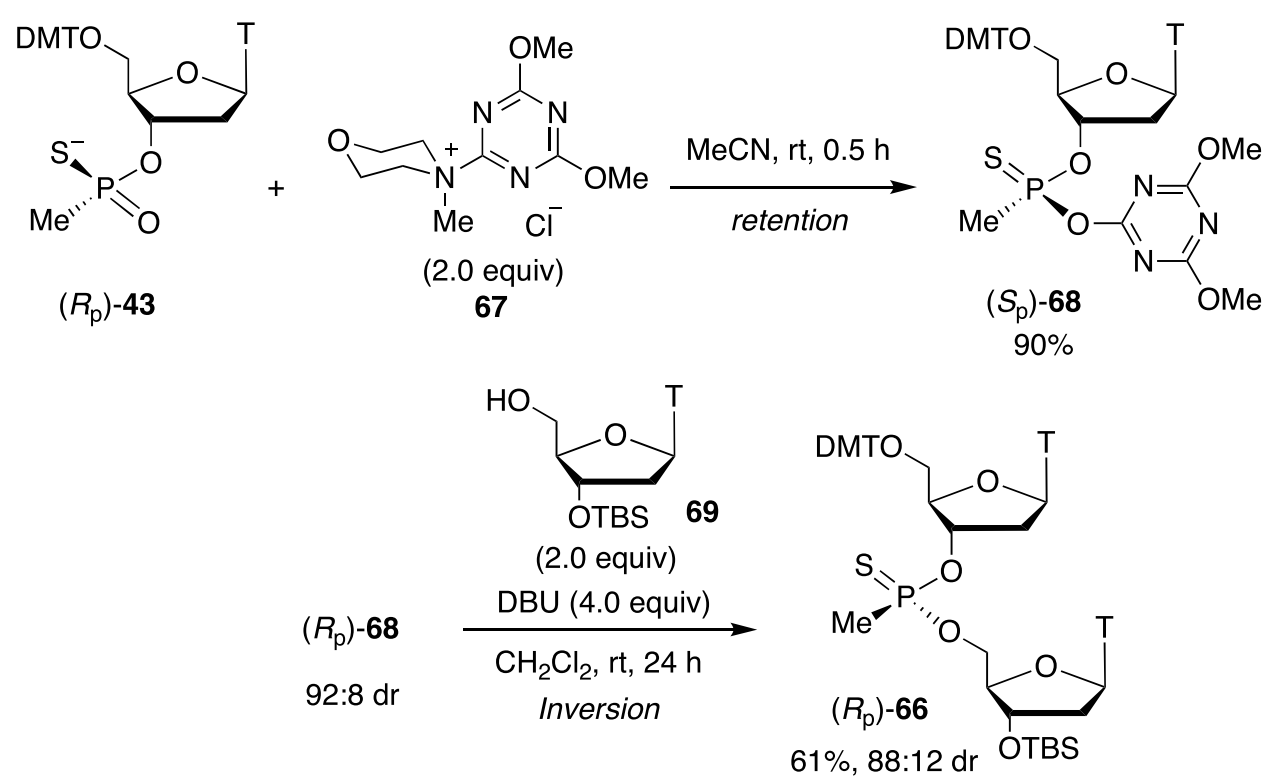


Scheme 19. The effect of the modification by "Thio" and "Methyl"

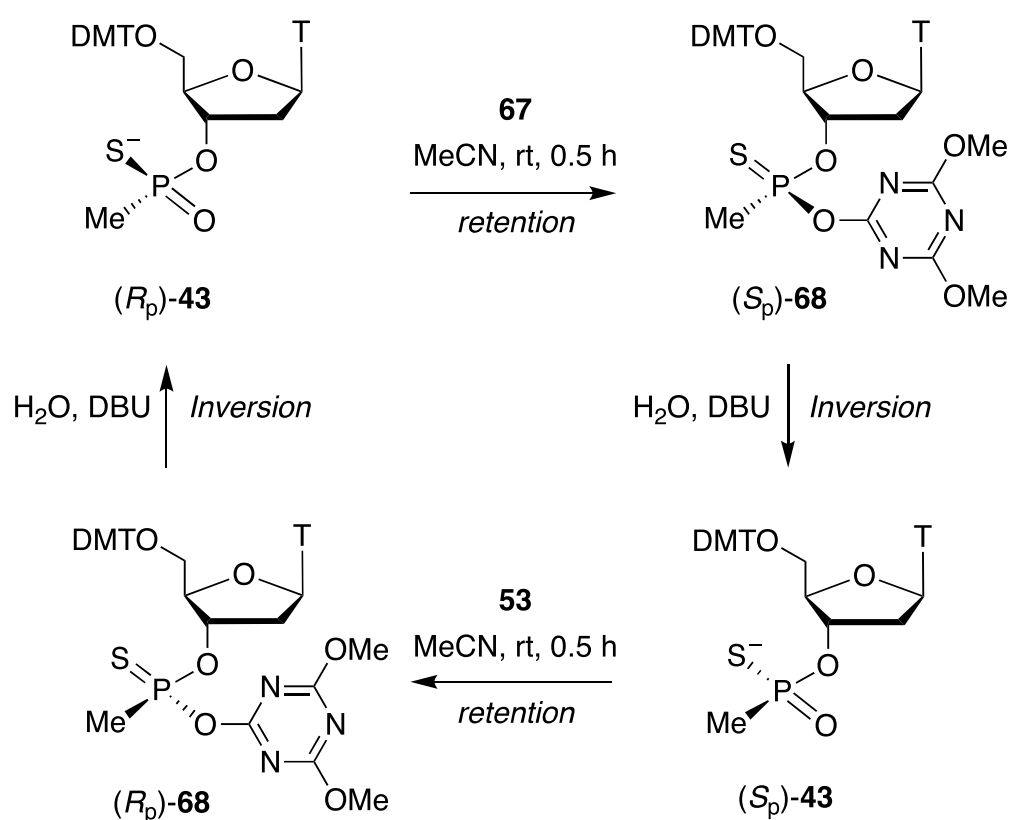


Scheme 20. Synthesis of enriched diastereomer **66** in one pot

Wozniak also demonstrated the synthesis of **66** via phosphonothioate **68** (Scheme 21).³⁷ The reaction of phosphonothioic acid (*R_p*)-**43** with morpholinium salt **67** proceeded with *retention* of configuration at the phosphorus center to give phosphonothioate (*S_p*)-**68**. The following reaction of the obtained ester (*S_p*)-**68** with nucleoside **69** occurred with *inversion* of configuration to give (*R_p*)-**66** with high diastereoselectivity. This method provided an access to both enantiomers of **66** from (*R_p*)-**43**. In fact, (*S_p*)-**68** was converted to (*R_p*)-**68** through the hydrolysis followed by the reaction with **67** (Scheme 22).

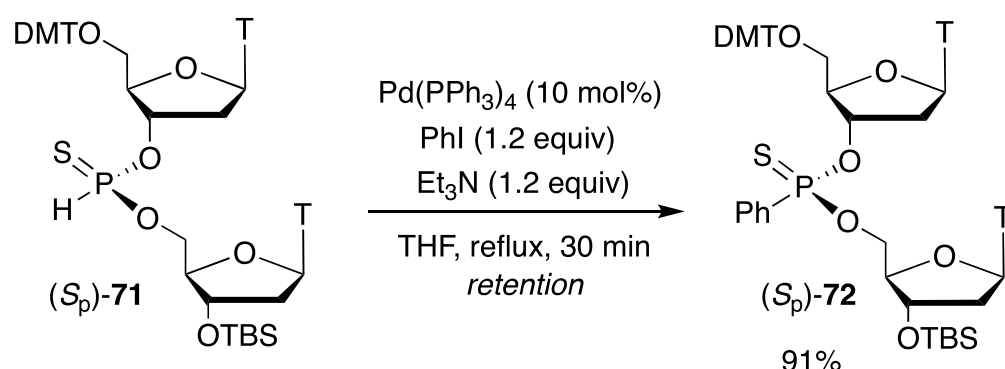


Scheme 21. Synthesis of **70** via phosphonothioate **66**



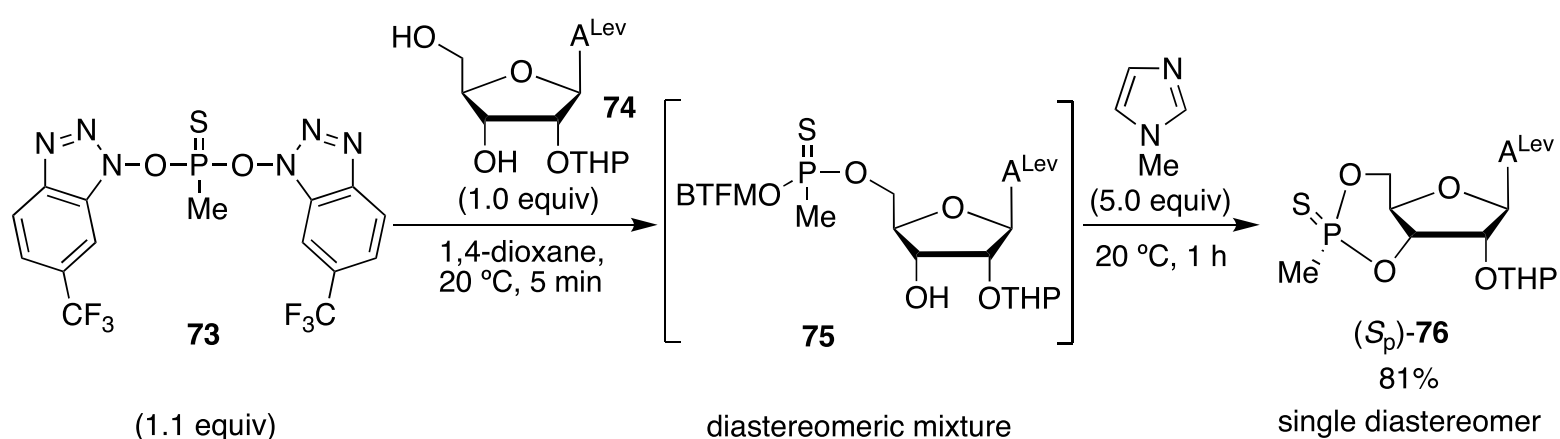
Scheme 22. Walden cycle

P-Stereogenic H-phosphonothioates (*S_p*)-**57** successfully was converted to phosphonothioate (*S_p*)-**58** by transition metal-catalyzed cross-coupling reaction with various aryl halides (Scheme 21).³⁸ The reaction was completely stereospecific and took place most likely with *retention* of configuration.

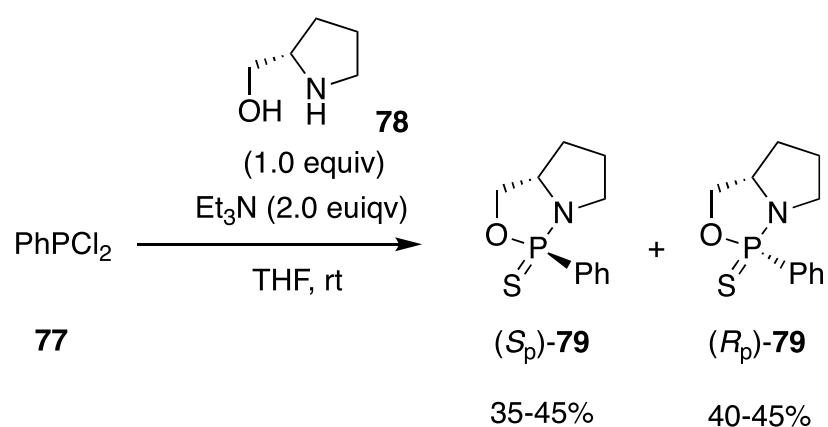


Scheme 23. Cross coupling reaction of H-phosphonothioate **71**

In addition to linear nucleotides, adenosine 3',5'-cyclic phosphate (cAMP) is known as a key regulator of metabolism.³⁹ In several studies of cAMP analogues, Van Boom reported the synthesis of the corresponding phosphonothioate analogues of cAMP (Scheme 24).⁴⁰ Interestingly, intramolecular alcoholysis of intermediate **75** proceeded as dynamic kinetic resolution-like process to give adenosine 3',5'-cyclic phosphonothioate (cAMPS) (*S_p*)-**76** as a single diastereomer although no stereoselectivity was observed in the intermolecular alcoholysis of activated ester **76** with nucleotide **74**. In contrast, the cyclization of phenylphosphonothioic dichloride **77** with *L*-prolinol **78** afforded oxazaphospholesulfide **79** as diastereomeric mixtures (Scheme 25).⁴¹

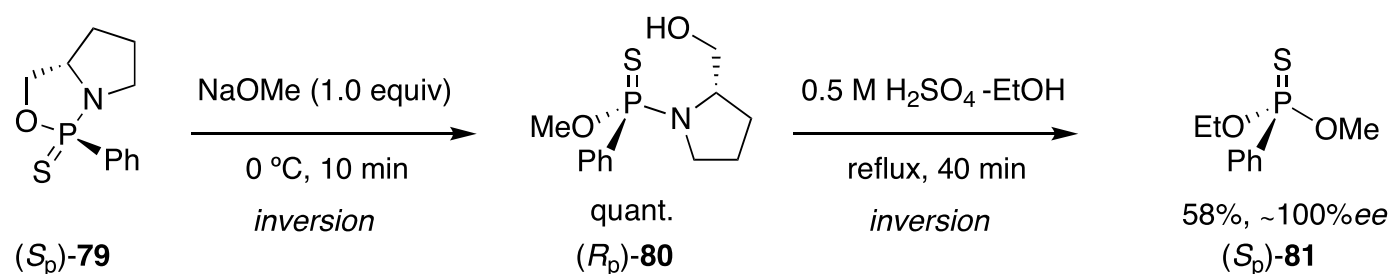


Scheme 24. Stereoselective synthesis of cAMPS **76**



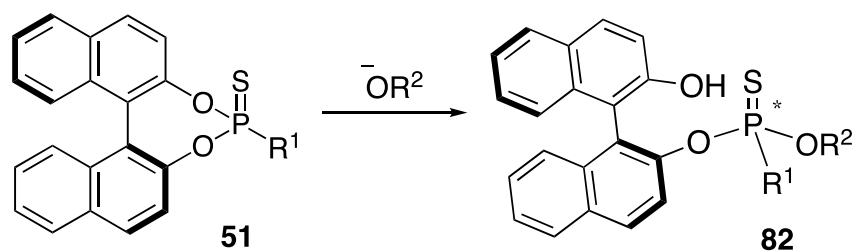
Scheme 25. Preparation of oxazaphospholesulfide **79**

Even so, after the separation of diastereomers of **79** by column chromatography, sequential methanolysis and ethanolysis of (*S_p*)-**79** stereospecifically proceeded with *inversion* of configuration to give phosphonothioates (*S_p*)-**81** with excellent enantiomeric excess (Scheme 26).



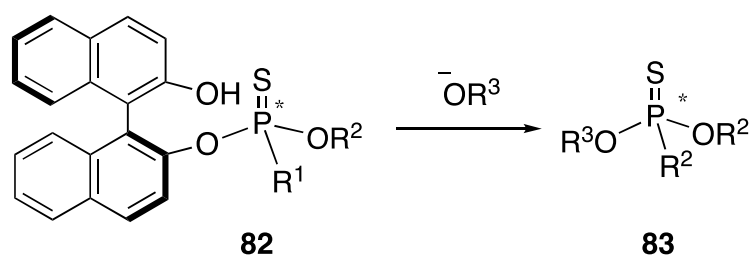
Scheme 26. Sequential alcoholysis of (*S_p*)-**79**

Almost all of the reactions as shown above contain diastereomeric separation step. In Chapter 3 is described a key step toward stereospecific synthesis of various *P*-stereogenic phosphonothioates. The reaction of phosphonothioates **51** with alcohols proceeded in the same fashion in the case of hydrolysis of **51** to give *P*-stereogenic phosphonothioates **82** with moderate to excellent diastereoselectivities (Scheme 27).



Scheme 27. Alcoholysis of phosphonothioates having a binaphthyl group

In Chapter 4 is described further alcoholysis of the obtained *P*-stereogenic phosphonothioates **68** (Scheme 26). The reaction proceeded with high stereoselectivities in the presence of strong base.



Scheme 28. Further alcoholysis of phosphonothioates **82**

References and notes

- (1) (a) Tröger, J. *J. Prakt. Chemie* **1887**, 36, 225. (b) Bucciarelli, M.; Forni, A.; Moretti, I.; Prati, F. *Tetrahedron: Asymmetry* **1990**, 1, 5.
- (2) Montgomery, C. D. *J. Chem. Educ.* **2013**, 90, 661.
- (3) (a) Knowles, W. S.; Sabacky, M. J.; Vineyard, B. D.; Weinkauff, D. J. *J. Am. Chem. Soc.* **1975**, 97, 2567. (b) Tamura, K.; Sugiyama, M.; Yoshida, K.; Yanagisawa, A.; Imamoto, T. *Org. Lett.* **2010**, 12, 4400. (c) Tang, W.; Qu, B.; Capacci, A. G.; Rodriguez, S.; Wei, X.; Haddad, N.; Narayanan, B.; Ma, S.; Grinberg, N.; Yee, N. K.; Krishnamurthy, D.; Senanayake, C. H. *Org. Lett.* **2010**, 12, 176. (d) Xiong, W.; Xu, G.; Yu, X.; Tng, W. *Organometallics* **2019**, doi.org/10.1021/acs.organomet.9b00194.
- (4) Deichl, K. D.; Ess, D. H.; Radosevich, A. T. *J. Am. Chem. Soc.* **2013**, 135, 9354.
- (5) Kimura, T.; Murai, T. *Chem. Commun.* **2005**, 4077.
- (6) (a) Tang, W.; Wang, W.; Zhang, X. *Angew. Chem. Int. Ed.* **2003**, 42, 943. (b) Kimura, T.; Murai, T. *Chem. Lett.* **2004**, 33, 878.
- (7) (a) Emmick, T.L.; Letsinger, R. L. *J. Am. Chem. Soc.* **1968**, 90, 3459. (b) Farnham, W. B.; Murray, R. K.; Mislow, K. *J. Am. Chem. Soc.* **1970**, 92, 5808. (c) Xu, Q.; Zgao, C.-Q.; Han, L.-B. *J. Am. Chem. Soc.* **2008**, 130, 12648. (d) Wang, W.-M.; Liu, L.-J.; Zhao, C.-Q.; Han, L.-B. *Eur. J. Org. Chem.* **2015**, 2015, 2342. For subsequent reactions, see reviews: (e) Kolodiazny, O. I. *Phosphorus Chemistry I Asymmetric Synthesis and Bioactive Compounds*; Montchamp, J.-L. Ed.; Springer International Publishing: Switzerland, 2014; pp161-236. (f) Dutartre, M.; Bayardon, J.; Jugé, S. *Chem. Soc. Rev.* **2016**, 45, 5771.
- (8) (a) Adams, H.; Collins, R. C.; Jones, S.; Warner, C. J. A. *Org. Lett.* **2011**, 13, 6576. (b) Han, Z. S.; Goyal, N.; Herbage, M. A.; Sieber, J. D.; Qu, B.; Xu, Y.; Li, Z.; Reeves, J. T.; Desrosiers, J.-N.; Ma, S.; Grinberg, N.; Lee, H.; Mangunuru, H. P. R.; Zhang, Y.; Krishnamurthy, D.; Lu, B. Z.; Song, J. L. Wang, G.; Senanayake, C. H. *J. Am. Chem. Soc.* **2013**, 135, 2474. (c) Li, S.-G.; Yuan, M.; Topic, F.; Han, Z. S.; Senanayake, C. H.; Tsantrizos, Y. S. *J. Org. Chem.* **2019**, 84, 7291.
- (9) (a) Casimiro, M.; Rocas, L.; Gracia-Granda, S.; Iglesias, M. J.; Oritz, F. L. *Org. Lett.* **2013**, 15, 2378. (b) Murai, T.; Hayashi, T.; Yamada, K.; Maekawa, Y.; Minoura, M. *Chem. Commun.* **2014**, 50, 12473. (c) Maekawa, Y.; Kuwabara, K.; Sugiyama, A.; Iwata, K.; Maruyama, T.; Murai, T. *Chem. Lett.* **2017**, 46, 1068.
- (10) (a) Lin, Z.-Q.; Wang, W.-Z.; Yan, S.-B.; Duan, W.-L. *Angew. Chem. Int. Ed.* **2015**,

- 54, 6265. (b) Huang, Z.; Huang, X.; Li, B.; Mou, C.; Yang, S.; Song, B.-A.; Chi, Y. R. *J. Am. Chem. Soc.* **2016**, *138*, 7524. (c) Beaud, R.; Phipps, R. J.; Gaunt, M. J.; *J. Am. Chem. Soc.* **2016**, *138*, 13183. (d) Jang, Y. S.; Wozniak, Ł.; Pedroni, J.; Cramer, N. *Angew. Chem. Int. Ed.* **2018**, *57*, 12901. (e) Zheng, Y.; Guo, L.; Zi, W. *Org. Lett.* **2018**, *20*, 7039. (f) Yang, G.-H.; Li, Y.; Li, X.; Cheng, J.-P. *Chem. Sci.* **2019**, *10*, 4322. (g) Trost, B. M.; Spohr, S. M.; Rolka, A. B.; Kalnmals, C. A. *J. Am. Chem. Soc.* **2019**, *141*, 14098. (h) Fernándy-Pérey, H.; Vida-Ferran, A. *Org. Lett.* **2019**, *21*, 7019.
- (11) Timperley, C. M. *Best Synthetic Methods Organophosphorus (V) Chemistry*; Elsevier Publishing: Amsterdam, 2001.
- (12) Jokanović, M. *Toxicology* **2018**, *410*, 125.
- (13) (a) Ooms, A. J. J.; Boter, H. L. *Biochem. Pharmacol.* **1965**, *14*, 1839. (b) Benschop, H. P.; Konings, C. A. G.; Van Genderen, J.; De Jong, L. P. A.; Kienhuis, H. *Phosphorus and Sulfur* **1983**, *18*, 345. (c) Benschop, H. P.; De Jong, L. P. A. *Acc. Chem. Res.* **1988**, *21*, 368.
- (14) (a) Sofia, M. J.; Bao, D.; Chang, W.; Du, J.; Nagarathnam, D.; Rachakonda, S.; Reddy, P. G.; Ross, B. S.; Wang, P.; Zhang, H.-R.; Bansal, S.; Espiritu, C.; Keilman, M.; Lam, A. M.; Micolochick Steuer, H. M.; Niu, C.; Otto, M. J.; Furman, P. A. *J. Med. Chem.* **2010**, *53*, 7202. (b) Reddy, P. G.; Bao, D.; Chang, W.; Chun, B.-K.; Du, J.; Nagarathnam, D.; Rachakonda, S.; Ross, B. S.; Zhang, H.-R.; Bansal, S.; Espiritu, C. L.; Keilman, M.; Lam, A. M.; Niu, C.; Micolochick Steure, H. M.; Furman, P. A.; Otto, M. J.; Sofia, M. j. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 7376. (c) Lam, A. M.; Espiritu, C.; Murakami, E.; Zennou, V.; Bansal, S.; Micolochick Steuer, H. M.; Niu, C.; keilman, M.; Bao, H.; Bourne, N.; Veselenak, R. L.; Reddy, P. G.; Chang, W.; Du, J.; Nagarathnam, D.; Sofia, M. J.; Otto, M. J.; Furman, P. A. *Antimicrob. Agents Chemother.* **2011**, *55*, 2566. (d) Ross, B. S.; Reddy, P. G.; Zhang, H.-R.; Rachakonda, S.; Sofia, M. J. *Org. Chem.* **2011**, *76*, 8311.
- (15) For reviews, see: (a) Shen, X.; Corey, D. R. *Nucleic Acids Res.* **2018**, *46*, 1584. (b) Goyal, N.; Natayanaswami, P. *Muscle Nerve* **2018**, *57*, 356.
- (16) (a) Knouse, K. W.; deGruyter, J. N.; Schmidt, M. A.; Zheng, B.; Vantourout, J. C.; Kingston, C.; Mercer, S. E.; Mcdonald, I. M.; Olson, R. E.; Zhu, Y.; Hang, C.; Zhu, J.; yuan, C.; Wang, Q.; Park, P.; Eastgate, M. D.; Baran, P. S. *Science* **2018**, *361*, 1234. (b) Bohr, H. G.; Shim, I.; Stein, C.; Ørum, H.; Hansen, H. F.; Koch, T. *Nucleic Acids* **2017**, *8*, 428. (c) Iwamoto, N.; Butler D. C.; Svrzikapa, N.; Mohapatra, S.; Zlatev, I.; Sah, D.

- W. Y.; Meena, Standley, S. M.; Lu, G.; Apponi, L. H.; Frank-Kamenetsky, M.; Zhang, J. J.; Vargeese, C.; Verdine, G. L. *Nat. Biotechnol.* **2017**, *35*, 845.
- (17) (a) Stec, W. J.; Karwowski, B.; Boczkowska, M.; Guga, P.; Koziołkiewicz, M.; Sochacki, M.; Wieczorek, M. W.; Błaszczuk, J. *J. Am. Chem. Soc.* **1998**, *120*, 7156. (b) Iyer, R. P.; Yu, D.; Ho, N.-H.; Tan, W.; Agrawal, S. *Tetrahedron: Asymmetry* **1995**, *6*, 1051. (c) Wilk, A.; Granjkowski, A.; Philips, L. R.; Beaucage, S. L. *J. Am. Chem. Soc.* **2000**, *122*, 2149. (d) Oka, N.; Wada, T.; Saigo, K. *J. Am. Chem. Soc.* **2002**, *124*, 4962. (e) Oka, N.; Wada, T.; Saigo, K. *J. Am. Chem. Soc.* **2003**, *125*, 8307.
- (18) Kabachnik, M. I.; Mastrukova, T. A.; Shipov, A. E.; Melentyeva, T. A. *Tetrahedron* **1960**, *9*, 10.
- (19) For reviews, see: (a) Parmar, D.; Sugiono, E.; Raja, S.; Rueping, M. *Chem. Rev.* **2014**, *114*, 9047. (b) Maji, R.; Mallojjala, S. C.; Wheele, S. E. *Chem. Soc. Rev.* **2018**, *47*, 1142.
- (20) (a) Akiyama, T.; Itoh, J.; Yokota, Fuchibe, K. *Angew. Chem. Int. Ed.* **2004**, *43*, 1566. (b) Uraguchi, D.; Terada, M.; *J. Am. Chem. Soc.* **2004**, *126*, 5356. (c) Rowland, G. B.; Zhang, H.; Rowland, E. B.; Chennamadhavuni, S.; Wang, Y.; Antilla, J. C. *J. Am. Chem. Soc.* **2005**, *127*, 15696. (d) Akiyama, T. *New Development of Organocatalyst*; Shibasaki, M., Supv.; CMC Publishing: Tokyo, 2006; pp 226. (e) Budragchaa, T.; Abraham, M.; Schöfberger, W.; Roller, A.; Widhalm, M. *Asymmetric Catal.* **2016**, *3*, 1. (c) Berger, O.; Montchamp, J.-L. *Angew. Chem. Int. Ed.* **2013**, *52*, 11377.
- (21) (a) Kobayashi, Y.; Morisawa, F.; Saigo, K. *Org. Lett.* **2004**, *6*, 4227. (b) Kobayashi, Y.; Morisawa, F.; Saigo, K. *J. Org. Chem.* **2006**, *71*, 606. (c) Kobayashi, Y.; Maeda, J.; Morisawa, F.; Saigo, K. *Tetrahedron: Asymmetry* **2006**, *17*, 967. (d) Kobayashi, Y.; Maeda, J.; Saigo, K. *Tetrahedron: Asymmetry* **2006**, *17*, 1617. (e) Ribeiro, N.; Kobayashi, Y.; Maeda, J.; Saigo, K. *Chirality* **2011**, *23*, 438.
- (22) Ferry, A.; Stemper, J.; Marinetti, A.; Voituriez, A.; Guinchard, X. *Eur. J. Org. Chem.* **2014**, *2014*, 188.
- (23) Malik, G.; Ferry, A.; Guinchard, X. *Molecules* **2015**, *20*, 21082.
- (24) Hamilton, G. L.; Kang, E. J.; Mba, M.; Toste, F. D. *Science* **2007**, *317*, 496.
- (25) Aaron, H.S.; Michel, H. O.; Witten, B.; Mille, J. I.; *J. Am. Chem. Soc.* **1958**, *80*, 456.
- (26) (a) Ohkawa, H.; Mikami, N.; Miyamoto, J.; *Agric. Bio. Chem.* **1977**, *41*, 369. (b) Lewis, V. E.; Donarski, W. J.; Wild, J. R.; Raushel, F. M. *Biochemistry* **1988**, *27*, 1591.

- (f) Kuo, L. Y.; Glazier, S. K. *Inorg. Chem.* **2012**, *51*, 328.
- (27) (a) Gray, M. D. M.; Smith, D. J. H. *Tetrahedron Lett.* **1989**, *21*, 859. (b) Wozniak, L. A.; Chworos, A.; Pyzowski, J.; Stec, W. J. *J. Org. Chem.* **1998**, *63*, 9109.
- (28) (a) Berger, O.; Montchamp, J.-L. *Angew. Chem. Int. Ed.* **2013**, *52*, 11377. (b) Wang, W.-M.; Liu, L.-J.; Yao, L.; Menf, F.-J.; Sun, Y.-M.; Zhao, C.-Q.; Xu, Q.; Han, L.-B. *J. Org. Chem.* **2016**, *81*, 6843.
- (25) Li, W.-S.; Li, Y.; Hill, C. M.; Lum, K. T.; Raushel, F. M. *J. Am. Chem. Soc.* **2002**, *124*, 3498.
- (30) (a) Ohkawa, H.; Mikami, N.; Okuno, Y.; Miyamoto, J. *J. Bull. Environ. Contam. Toxicol.* **1977**, *18*, 534. (b) Mikołajczyk, M.; Omelanczuk, J.; Para, M. *Tetrahedron* **1972**, *28*, 3855. (c) Allahyari, R.; Hoolingshaus, J. G.; Rapp, R. L.; Timm, E.; Jacobsen, R. A.; Fukuto, T. R. *J. Agric. Food. Chem.* **1980**, *28*, 594. (d) Yoshikawa, H.; Shono, T.; Eto, M. *J. Pesticide. Sci.* **1984**, *9*, 455.
- (31) Yoshikawa, H. *Biosci. Biotechnol. Biochem.* **1999**, *63*, 424.
- (32) (a) Batra, P. B. S.; Lal, G. *Tetrahedron Lett.* **1994**, *35*, 4641. (b) Reddy, P. M.; Kovach, I. M. *Tetrahedron Lett.* **2002**, *43*, 4063.
- (33) (a) Vosberg, H.-P.; Eckstein, F. *J. Biolog. Chem.* **1982**, *257*, 6596. (b) Wickstrom, E. *J. Biochem. Biophys. Methods* **1986**, *13*, 97.
- (34) (a) Reynolds, M.A.; Hogrefe, R. I.; Jaeger, J. A.; Schwartz, D. A.; Riely, T. A.; Marvin, W. B.; Daily, W. J.; Vaghefi, M. M.; Beck, T. A.; Knowles, S. K.; Klem, R. E.; Arnold, L. J. Jr. *Nucleic Acids Res.* **1996**, *24*, 4584. (b) Giles, R. V.; Spiller, D. V.; Grzybowski, J.; Clark, R. E.; Nicklin, P.; Tidd, D. M. *Nucleic Acids Res.* **1998**, *26*, 1567. (c) Miller, P. S.; Hamma, T. *Antisense & Nucl. Acids Drug Dev.* **1999**, *9*, 367. (d) Lloyd, B. H.; Giles, R. V.; Spiller, D. V.; Grzybowski, J.; Tidd, D. M.; Sibson, D. R. *Nucleic Acids Res.* **2001**, *29*, 3664.
- (35) Wozniak, L. A.; Majzner, W.; Stec, W. J. *ARKIVOC* **2004**, (iii), 101.
- (36) (a) Olejniczak, S.; Potrzebowski, M. J. Wozniak, L. A. *Eur. J. Org. Chem.* **2004**, *2004*, 1985. (b) Wozniak, L. A.; Bukowiecka-Matusiak, M.; Gora, M.; Stec, W. J. *Synlett* **2006**, *9*, 1331.
- (37) Wozniak, L. A.; Góra, M.; Stec, W. J. *J. Org. Chem.* **2007**, *72*, 8584.
- (38) Sobczak, M.; Johansson, T.; Bulkowski, M.; Sochacki, M.; Lavén, G.; Mikołajczyk, B.; Stawinski, J.; Nawrot, B. *ARKIVOC* **2012**, (iv), 63.
- (39) Brun, P.-J.; Yang, K. J. Z.; Lee, S.-A.; Yuen, J. J.; Blane, W. S. *Biofactors* **2013**,

39, 151.

(40) (a) Van Haasstert, P. J. M. *J. Biol. Chem.* **1983**, 258, 9643. (b) Roelen, H. C. P. F.; De Vroom, E.; Van Der Marel, G. A.; Van Boom, J. H. *Nucleic Acids Res.* **1988**, 16, 7633. (c) Roelen, H. C. P. F.; De Vroom, E.; Wang, A. H. J.; Van Der Marel, G. A.; Van Boom, J. H. *Nucleosides & Nucleotides* **1992**, 11, 141. For similar observation of stereoselectivity, also see ref. 10b.

(41) Koizumi, T.; Yanada, R.; Takagi, H.; Hirai, H.; Yoshii, E. *Tetrahedron Lett.* **1981**, 22, 477.

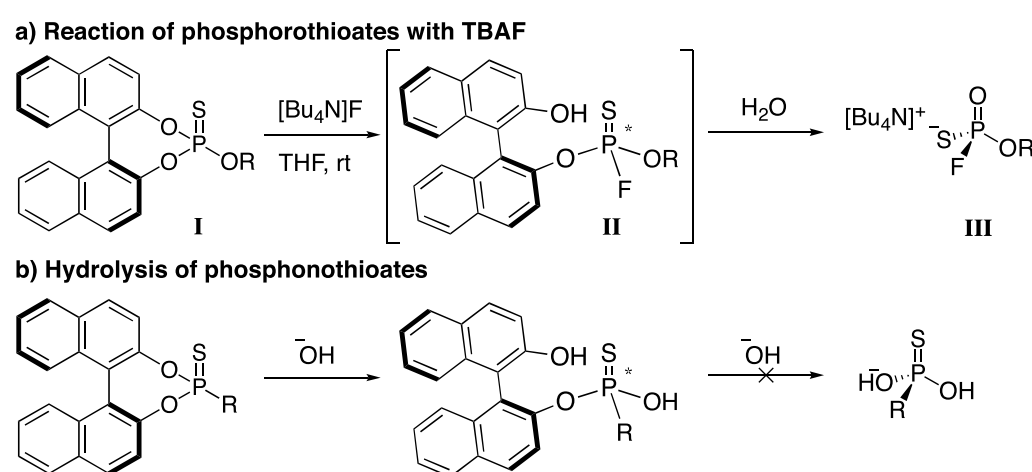
Chapter 2

Hydrolysis of Phosphonothioates with a Binaphthyl Group

The hydrolysis of phosphonothioates with a binaphthyl group afforded the first example of *O*-(2'-hydroxy)binaphthyl phosphonothioic acids in good to high yields and >95:5 diastereoselectivity. The reaction proceeds via an axis-to-center chirality-transfer reaction. The ability of these acids to act as chiral molecular auxiliaries was demonstrated by using them as optically active ligands for the asymmetric ethylation of benzaldehyde and as a chiral discriminating agent for chiral aliphatic amines.

2.1. Introduction

As mentioned in the Chapter 1, *P*-Stereogenic phosphonothioic acids have attracted increasing attention due to their diverse applications in a variety of research area related to chirality. More interestingly, if such compounds possess not only chirality on the phosphorus atom, but also on the carbon chains attached to the phosphorus atom, they may provide well-organized chiral environments. In fact, such types of derivatives, which exhibit carbon chains with central chirality have been developed,¹ but their applications as chiral molecular tools remain somewhat under-developed. On the other hand, an axis-to-center chirality-transfer strategy has been developed for the synthesis of *P*-stereogenic compounds from organophosphorus substrates bearing a binaphthyl group. For example, the reaction of phosphorothioates **I** with a THF solution of [Bu₄N]F containing 10% of H₂O furnished acid salts **III** with high efficiency and high enantiomeric excess (Scheme 1a).^{2a} In this reaction, fluoride **II** may be initially formed, but the high electrophilicity of the phosphorus atom in **II** may cause further hydrolysis. The author envisaged that acids possessing skeletons analogous to **II**, provided that they are sufficiently stable to be isolated, could serve as highly versatile chiral molecular tools given the presence of an axially chiral binaphthyl group, a *P*-stereogenic center, and acidic protons (Scheme 1b). In this chapter, the author describes the diastereoselective synthesis of *O*-binaphthyl phosphonothioic acids via an axis-to-center chirality transfer, and their applications as optically active ligands and as chiral discriminating agents.

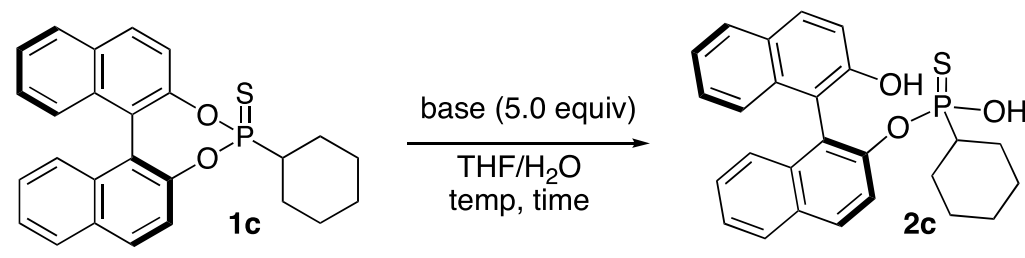


Scheme 1. Axis-to-Center Chirality Transfer from Phosphorothioates and Phosphonothioates

2.2. Hydrolysis of Phosphonothioates

Initially, the author reacted phosphonothioate **1c** with metal hydroxides (Table 1). The hydrolysis of **1c** occurred at room temperature to give the desired product **2c** in 88% yield with a diastereoselectivity of >95:5, albeit that prolonged reaction times (>140 h) were required when LiOH was used (entry 1). In this reaction, the axial chirality of the binaphthyl group was clearly transferred to the central chirality at the phosphorus atom, and products derived from a further hydrolysis of **2c** did not form. In order to shorten the reaction time, more basic metal hydroxides such as NaOH, KOH, and CsOH were examined, but the reaction did not reach completion, and the starting material **1c** was partially recovered (entries 3–5). In contrast, a reaction at higher temperature (70 °C) accelerated the reaction (18 h) under retention of the high diastereoselectivity (entry 2).

Table 1. Hydrolysis of Cyclohexylphosphonothioate **1c**



entry	base	temp	time (h)	yield (%) ^b	recovery of 1c (%) ^b	dr ^c
1	LiOH	rt	144	88	0	>95:5
2	LiOH	70 °C	18	78	0	>95:5
3	NaOH	rt	144	67	33	>95:5
4	KOH	rt	144	47	53	>95:5
5	CsOH	rt	144	48	52	>95:5

^aThe reaction was carried out with **1** (0.5 mmol) and LiOH (5.0 equiv) in THF/H₂O (1 mL/1 mL) at room temperature unless otherwise noted. ^bIsolated yield.

^cDetermined by ³¹P NMR analysis of the crude reaction mixtures.

The author then subjected a range of phosphonothioates **1** to these hydrolysis conditions (Table 2). The hydrolysis of methylphosphonothioate **1a** reached completion within 30 min to quantitatively afford the corresponding product **2a** with slightly reduced diastereoselectivity (entry 1). Longer reaction times were required for the reaction of **1b**, albeit that **2b** was obtained almost exclusively as a single diastereoisomer (entry 2). The reaction of **1d**, which carries a *tert*-butyl group did not proceed at room temperature, and the starting material **1d** was completely recovered, while the reaction at 100 °C proceeded smoothly to give the corresponding product **2d** in 94% yield with high diastereoselectivity (entry 3). Arylphosphonothioates **1e–1j** were also susceptible to these hydrolysis conditions (entries 4–9). We also discovered that the

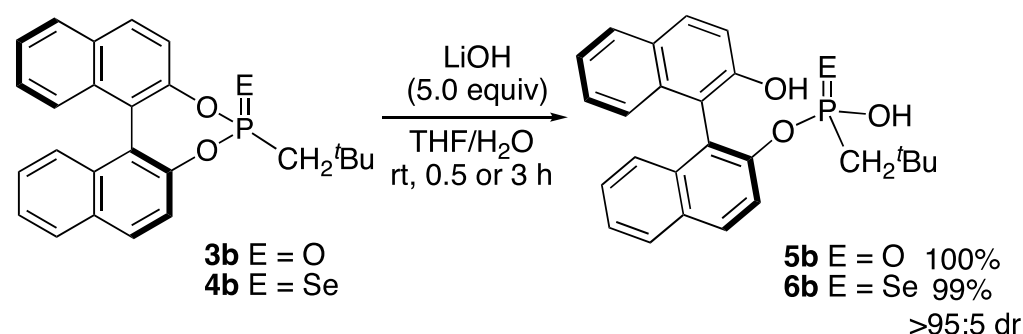
substituents at the *ortho*-position of the aromatic groups affected the diastereoselectivity. Esters with no *ortho*-substituents (entries 4 and 8) afforded **2e** and **2i** with a diastereoselectivity of ~73:27, whereas substrates **1f**, **1g**, **1h**, and **1j** exhibited higher diastereoselectivity (entries 5, 6, and 9). Among these, esters **1h** and **1j**, which carry 1-naphthyl and mesityl groups, respectively, furnished **2h** and **2i** with a diastereoselectivity of >95:5 (entries 7 and 9).

Table 2. Hydrolysis of a Range of Phosphonothioates **1**

<div style="text-align: center;"> </div>						
entry	1	R	product	time (h)	yield (%) ^b	dr ^c
1	1a	Me		0.5	quant	85:15
2	1b	CH ₂ Bu ^t		24	85	>95:5
3 ^d	1d	^t Bu		24	94	>95:5
4	1e			6	80	71:29
5	1f			12	61	>95:5
6	1g			6	60	17:83
7	1h			8	82	>95:5
8	1i			6	72	74:26
9	1j			24	67	>95:5

^aThe reaction was carried out with **1** (0.5 mmol) and LiOH (5.0 equiv) in THF/H₂O (1.0 mL/1.0 mL) at room temperature unless otherwise noted. ^bIsolated yield. ^cDetermined by ³¹P NMR analysis of the crude reaction mixtures. ^dThe reaction was carried out in 1,4-dioxane/H₂O (0.6 mL/0.6 mL) at 100 °C.

The hydrolysis of phosphonate **3b** and phosphonoselenoate **4b** also proceeded smoothly to quantitatively furnish the corresponding acids **5b** and **6b** (Scheme 2). Due to the fast tautomerization, the phosphorus atom in **5b** is readily racemized, while the product **6b** exhibited high levels of diastereoselectivity.



Scheme 2. Hydrolysis of Phosphonate **3b** and Phosphonoselenoate **4b**

At this point, the reaction pathway of the present reaction still remains unclear. Such substitution reactions³ generally proceed via S_N2 -type reactions and/or S_N1 -type reactions that may involve pentacoordinate intermediates, but the environment around the phosphorus atom might affect the reaction pathway. Indeed, the high influence of the substituents at the phosphorus atom with respect to reaction times and diastereoselectivity of the reactions imply that the reaction may proceed in a S_N2 -type fashion.

The absolute configuration of the major isomer of **2i** was unequivocally determined by a single-crystal X-ray diffraction analysis (Figure 1). The tetrahedral phosphorus atom in **2i** exhibited an *R*-configuration. The bond length of the P=S bond (1.9355(5) Å), is closer to typical P=S double bonds (~1.9 Å)⁴ than to typical P-S single bonds (~2.1 Å),⁵ which suggests the presence of a P=S double bond while the proton should reside on the oxygen atom.

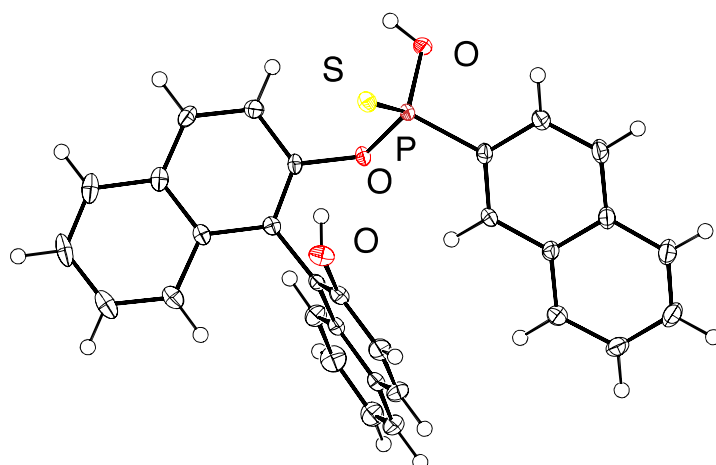
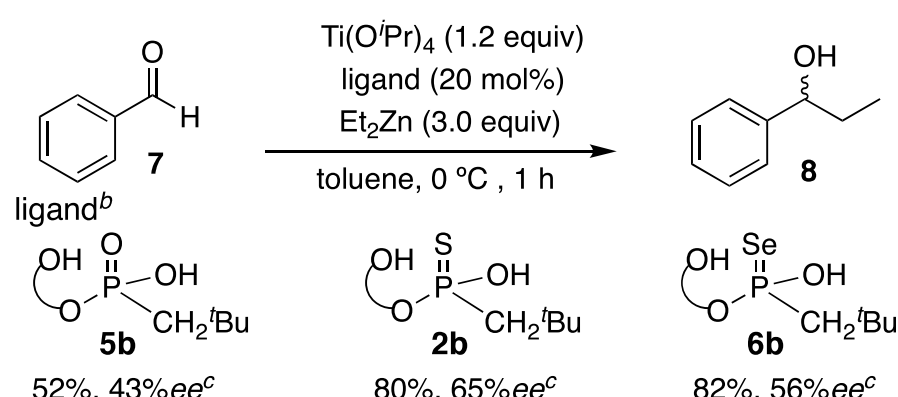


Figure 1. Molecular structure of **2i** with thermal ellipsoids set to 50% probability

2.3. Applications: Use as Optically Active Ligands

Subsequently, the author tested the resulting products **2**, **5b**, and **6b** with respect to their potential to serve as optically active ligands. For that, the ethylation of benzaldehyde (**7**) with Et₂Zn in the presence of Ti(O^{*i*}Pr)₄ was chosen as a model reaction.⁶ Acids **5b**, **2b**, and **6b** (20 mol%) were able to promote the ethylation to give **8** in good yield (Table 4). The enantiomeric excess of **8** derived from **2b** and **6b** was higher than that from **5**, which reflects the importance of the central chirality at the phosphorus atom for the asymmetric reactions. We then used a range of phosphonothioic acids **2** as optically active ligands (Table 5). Among these, the acids that carry aromatic rings with *ortho*-substituents enhanced the enantioselectivity. In particular, acid **2j**, which carries a mesityl group furnished **8** in up to 94% ee. Many types of optically active ligands with a binaphthyl group catalyze the asymmetric alkylation of aromatic aldehydes with zinc reagents. To achieve highly enantioselectivity, multiple biphenyl groups were incorporated in the ligands,⁷ or substituents were introduced at the 3,3'-positions of the binaphthyl group.⁸ Unlike these precedents, the present optically active ligands possess axial chirality and central chirality at the phosphorus atom, and the enantioselectivity was controlled by the achiral substituents on the chiral phosphorus atom.

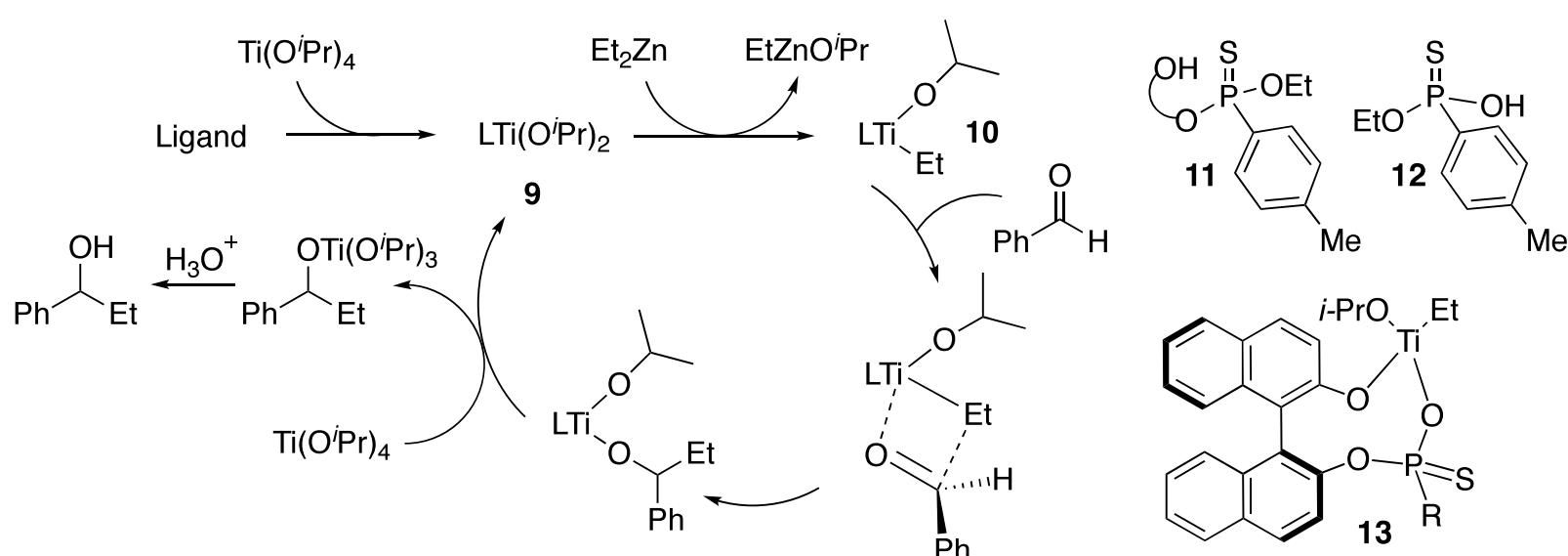
Table 3. Asymmetric Ethylation of **7**



^aThe reaction was carried out with **7** (0.5 mmol), Ti(O^{*i*}Pr)₄ (1.2 equiv), ligand (20 mol%), and Et₂Zn (3.0 equiv) in toluene (1.5 mL) at 0 °C for 1 h. ^bRatio of the diastereomers of ligands: >95:5. ^cThe enantiomeric excess was determined by HPLC on a chiral stationary phase (CHIRALPAK OD-H, ^{*i*}PrOH/hexane = 10/90, flow rate 1.0 mL/min).

On the basis of the literature,⁹ the plausible reaction pathway is proposed in Scheme 3. Initially, phosphonothioic acids **2** react with Ti(OPr-*i*)₄ to generate **9**, and it reacted with Et₂Zn to form **10**. The oxygen atom of benzaldehyde may coordinate to the titanium

atom followed by the transfer of the ethyl group on the titanium atom to the carbonyl carbon atom. In this step, the enantiotopic face of the carbonyl group may be differentiated by the chirality in the ligands. To prove the formation and importance of the hydroxyl and phosphonothioic groups, **11** and **12** were used as a ligand. As a result, ethylation did not take place at all. Therefore, the titanium complexes **13** wherein two oxygen atoms coordinate to the titanium atom may play important roles to facilitate the reaction and to control the stereoselectivity.



Scheme 2. Plausible Reaction Pathway for Asymmetric Ethylation

2.4. Applications: Use as Chiral Discriminating Agents

Finally, the efficiency of phosphonothioic acids **2** to discriminate the chirality of chiral aliphatic amines¹⁰ was tested, as this is an important research field to develop readily available chiral agents that can quickly discriminate enantiomers of racemic mixtures.¹¹ The ¹H NMR spectra of a 1:1 mixture of **2j** and racemic 1-phenethylamine (**9a**) clearly showed two doublet signals of the diastereomeric salts at 1.05 ppm and 1.13 ppm ($\Delta\delta = 0.08$) derived from **2j** and **9a** (Figure 2A). To demonstrate the importance of the chirality on the phosphorus atom for the chiral discrimination, phosphonic acid **5j** was mixed with **9b**, and the resulting salts also showed similar two similar doublets at 1.12 ppm and 1.18 ppm ($\Delta\delta = 0.06$) (Figure 2B), but the signals are broader than in the case of **2j**. The critical importance of the *P*-stereogenic centers was highlighted by the discrimination of 2-aminobutane (**9b**) and 3-methylpyrrolidine (**9c**). The ¹H NMR spectra of the 1:1 mixtures of **5j** and **9b** or **9c** were broad, and methyl signals

corresponding to each diastereomer were not observed. In contrast, 1:1 mixture of **2j** and **9b** exhibited two triplets and two doublets at 0.64 ppm and 0.82 ppm ($\Delta\delta = 0.18$) and at 0.93 ppm and 1.00 ppm ($\Delta\delta = 0.07$), respectively (Figure 2C). Likewise, the ^1H NMR spectra of a mixture of **2j** and **9c** showed two doublets at 0.59 ppm and 0.65 ppm ($\Delta\delta = 0.06$) (Figure 2D). It should be noted here that the chromatographic detection of simple alkyl amines such as **9b** and **9c** is nontrivial due to the lack of UV-active functional groups. Furthermore, the chiral carbon atom in **9c** is removed from the amino

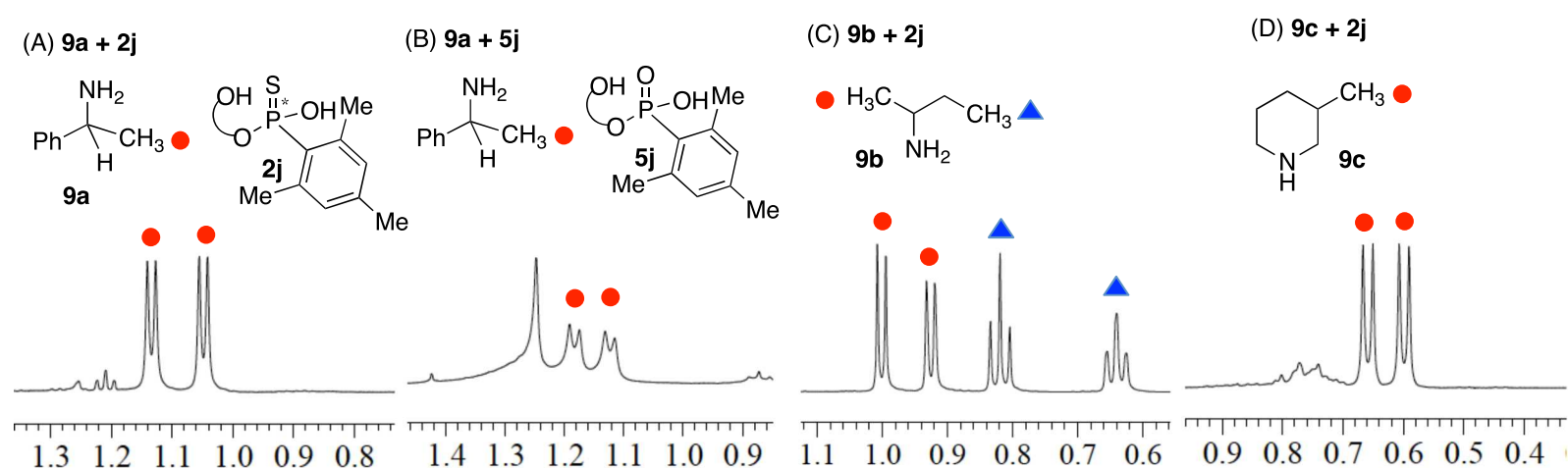


Figure 2. ^1H NMR spectra of 1:1 mixtures of (A) **9a** + **2j** (0.02 mmol each), (B) **9a** + **5j**, (C), **9b** + **2j** and (D) **9c** + **2j** in CDCl_3 (0.5 mL).

group, where the protonation occurs to form diastereomers

In summary, the author has demonstrated that the hydrolysis of phosphonothioates **1** that carry a binaphthyl group proceeds via axis-to-center chirality-transfer with high efficiency and diastereoselectivity. In these reactions, only one P-O bond in the starting material **1** is cleaved selectively. The resulting acids **2** can be used as optically active ligands for the Ti-mediated asymmetric ethylation of benzaldehyde with Et_2Zn . The enantiomeric excess of the product was optimized by changing the substituents on the phosphorus atom in **2** without the need to modify the substituents on the binaphthyl group. The utility of acids **2** was further demonstrated by using them as chiral discriminating agents for racemic aliphatic amines.

2.5. Experimental Section

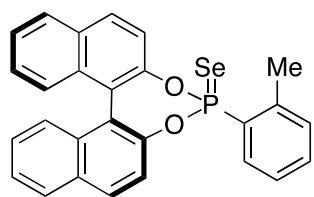
General Remarks: The IR spectra were obtained on a JASCO FT/IR 410 spectrometer. ^1H NMR spectra were recorded on a JEOL ECX-400P (400 MHz) in CDCl_3 . Chemical shifts of protons are reported in δ values referred to tetramethylsilane as an internal standard in CDCl_3 , and the following abbreviations are used: s: singlet, d: doublet, t: triplet, m: multiplet, br: broad. The ^{13}C NMR spectra were measured on a JEOL ECX-400P (100 MHz) in CDCl_3 . ^{31}P NMR were measured on a JEOL ECX-400P (162 MHz) in CDCl_3 with 85% H_3PO_4 as an external standard. ^{77}Se NMR spectra were measured on a JEOL ECX-400P (76 MHz) with Me_2Se as an external standard. All spectra were acquired in the proton-decoupled mode. The mass spectra (MS) and high resolution mass spectra (HRMS) were taken on a JMS-700 mass spectrometers. Melting point were determined using a Yanaco seisakusho MP-S2 micro melting point apparatus and are uncorrected.

Materials: Unless otherwise noted, materials were purchased from commercial supplies and used as received. Dichloromethane (Kanto Chemical Co., Ltd.) was distilled from P_2O_5 . Ethanol (Japan Alcohol Corporation) was distilled from magnesium. Toluene (Kanto Chemical Co., Ltd.) was distilled from sodium metal. The detail for the preparation of phosphonothioates **1** has been describe in the following chapter. Phosphonoselenoates **4a-4e**, **4i** were previously prepared.¹² Flash column chromatography was run on silica gel 60 N (spherical neutral) 40-50 μm (Kanto Chemical Co., Ltd.) and silica gel 120 (spherical) RP-18 40-50 μm (Kanto Chemical Co., Ltd.) All manipulations were carried out under argon atmosphere.

General Procedure for the synthesis of phosphonoselenoate **4**

To a solution of (S_{ax})-binaphtyloxy-phosphonoselenoic chloride in toluene was added Grignard reagents via syringe pump at 40 $^\circ\text{C}$ over 20 min, and it was stirred at that temperature for 30 min. After that, saturated NH_4Cl aqueous solution was added to the resulting mixture, and water was further added to dilute the solution. the aqueous phase was extracted with ether three times. The combined organic layer was dried over MgSO_4 , filtered, and concentrated. The crude product was purified by column chromatography on silica gel to give phosphonoselenoate **4**.

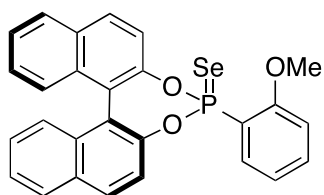
(*S*_{ax})-4-(*o*-Tolyl)binaphtho[2,1-*d*:1',2'-*f*][1,3,2]dioxaphosphepine-4-selenide (4f)



Chemical Formula: C₂₇H₁₉O₂PSe
Exact Mass: 486.0288
Molecular Weight: 485.3808

The compound was synthesized *via* General Procedure, with (*S*_{ax})-binaphtyloxy-phosphonoselenoic chloride (645 mg, 1.5 mmol), toluene (15 mL), and *o*-tolylmagnesium bromide (0.49 M THF solution, 3.1 mL, 1.5 mmol). Purification by column chromatography on silica gel (CH₂Cl₂:hexane =1:3, R_f = 0.33) gave **4f** (368 mg, 51%) as a colorless solid.: mp: 165-167 °C; IR (KBr): 3055, 1589, 1508, 1461, 1321, 1220, 949, 836, 613 cm⁻¹; ¹H NMR (CDCl₃): δ 2.95 (s, 3H, CH₃), 7.09 (d, *J* = 8.7 Hz, 1H), 7.13 (m, 1H, Ar), 7.27-7.52 (m, 8H, Ar), 7.72-7.77 (m, 3H, Ar), 7.83 (d, *J* = 8.2 Hz, 1H), 8.00 (d, *J* = 8.2 Hz, 1H), 8.11 (d, *J* = 8.7 Hz, 1H); ¹³C NMR (CDCl₃): δ 22.0 (CH₃), 120.1, 122.5, 122.9, 123.2, 125.7, 125.8, 126.7, 126.7, 127.2, 127.4, 128.5, 128.8, 130.4, 130.8, 131.0, 131.6, 132.2, 132.4, 132.7, 132.8, 140.8, 140.9, 145.8, 145.9, 148.6, 148.8; ³¹P NMR (CDCl₃): δ 102.0 (¹*J*_{P-Se} = 919.9 Hz); ⁷⁷Se NMR (CDCl₃): δ -150.1 (¹*J*_{P-Se} = 921.4 Hz); MS (EI) *m/z* 486 (M⁺); HRMS Calcd for C₂₇H₁₉O₂PSe: 486.0288, Found: 486.0278.

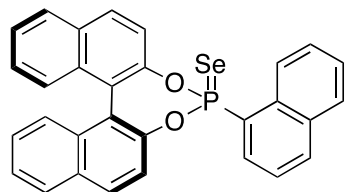
(*S*_{ax})-4-(2-Methoxyphenyl)binaphtho[2,1-*d*:1',2'-*f*][1,3,2]dioxaphosphepine-4-selenide (4g)



Chemical Formula: C₂₇H₁₉O₃PSe
Exact Mass: 502.0237
Molecular Weight: 501.3798

The compound was synthesized *via* General Procedure, with (*S*_{ax})-binaphtyloxy-phosphonoselenoic chloride (2.15 g, 5.0 mmol), toluene (15 mL), and 2-methoxyphenylmagnesium bromide (0.94 M THF solution, 5.3 mL, 5.0 mmol). Purification by column chromatography on silica gel (EtOAc:hexane =1:20, R_f = 0.33) gave **4g** (1.79 g, 71%) as a colorless solid.: mp: 167-168 °C; IR (KBr): 3058, 2935, 1588, 1461, 1220, 950, 837, 751, 612 cm⁻¹; ¹H NMR (CDCl₃): δ 3.74 (s, 3H, OCH₃), 6.88-6.97 (m, 2H, Ar), 7.18-7.19 (m, 1H, Ar), 7.29-7.30 (m, 2H, Ar), 7.35-7.37 (m, 1H, Ar), 7.39-7.53 (m, 5H, Ar), 7.70 (d, *J* = 8.0 Hz, 1H), 7.77-7.78 (m, 1H, Ar), 7.85 (d, *J* = 8.0 Hz, 1H), 7.98-7.99 (m, 1H, Ar), 8.07-8.09 (m, 1H, Ar); ¹³C NMR (CDCl₃): δ 56.0 (OCH₃), 111.9, 120.5, 120.7, 121.1, 122.5, 123.2, 124.1, 124.4, 125.6, 126.6, 127.3, 128.4, 128.7, 130.5, 130.7, 131.6, 132.1, 132.6, 132.9, 134.2, 135.0, 146.3, 146.4, 149.4, 149.5, 160.7; ³¹P NMR (CDCl₃): δ 102.4 (¹*J*_{P-Se} = 928.6 Hz); ⁷⁷Se NMR (CDCl₃): δ -173.9 (¹*J*_{P-Se} = 927.3 Hz); MS (EI) *m/z* 502 (M⁺); HRMS Calcd for C₂₇H₁₉O₃PSe: 502.0237, Found: 502.0227.

(*S*_{ax})-4-(Naphthalene-1-yl)binaphtho[2,1-*d*:1',2'-*f*][1,3,2]dioxaphosphepine-4-selenide (4h)



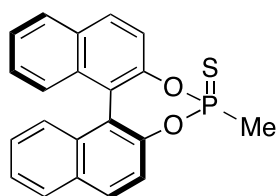
Chemical Formula: C₃₀H₁₉O₂PSe
Exact Mass: 522.0288
Molecular Weight: 521.4138

The compound was synthesized *via* General Procedure, with (*S*_{ax})-binaphthoxy-phosphonoselenoic chloride (1.29 g, 3.0 mmol), toluene (10 mL), and 1-naphthylmagnesium bromide (0.77 M THF solution, 3.9 mL, 3.0 mmol). Purification by column chromatography on silica gel (EtOAc:hexane =1:10, R_f = 0.38) gave **4h** (0.90 g, 57%) as a colorless solid.: mp: 230-232 °C; IR (KBr): 3054, 1507, 1323, 1220, 1068, 948, 907, 840, 606 cm⁻¹; ¹H NMR (CDCl₃): δ 6.73-6.76 (m, 1H, Ar), 7.27-7.44 (m, 6H, Ar), 7.50-7.53 (m, 2H, Ar), 7.64-7.67 (m, 1H, Ar), 7.33-7.80 (m, 3H, Ar), 7.94-8.03 (m, 4H, Ar), 8.14 (d, *J* = 8.6 Hz, 1H), 9.19 (d, *J* = 8.6 Hz, 1H); ¹³C NMR (CDCl₃): δ 119.9, 122.4, 122.7, 123.3, 124.5, 125.7, 125.9, 126.5, 126.7, 126.9, 127.2, 127.7, 128.0, 128.4, 128.8, 129.0, 129.3, 130.6, 130.9, 131.0, 131.5, 131.6, 132.2, 132.4, 133.9, 134.0, 145.8, 145.8, 148.6, 148.7; ³¹P NMR (CDCl₃): δ 102.4 (¹*J*_{P-Se} = 926.4 Hz); ⁷⁷Se NMR (CDCl₃): δ -127.3 (¹*J*_{P-Se} = 920.7 Hz); MS (EI) *m/z* 522 (M⁺); HRMS Calcd for C₃₀H₁₉O₂PSe: 522.0288, Found: 522.0292.

General Procedure for the synthesis of phosphonothioates 1a-i

To a solution of phosphonoselenoates in THF degassed via three freeze-pump-thaw cycles was added tri-*n*-butylphosphine, and it was stirred at room temperature for 2 h. After that, elemental sulfur was added to the mixture, and it was further stirred for 30 min. The reaction mixture was concentrated and was purified by recrystallization from hexane or column chromatography on silica gel.

(*S*_{ax})-4-Methylbinaphtho[2,1-*d*:1',2'-*f*][1,3,2]dioxaphosphepine-4-sulfide (1a)

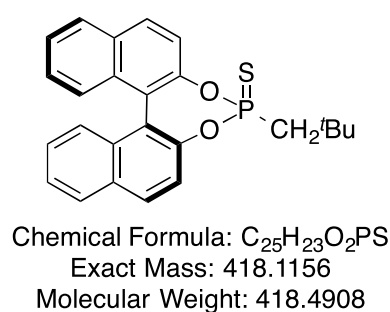


Chemical Formula: C₂₁H₁₅O₂PS
Exact Mass: 362.0530
Molecular Weight: 362.3828

The compound was synthesized *via* General Procedure, with phosphonoselenoate¹⁷ (1.23 g, 3.0 mmol), THF (9.0 mL), tri-*n*-butylphosphine (1.5 mL, 6.0 mmol), and elemental sulfur (0.20 g, 6.3 mmol). Purification by recrystallization from hexane (3.0 mL) for three times gave **1a** (0.76 g, 70%) as a colorless solid.: mp: 233-236 °C; IR (KBr): 3063, 2914, 2359, 1588, 1506, 1461, 1321, 1222, 1069, 953, 911, 889, 812, 750, 652 cm⁻¹; ¹H NMR (CDCl₃): δ 2.05 (d, *J* = 14.8 Hz, 3H, CH₃), 7.27-7.37 (m, 3H, Ar), 7.42 (d, *J* = 8.5 Hz, 1H), 7.44-7.52 (m, 3H, Ar), 7.57 (d, *J*

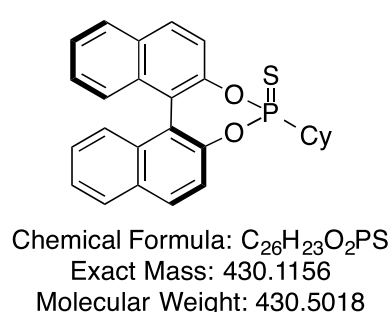
= 9.0 Hz, 1H), 7.96 (d, J = 8.5 Hz, 2H), 8.03 (d, J = 8.5 Hz, 1H), 8.04 (d, J = 9.0 Hz, 1H, Ar); ^{13}C NMR (CDCl_3): δ 19.4 (d, $^1J_{\text{C-P}}$ = 102.4 Hz, CH_3), 120.4, 121.8, 122.7, 125.8, 126.0, 126.7, 127.0, 127.4, 128.6, 128.7, 131.0, 131.2, 131.8, 132.0, 132.7, 132.8, 146.1, 146.2, 148.2, 148.3; ^{31}P NMR (CDCl_3): δ 111.8 (s); MS (EI) m/z 362 (M^+); HRMS Calcd for $\text{C}_{21}\text{H}_{15}\text{O}_2\text{PS}$: 362.0530, Found: 362.0527.

(S_{ax})-4-Neopentylbinaphtho[2,1- d :1',2'- f][1,3,2]dioxaphosphepine-4-sulfide (1b**)**



The compound was synthesized *via* General Procedure, with phosphonoselenoate¹⁷ (455 mg, 1.0 mmol), THF (2.0 mL), tri-*n*-butylphosphine (0.5 mL, 2.0 mmol), and elemental sulfur (65 mg, 2.1 mmol). Purification by recrystallization from hexane (3.0 mL) for three times gave **1b** (288 mg, 69%) as a colorless solid.: mp: 178-179 °C; IR (KBr): 3064, 2960, 2901, 2877, 1588, 1509, 1462, 1323, 1223, 1069, 953, 856, 751, 699, 633 cm^{-1} ; ^1H NMR (CDCl_3): δ 1.28 (d, J = 0.9 Hz, 9H, $\text{CH}_2\text{C}(\text{CH}_3)_3$), 2.19 (dd, J = 15.5 Hz, 14.9 Hz, 1H, $\text{CH}_2\text{C}(\text{CH}_3)_3$), 2.26 (dd, J = 15.5 Hz, 14.9 Hz, 1H, $\text{CH}_2\text{C}(\text{CH}_3)_3$), 7.28-7.34 (m, 3H, Ar), 7.41-7.52 (m, 4H, Ar), 7.56-7.57 (m, 1H, Ar), 7.95-7.98 (m, 2H, Ar), 8.02-8.05 (m, 2H, Ar); ^{13}C NMR (CDCl_3): δ 30.7 ($\text{CH}_2\text{C}(\text{CH}_3)_3$), 31.1 (d, $^3J_{\text{C-P}}$ = 8.4 Hz, $\text{CH}_2\text{C}(\text{CH}_3)_3$), 31.2, 44.5 (d, $^1J_{\text{C-P}}$ = 91.2 Hz, $\text{CH}_2\text{C}(\text{CH}_3)_3$), 120.7, 122.3, 122.6, 122.8, 125.7, 125.8, 126.6, 126.9, 127.1, 127.5, 128.5, 128.7, 130.7, 131.0, 131.6, 132.0, 132.7, 132.8, 146.1, 146.2, 148.5, 148.6; ^{31}P NMR (CDCl_3): δ 113.7 (s); MS (EI) m/z 418 (M^+); HRMS Calcd for $\text{C}_{25}\text{H}_{23}\text{O}_2\text{PS}$: 418.1156, Found: 418.1145.

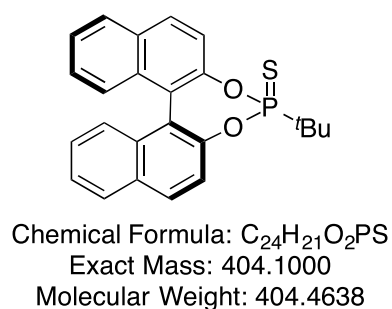
(S_{ax})-4-Cyclohexylbinaphtho[2,1- d :1',2'- f][1,3,2]dioxaphosphepine-4-sulfide (1c**)**



The compound was synthesized *via* General Procedure, with phosphonoselenoate¹⁷ (952 mg, 2.0 mmol), THF (2.0 mL), tri-*n*-butylphosphine (1.0 mL, 4.0 mmol), and elemental sulfur (142 mg, 4.4 mmol). Purification by column chromatography on silica gel (CH_2Cl_2 :hexane = 1:5, R_f = 0.25) gave **1c** (639 mg, 74%) as a colorless solid.: mp: 214-215 °C; IR (KBr): 3053, 1732, 1620, 1588, 1507, 1462, 1432, 1092, 1068, 956, 872, 840, 812, 732, 687, 567 cm^{-1} ; ^1H NMR (CDCl_3): δ 1.16-1.36 (m, 3H), 1.67-1.82 (m, 4H), 1.93-2.24 (m, 4H), 7.27-7.34 (m, 3H, Ar), 7.40-7.52 (m, 4H, Ar), 7.56 (m, 1H, Ar), 7.95-7.98 (m, 2H, Ar), 8.01-8.05 (m, 2H, Ar)

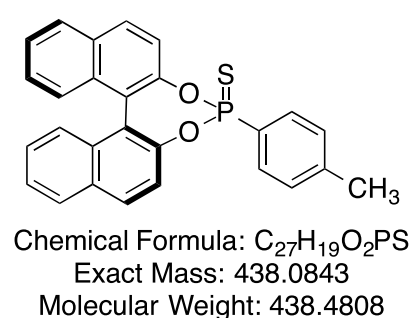
^{13}C NMR (CDCl_3): δ 25.7, 25.75, 25.83, 26.1, 39.9 (d, $^1J_{\text{C-P}} = 95.9$ Hz, $\underline{\text{CHCH}_2\text{CH}_2}$), 120.4, 122.1, 122.6, 125.8, 126.6, 126.9, 127.1, 127.5, 128.5, 128.7, 130.8, 131.0, 131.6, 132.0, 132.7, 132.9, 146.2, 146.4, 148.6, 148.7; ^{31}P NMR (CDCl_3): δ 122.8 (s); MS (EI) m/z 430 (M^+); HRMS Calcd for $\text{C}_{26}\text{H}_{23}\text{O}_2\text{PS}$: 430.1156, Found: 430.1136.

(*S*_{ax})-4-(*tert*-Butyl)binaphtho[2,1-*d*:1',2'-*f*][1,3,2]dioxaphosphepine-4-sulfide (1d)



The compound was synthesized *via* General Procedure, with phosphonoselenoate¹ (975 mg, 2.2 mmol), THF (4.0 mL), tri-*n*-butylphosphine (1.1 mL, 4.4 mmol), and elemental sulfur (160 mg, 5.0 mmol). Purification by recrystallization from hexane for three times gave **1d** (603 mg, 69%) as a colorless solid.: mp: 248-251 °C; IR (KBr): 3064, 2960, 2877, 1588, 1509, 1462, 1323, 1223, 1069, 953, 856, 751, 699, 634 cm^{-1} ; ^1H NMR (CDCl_3): δ 1.35 (d, $J = 18.9$ Hz, 9H, $\text{C}(\underline{\text{CH}_3})_3$), 7.19 (d, $J = 8.6$ Hz, 1H), 7.22-7.34 (m, 3H, Ar), 7.43-7.56 (m, 4H, Ar), 7.92-7.98 (m, 3H, Ar), 8.04 (d, $J = 8.6$ Hz, 1H); ^{13}C NMR (CDCl_3): δ 26.1 ($\text{C}(\underline{\text{CH}_3})_3$), 39.9 ($^3J_{\text{C-P}} = 90.0$ Hz, $\underline{\text{C}}(\text{CH}_3)_3$), 120.9, 121.1, 122.3, 122.7, 125.7, 126.5, 126.8, 127.1, 127.7, 128.4, 128.7, 130.6, 130.8, 131.3, 132.0, 132.9, 146.5, 146.6, 150.8, 150.9; ^{31}P NMR (CDCl_3): δ 128.8 (s); MS (EI) m/z 404 (M^+); HRMS Calcd for $\text{C}_{24}\text{H}_{21}\text{O}_2\text{PS}$: 404.1000, Found: 404.0986.

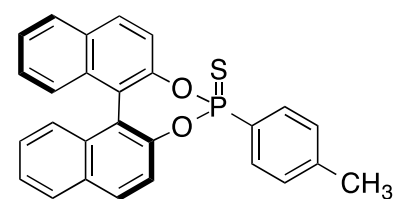
(*S*_{ax})-4-(*p*-Tolyl)binaphtho[2,1-*d*:1',2'-*f*][1,3,2]dioxaphosphepine-4-sulfide (1e)



The compound was synthesized *via* General Procedure, with phosphonoselenoate¹⁷ 1.22 g, 2.5 mmol), THF (5.0 mL), tri-*n*-butylphosphine (1.3 mL, 5.0 mmol), and elemental sulfur (0.17 g, 5.3 mmol). Purification by recrystallization from hexane for three times gave **1e** (0.97 g, 88%) as a colorless solid.: mp: 208-210 °C; IR (KBr): 3077, 2919, 2360, 1915, 1589, 1508, 1462, 1322, 1222, 1119, 1068, 861, 734, 688 cm^{-1} ; ^1H NMR (CDCl_3): δ 2.38 (s, 3H, $\underline{\text{CH}_3}$), 6.92 (d, $J = 9.0$, 1H), 7.12-7.17 (m, 2H, Ar), 7.29-7.40 (m, 3H, Ar), 7.47-7.52 (m, 3H, Ar), 7.58 (d, $J = 8.1$ Hz, 1H), 7.61 (d, $J = 8.1$ Hz, 1H), 7.64-7.66 (m, 1H, Ar), 7.80 (d, $J = 9.0$ Hz, 1H), 7.91-8.08 (m, 3H, Ar); ^{13}C NMR (CDCl_3): δ 21.8 ($\underline{\text{CH}_3}$), 121.3, 122.1, 122.4, 122.7, 125.8, 126.1, 126.7, 127.2, 127.3, 127.4, 128.6, 128.7, 129.0, 129.1, 130.6, 131.0, 131.7, 132.0, 132.1, 132.6, 132.7, 144.3, 146.1, 146.1, 148.5, 148.6; ^{31}P NMR (CDCl_3):

δ 102.1 (s); MS (EI) m/z 438 (M^+); HRMS Calcd for $C_{27}H_{19}O_2PS$: 438.0843, Found: 438.0831.

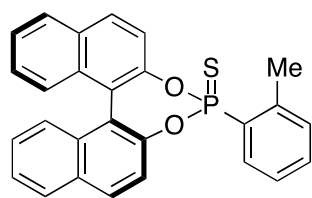
(*S*_{ax})-4-(*p*-Tolyl)binaphtho[2,1-*d*:1',2'-*f*][1,3,2]dioxaphosphepine-4-sulfide (1e**)**



Chemical Formula: $C_{27}H_{19}O_2PS$
Exact Mass: 438.0843
Molecular Weight: 438.4808

The compound was synthesized *via* General Procedure, with phosphonoselenoate¹⁷ (1.22 g, 2.5 mmol), THF (5.0 mL), tri-*n*-butylphosphine (1.3 mL, 5.0 mmol), and elemental sulfur (0.17 g, 5.3 mmol). Purification by recrystallization from hexane for three times gave **1e** (0.97 g, 88%) as a colorless solid.: mp: 208-210 °C; IR (KBr): 3077, 2919, 2360, 1915, 1589, 1508, 1462, 1322, 1222, 1119, 1068, 861, 734, 688 cm^{-1} ; 1H NMR ($CDCl_3$): δ 2.38 (s, 3H, CH_3), 6.92 (d, J = 9.0, 1H), 7.12-7.17 (m, 2H, Ar), 7.29-7.40 (m, 3H, Ar), 7.47-7.52 (m, 3H, Ar), 7.58 (d, J = 8.1 Hz, 1H), 7.61 (d, J = 8.1 Hz, 1H), 7.64-7.66 (m, 1H, Ar), 7.80 (d, J = 9.0 Hz, 1H), 7.91-8.08 (m, 3H, Ar); ^{13}C NMR ($CDCl_3$): δ 21.8 (CH_3), 121.3, 122.1, 122.4, 122.7, 125.8, 126.1, 126.7, 127.2, 127.3, 127.4, 128.6, 128.7, 129.0, 129.1, 130.6, 131.0, 131.7, 132.0, 132.1, 132.6, 132.7, 144.3, 146.1, 146.1, 148.5, 148.6; ^{31}P NMR ($CDCl_3$): δ 102.1 (s); MS (EI) m/z 438 (M^+); HRMS Calcd for $C_{27}H_{19}O_2PS$: 438.0843, Found: 438.0831.

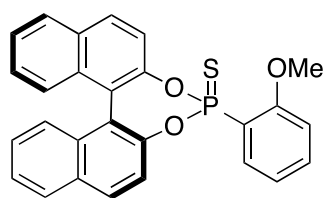
(*S*_{ax})-4-(*o*-Tolyl)binaphtho[2,1-*d*:1',2'-*f*][1,3,2]dioxaphosphepine-4-sulfide (1f**)**



Chemical Formula: $C_{27}H_{19}O_2PS$
Exact Mass: 438.0843
Molecular Weight: 438.4808

The compound was synthesized *via* General Procedure, with phosphonoselenoate **4f** (294 mg, 0.6 mmol), THF (1.5 mL), tri-*n*-butylphosphine (0.35 mL, 1.4 mmol), and elemental sulfur (50 mg, 1.5 mmol). Purification by column chromatography on silica gel (EtOAc:hexane = 1:10, R_f = 0.25) gave **1f** (210 mg, 79%) as a colorless solid.: mp: 208-210 °C; IR (KBr): 3057, 2924, 2853, 1589, 1508, 1462, 1223, 1070, 953, 738 cm^{-1} ; 1H NMR ($CDCl_3$): δ 2.92 (s, 3H, CH_3), 7.04-7.06 (m, 2H, Ar), 7.27-7.51 (m, 8H, Ar), 7.69-7.77 (m, 3H, Ar), 7.82-7.84 (m, 1H, Ar), 7.98-8.00 (m, 1H, Ar), 8.09-8.11 (m, 1H, Ar); ^{13}C NMR ($CDCl_3$): δ 22.1 (CH_3), 120.1, 122.4, 122.7, 123.0, 125.7, 125.8, 126.7, 127.2, 127.4, 128.5, 128.7, 130.7, 130.9, 131.4, 131.6, 132.0, 132.1, 132.5, 132.7, 133.3, 141.1, 141.2, 145.8, 145.9, 148.5, 148.6; ^{31}P NMR ($CDCl_3$): δ 102.1 (s); MS (EI) m/z 438 (M^+); HRMS Calcd for $C_{27}H_{19}O_2PS$: 438.0843, Found: 438.0828.

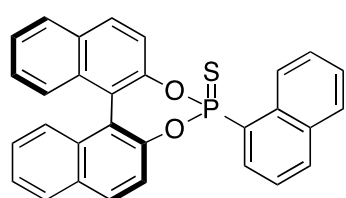
(S_{ax})-4-(2-Methoxyphenyl)binaphtho[2,1-*d*:1',2'-*f*][1,3,2]dioxaphosphepine-4-sulfide (1g)



Chemical Formula: C₂₇H₁₉O₃PS
Exact Mass: 454.0793
Molecular Weight: 454.4798

The compound was synthesized *via* General Procedure, with phosphonoselenoate **4g** (1.51 g, 3.0 mmol), THF (6.0 mL), tri-*n*-butylphosphine (1.5 mL, 6.0 mmol), and elemental sulfur (0.23 g, 6.3 mmol). Purification by column chromatography on silica gel (EtOAc:hexane =1:10, R_f = 0.19) gave **1g** (1.14 g, 83%) as a colorless solid.: mp: 173-175 °C; IR (KBr): 3055, 2007, 1589, 1462, 1403, 1223, 954, 858, 842, 745, 698 cm⁻¹; ¹H NMR (CDCl₃): δ 3.66 (s, 3H, OCH₃), 6.93-6.96 (m, 2H, Ar), 7.17 (d, *J* = 9.2 Hz, 1H), 7.26-7.30 (m, 2H, Ar), 7.36 (d, *J* = 8.2 Hz, 1H), 7.41-7.51 (m, 4H, Ar), 7.67 (d, *J* = 8.7 Hz, 1H), 7.78 (d, *J* = 8.7 Hz, 1H), 7.84-7.92 (m, 2H, Ar), 7.98 (d, *J* = 8.2 Hz, 1H), 8.07 (d, *J* = 9.2 Hz, 1H); ¹³C NMR (CDCl₃): δ 55.9 (OCH₃), 111.6, 118.3, 119.7, 120.6, 120.7, 122.3, 122.5, 122.9, 125.6, 126.3, 127.3, 128.4, 128.7, 130.4, 130.8, 131.5, 132.0, 132.6, 132.8, 134.6, 135.0, 146.3, 146.4, 149.3, 149.4, 160.8; ³¹P NMR (CDCl₃): δ 98.1 MS (EI) *m/z* 454 (M⁺); HRMS Calcd for C₂₇H₁₉O₃PS: 454.0793, Found: 454.0819.

(S_{ax})-4-(Naphthalene-1-yl)binaphtho[2,1-*d*:1',2'-*f*][1,3,2]dioxaphosphepine-4-sulfide (1h)

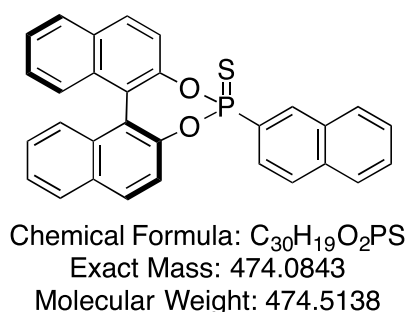


Chemical Formula: C₃₀H₁₉O₂PS
Exact Mass: 474.0843
Molecular Weight: 474.5138

The compound was synthesized *via* General Procedure, with phosphonoselenoate **1h** (0.77 g, 1.5 mmol), THF (1.5 mL), tri-*n*-butylphosphine (0.75 mL, 3.0 mmol), and elemental sulfur (0.10 g, 3.2 mmol). Purification by column chromatography on silica gel (EtOAc:hexane =1:10, R_f = 0.25) gave **1h** (0.49 g, 69%) as a colorless solid.: mp: 222-225 °C; IR (KBr): 3054, 1589, 1507, 1461, 1322, 1223, 1069, 952, 856, 842, 771 cm⁻¹; ¹H NMR (CDCl₃): δ 6.72 (d, *J* = 8.6 Hz, 1H), 7.28-7.45 (m, 6H, Ar), 7.50-7.53 (m, 2H, Ar), 7.64-7.67 (m, 1H, Ar), 7.74-7.78 (m, 3H, Ar), 7.94-8.03 (m, 4H, Ar), 8.12-8.14 (m, 1H, Ar), 9.09 (d, *J* = 8.6 Hz, 1H); ¹³C NMR (CDCl₃): δ 120.1, 122.4, 122.6, 123.1, 124.5, 124.6, 125.7, 125.9, 126.8, 127.2, 127.3, 127.9, 128.5, 128.6, 128.8, 129.3, 130.6, 131.0, 131.6, 131.7, 131.8, 131.9, 132.2, 132.4, 132.8, 133.9, 145.8, 145.9, 148.5, 148.6; ³¹P NMR (CDCl₃): δ 96.0 (s); MS (EI) *m/z* 474 (M⁺); HR

MS Calcd for C₃₀H₁₉O₂PS: 474.0843, Found: 474.0837.

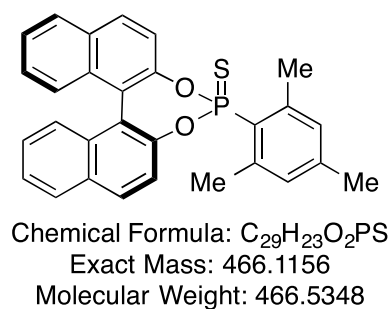
(S_{ax})-4-(Naphthalene-2-yl)binaphtho[2,1-*d*:1',2'-*f*][1,3,2]dioxaphosphepine-4-sulfide (1i)



The compound was synthesized *via* General Procedure, with phosphonoselenoate¹⁷ (2.63 g, 5.0 mmol), THF (10.0 mL), tri-*n*-butylphosphine (2.5 mL, 10.0 mmol), and elemental sulfur (0.37 g, 10.5 mmol). Purification by column chromatography on silica gel (CH₂Cl₂:hexane =1:3, R_f = 0.25) gave **1i** (2.19 g, 92%) as a colorless solid.: mp: 178-182 °C; IR (KBr): 3067, 2969, 2927, 2898, 2867, 1590, 1507, 1464, 1322, 1227, 1072, 956, 856, 842, 819, 734 cm⁻¹; ¹H NMR (CDCl₃): δ 6.88 (d, *J* = 8.6 Hz, 1H), 7.33 (dd, *J* = 7.5 Hz, *J* = 7.5 Hz, 1H), 7.35-7.38 (m, 1H, Ar), 7.41 (d, *J* = 8.6 Hz, 1H), 7.50-7.55 (m, 5H, Ar), 7.60-7.63 (m, 1H, Ar), 7.70 (d, *J* = 9.2 Hz, 1H), 7.73-7.76 (m, 2H, Ar), 7.82 (d, *J* = 8.6 Hz, 1H), 7.85 (d, *J* = 8.0 Hz, 1H), 7.90 (d, *J* = 7.5 Hz, 1H), 8.01 (d, *J* = 8.0 Hz, 1H), 8.11 (d, *J* = 9.2 Hz, 1H), 8.43-8.47 (m, 1H, Ar); ¹³C NMR (CDCl₃): δ 121.2, 122.2, 122.4, 122.8, 125.9, 126.1, 126.5, 126.8, 127.2, 127.4, 127.6, 127.9, 128.0, 128.7, 129.0, 129.5, 130.7, 131.1, 131.7, 132.0, 132.2, 132.6, 132.7, 134.8, 134.9, 135.4, 146.0, 146.1, 148.5, 148.7; ³¹P NMR (CDCl₃): δ 97.0 (s); MS (EI) *m/z* 474 (M⁺); HRMS Calcd for C₃₀H₁₉O₂PS: 474.0843, Found: 474.0817.

2.6.4 Synthesis of Phosphonothioate 1j

(S_{ax})-4-Mesitylbinaphtho[2,1-*d*:1',2'-*f*][1,3,2]dioxaphosphepine-4-sulfide (1j)

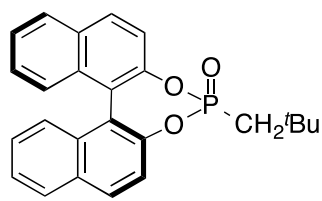


To a 50 mL two-necked flask were added (S_{ax})-4-chlorobinaphtho[2,1-*d*:1',2'-*f*][1,3,2]dioxaphosphepines (1.0 M toluene solution, 1.0 mL, 1.0 mmol) under Ar atmosphere. The solution was heated to 40 °C. Mesitylmagnesium bromide (0.90 M Et₂O solution, 1.1 mL, 1.0 mmol) was added dropwise for 10 min to the heated solution, and it was stirred at 30 min. Then sulfur (36 mg, 1.1 mmol) was added to the solution. After that, the reaction mixture was added sat. NH₄Cl aqueous and it was extracted with Et₂O three times. The combined organic layer was dried over MgSO₄, filtrate, and concentrated. Purification by column chromatography on silica gel (EtOAc : hexane = 1 : 50, R_f = 0.15) gave **1j**

(240 mg, 52%) as a colorless solid.: mp: 200-202 °C; IR (KBr): 3054, 2971, 2933, 1604, 1589, 1507, 1461, 1322, 1221, 1070, 951, 857, 736 cm⁻¹; ¹H NMR (CDCl₃): δ 2.27 (s, 3H, CH₃), 2.76 (s, 6H, CH₃), 6.90 (s, 1H), 6.91 (s, 1H), 7.17 (d, *J* = 8.7 Hz, 1H), 7.24-7.32 (m, 2H, Ar), 7.38 (d, *J* = 8.2 Hz 1H), 7.40-7.51 (m, 3H, Ar), 7.71 (d, *J* = 8.7 Hz, 1H), 7.77 (d, *J* = 8.7 Hz, 1H), 7.84 (d, *J* = 8.2 Hz, 1H), 7.99 (d, *J* = 8.7 Hz, 1H), 8.08 (d, *J* = 8.7 Hz, 1H); ¹³C NMR (CDCl₃): δ 21.2 (CH₃), 23.9 (CH₃), 119.7, 122.7, 123.1, 125.7, 125.8, 126.1, 126.6, 127.2, 127.4, 128.4, 128.7, 130.6, 130.7, 130.9, 131.1, 131.5, 132.1, 132.4, 132.7, 141.2, 141.3, 142.0, 145.6, 145.6, 148.9, 149.0; ³¹P NMR (CDCl₃): δ 102.9 (s); MS (EI) *m/z* 474 (M⁺); HRMS Calcd for C₂₉H₂₃O₂PS: 466.1156, Found: 466.1140.

2.6.5 Synthesis of Phosphonates 3

(*S*_{ax})-4-Neopentylbinaphtho[2,1-*d*:1',2'-*f*][1,3,2]dioxaphosphepine-4-oxide (**3b**)

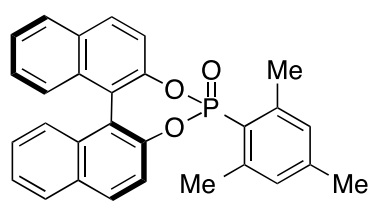


Chemical Formula: C₂₅H₂₃O₃P
Exact Mass: 402.1385
Molecular Weight: 402.4298

To a round-bottom flask were added phosphonoselenoate¹⁷ (470 mg, 1.0 mmol), CH₂Cl₂ (2.0 mL) and hydrogen peroxide (35% aqueous solution, 0.42 mL, 6.0 mmol), and the mixture was stirred at room temperature for 7 h. After that, the mixture was filtered, washed with CH₂Cl₂, and the filtrate was concentrated.

The resulting solid was passed through column chromatography on silica gel (CH₂Cl₂ : hexane = 1 : 2, R_f = 0.18) to give **3b** (280 mg, 70%) as a colorless solid. mp: 210-213 °C; IR (KBr): 3057, 2966, 1466, 1225, 960, 858, 818 cm⁻¹; ¹H NMR (CDCl₃): δ 1.27 (s, 9H, CH₂C(CH₃)₃), 1.91 (dd, *J* = 18.0 Hz, 15.3 Hz, 1H, CH₂C(CH₃)₃), 2.03 (dd, *J* = 18.0 Hz, 15.3 Hz, 1H, CH₂C(CH₃)₃), 7.24 (d, *J* = 8.5 Hz, 1H), 7.25-7.33 (m, 2H, Ar), 7.39-7.49 (m, 4H, Ar), 7.60 (d, *J* = 8.5 Hz, 1H), 7.92-7.96 (m, 2H, Ar), 8.02 (d, *J* = 9.0 Hz, 2H); ¹³C NMR (CDCl₃): δ 30.3 (CH₂C(CH₃)₃), 31.1 (³*J*_{P-C} = 9.4 Hz, CH₂C(CH₃)₃), 37.4 (¹*J*_{P-C} = 127.8 Hz, CH₂C(CH₃)₃), 120.2, 121.4, 122.0, 125.6, 125.8, 126.6, 126.9, 126.9, 127.3, 128.5, 128.6, 131.2, 131.5, 131.8, 132.5, 132.6, 145.9, 146.0, 147.7, 147.8; ³¹P NMR (CDCl₃): δ 41.6 (s); MS (EI) *m/z* 402 (M⁺); HRMS Calcd for C₂₅H₂₃O₃PS: 402.1385, Found: 402.1399.

(*S*_{ax})-4-Mesitylbinaphtho[2,1-*d*:1',2'-*f*][1,3,2]dioxaphosphepine-4-oxide (3j)



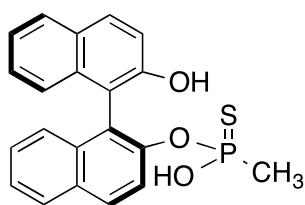
Chemical Formula: C₂₉H₂₃O₃P
Exact Mass: 450.1385
Molecular Weight: 450.4738

2-Mesitylmagnesium bromide (1.2 M Et₂O solution, 1.7 mL, 2.0 mmol) was added to a THF solution (8.0 mL) of (*S*_{ax})-binaphthylphosphoric acid chloride (730 mg, 2.0 mmol) via syringe pump at rt over 20 minutes, and it was stirred at that temperature for 30 min. After that, saturated NH₄Cl aqueous solution was added to the resulting mixture and water was further added to dilute the solution. The aqueous phase was extracted with ether three times. The combined organic layer was dried over MgSO₄, filtered, and concentrated. The crude product was purified by column chromatography on silica gel (EtOAc : hexane = 1 : 5, R_f = 0.16) to give **3j** (372 mg, 42%) as a colorless solid. mp: 229-230 °C; IR (KBr): 3055, 1735, 1507, 1277, 1225, 957, 839, 646 cm⁻¹; ¹H NMR (CDCl₃): δ 2.28 (s, 3H, CH₃), 2.45 (s, 6H, CH₃), 6.86 (s, 1H), 6.87 (s, 1H), 6.94-6.96 (m, 1H, Ar), 7.28-7.32 (m, 2H, Ar), 7.37-7.50 (m, 4H, Ar), 7.70 (d, *J* = 8.7 Hz, 1H), 7.74-7.76 (m, 1H, Ar), 7.86 (d, *J* = 8.2 Hz, 1H), 7.98 (d, *J* = 8.2 Hz, 1H), 8.07 (d, *J* = 8.7 Hz, 1H); ¹³C NMR (CDCl₃): δ 21.3 (CH₃), 23.9 (CH₃), 119.6, 120.3, 121.4, 121.7, 122.1, 122.3, 125.7, 126.7, 127.1, 127.2, 128.5, 128.6, 130.6, 130.8, 131.2, 131.5, 131.9, 132.4, 132.5, 142.8, 143.1, 143.2, 145.8, 145.9, 147.4, 147.5; ³¹P NMR (CDCl₃): δ 23.2 (s); MS (EI) *m/z* 450 (M⁺); HRMS Calcd for C₂₉H₂₃O₃P: 450.1385, Found: 450.1395.

General Procedure for Hydrolysis

To a solution of phosphonothioates **1**, phosphonates **3**, or phosphonoselenoate **4** in THF or 1,4-dioxane was added LiOH and water, and it was stirred for 1-144 h. After that, to the mixture was added 1N HCl until pH reached 1~2 and it was extracted with Et₂O three times. The combined organic layer was dried over MgSO₄, filtered, and concentrated to give phosphonothioic acids **2**.

(*S*_{ax})-*O*-(2'-Hydroxy-[1,1'-binaphthalen]-2-yl)-*O*-hydrogen-methylphosphonothioate (2a)

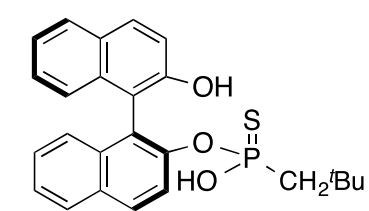


Chemical Formula: C₂₁H₁₇O₃PS
Exact Mass: 380.0636
Molecular Weight: 380.3978

The compound was synthesized *via* General Procedure, with phosphonothioate **1a** (183 mg, 0.50 mmol), THF (1.0 mL), LiOH (97 mg, 2.4 mmol), and water (1.0 mL) at room temperature for 1

h to give **2a** (208 mg, quant, 88:12 dr) as a colorless solid.: mp; 111-113 °C; IR (KBr): 3282, 3058, 2961, 2922, 2854, 1621, 1593, 1506, 1433, 993, 816, 749 cm⁻¹; ¹H NMR (CDCl₃): δ 1.62 (d, *J* = 17.5 Hz, 3H, CH₃), 4.77 (br, 2H, OH), 7.07-7.09 (m, 1H, Ar), 7.23-7.28 (m, 2H, Ar), 7.31-7.38 (m, 3H, Ar), 7.47-7.51 (m, 1H, Ar), 7.60-7.62 (m, 1H, Ar), 7.85-7.87 (m, 1H, Ar), 7.91-7.96 (m, 2H, Ar), 8.01-8.04 (m, 1H, Ar); ¹³C NMR (CDCl₃): δ 22.4 (d, ¹*J*_{C-P} = 149.3 Hz, CH₃), 115.0, 117.9, 125.2, 125.9, 126.1, 126.9, 127.5, 128.1, 128.4, 129.2, 130.5, 130.6, 131.7, 133.6, 133.6, 148.1, 148.1, 151.0; ³¹P NMR (CDCl₃): δ 91.2 (s, major), 92.1 (s, minor); MS (EI) *m/z* 364 (M⁺); HRMS Calcd for C₂₁H₁₇O₃PS: 380.0636, Found: 380.0622.

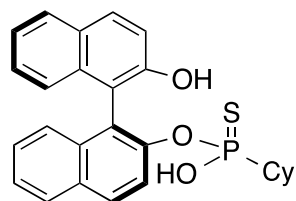
(*S*_{ax})-*O*-(2'-Hydroxy-[1,1'-binaphthalen]-2-yl)-*O*-hydrogen-neopentylphosphonothioate (2b**)**



Chemical Formula: C₂₅H₂₅O₃PS
Exact Mass: 436.1262
Molecular Weight: 436.5058

The compound was synthesized *via* General Procedure, with phosphonothioate **1b** (105 mg, 0.25 mmol), THF (0.5 mL), LiOH (31 mg, 1.3 mmol), and water (0.5 mL) at room temperature for 24 h to give **2b** (78 mg, 69%, >95:5 dr) as a colorless solid.: mp: 225-228 °C; IR (KBr): 3420, 3058, 2957, 1621, 1596, 1506, 1472, 1217, 988, 816 cm⁻¹; ¹H NMR (CDCl₃): δ 0.79 (s, 9H, CH₂(CH₃)₃), 1.64 (dd, *J* = 15.6 Hz, *J* = 15.6 Hz, 1H, CH₂(CH₃)₃), 1.76 (dd, *J* = 15.6 Hz, *J* = 15.6 Hz, 1H, CH₂(CH₃)₃), 5.20 (br, 2H, OH), 7.09-7.11 (m, 1H, Ar), 7.23-7.38 (m, 5H, Ar), 7.46-7.49 (m, 1H, Ar), 7.71-7.73 (m, 1H, Ar), 7.84-7.86 (m, 1H, Ar), 7.90 (d, *J* = 8.6 Hz, 1H, Ar), 7.93 (d, *J* = 8.6 Hz, 1H, Ar), 7.96-7.89 (m, 1H, Ar); ¹³C NMR (CDCl₃): δ 30.6 (d, ³*J*_{C-P} = 9.6 Hz, CH₂C(CH₃)₃), 30.7 (CH₂C(CH₃)₃), 48.7 (d, ¹*J*_{C-P} = 104.4 Hz, CH₂C(CH₃)₃), 115.3, 117.9, 122.7, 123.9, 125.3, 125.8, 126.0, 126.9, 127.5, 128.1, 128.4, 129.3, 130.5, 131.5, 131.6, 133.6, 133.7, 148.2, 148.3, 151.1 (Ar); ³¹P NMR (CDCl₃): δ 91.3 (s, major), 93.3 (s, minor); MS (EI) *m/z* 436 (M⁺); HRMS Calcd for C₂₅H₂₅O₃PS: 436.1262, Found: 436.1233.

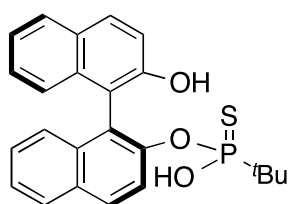
(*S*_{ax})-*O*-(2'-Hydroxy-[1,1'-binaphthalen]-2-yl)-*O*-hydrogen-cyclohexylphosphonothioate (2c)



Chemical Formula: C₂₆H₂₅O₃PS
Exact Mass: 448.1262
Molecular Weight: 448.5168

The compound was synthesized *via* General Procedure, with phosphonothioate **1c** (218 mg, 0.50 mmol), THF (1.0 mL), LiOH (62 mg, 2.5 mmol), and water (1.0 mL) at room temperature for 144 h to give **2c** (199 mg, 88%, >95:5 dr) as a colorless solid.: mp: 175-178 °C; IR (KBr): 3426, 3057, 2928, 2853, 1591, 1506, 1208, 1146, 988, 814, 748 cm⁻¹; ¹H NMR (CDCl₃): δ 0.84-1.00 (m, 5H), 1.26-1.49 (m, 6H), 7.09 (d, *J* = 8.6 Hz, 1H), 7.29-7.37 (m, 5H, Ar), 7.48-7.51 (m, 1H, Ar), 7.65-7.87 (m, 2H, Ar), 7.92-7.97 (m, 2H, Ar), 8.02 (d, *J* = 8.6 Hz, 1H); ¹³C NMR (CDCl₃): δ 25.1, 25.2, 25.5, 25.8, 25.9, 42.9 (d, ¹*J*_{C-P} = 108.0 Hz, CHCH₂CH₂), 115.0, 117.8, 121.8, 122.2, 123.9, 125.3, 125.8, 126.0, 126.9, 127.5, 128.0, 128.4, 129.3, 130.4, 130.6, 131.5, 133.7, 148.0, 148.1, 151.2; ³¹P NMR (CDCl₃): δ 96.7 (s, major), 98.4 (s, minor); MS (EI) *m/z* 448 (M⁺); HRMS Calcd for C₂₆H₂₅O₃PS: 448.1262, Found: 448.1241.

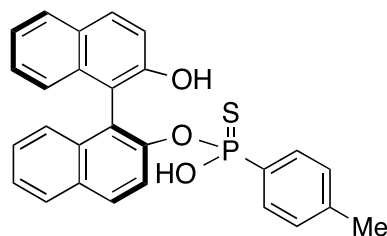
(*S*_{ax})-*O*-(2'-Hydroxy-[1,1'-binaphthalen]-2-yl)-*O*-hydrogen-*tert*-butylphosphonothioate (2d)



Chemical Formula: C₂₄H₂₃O₃PS
Exact Mass: 422.1106
Molecular Weight: 422.4788

The compound was synthesized *via* General Procedure, with phosphonothioate **1d** (125 mg, 0.30 mmol), 1,4-dioxane (0.6 mL), LiOH (39 mg, 1.6 mmol), and water (0.6 mL) at 100 °C for 24 h to give **2d** (120 mg, 94%, >95:5 dr) as a colorless solid.: mp: 139-141 °C; IR (KBr): 3408, 3058, 1621, 1592, 1506, 1212, 988, 935, 816, 716 cm⁻¹; ¹H NMR (CDCl₃): δ 0.86 (d, *J* = 18.9 Hz, 9H, C(CH₃)₃), 3.97 (br, 2H, OH), 7.10 (d, *J* = 8.5 Hz, 1H), 7.23-7.26 (m, 1H, Ar), 7.30-7.37 (m, 4H, Ar), 7.46-7.50 (m, 1H, Ar), 7.79 (d, *J* = 9.0 Hz, 1H), 7.83 (d, *J* = 8.1 Hz, 1H), 7.90 (d, *J* = 9.0 Hz, 1H), 7.94 (d, *J* = 8.1 Hz, 1H), 7.99 (d, *J* = 8.5 Hz, 1H); ¹³C NMR (CDCl₃): δ 24.0 (C(CH₃)₃), 36.8 (d, ¹*J*_{P-C} = 106.2 Hz, C(CH₃)₃), 114.5, 117.8, 121.9, 122.0, 123.8, 125.2, 125.8, 126.0, 126.8, 127.5, 128.0, 128.4, 129.2, 130.5, 131.6, 133.6, 133.7, 148.1, 148.3, 151.3; ³¹P NMR (CDCl₃): δ 103.5 (s); MS (EI) *m/z* 422 (M⁺); HRMS Calcd for C₂₄H₂₃O₃PS: 422.1106, Found: 422.1091.

(S_{ax})-O-(2'-hydroxy-[1,1'-binaphthalen]-2-yl)-O-hydrogen-*p*-tolylphosphonothioate



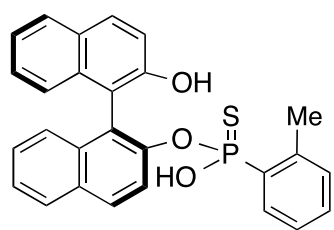
Chemical Formula: C₂₇H₂₁O₃PS
Exact Mass: 456.0949
Molecular Weight: 456.4958

(2e)

The compound was synthesized *via* General Procedure, with phosphonothioate **1e** (214 mg, 0.50 mmol), THF (1.0 mL), LiOH (60 mg, 2.5 mmol), and water (1.0 mL) at room temperature for 24 h. Purification by column chromatography on silica gel (Acetone/H₂O = 1:1, R_f = 0.18). The eluted fraction was concentrated to remove acetone, and it was extracted with Et₂O three times. The combined organic layer was dried over MgSO₄, filtered, and concentrated to give **2e** (181 mg, 80%, 71:29 dr) as a colorless solid.: mp: 158-160 °C; IR (KBr): 3400, 3063, 1590, 1506, 1471, 1216, 1126, 940, 834, 722 cm⁻¹; ¹H NMR (CDCl₃): δ 2.26 (s, 3H, CH₃), 5.16 (br, 2H, OH), 6.84-6.87 (m, 1H, Ar), 7.00-7.09 (m, 3H, Ar), 7.17-7.38 (m, 6H, Ar), 7.43-7.51 (m, 1H, Ar), 7.61-7.95 (m, 5H, Ar); ¹³C NMR (CDCl₃): δ 21.6 (CH₃), 115.1, 118.7, 122.1, 122.5, 123.6, 125.0, 125.9, 126.0, 126.7, 127.5, 128.0, 128.4, 128.7, 128.8, 129.0, 129.2, 130.0, 130.2, 130.7, 131.7, 133.6, 133.7, 142.6, 148.3, 148.4, 151.7; ³¹P NMR (CDCl₃): δ 80.0 (s, major), 80.4 (s, minor); MS (EI) m/z 456 (M⁺); HRMS Calcd for C₂₇H₂₁O₃PS: 492.0949, Found: 456.0941.

(S_{ax})-O-(2'-hydroxy-[1,1'-binaphthalen]-2-yl)-O-hydrogen-*o*-tolylphosphonothioate

(2f)



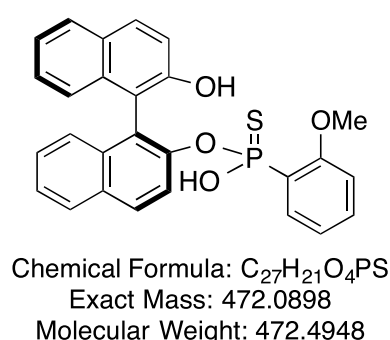
Chemical Formula: C₂₇H₂₁O₃PS
Exact Mass: 456.0949
Molecular Weight: 456.4958

The compound was synthesized *via* General Procedure, with phosphonothioate **1f** (174 mg, 0.40 mmol), THF (0.4 mL), LiOH (52 mg, 2.2 mmol), and water (0.4 mL) at room temperature for 12 h. Purification by column chromatography on silica gel (Acetone/H₂O = 1:1, R_f = 0.18). The eluted fraction

was concentrated to remove acetone, and it was extracted with Et₂O three times. The combined organic layer was dried over MgSO₄, filtered, and concentrated to give **2f** (111 mg, 61%, 95:5 dr) as a colorless solid.: mp: 208-210 °C; IR (KBr): 3405, 3058, 1593, 1431, 1381, 1211, 1071, 984, 814, 725 cm⁻¹; ¹H NMR (CDCl₃): δ 2.13 (s, CH₃, 3H), 4.13 (br, 2H, OH), 6.91 (m, 2H, Ar), 7.09-7.12 (m, 2H, Ar), 7.21-7.43 (m, 2H, Ar), 7.29-7.43 (m, 4H, Ar), 7.48-7.52 (m, 1H, Ar), 7.66 (d, *J* = 8.6 Hz, 1H), 7.69-7.71 (m, 1H, Ar), 7.78 (d, *J* = 8.0 Hz, 1H), 7.95 (d, *J* = 8.0 Hz, 1H), 7.98 (d, *J* = 8.6 Hz, 1H) ¹³C NMR (CDCl₃): δ 20.9 (CH₃), 115.8, 118.6, 122.6, 123.6, 124.9, 125.1, 125.2, 125.9,

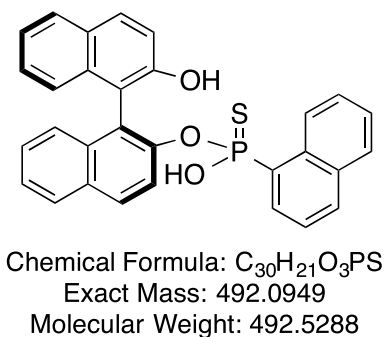
126.1, 126.7, 127.5, 128.0, 128.4, 129.1, 130.4, 130.6, 131.2, 131.3, 131.7, 132.3, 133.7, 140.6, 140.7, 148.4, 148.5, 151.5; ^{31}P NMR (CDCl_3): δ 79.6 (s); MS (EI) m/z 456 (M^+); HRMS Calcd for $\text{C}_{27}\text{H}_{21}\text{O}_3\text{PS}$: 456.0949, Found: 456.0934.

(*S*_{ax})-*O*-(2'-hydroxy-[1,1'-binaphthalen]-2-yl)-*O*-hydrogen-(2-methoxyphenyl)phosphonothioate (2g**)**



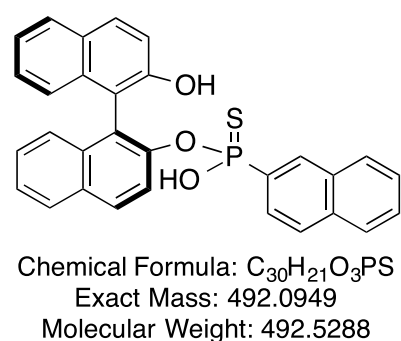
The compound was synthesized *via* General Procedure, with phosphonothioate **1g** (227 mg, 0.50 mmol), THF (1.0 mL), LiOH (61 mg, 2.5 mmol), and water (1.0 mL) at room temperature for 6 h. Purification by column chromatography on silica gel (Acetone/ H_2O = 1:1, R_f = 0.18). The eluted fraction was concentrated to remove acetone, and it was extracted with Et_2O three times. The combined organic layer was dried over MgSO_4 , filtered, and concentrated to give **2g** (142 mg, 60%, 17:83 dr) as a colorless solid. To a solution of diastereomixture **2g** (722 mg, 1.5 mmol) in Et_2O were added dicyclohexylamine (0.40 mL, 2.0 mmol), and the mixture was stirred at rt for 1 h. The precipitate was collected by filtration. To the obtained salt was added 3N HCl (18 mL), and the mixture was stirred for 1 h and extracted with Et_2O three times. The combined organic layer was dried over MgSO_4 , filtered, and concentrated to give diastereomerically pure **2g** (266 mg, 28%, dr = 5: >95).: mp: 207-210 °C; IR (KBr): 3455, 3060, 1620, 1590, 1474, 1216, 984, 813, 721 cm^{-1} ; ^1H NMR (CDCl_3): δ 3.48 (s, OCH_3 , 3H), 6.56-6.60 (m, 1H, Ar), 6.77-6.82 (m, 1H, Ar), 7.06 (d, J = 8.7 Hz, 1H), 7.09 (d, J = 8.7 Hz, 1H), 7.20- 7.27 (m, 3H, Ar), 7.30-7.39 (m, 3H, Ar), 7.56-7.49 (m, 1H, Ar), 7.64 (d, J = 8.7 Hz, 1H), 7.71 (d, J = 9.2 Hz, 1H), 7.75 (d, J = 9.2 Hz, 1H), 7.95-7.97 (m, 1H, Ar), 8.06 (d, J = 8.7 Hz, 1H); ^{13}C NMR (CDCl_3): δ 60.0 (OCH_3), 110.9, 114.9, 118.4, 121.1, 121.2, 122.3, 123.0, 123.3, 124.9, 125.8, 126.0, 126.4, 127.5, 127.9, 128.4, 128.9, 130.2, 130.5, 131.8, 133.4, 133.6, 134.1, 148.5, 148.6, 151.7, 158.6; ^{31}P NMR (CDCl_3): δ 81.7(s, minor), 82.9 (s, major); MS (EI) m/z 472 (M^+); HRMS Calcd for $\text{C}_{27}\text{H}_{21}\text{O}_4\text{PS}$: 472.0898, Found: 472.0901.

(S_{ax})-O-(2'-hydroxy-[1,1'-binaphthalen]-2-yl)-O-hydrogen-naphthalen-1-ylphosphonothioate (2h)



The compound was synthesized *via* General Procedure, with phosphonothioate **1h** (236 mg, 0.50 mmol), THF (0.5 mL), LiOH (59 mg, 2.5 mmol), and water (0.5 mL) at room temperature for 8 h. Purification by column chromatography on silica gel (Acetone/H₂O = 1:1, R_f = 0.08). The eluted fraction was concentrated to remove acetone, and it was extracted with Et₂O three times. The combined organic layer was dried over MgSO₄, filtered, and concentrated to give **2h** (217 mg, 82%, >95:5 dr) as a colorless solid.: mp: 146-148 °C; IR (KBr): 3402, 3056, 1591, 1507, 1378, 1205, 1149, 986, 932, 835, 712 cm⁻¹; ¹H NMR (CDCl₃): δ 4.13 (br, 2H, OH), 6.95 (d, *J* = 8.7 Hz, 1H), 7.04-7.24 (m, 5H, Ar), 7.29-7.36 (m, 5H, Ar), 7.53 (d, *J* = 8.2 Hz, 1H), 7.70-7.72 (m, 2H, Ar), 7.80-7.87 (m, 2H, Ar), 7.93 (d, *J* = 8.2 Hz, 1H), 7.99-8.01 (m, 1H, Ar), 8.14 (d, *J* = 8.7 Hz, 1H); ¹³C NMR (CDCl₃): δ 114.9, 118.1, 122.7, 123.0, 123.3, 124.0, 124.2, 124.6, 125.9, 126.0, 126.4, 126.5, 126.9, 127.4, 127.9, 128.3, 128.8, 129.9, 130.2, 130.4, 130.9, 131.0, 131.8, 133.2, 133.4, 133.6, 133.7, 148.7, 148.8, 151.6; ³¹P NMR (CDCl₃): δ 79.6 (s); MS (EI) *m/z* 492 (M⁺); HRMS Calcd for C₃₀H₂₁O₃PS: 492.0949, Found: 492.0923.

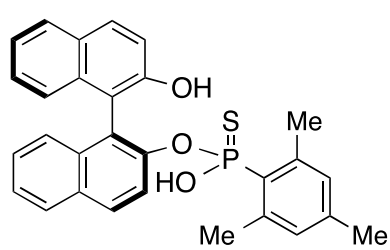
(S_{ax})-O-(2'-Hydroxy-[1,1'-binaphthalen]-2-yl)-O-hydrogen-naphthalen-2-ylphosphonothioate (2i)



The compound was synthesized *via* General Procedure, with phosphonothioate **1i** (231 mg, 0.49 mmol), THF (1.0 mL), LiOH (62 mg, 2.5 mmol), and water (1.0 mL) at room temperature for 6 h. Purification by column chromatography on silica gel (Acetone/H₂O = 1:1, R_f = 0.17). The eluted fraction was concentrated to remove acetone, and it was extracted with Et₂O three times. The combined organic layer was dried over MgSO₄, filtered, and concentrated to give **2i** (173 mg, 72%, 79:21 dr) as a colorless solid.: mp: 176-178 °C; IR (KBr): 3057, 1620, 1504, 1216, 984, 932, 834, 750, 717 cm⁻¹; ¹H NMR (DMSO-d₆): δ 4.41 (br, 2H, OH), 6.95 (d, *J* = 8.6 Hz, 1H), 7.12 (d, *J* = 8.6 Hz, 1H), 7.15-7.19 (m, 2H, Ar), 7.23-7.26 (m, 1H, Ar), 7.29-7.33 (m, 2H, Ar), 7.32-7.46 (m, 1H, Ar), 7.54-7.60 (m, 2H, Ar), 7.64-7.72 (m, 3H, Ar), 7.87-7.89 (m, 2H, Ar), 7.92 (d, *J* = 9.2 Hz, 1H), 8.06 (d, *J* = 9.2 Hz, 1H);

^{13}C NMR (DMSO- d_6): δ 114.3, 118.5, 120.6, 122.5, 123.6, 124.4, 124.9, 125.4, 125.6, 126.2, 126.5, 126.8, 127.4, 127.5, 127.9, 128.0, 128.4, 128.7, 129.3, 130.4, 130.6, 131.3, 131.5, 132.4, 133.5, 133.8, 133.9, 147.4, 147.5, 153.1; ^{31}P NMR (CDCl_3): δ 80.0 (s, major), 80.4 (s, minor); MS (EI) m/z 492 (M^+); HRMS Calcd for $\text{C}_{30}\text{H}_{21}\text{O}_3\text{PS}$: 492.0949, Found: 492.0923.

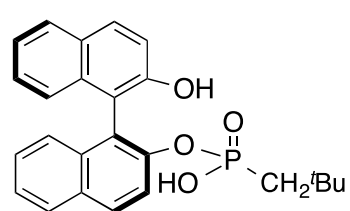
(S_{ax})-*O*-(2'-Hydroxy-[1,1'-binaphthalen]-2-yl)-*O*-hydrogen-mesitylphosphonothioate (2j**)**



Chemical Formula: $\text{C}_{29}\text{H}_{25}\text{O}_3\text{PS}$
Exact Mass: 484.1262
Molecular Weight: 484.5498

The compound was synthesized *via* General Procedure, with phosphonothioate **1j** (58 mg, 0.12 mmol), THF (0.2 mL), LiOH (14 mg, 0.6 mmol), and water (0.2 mL) at room temperature for 24 h. Purification by column chromatography on silica gel (Acetone/ H_2O = 1:1, R_f = 0.08). The eluted fraction was concentrated to remove acetone, and it was extracted with Et_2O three times. The combined organic layer was dried over MgSO_4 , filtered, and concentrated to give **2j** (38 mg, 67%, >95:5 dr) as a colorless solid.: mp: 185-187 $^\circ\text{C}$; IR (KBr): 3450, 3055, 2977, 2930, 1606, 1199, 1070, 969, 830, 682 cm^{-1} ; ^1H NMR (CDCl_3): δ 2.20 (s, 9H, CH_3), 4.24 (br, 2H, OH), 6.66 (s, 1H), 6.67 (s, 1H), 7.00 (d, J = 8.7 Hz, 1H), 7.17 (dd, J = 8.7 Hz, 7.8 Hz, 1H), 7.25 (d, J = 8.7 Hz, 1H), 7.25 (d, J = 9.2 Hz, 1H), 7.27 (dd, J = 8.2 Hz, 7.8 Hz, 1H), 7.31 (dd, J = 8.2 Hz, 7.8 Hz, 1H), 7.46 (dd, J = 8.7 Hz, 7.8 Hz, 1H), 7.64 (d, J = 9.2 Hz, 1H), 7.78 (d, J = 7.8 Hz, 1H), 7.80 (d, J = 9.2 Hz, 1H), 7.90 (d, J = 7.8 Hz, 1H), 7.93 (d, J = 9.2 Hz, 1H); ^{13}C NMR (CDCl_3): δ 21.1 (CH_3), 23.2 (CH_3), 115.9, 118.6, 122.2, 123.0, 123.5, 125.0, 126.0, 126.6, 127.4, 128.0, 128.2, 129.3, 130.0, 130.5, 130.6, 130.7, 131.6, 133.9, 134.0, 141.2, 141.3, 141.5, 148.2, 148.3, 151.6; ^{31}P NMR (CDCl_3): δ 76.3 (s); MS (EI) m/z 484 (M^+); HRMS Calcd for $\text{C}_{29}\text{H}_{25}\text{O}_3\text{PS}$: 484.1262, Found: 484.1270.

(S_{ax})-*O*-(2'-Hydroxy-[1,1'-binaphthalen]-2-yl)-*O*-hydrogen-2,2-dimethylethylphosphonate (5b**)**

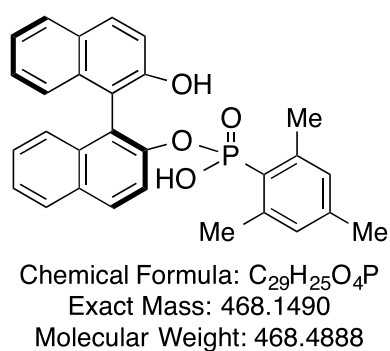


Chemical Formula: $\text{C}_{25}\text{H}_{25}\text{O}_4\text{P}$
Exact Mass: 420.1490
Molecular Weight: 420.4448

The compound was synthesized *via* General Procedure, with phosphonate **3b** (237 mg, 0.60 mmol), THF (1.0 mL), LiOH (63 mg, 2.5 mmol), and water (1.0 mL) at room temperature for 0.5 h

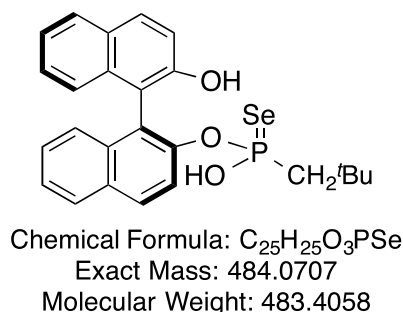
to give **5b** (255 mg, quant) as a colorless solid.: mp: 206-209 °C; IR (KBr): 3266, 2982, 2956, 1697, 1506, 1227, 996, 809 cm⁻¹; ¹H NMR (DMSO-d₆): δ 0.68 (s, 9H, CH₂C(CH₃)₃), 1.00 (dd, *J* = 18.8 Hz, *J* = 15.6 Hz, 1H, CH₂(CH₃)₃), 1.12 (dd, *J* = 18.8 Hz, *J* = 15.6 Hz, 1H, CH₂(CH₃)₃), 3.53 (br, 2H, OH), 6.87 (d, *J* = 8.7 Hz, 1H), 7.07 (d, *J* = 8.2 Hz, 1H), 7.18-7.34 (m, 4H, Ar), 7.41-7.45 (m, 1H, Ar), 7.72 (d, *J* = 8.7 Hz, 1H), 7.87 (d, *J* = 8.2 Hz, 1H), 7.89-8.03 (m, 3H, Ar); ¹³C NMR (DMSO-d₆): δ 29.0 (d, ³*J*_{C-P} = 3.8 Hz, CH₂C(CH₃)₃), 30.3, (d, ¹*J*_{C-P} = 9.6 Hz, CH₂C(CH₃)₃), 30.7 (CH₂C(CH₃)₃), 144.5, 118.5, 121.5, 122.5, 123.1, 124.3, 124.7, 125.5, 126.2, 126.4, 127.9, 128.0, 128.7, 129.3, 130.4, 133.4, 133.9, 147.2, 147.3, 153.0; ³¹P NMR (DMSO-d₆): δ 25.6 (s); MS (EI) *m/z* 420 (M⁺); HRMS Calcd for C₂₅H₂₅O₄PS: 420.1490, Found: 420.1479.

(*S*_{ax})-*O*-(2'-Hydroxy-[1,1'-binaphthalen]-2-yl)-*O*-hydrogen-mesitylphosphonate (5j**)**



The compound was synthesized *via* General Procedure, with phosphonothioate **3b** (61 mg, 0.13 mmol), THF (0.1 mL), LiOH (15 mg, 0.7 mmol), and water (0.1 mL) at room temperature for 24 h. Purification by column chromatography on silica gel (Acetone/H₂O = 1:1, *R_f* = 0.38). The eluted fraction was concentrated to remove acetone, and it was extracted with Et₂O three times. The combined organic layer was dried over MgSO₄, filtered, and concentrated to give **5b** (33 mg, 54%) as a colorless solid.: mp: 167-169 °C; IR (KBr): 3505, 1594, 1507, 1459, 1211, 1145, 984, 814 cm⁻¹; ¹H NMR (CDCl₃): δ 2.03 (s, 6H, CH₃), 2.17 (s, 3H, CH₃), 4.92 (br, 2H, OH), 6.52 (s, 1H), 6.54 (s, 1H), 6.80 (d, *J* = 8.2 Hz, 1H), 6.99-7.03 (m, 1H, Ar), 7.11 (d, *J* = 9.2 Hz, 1H), 7.15 (d, *J* = 8.2 Hz, 1H), 7.18-7.22 (m, 1H, Ar), 7.26-7.30 (m, 1H, Ar), 7.400-7.44 (m, 1H, Ar), 7.56-7.58 (m, 1H, Ar), 7.64 (d, *J* = 9.2 Hz, 1H), 7.67-7.70 (m, 2H, Ar), 7.75-7.77 (m, 1H, Ar); ¹³C NMR (CDCl₃): δ 21.2 (CH₃), 22.7 (CH₃), 115.2, 118.6, 120.4, 122.0, 122.3, 123.3, 124.9, 125.8, 126.0, 126.4, 127.3, 127.8, 128.2, 129.1, 130.0, 130.1, 130.2, 130.5, 131.6, 133.8, 141.9, 142.9, 143.1, 147.5, 147.6, 151.8; ³¹P NMR (CDCl₃): δ 23.2 (s); MS (EI) *m/z* 468 (M⁺); HRMS Calcd for C₂₉H₂₅O₄P: 468.1490, Found: 468.1483.

(S_{ax})-O-(2'-Hydroxy-[1,1'-binaphthalen]-2-yl)-O-hydrogen-neopentylphosphonosel enonate (6b)



The compound was synthesized *via* General Procedure, with phosphonothioate **4b** (120 mg, 0.3 mmol), THF (0.5 mL), LiOH (32 mg, 1.3 mmol), and water (0.5 mL) at room temperature for 3 h. Purification by column chromatography on silica gel (Acetone/H₂O = 1:1, R_f = 0.38). The eluted fraction was concentrated to remove acetone, and it was extracted with Et₂O three times. The combined organic layer was dried over MgSO₄, filtered, and concentrated to give **6b** (123 mg, 99%, >95:d dr) as a colorless solid.: mp: decomp (110 °C-); IR (KBr): 3390, 3058, 2956, 1621, 1592, 1505, 1366, 1210, 987, 814, 748 cm⁻¹; ¹H NMR (CDCl₃): δ 0.86 (s, 9H, CH₂C(CH₃)₃), 1.88-2.05 (m, 2H), 4.48 (br, 2H, OH), 7.10-7.12 (m, 1H, Ar), 7.25-7.40 (m, 5H, Ar), 7.48-7.51 (m, 1H, Ar), 7.65-7.68 (m, 1H, Ar), 7.86 (d, *J* = 8.1 Hz, 1H), 7.93 (d, *J* = 9.0 Hz, 1H, Ar), 7.95 (d, *J* = 8.1 Hz, 1H), 8.02 (d, *J* = 9.0 Hz, 1H); ¹³C NMR (CDCl₃): δ 30.6 (d, ³*J*_{C-P} = 8.4 Hz, CH₂C(CH₃)₃), 31.4 (CH₂C(CH₃)₃), 50.4 (d, ¹*J*_{C-P} = 92.4 Hz, CH₂C(CH₃)₃), 115.6, 118.5, 122.4, 122.6, 123.9, 125.2, 125.9, 126.2, 127.0, 127.6, 128.1, 128.4, 129.4, 130.6, 131.8, 133.6, 133.7, 148.3, 148.4, 151.5; ³¹P NMR (CDCl₃): δ 93.5 (br); ⁷⁷Se NMR (CDCl₃): n.d.; MS (EI) *m/z* 484 (M⁺); HRMS Calcd for C₂₅H₂₅O₃PSe: 484.0707, Found: 484.0701.

X-ray Structure Analysis

Phosphonothioic acid (S_{ax}, R)-2i: Crystal samples were cut from the grown crystals and mounted on a glass fiber. The crystals were coated with an epoxy resin because they were air sensitive. Measurements were carried out on a Rigaku/MSM Mercury CCD using a graphite-monochromator with Mo Kα radiation (λ = 0.71069 Å). The structure was solved by direct methods (SIR97)¹³ and refined by full-matrix least-squares procedures (SHELXL-97)¹⁴ using the Yadokari-XG 2009.¹⁵ The crystal data are shown Table 4.

References and Notes

- (1) (a) Ferry, A.; Stemper, J.; Marinetti, A.; Voituriez, A.; Guinchard, X. *Eur. J. Org. Chem.* **2014**, 188. (b) Malik, G.; Ferry A.; Guinchard, X. *Molecules* **2015**, *20*, 21082.

(2) (a) Murai, T.; Hayashi, T.; Yamada, K.; Maekawa, Y.; Minoura, M. *Chem. Commun.* **2014**, 50, 12473. (b) Maekawa, Y.; Kuwabara, K.; Sugiyama, A.; Iwata, K.; Maruyama, T.; Murai, T. *Chem. Lett.* **2017**, 46, 1068.

(3) For a review, see: Kolodiazhnyi, O. I.; Kolodiazhna, A. *Tetrahedron: Asymmetry* **2017**, 28, 1651.

(4) Grand, A.; Robert, J. B. *Acta. Cryst.* **1978**, B34, 199.

(5) Odinets, I. L.; Vinogradova, N. M.; Lyssenko, K. A.; Petrovskii, P. V.; Mastryukova, T. A. *Heteroat. Chem.* **2000**, 11, 163.

(6) For recent examples, see: (a) Szakonyi, Z.; Csor, A.; Csampai, A.; Fuleop, F. *Chem. Eur. J.* **2016**, 22, 7163. (b) Botta, M. C.; Biava, H. D.; Spanevello, R. A.; Mata, E. G.; Suarez, A. G. *Tetrahedron Lett.* **2016**, 57, 2186. (c) Gonda, T.; Szakonyi, Z.; Csampai, A.; Haukka, M.; Fulop, F. *Tetrahedron: Asymmetry* **2016**, 27, 480. (d) Goek, Y.; Kilicarslan, S.; Goek, H. Z.; Karayigit, I. U. *Chirality* **2016**, 28, 593. (e) Huynh, K.-D.; Ibrahim, H.; Bouchardy, L.; Bournaud, C.; Kolodziej, E.; Toffano, M.; Vo-Thanh, G. *Asian J. Org. Chem.* **2016**, 5, 1242. (f) Kamenova-Nacheva, M.; Dobrikov, G. M.; Dimitrov, V. *Tetrahedron: Asymmetry* **2016**, 27, 852. (g) Serra, M. E. S.; Costa, D.; Murtinho, D.; Tavares, N. C. T.; Pinho e Melo, T. M. V. D. *Tetrahedron* **2016**, 72, 5923. (h) Wang, X.; Han, X.; Zhang, J.; Wu, X.; Liu, Y.; Cui, Y. *J. Am. Chem. Soc.* **2016**, 138, 12332. (i) Zhang, P.; Yu, J.; Peng, F.; Wu, X.; Jie, J.; Liu, C.; Tian, H.; Yang, H.; Fu, H. *Chem. -Eur. J.* **2016**, 22, 17477. (j) Zhao, W.-X.; Liu, G.-J.; Wang, J.; Li, F.; Liu, L. *Tetrahedron: Asymmetry* **2016**, 27, 1139. (k) Escorihuela, J.; Burguete, M. I.; Ujaque, G.; Lledos, A.; Luis, S. V. *Org. Biomol. Chem.* **2016**, 14, 11125. (l) Serra, M. E. S.; Murtinho, D.; Paz, V. *Tetrahedron: Asymmetry* **2017**, 28, 381. (m) Sanchez-Carnerero, E. M.; Sandoval-Torrientes, R.; Urieta-Mora, J.; Moreno, F.; Maroto, B. L.; de la Moya, S. *Reactive and Functional Polymers* **2017**, 113, 23. (n) Gonda, T.; Balazs, A.; Toth, G.; Fulop, F.; Szakonyi, Z. *Tetrahedron* **2017**, 73, 2638. Bouhachicha, M.; Ngo N., A.; Roisnel, T.; Lalli, C.; Argouarch, G. *New J. Chem.* **2017**, 41, 4767.

(7) (a) Liu, X.; Wang, P.; Yang, Y.; Wang, P. Yang, Q. *Chem. Asian J.* **2010**, 5, 1232. (b) Abreu, A. R.; Lourenco, M.; Peral, D.; Rosado, M. T. S.; Eusebio, M. E. S.; Palacios, O.; Bayon, J. C.; Pereira, M. M. *J. Mol. Cat. A* **2010**, 325, 91. (c) Liu, X.; Wang, P.; Zhang, L.; Yang, J.; Li, C.; Yang, Q. *Chem. -Eur. J.* **2010**, 16, 12727. (k) Gao, G.; Bai, X.-F.; Yang, H.-M.; Jiang, J.-X.; Lai, G.-Q.; Xu, L.-W. *Eur. J. Org. Chem.* **2011**, 5039. (d) Ma, L.; Wanderley, M. M.; Lin, W. *ACS Cat.* **2011**, 1, 691. (e) Bian, G.; Huang, H.;

Zong, H.; Song, L. *Chirality* **2012**, *24*, 825. (f) Vidal, M.; Schmitzer, A. R. *Organometallics* **2014**, *33*, 3328. (g) Liu, D.; Ouyang, K.; Yang, N. *Tetrahedron* **2016**, *72*, 1018.

(8) (a) Hatano, M.; Miyamoto, T.; Ishihara, K. *Adv. Synth. Cat.* **2005**, *347*, 1561. (b) Guo, Q.-S.; Liu, B.; Lu, Y.-N.; Jiang, F.-Y.; Song, H.-B.; Li, J.-S. *Tetrahedron: Asymmetry* **2005**, *16*, 3667. (b) Guo, Q.-S.; Lu, Y.-N.; Liu, B.; Xiao, J.; Li, J.-S. *J. Organomet. Chem.* **2006**, *691*, 1282. (c) Hatano, M.; Miyamoto, T.; Ishihara, K. *J. Org. Chem.* **2006**, *71*, 6474. (d) Arai, T.; Endo, Y.; Yanagisawa, A. *Tetrahedron: Asymmetry* **2007**, *18*, 165. (e) Liu, G.-H.; Yu, H.; Yang, L.-Z.; Yao, M.; Fang, H.-B.; Xue, Y.-N. *Chin. J. Struct. Chem.* **2007**, *26*, 477. (f) Liu, B.; Fang, C.; Dong, Z.-B.; Li, J.-S. *Appl. Organomet. Chem.* **2008**, *22*, 55. (g) Beckendorf, S.; Mancheno, O. G. *Synthesis*. **2012** *44*, 2162.

(9) Gadenne, B.; Hesemann, P.; Moreau, J. J. E. *Tetrahedron: Asymmetry* **2005**, *16*, 2001.

(10) The discrimination of chiral aliphatic amines is nontrivial; for examples, see: (a) Kumari, D.; Sachin, S. L.; Suryaprakash, N. *Chem. Phys. Lett.* **2015**, *636*, 72. (h) Zhao, Y.; Swager T. M. *J. Am. Chem. Soc.* **2015**, *137*, 3221. (i) Seo, M.-S.; Kim, H. *J. Am. Chem. Soc.* **2015**, *137*, 14190. (j) Oliveira, S. S.; Cunha, R. L. O. R.; Silva, M. S. *Tetrahedron Lett.* **2016**, *57*, 4556. (k) Li, L.-P.; Ye, B.-H. *Inorg. Chem.* **2017**, *56*, 10717.

(11) For a review, see: Wenzel, T. J. *Tetrahedron: Asymmetry* **2017**, *28*, 1212.

(12) Murai, T.; Maekawa, Y.; Hirai, Y.; Kuwabara, K.; Minoura, M. *RSC Adv.* **2016**, *6*, 15180.

(13) Altomare, A.; Burla, M. C.; Camalli, M.; Casacaro, G. L.; Giacovazzo, C.; Guagliardi, A.; Moliterni, A. G. G.; Polidori, G.; Spagna, R. *J. Appl. Cryst.* **1999**, *32*, 115.

(14) Sheldrick, G. M. SHELXL-97, *A Program for the Refinement of Crystal Structures*; University of Göttingen: Göttingen, Germany, **1997**.

(15) (a) Wakita, K.; Yadokari-XG, *Software for Crystal Structure Analysis*, **2001**. (b) Kabuto, C.; Akine, S.; Nemoto, T.; Kwon, E. *J. Cryst. Soc. Jpn.* **2009**, *51*, 218.

Chapter 3

Alcoholysis of Phosphonothioates with a Binaphthyl Group

The reaction of phosphonothioates having a binaphthyl group with alkoxides proceeded via transfer of the axial chirality of the binaphthyl group to the central chirality of the phosphorus atom to give *P*-stereogenic phosphonothioates with moderate to excellent diastereoselectivities. The reaction of phosphonoselenoates also proceeded in a similar fashion. The selenium atom of the obtained product could be extruded with tributylphosphine to give a trivalent phosphonite, which was then isolated as a boron complex.

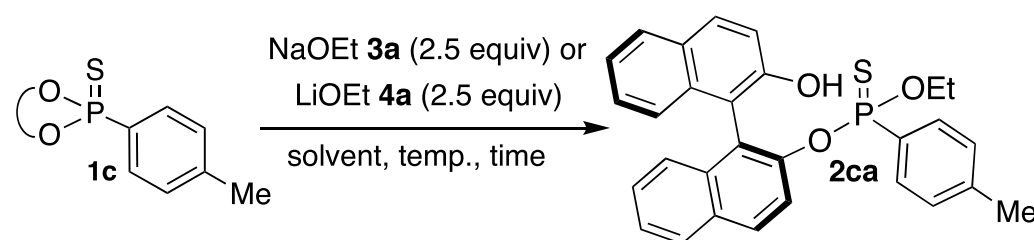
3.1 Introduction

As mentioned in the Chapter 1, despite the utilities of *P*-stereogenic phosphonothioates, the stereoselective synthetic approach is still lacking. In the previous chapter, the author described stereoselective hydrolysis of the phosphonothioates having a binaphthyl group via axis-to-center chirality transfer. In this chapter, the author describes stereoselective alcoholysis of the phosphonothioates having a binaphthyl group via the chirality transfer.

3.2 Alcoholysis of Phosphonothioates

To optimize the alcoholysis of phosphonothioates **1**, the author initially reacted phosphonothioate **1c** with sodium ethoxide **3a** at room temperature for 0.5 h to give the desired *P*-stereogenic phosphonothioate **2ca** in high yield with moderate diastereoselectivity (Table 1, entry 1). As in the hydrolysis of **1**, an axis-to-center chirality transfer takes place in the alcoholysis. To further improve the yields and stereoselectivity, the author used mixed solvents (entries 2–4), but the reaction gave the products in lower yields and with lower diastereoselectivity. Therefore, instead of **3a**, lithium ethoxide **4a** was used to improve the diastereoselectivity (entry 5). While the alcoholysis of **1c** at -20 °C gave **2ca** in moderate yield, the reaction at 0 °C showed comparable diastereoselectivity in high yield (entries 6 and 7).

Table 1. Optimization of the ethanolysis of phosphonothioates **1c**



entry	base	solvent	temp. (°C)	time (h)	yield (%)	dr
1	3a	EtOH	rt	0.5	97	81:19
2	3a	EtOH/toluene 1/1	rt	3	34	71:29
3	3a	EtOH/THF 1/1	rt	2	57	60:40
4	3a	EtOH/hexane 1/1	rt	1	73	55:45
5	4a	EtOH	rt	2	76 ^a	90:10
6	4a	EtOH	0	13	88 ^a	94:6
7	4a	EtOH	-20	70	49 ^a	>95:5

Note. Yield and diastereoselectivities were determined by ³¹P NMR analysis of the crude reaction mixtures. ^aIsolated yields.

With the optimal reaction conditions in hand, we then explored the substrate scope of phosphonothioates (Table 2). The phosphonothioate **1a** showed modest diastereoselectivity (entry 1). The reactions of **1b** and **1d** with **4a** gave the corresponding products **2ba** and **2da** with better diastereoselectivities even when the reaction was performed for longer reaction times, whereas the reaction of **1e** was complete within 4 h in 84% yield with excellent diastereoselectivity (entries 2-4). Even though the reaction of **1f** required a higher reaction temperature, the diastereoselectivity was completely controlled (entry 5).

Table 2. Substrate scope of phosphonothioates **1**

entry	R	product	time (h)	yield (%)	dr	entry	R	product	time (h)	yield (%)	dr
1	Me		3	88	40:60	4			4	84	>95:5
2 ^a	Cy		96	75	88:12	5 ^b			0.2	73	>95:5
3			36	90	16:84						

Note. Isolated yields are shown. Diastereoselectivities were determined by ³¹P NMR analysis of the crude reaction mixtures. ^aReaction was carried out at rt. ^bReaction was carried out at 80 °C.

The author then explored the substrate scope of alkoxides **4** in the reaction of **1** (Table 3). The use of lithium alkoxide **4b** derived from secondary alcohols such as cyclohexanol improved the diastereoselectivity (entry 1). Notably, (*l*)-menthol **4c** was successfully installed to the phosphorus atom to afford **2ac** with excellent diastereoselectivity (entry 2). With the expectation of kinetic resolution of racemic alcohols, 1-phenylethyl alcohol **4d** reacted with **1a**, but four diastereomers were obtained in a nearly equal ratio (entry 3). To improve the selectivity, we then used ester **1f** having a mesityl group, but could not discriminate the enantiomers to recover the alcohol **4d** as a racemic mixture (entry 4). Even so, the diastereomers **2fd** were separated by column chromatography to give a single diastereomer with multiple

chiralities that correspond to the axial chirality of the binaphthyl group and the central chiralities of phosphorus and carbon atoms. Therefore, their application as chiral ligands is highly promising.

Table 3. Substrate scope of alkoxides **4**

entry	R	base	X	product	time (h)	yield (%)	dr
1	Me	LiOCy 4b	1.5	 2ab	0.5	82	83:13
2	Me	 4c	1.5	 2ac	0.5	69	>95:5
3	Me	 4d	2.0	 2ad	0.5	59	29:30:29:12
4	 Me	 4d	2.0	 2fd	48	42	50:50:0:0

Note. Isolated yields are shown. Diastereoselectivities were determined by ^{31}P NMR analysis of the crude reaction mixtures.

The absolute configuration of the major isomer of **2ca** was determined by a single-crystal X-ray diffraction analysis (Figure 1).¹ The tetrahedral phosphorus atom in **2ca** adopts an *R* configuration.

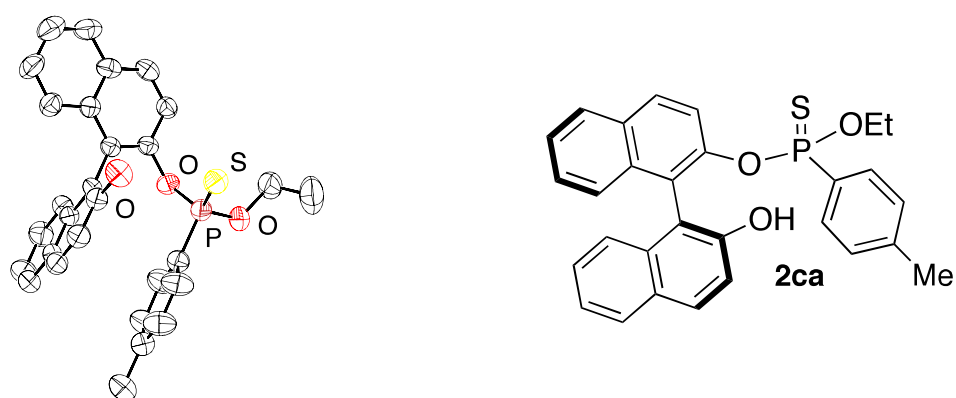
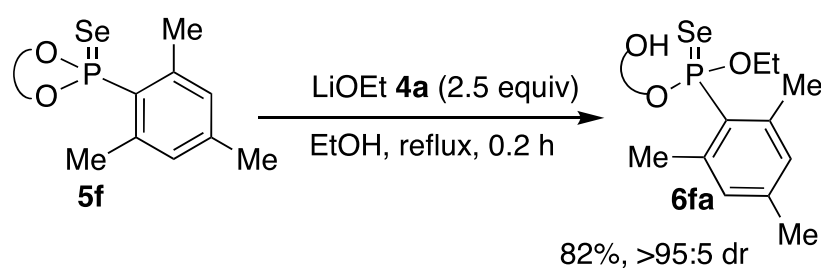
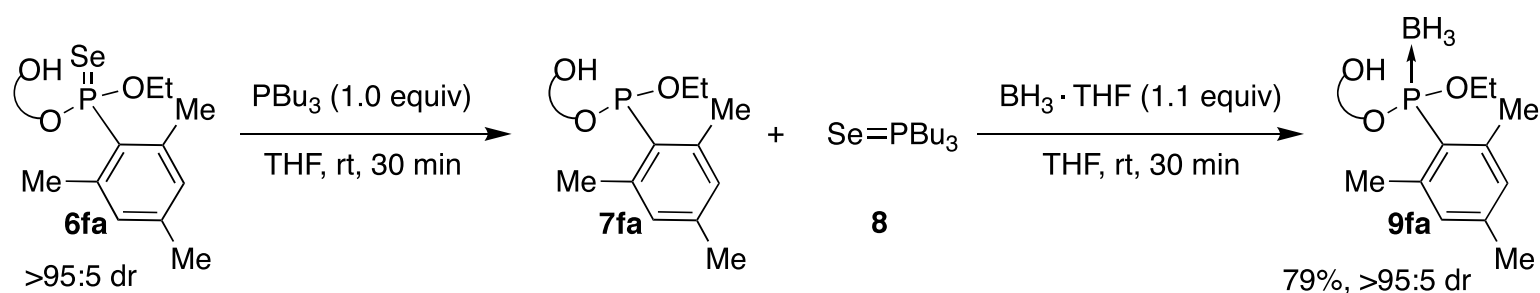


Figure 1. Molecular structure of **2ca** with thermal ellipsoids set to 50% probability

The author also subjected the phosphonoselenoate **5f**, which is a selenium isologue of **1f**, to this alcoholysis (Scheme 2). The reaction of **5f** proceeded smoothly to afford **6fa** with high yield and excellent diastereoselectivity. To show the synthetic utility of this alcoholysis, the author then examined the reduction of **6fa** to convert it to a trivalent phosphonite **7fa** (Scheme 3). A peak corresponding to phosphonite **7fa** was observed in the ^{31}P NMR spectra by reacting **6fa** and tributylphosphine, but the author could not separate **7fa** and tributylphosphine selenide **8**. Nevertheless, the author successfully isolated **7fa** as a boron complex **9fa** by reacting with $\text{BH}_3 \cdot \text{THF}$ without a decrease in the diastereomeric ratio.² A series of reactions to give **9fa**, which is a precursor of phosphonite **7fa**, emphasize the utility of this chirality-transfer strategy to access a range of *P*-stereogenic phosphonites.



Scheme 2. Alcoholysis of phosphonoselenoate **5f**



Scheme 3. Synthesis of boron complex of **9fa**

In summary, the author has demonstrated that the alcoholysis of phosphonothioates proceeds via transfer of the axial chirality of the binaphthyl group to the central chirality of the phosphorus atom with moderate to high yields and diastereoselectivities. Although the reaction of **1f** with racemic 1-phenylethyl alcohol **4d** gave two diastereomers in a nearly equal ratio, the obtained diastereomers could be separated by column chromatography. The alcoholysis of phosphonoselenoates **5f** also proceeded via a transfer of chirality. The selenium atom of the obtained **6fa** could be easily excluded to afford the trivalent phosphonite **7fa** *in situ*, and was isolated as boron complex **9fa** without a decrease in the diastereomeric ratio.

3.3 Experimental Section

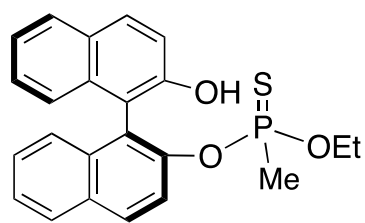
Unless otherwise noted, materials were purchased from commercial supplies and used as received. Ethanol (Japan Alcohol Corporation) was distilled from magnesium. Toluene (Kanto Chemical Co., Ltd.) was distilled from sodium metal. *n*-BuLi 1.6 M solution in hexane was purchased from Mituwa Chemical Co., Ltd. Phosphonothioates **1a-1f** were previously prepared.³ Flash column chromatography was run on silica gel 60 N (spherical neutral) 40-50 μ m of Kanto Chemical Co., Ltd. All manipulations were carried out under argon atmosphere.

The ^1H NMR spectra were recorded on JEOL ECX-400P (400 MHz) in CDCl_3 . Chemical shifts of protons are recorded in δ values referred to chloroform as an internal standard in CDCl_3 , and the following abbreviations are used: s: singlet, d: doublet, t: triplet, q: quartet, m: multiplet, br: broad. The ^{13}C NMR spectra were measured on a JEOL ECX-400P (100 MHz) in CDCl_3 . The ^{31}P NMR spectra were measured on a JEOL ECX-400P (162 MHz) in CDCl_3 and with 85% H_3PO_4 as an external standard. The ^{77}Se NMR spectra were measured on a JEOL ECX-400P (76 MHz) in CDCl_3 and with Me_2Se as an external standard. All spectra were acquired in the proton-decoupled mode. The high-resolution mass spectra (HRMS) were taken on a JMS-700 mass spectrometer.

General procedure 1 for the preparation of phosphonothioates **2** (GP1)

To a 20 mL Schlenk tube were added phosphonothioates **1** (0.50 mmol) and ethanol (0.5 mL). The reaction mixture was cooled to 0 $^\circ\text{C}$. Then, lithium ethoxide **4a** (1.0 M ethanol solution, 0.75 mL, 0.75 mmol) was added to the cooled solution. After that, the mixture was added 1N HCl (3.0 mL), and it was extracted with Et_2O (5 mL \times 3). The combined organic layer was dried over MgSO_4 , filtered, and concentrated. Purification by column chromatography on silica gel (EtOAc :hexane = 1:10) provided **2**.

(*S*_{ax})-Ethyl(2'-hydroxy-[1,1'-binaphthalen]-2-yl) methylphosphonothioate (**2aa**)

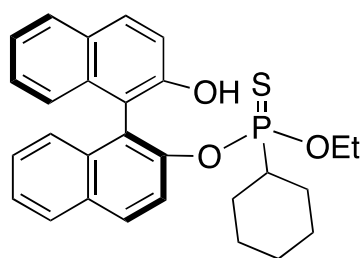


Chemical Formula: $\text{C}_{23}\text{H}_{21}\text{O}_3\text{PS}$
Exact Mass: 408.0949
Molecular Weight: 408.4518

According to GP1, **2aa** (181 mg, 88%, 40:60 dr) was obtained as a colorless solid. ^1H NMR (CDCl_3): δ 0.91 (t, J = 7.2 Hz, 1.8H, OCH_2CH_3), 1.21-1.28 (m, 3H, CH_3 , OCH_2CH_3), 1.68 (d, J = 15.3 Hz, 1.2H, CH_3), 3.21 (ddq, J

= 21.5 Hz, 7.2 Hz, 2.5 Hz, 0.6H, OCH₂CH₃), 3.81 (ddq, J = 21.1 Hz, 7.2 Hz, 3.0 Hz, 0.4H, OCH₂CH₃), 3.93 (ddq, J = 21.1 Hz, 7.2 Hz, 1.7 Hz, 0.4H, OCH₂CH₃), 4.13 (ddq, J = 21.5 Hz, 7.2 Hz, 1.8 Hz, 0.6H, OCH₂CH₃), 5.33-5.35 (br, 1H, OH), 7.10-7.12 (m, 1H, Ar), 7.25-7.39 (m, 5H, Ar), 7.42-7.51 (m, 2H, Ar), 7.34-7.86 (m, 1H, Ar), 7.90-7.96 (m, 2H, Ar), 8.02-8.05 (m, 1H, Ar); ¹³C NMR (CDCl₃): δ 15.8 (d, $^3J_{C-P}$ = 8.5 Hz, OCH₂CH₃), 16.1 (d, $^3J_{C-P}$ = 8.5 Hz, OCH₂CH₃), 21.6 (d, $^1J_{C-P}$ = 116.5 Hz, CH₃), 23.1 (d, $^1J_{C-P}$ = 114.6 Hz, CH₃), 62.0 (d, $^2J_{C-P}$ = 7.5 Hz, OCH₂CH₃), 62.4 (d, $^2J_{C-P}$ = 7.5 Hz, OCH₂CH₃), 115.0, 115.3, 118.5, 118.7, 121.7, 122.4, 122.7, 123.8, 124.9, 125.0, 125.9, 126.1, 126.9, 127.0, 127.7, 128.1, 128.4, 129.2, 129.2, 130.4, 130.6, 130.7, 130.8, 131.7, 133.6, 133.7, 133.7, 133.8, 148.3, 148.4, 148.5, 148.6, 151.7, 151.9; ³¹P NMR (CDCl₃): δ 95.5 (s, minor), 96.2 (s, major); HRMS Calcd for C₂₃H₂₁O₃PS: 408.0949, Found: 408.0947.

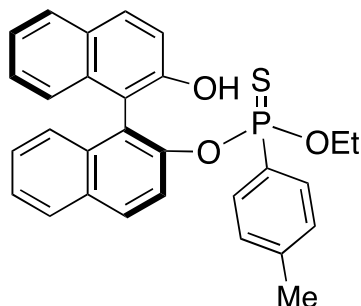
(S_{ax})-Ethyl(2'-hydroxy-[1,1'-binaphthalen]-2-yl) cyclohexylphosphonothioate (2b a)



Chemical Formula: C₂₈H₂₉O₃PS
Exact Mass: 476.1575
Molecular Weight: 476.5708

According to GP1, **2ba** (179 mg, 75%, 84:16 dr) was obtained as a colorless solid. ¹H NMR (CDCl₃): δ 0.89-0.95 (m, 5H, Cy), 1.05 (t, J = 7.2 Hz, 3H, OCH₂CH₃), 1.49-1.68 (m, 6H, Cy), 3.53-3.65 (m, 1H, OCH₂CH₃), 3.94-4.04 (m, 1H, OCH₂CH₃), 5.18 (br, 1H, OH), 7.12 (d, J = 8.5 Hz, 1H), 7.25-7.36 (m, 5H, Ar), 7.46-7.50 (m, 1H, Ar), 7.62 (d, J = 9.0 Hz, 1H), 7.85 (d, J = 8.5 Hz, 1H), 7.90-7.96 (m, 2H, Ar), 8.02 (d, J = 9.0 Hz, 1H); ¹³C NMR (CDCl₃): δ 16.0 (d, $^3J_{C-P}$ = 7.2 Hz, OCH₂CH₃), 25.5, 25.6, 25.8, 26.0, 26.2, 44.2 (d, $^1J_{C-P}$ = 110.4 Hz, CHCH₂CH₂), 62.7 (d, $^2J_{C-P}$ = 7.2 Hz, OCH₂CH₃), 114.9, 118.1, 122.1, 123.7, 125.3, 125.7, 126.0, 126.9, 127.6, 128.0, 128.4, 129.2, 130.3, 130.5, 131.5, 133.7, 133.8, 148.4, 148.5, 151.6; ³¹P NMR (CDCl₃): δ 102.1 (s, major), 109.7 (s, minor); HRMS Calcd for C₂₈H₂₉O₃PS: 476.1575, Found: 476.1564.

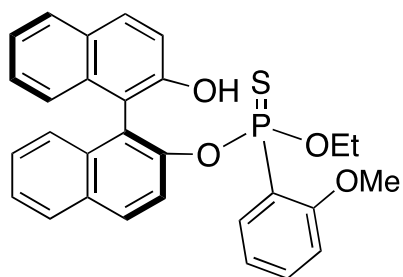
(S_{ax})-Ethyl(2'-hydroxy-[1,1'-binaphthalen]-2-yl) (*p*-tolyl)phosphonothioate (2ca)



Chemical Formula: C₂₉H₂₅O₃PS
Exact Mass: 484.1262
Molecular Weight: 484.5498

According to GP1, **2ca** (211 mg, 88%, 94:6 dr) was obtained as a colorless solid. ¹H NMR (CDCl₃): δ 1.12 (t, *J* = 7.2 Hz, 3H, OCH₂CH₃), 2.32 (s, 3H, CH₃), 3.80 (ddq, *J* = 14.3 Hz, 7.2 Hz, 2.3 Hz, 1H, OCH₂CH₃), 3.93 (ddq, *J* = 14.3 Hz, 7.2 Hz, 2.3 Hz, 1H, OCH₂CH₃), 5.16 (br, 1H, OH), 6.91 (d, *J* = 7.5 Hz, 1H), 6.92 (d, *J* = 7.5 Hz, 1H), 7.12 (d, *J* = 9.2 Hz, 1H), 7.14 (d, *J* = 8.0 Hz, 1H), 7.19 (d, *J* = 8.0 Hz, 1H), 7.22 (d, *J* = 8.0 Hz, 1H), 7.24-7.35 (m, 4H, Ar), 7.47 (t, *J* = 7.5 Hz, 1H, Ar), 7.56-7.58 (m, 1H, Ar), 7.71 (d, *J* = 9.2 Hz, 1H), 7.75 (d, *J* = 8.0 Hz, 1H), 7.95 (d, *J* = 8.0 Hz, 1H), 8.02 (d, *J* = 9.2 Hz, 1H); ¹³C NMR (CDCl₃): δ 16.0 (d, ³*J*_{C-P} = 8.4 Hz, OCH₂CH₃), 21.7 (CH₃), 63.1 (d, ²*J*_{C-P} = 7.2 Hz, OCH₂CH₃), 114.9, 118.4, 122.1, 123.6, 125.1, 125.9, 126.1, 126.7, 127.6, 127.9, 128.4, 128.7, 128.8, 129.2, 130.4, 130.5, 130.6, 131.7, 133.6, 133.8, 142.7, 148.7, 148.7, 151.7; ³¹P NMR (CDCl₃): δ 86.5 (s, major), 87.2 (s, minor); HRMS Calcd for C₂₉H₂₅O₃PS: 484.1262, Found: 484.1273.

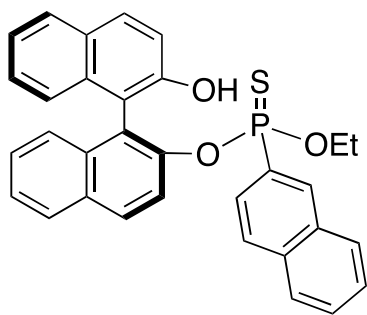
(S_{ax})-Ethyl(2'-hydroxy-[1,1'-binaphthalen]-2-yl) (2-methoxyphenyl)phosphonothioate (2da)



Chemical Formula: C₂₉H₂₅O₄PS
Exact Mass: 500.1211
Molecular Weight: 500.5488

According to GP1, **2da** (226 mg, 90%, 14:84 dr) was obtained as a colorless solid. ¹H NMR (CDCl₃): δ 1.27 (t, *J* = 7.3 Hz, 3H, OCH₂CH₃), 3.34 (s, 3H, OCH₃), 4.07 (q, *J* = 7.3 Hz, 1H, OCH₂CH₃), 4.09 (dq, *J* = 7.3 Hz, 1H, OCH₂CH₃), 5.34 (br, 1H, OH), 6.94-6.53 (m, 1H, Ar), 6.95-6.70 (m, 1H, Ar), 6.95-6.98 (m, 1H, Ar), 7.13 (d, *J* = 8.2 Hz, 1H), 7.22-7.33 (m, 6H, Ar), 7.45-7.49 (m, 1H, Ar), 7.56-7.60 (m, 2H, Ar), 7.75 (d, *J* = 8.2 Hz, 1H), 7.94-8.06 (m, 2H, Ar); ¹³C NMR (CDCl₃): δ 16.1 (d, ³*J*_{C-P} = 7.2 Hz, OCH₂CH₃), 55.3 (OCH₃), 63.5 (d, ²*J*_{C-P} = 6.0 Hz, OCH₂CH₃), 110.9, 115.3, 118.7, 120.0, 120.1, 122.9, 123.4, 125.1, 125.8, 126.0, 126.5, 127.4, 127.8, 128.3, 129.0, 130.2, 130.3, 131.7, 133.6, 133.8, 134.2, 134.8, 148.65, 148.73, 151.8, 160.0; ³¹P NMR (CDCl₃): δ 84.9 (s, minor), 86.4 (s, major); HRMS Calcd for C₂₉H₂₅O₄PS: 500.1211, Found: 500.1220.

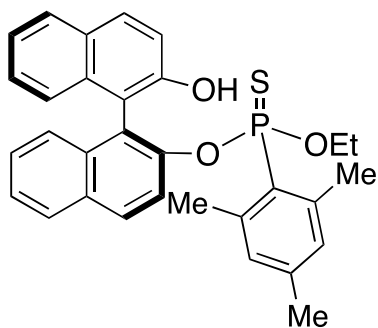
(S_{ax})-Ethyl(2'-hydroxy-[1,1'-binaphthalen]-2-yl) (naphthalene-2-yl)phosphonothioate (2ea)



Chemical Formula: C₃₂H₂₅O₃PS
Exact Mass: 520.1262
Molecular Weight: 520.5828

According to GP1, **2ea** (216 mg, 84%, >95:5 dr) was obtained as a colorless solid. ¹H NMR (CDCl₃): δ 1.12 (t, *J* = 7.2 Hz, 3H, OCH₂CH₃), 3.83-3.99 (m, 2H, OCH₂CH₃), 5.12 (br, 1H, OH), 6.83-6.84 (m, 1H, Ar), 7.07-7.08 (m, 1H, Ar), 7.15-7.24 (m, 6H, Ar), 7.36-7.53 (m, 7H, Ar), 7.67 (d, *J* = 8.6 Hz, 1H), 7.74-7.77 (m, 1H, Ar), 7.85-7.86 (m, 1H, Ar), 7.95 (d, *J* = 8.6 Hz, 1H); ¹³C NMR (CDCl₃): δ 16.1 (d, ³*J*_{C-P} = 8.4 Hz, OCH₂CH₃), 63.2 (d, ²*J*_{C-P} = 7.2 Hz, OCH₂CH₃), 114.8, 118.3, 122.3, 122.7, 123.5, 124.8, 124.9, 125.9, 126.1, 126.6, 127.7, 127.8, 128.0, 128.3, 128.4, 128.8, 129.0, 129.4, 130.1, 130.4, 130.7, 131.8, 132.0, 132.1, 133.4, 133.7, 134.8, 148.7, 148.8, 151.7; ³¹P NMR (CDCl₃): δ 86.3 (s); HRMS Calcd for C₃₂H₂₅O₃PS: 520.1262, Found: 520.1270.

(S_{ax})-Ethyl(2'-hydroxy-[1,1'-binaphthalen]-2-yl) mesitylphosphonothioate (2fa)



Chemical Formula: C₃₁H₂₉O₃PS
Exact Mass: 512.1575
Molecular Weight: 512.6038

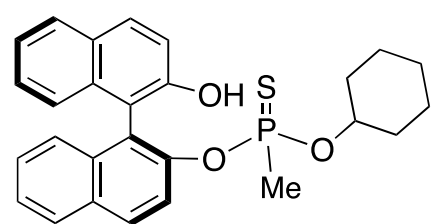
According to GP1, **2fa** (187 mg, 73%, >95:5 dr) was obtained as a colorless solid. ¹H NMR (CDCl₃): δ 1.08 (t, *J* = 7.1 Hz, 3H, OCH₂CH₃), 2.21 (s, 3H, CH₃), 2.28 (s, 6H, CH₃), 3.78 (ddq, *J* = 22.0 Hz, 7.1 Hz, 1.8 Hz, 1H, OCH₂CH₃), 3.96 (ddq, *J* = 22.0 Hz, 7.1 Hz, 1.8 Hz, 1H, OCH₂CH₃), 5.25 (br, 1H, OH), 6.58 (s, 1H), 6.60 (s, 1H), 7.06 (d, *J* = 7.8 Hz, 1H), 7.11 (d, *J* = 8.7 Hz, 1H), 7.19 (t, *J* = 8.2 Hz, 1H), 7.24 (d, *J* = 8.2 Hz, 1H), 7.25 (t, *J* = 8.2 Hz, 1H), 7.31 (t, *J* = 8.2 Hz, 1H), 7.46 (t, *J* = 8.2 Hz, 1H), 7.58 (d, *J* = 9.2 Hz, 1H), 7.64 (d, *J* = 8.7 Hz, 1H), 7.68 (d, *J* = 7.8 Hz, 1H), 7.94 (d, *J* = 8.2 Hz, 1H), 8.01 (d, *J* = 9.2 Hz, 1H); ¹³C NMR (CDCl₃): δ 15.7 (d, ³*J*_{C-P} = 9.6 Hz, OCH₂CH₃), 21.1 (CH₃), 23.6 (CH₃), 62.1 (d, ³*J*_{C-P} = 6.7 Hz, OCH₂CH₃), 115.1, 118.3, 122.7, 123.4, 125.1, 125.9, 126.1, 126.4, 127.5, 127.6, 127.8, 128.3, 129.2, 130.2, 130.3, 130.9, 131.0, 131.5, 133.7, 133.9, 141.2, 141.6, 141.7, 148.6, 148.7, 151.7; ³¹P NMR (CDCl₃): δ 84.3 (s); HRMS Calcd for C₃₁H₂₉O₃PS: 512.1575, Found: 512.1589.

General procedure 2 for the preparation of phosphonothioates 2 (GP2)

To a 20 mL Schlenk tube were added phosphonothioates **1** (0.50 mmol) and THF (1.0 mL). The reaction mixture was cooled to 0 °C. Then, lithium alkoxide **4** (1.0 M THF

solution) was added to the cooled solution. After that, the mixture was added 1N HCl (3.0 mL), and it was extracted with Et₂O (5 mL × 3). The combined organic layer was dried over MgSO₄, filtered, and concentrated. Purification by column chromatography on silica gel (EtOAc:hexane = 1:10) provided **2**.

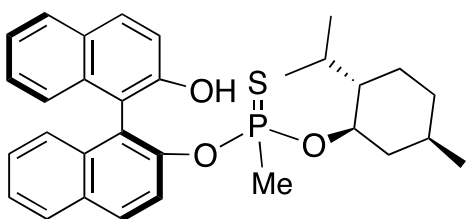
(*S*_{ax})-*O*-Cyclohexyl-*O*-(2'-hydroxy-[1,1'-binaphthalen]-2-yl) methylphosphonothioate (2ab**)**



Chemical Formula: C₂₇H₂₇O₃PS
Exact Mass: 462.1419
Molecular Weight: 462.5438

According to GP2, **2ab** (188 mg, 82%, 86:14 dr) was obtained as a colorless solid. ¹H NMR (CDCl₃): δ 0.86-1.39 (m, 9H, Cy), 1.56-1.59 (m, 1H, Cy), 1.76 (d, *J* = 15.1 Hz, 3H, CH₃), 3.89-3.98 (m, 1H, Cy), 5.45 (br, 1H, OH), 7.09-7.11 (m, 1H, Ar), 7.24-7.40 (m, 5H, Ar), 7.46-7.51 (m, 2H, Ar), 7.84 (d, *J* = 7.8 Hz, 1H), 7.92 (d, *J* = 8.7 Hz, 1H), 7.94 (d, *J* = 7.8 Hz, 1H), 8.03 (d, *J* = 8.7 Hz, 1H); ¹³C NMR (CDCl₃): δ 23.3, 23.5, 24.5, 25.1 33.1 (d, ¹*J*_{C-P} = 63.3 Hz, CH₃), 115.3, 118.7, 121.1, 122.8, 123.5, 124.9, 125.9, 126.1, 126.9, 127.6, 128.1, 128.4, 129.2, 130.5, 130.8, 131.7, 133.7, 148.36, 148.44, 151.7; ³¹P NMR (CDCl₃): δ 93.6 (s, major), 95.6 (s, minor); HRMS Calcd for C₂₇H₂₇O₃PS: 462.1419, Found: 462.1396.

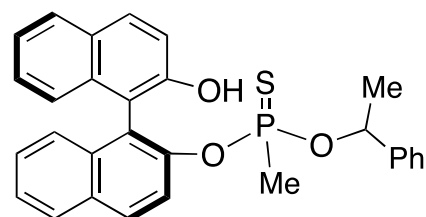
(*S*_{ax})-*O*-(2'-hydroxy-[1,1'-binaphthalen]-2-yl)-*O*-((1*R*,2*S*,5*R*)-2-isopropyl-5-methyl-cyclohexyl) methylphosphonothioate (2ac**)**



Chemical Formula: C₃₁H₃₅O₃PS
Exact Mass: 518.2045
Molecular Weight: 518.6518

According to GP2, **2ac** (108 mg, 69%, >95:5 dr) was obtained as a colorless solid. ¹H NMR (CDCl₃): δ 0.43 (d, *J* = 6.7 Hz, 3H, CH(CH₃)₂), 0.67 (d, *J* = 6.7 Hz, 3H, CH(CH₃)₂), 0.74-0.80 (m, 2H), 0.87 (d, *J* = 6.3 Hz, 3H), 0.92-1.01 (m, 1H), 1.15-1.21(m, 1H), 1.39 (d, *J* = 15.3 Hz, 3H, CH₃), 1.49-1.65 (m, 4H), 2.18-2.21 (m, 1H), 3.99 (dq, *J* = 10.3 Hz, 4.5 Hz, 1H, OCHCH₂), 5.35 (br, 1H, OH), 7.04-7.06 (m, 1H, Ar), 7.21-7.26 (m, 2H, Ar), 7.29-7.32 (m, 2H, Ar), 7.35 (d, *J* = 9.0 Hz, 1H), 7.46-7.49 (m, 1H, Ar), 7.68 (d, *J* = 9.0 Hz, 1H), 7.83 (d, *J* = 8.1 Hz, 1H), 7.91 (d, *J* = 9.0 Hz, 1H), 7.95 (d, *J* = 8.1 Hz, 1H), 8.03 (d, *J* = 9.0 Hz, 1H); ¹³C NMR (CDCl₃): δ 15.8, 21.0, 22.1, 23.0, 24.2 (d, ¹*J*_{C-P} = 114.0 Hz, CH₃), 25.5, 31.5, 34.1, 42.6, 48.5, 80.0, 114.7, 118.4, 121.8, 122.2, 123.8, 125.2, 126.0, 127.0, 127.5, 128.1, 128.4, 129.2, 130.5, 130.6, 131.7, 133.9, 134.0, 148.37, 148.44, 151.7; ³¹P NMR (CDCl₃): δ 91.5 (s); HRMS Calcd for C₃₁H₃₅O₃PS: 518.2045, Found: 518.2039.

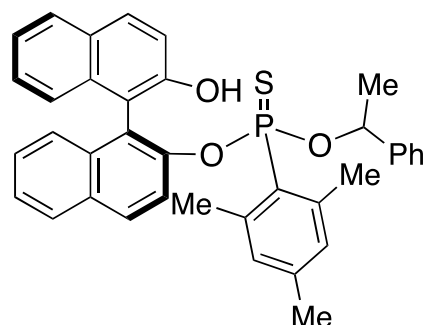
(*S*_{ax})-*O*-(2'-hydroxy-[1,1'-binaphthalen]-2-yl)-*O*-(1-phenylethyl) methylphosphono thioate (2ad)



Chemical Formula: C₂₉H₂₅O₃PS
Exact Mass: 484.1262
Molecular Weight: 484.5498

According to GP2, **2ad** (142 mg, 59%, 29:30:29:12 dr) was obtained as a colorless solid. ¹H NMR (CDCl₃): δ 0.88 (t, *J* = 6.4 Hz, 0.9 H, OCHCH₃), 1.12 (d, *J* = 15.6 Hz, 0.3H, PCH₃), 1.15 (d, *J* = 15.6 Hz, 0.9H, PCH₃), 1.45 (d, *J* = 15.1 Hz, 0.9H, PCH₃), 1.49 (d, *J* = 6.4 Hz, 0.9H, OCHCH₃), 1.53 (d, *J* = 6.4 Hz, 0.3H, OCHCH₃), 1.55 (d, *J* = 6.4 Hz, 0.9H, OCHCH₃), 1.64 (d, *J* = 15.6 Hz, 0.9H, PCH₃), 5.06 (dq, *J* = 13.1 Hz, 6.4 Hz, 0.3H, OCHCH₃), 5.15 (dq, *J* = 13.1 Hz, 6.4 Hz, 0.3H, OCHCH₃), 5.24-5.43 (br, 1H, OH), 5.55 (dq, *J* = 13.1 Hz, 6.4 Hz, 0.1H, OCHCH₃), 5.73 (dq, *J* = 13.1 Hz, 6.4 Hz, 0.3H, OCHCH₃), 6.48-6.51 (m, 0.3H, Ar), 6.93-7.09 (m, 1.5 H, Ar), 7.16-7.56 (m, 10.4H, Ar), 7.73-8.06 (m, 5.1H, Ar); ¹³C NMR (CDCl₃): δ 20.0, 20.2, 20.3, 21.0, 21.2, 22.6, 22.9, 23.2, 13.8, 24.0, 24.1, 24.3, 24.4, 24.6, 24.8, 24.9, 25.2, 25.7, 45.5, 46.0, 68.1, 75.8, 76.3, 76.5, 113.9, 114.7, 115.1, 115.2, 115.3, 116.0, 116.5, 117.9, 118.3, 118.5, 118.7, 118.8, 118.9, 119.6, 119.9, 120.6, 120.9, 121.1, 121.3, 121.5, 122.2, 123.6, 123.7, 123.8, 124.1, 124.4, 124.8, 125.0, 125.3, 125.5, 125.8, 125.9, 126.0, 126.1, 126.2, 126.3, 126.4, 126.6, 126.8, 126.9, 127.2, 127.5, 127.6, 127.7, 127.9, 128.0, 128.1, 128.2, 128.3, 128.4, 128.5, 128.6, 128.7, 128.8, 129.0, 129.1, 129.2, 129.3, 129.5, 129.9, 130.3, 130.4, 130.5, 130.6, 130.7, 130.8, 131.9, 131.4, 131.6, 131.7, 131.9, 133.4, 133.6, 133.7, 133.8, 143.0, 143.5, 147.0, 147.7, 148.3, 148.6, 151.8, 152.3, 152.9; ³¹P NMR (CDCl₃): δ 93.7 (s), 94.9 (s), 95.4 (s), 96.4 (s); HRMS Calcd for C₂₉H₂₅O₃PS: 484.1262, Found: 484.1264.

(*S*_{ax})-*O*-(2'-hydroxy-[1,1'-binaphthalen]-2-yl)-*O*-(1-phenylethyl) mesityllphosphon othioate (2fd)

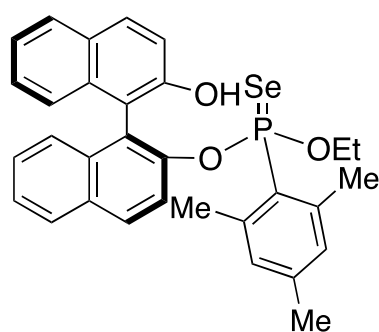


Chemical Formula: C₃₇H₃₃O₃PS
Exact Mass: 588.1888
Molecular Weight: 588.7018

According to GP2, **2fd** (52 mg, 22%, >95:5 dr, The first fraction on TLC), (47 mg, 20%, 5:>95 dr, The second fraction on TLC) was obtained as a colorless solid. (>95:d dr) ¹H NMR (CDCl₃): δ 1.38 (d, *J* = 6.8 Hz, 3H, OCHCH₃), 2.08 (s, 3H, CH₃), 2.20 (s, 6H, CH₃), 5.23 (br, 1H, OH), 5.66 (dq, *J* = 12.3 Hz, 6.8 Hz, 1H, OCHCH₃), 6.33 (s, 1H), 6.34 (s, 1H), 6.60-6.63 (m, 1H, Ar), 6.85 (d, *J* = 8.7 Hz, 1H), 6.86 (d, *J* = 8.7 Hz, 1H), 6.98-7.31 (m, 10H, Ar), 7.34 (d, *J* = 9.2 Hz, 1H), 7.45 (d, *J* = 8.2 Hz,

1H), 7.79 (d, $J = 9.2$ Hz, 1H), 7.74 (d, $J = 8.2$ Hz, 1H); ^{13}C NMR (CDCl_3): δ 21.0 ($\underline{\text{CH}_3}$), 24.19 ($\underline{\text{CH}_3}$), 24.22 ($\underline{\text{CH}_3}$), 24.8 (d, $^3J_{\text{C-P}} = 5.6$ Hz, $\text{OCH}\underline{\text{CH}_3}$), 76.1 ($^2J_{\text{C-P}} = 7.5$ Hz, OCHCH_3), 115.2, 118.4, 122.8, 123.1, 123.3, 125.0, 125.8, 126.2, 126.6, 127.3, 127.7, 128.2, 128.7, 129.1, 130.0, 130.2, 130.8, 131.0, 131.5, 133.5, 133.6, 140.7, 140.8, 141.6, 141.7, 142.0, 142.1, 149.3, 149.4, 151.6; ^{31}P NMR (CDCl_3): δ 81.7 (s); HRMS Calcd for $\text{C}_{37}\text{H}_{33}\text{O}_3\text{PS}$: 588.1888, Found: 588.1891. (5:>95 dr): ^1H NMR (CDCl_3): δ 1.22 (t, $J = 6.4$ Hz, 3H, OCHCH_3), 2.23 (s, 3H, $\underline{\text{CH}_3}$), 2.40 (s, 6H, $\underline{\text{CH}_3}$), 5.20-5.28 (m, 2H), 6.63 (s, 1H), 6.65 (s, 1H), 7.03-7.06 (m, 2H, Ar), 7.13-7.36 (m, 9H, Ar), 7.39-7.48 (m, 2H, Ar), 7.69 (d, $J = 9.2$ Hz, 1H), 7.73 (d, $J = 8.2$ Hz, 1H), 7.92 (d, $J = 8.2$ Hz, 1H), 7.96 (d, $J = 9.2$ Hz, 1H); ^{13}C NMR (CDCl_3): δ 21.1 ($\underline{\text{CH}_3}$), 23.7 (d, $^3J_{\text{C-P}} = 4.8$ Hz, $\text{OCH}\underline{\text{CH}_3}$), 24.17 ($\underline{\text{CH}_3}$), 24.20 ($\underline{\text{CH}_3}$), 75.1 ($^2J_{\text{C-P}} = 7.3$ Hz, OCHCH_3), 114.9 118.1, 122.1, 122.5, 125.5, 125.7, 125.9, 126.2, 126.6, 127.4, 127.8, 127.9, 128.2, 128.3, 129.3, 130.21, 130.24, 131.1, 131.2, 131.4, 133.7, 133.9, 141.3, 141.76, 141.80, 142.1, 142.2, 149.0, 149.1, 151.7; ^{31}P NMR (CDCl_3): δ 83.3 (s); HRMS Calcd for $\text{C}_{37}\text{H}_{33}\text{O}_3\text{PS}$: 588.1888, Found: 588.1862.

(S_{ax})-Ethyl(2'-hydroxy-[1,1'-binaphthalen]-2-yl) mesitylphosphonoselenoate (6fa)

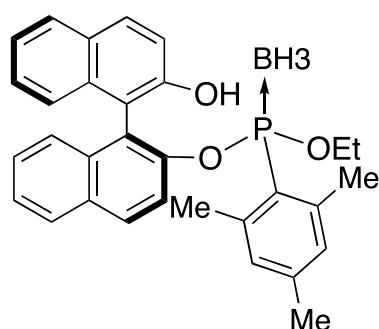


Chemical Formula: $\text{C}_{31}\text{H}_{29}\text{O}_3\text{PSe}$
 Exact Mass: 560.1020
 Molecular Weight: 559.5038

To a 20 mL Schlenk tube were added phosphonoselenoate **5f** (1.29 g, 2.5 mmol) and ethanol (5.0 mL) under Ar atmosphere. Then, lithium ethoxide **4a** (1.0 M ethanol solution, 6.3 mL, 6.3 mmol) was added to the solution, and it was stirred for 10 min at 80 °C. After that, the mixture was added 1N HCl (6.0 mL) and it was extracted with Et_2O (7 mL \times 3). The combined organic layer was dried over MgSO_4 , filtered, and concentrated. Purification by column chromatography on silica gel (EtOAc :hexane = 1:10, R_f = 0.28) gave **6fa** (1.14 g, 82%, dr = >95 : 5) as a colorless solid. ^1H NMR (CDCl_3): δ 1.10 (t, $J = 7.3$ Hz, 3H, $\text{OCH}_2\underline{\text{CH}_3}$), 2.21 (s, 3H, $\underline{\text{CH}_3}$), 2.27 (s, 6H, $\underline{\text{CH}_3}$), 3.76-3.86 (m, 1H), 3.90-4.06 (m, 1H), 5.29 (br, 1H, OH), 6.60 (s, 1H), 6.62 (s, 1H), 7.05 (d, $J = 8.2$ Hz, 1H), 7.17 (d, $J = 9.2$ Hz, 1H), 7.21-7.34 (m, 4H, Ar), 7.46-7.50 (m, 1H, Ar), 7.69-7.72 (m, 3H, Ar), 7.95 (d, $J = 8.2$ Hz, 1H), 8.02 (d, $J = 9.2$ Hz, 1H); ^{13}C NMR (CDCl_3): δ 15.5 (d, $^3J_{\text{C-P}} = 4.8$ Hz, $\text{OCH}_2\underline{\text{CH}_3}$), 21.0 ($\underline{\text{CH}_3}$), 23.3 ($\underline{\text{CH}_3}$), 23.4 ($\underline{\text{CH}_3}$), 63.8 (d, $^2J_{\text{C-P}} = 7.2$ Hz, $\text{OCH}_2\underline{\text{CH}_3}$), 115.1, 118.3, 122.4, 122.8, 123.4, 125.1, 126.0, 126.4, 127.5, 127.9, 128.3, 128.8, 129.2, 130.2, 130.3, 130.9, 131.0, 131.5,

133.7, 134.0, 140.9, 141.0, 141.2, 148.7, 148.8, 151.7; ^{31}P NMR (CDCl_3): δ 87.4 (d, $J_{\text{P-Se}} = 867.6$ Hz); ^{77}Se NMR (CDCl_3): δ -141.6 (d, $J_{\text{P-Se}} = 865.6$ Hz); HRMS Calcd for $\text{C}_{31}\text{H}_{29}\text{O}_3\text{PSe}$: 560.1020, Found: 560.1040.

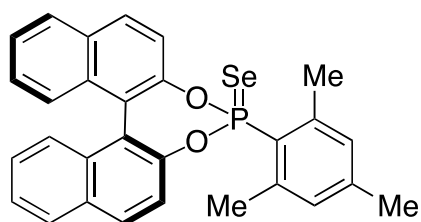
(*S*_{ax})-Ethyl(2'-hydroxy-[1,1'-binaphthalen]-2-yl) mesitylphosphoniteboron (9fa)



Chemical Formula: $\text{C}_{31}\text{H}_{32}\text{BO}_3\text{P}$
Exact Mass: 494.2182
Molecular Weight: 494.3778

To a 20 mL Schlenk tube were added **6fa** (58 mg, 0.1 mmol), tributylphosphine (25 μL , 0.1 mmol) and THF (0.2 mL) under Ar atmosphere, and it was stirred for 30 min at rt. Then, $\text{BH}_3 \cdot \text{THF}$ complex (0.93 M THF solution, 0.11 mL, 0.11 mmol) was added to the solution, and it was stirred for 30 min at rt. After that, the mixture was concentrated *in vacuo*. Purification by column chromatography on silica gel (EtOAc : hexane = 1 : 20) gave **9fa** (41 mg, 79%, dr = >95 : 5) as a colorless solid. ^1H NMR (CDCl_3): δ 0.25-0.81 (br, 3H, BH_3), 0.86 (d, $J = 7.3$ Hz, 3H, OCH_2CH_3), 2.14 (s, 3H, CH_3), 2.21 (s, 6H, CH_3), 3.47 (ddq, $J = 10.0$ Hz, 7.3 Hz, 7.1 Hz, 1H, OCH_2CH_3), 3.67 (ddq, $J = 10.0$ Hz, 7.3 Hz, 7.1 Hz, 1H, OCH_2CH_3), 4.83 (br, 1H, OH), 6.55 (s, 1H), 6.56 (s, 1H), 7.02 (d, $J = 8.7$ Hz, 1H), 7.05 (d, $J = 9.2$ Hz, 1H), 7.11-7.25 (m, 4H, Ar), 7.34-7.40 (m, 2H, Ar), 7.58 (d, $J = 9.2$ Hz, 1H), 7.60 (d, $J = 8.2$ Hz, 1H), 7.83 (d, $J = 8.2$ Hz, 1H), 7.88 (d, $J = 8.7$ Hz, 1H); ^{13}C NMR (CDCl_3): δ 16.0 (d, $^3J_{\text{C-P}} = 7.2$ Hz, OCH_2CH_3), 21.2 (CH_3), 22.92 (CH_3), 22.94 (CH_3), 62.9 (d, $^2J_{\text{C-P}} = 6.0$ Hz, OCH_2CH_3), 114.2, 117.6, 121.0, 122.0, 123.5, 125.3, 125.8, 125.9, 126.6, 127.6, 127.9, 128.4, 129.1, 130.3, 130.5, 130.7, 130.8, 131.4, 133.6, 133.7, 142.0, 142.5, 142.6, 149.36, 149.39, 151.5 ; ^{31}P NMR (CDCl_3): δ 140.4-141.7 (br); HRMS Calcd for $\text{C}_{31}\text{H}_{32}\text{BO}_3\text{P}$: 494.2182, Found: 494.2167.

(*S*_{ax})-4-Mesitylbinaphtho[2,1-d:1',2'-f][1,3,2]dioxaphosphepine-4-selenide (5f)



Chemical Formula: $\text{C}_{29}\text{H}_{23}\text{O}_2\text{PSe}$
Exact Mass: 514.0601
Molecular Weight: 513.4348

To a 300 mL three-necked flask were added (*S*_{ax})-4-chlorobinaphtho[2,1-*d*:1',2'-*f*][1,3,2]dioxaphosphepines (1.0 M toluene solution, 7.0 mL, 7.0 mmol) under Ar atmosphere. The solution was heated to 40 °C. Mesitylmagnesium bromide (1.0 M Et_2O solution, 7.0 mL, 7.0 mmol) was added dropwise for 10 min to the heated solution, and it was stirred at 30 min. Then selenium powder (0.60 g, 7.7 mmol) was added to the solution. After that,

the reaction mixture was added sat. NH_4Cl aqueous and it was extracted with Et_2O ($15\text{ mL} \times 3$). The combined organic layer was dried over MgSO_4 , filtrate, and concentrated. Purification by column chromatography on silica gel ($\text{EtOAc}:\text{hexane} = 1:10$) gave **5f** (2.08 g, 58%) as a colorless solid. ^1H NMR (CDCl_3): δ 2.17 (s, 3H, CH_3), 2.70 (s, 6H, CH_3), 6.80 (s, 1H), 6.81 (s, 1H), 7.10-7.41 (m, 7H, Ar), 7.63 (d, $J = 8.7$ Hz, 1H), 7.67 (d, $J = 8.7$ Hz, 1H), 7.72-7.74 (m, 1H, Ar), 7.88-8.00 (m, 2H, Ar); ^{13}C NMR (CDCl_3): δ 21.2 (CH_3), 23.7 (CH_3), 23.8 (CH_3), 117.9, 119.7, 122.8, 123.4, 124.2, 124.3, 125.8, 126.6, 127.2, 127.4, 128.4, 128.7, 130.5, 130.7, 131.1, 131.2, 131.5, 132.1, 132.4, 132.8, 140.9, 142.1, 145.6, 145.7, 149.1, 149.2; ^{31}P NMR (CDCl_3): δ 108.5 (d, $J_{\text{P-Se}} = 906.8$ Hz); ^{77}Se NMR (CDCl_3): δ -109.9 (d, $J_{\text{P-Se}} = 907.4$ Hz); HRMS Calcd for $\text{C}_{29}\text{H}_{23}\text{O}_2\text{PSe}$: 514.0601, Found: 514.0604.

Preparation of lithium ethoxide **4a**

To a 10 mL Schlenk tube were added ethanol (0.5 mL) and *n*-BuLi (1.6 M hexane solution, 0.78 mL, 1.3 mmol) at 0 °C for 15 min under Ar atmosphere. The solution was concentrated *in vacuo*. for 1 h. After that, it was refilled with Ar and was added ethanol 1.3 mL to give lithium ethoxide **4a** (1.0 M ethanol solution).

Preparation of lithium alkoxide **4b-d**

To a 10 mL Schlenk tube were added alcohol **4b-d** (2.0 mmol), THF (2.0 mL) and *n*-BuLi (1.6 M hexane solution, 1.3 mL, 2.0 mmol) at 0 °C for 15 min under Ar atmosphere. The solution was concentrated *in vacuo*. for 1 h. After that, it was refilled with Ar and was added THF 2.0 mL to give lithium alkoxide **4b-d** (1.0 M THF solution).

Reference and Notes

(1) **2ca**: $\text{C}_{29}\text{H}_{25}\text{O}_3\text{PS}$, $M_r = 484.52$, orthorhombic, $P2_12_12_1$, $a = 9.2517(7)$ Å, $b = 13.8653(11)$ Å, $c = 19.1250(18)$ Å, $V = 2453.3(4)$ Å³, $T = 296$ K, $Z = 4$, $\rho_{\text{calcd}} = 1.312$ g cm⁻³, 5566 unique reflections out of 21980 with $I > 2\sigma(I)$, 310 parameters, $R_1 = 0.0995$, $wR_2 = 0.1821$, GOF = 0.990. Crystallographic data have been deposited with the Cambridge Crystallographic Data Center: deposition number CCDC-1867411.

(2) To confirm the stereochemistry of reduction of phosphonoselenoate **6fa** with tributylphosphine, phosphonite **7fa** was treated with elemental selenium to give **6fa**

with >95:5 dr. This indicates that the reduction of **6fa** to **7fa** proceeded with retention of configuration at the phosphorus atom.

(3) K. Kuwabara, Y. Maekawa, M. Minoura, T. Murai, *Org. Lett.* **2018**, *20*, 1375.

Chapter 4

Sequential Alcoholysis of Phosphonothioates with a Binaphthyl Group

P-Stereogenic phosphonothioates have attracted much attention due to their potent biological activities as analogs of phosphoric acids and phosphorothioates. The author demonstrate here straightforward access to *P*-stereogenic phosphonothioates through the use of binaphthyl phosphonothioates as a chiral template. The 1st-step alcoholysis of binaphthyl phosphonothioates proceeded via a transfer of the axial chirality of a binaphthyl group to the central chirality of a phosphorus atom to give only mono-alcohol adducts with moderate to excellent diastereoselectivities. Further alcoholysis of the obtained products in the presence of a small excess of alcohol and base proceeded with complete elimination of a binaphthyl group to give the corresponding *P*-stereogenic phosphonothioates with high enantiomeric excess. A DFT study of the reaction mechanisms in 1st-step alcoholysis indicated that the coordination of a sulfur atom to a sodium cation is the key factor to control the diastereoselectivities. This method can be applied to prepare both stereoisomers of a G6P analog with high diastereomeric purity.

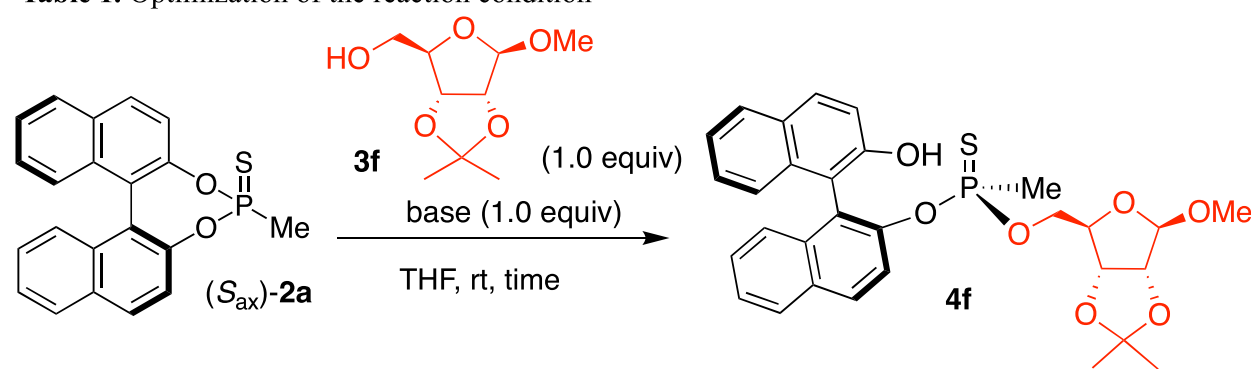
4.1. Introduction

As described in Chapter 3, the alcoholysis of phosphonothioates having a binaphthyl group provide useful access to the *P*-stereogenic phosphonothioates. However, as mentioned in Chapter 1, the target *P*-stereogenic phosphonothioates contain not only simple alcohols such as methanol and ethanol, but also functionalized alcohols such as nucleotides. In this chapter, the author describes 1st step alcoholysis with functionalized alcohols and the following alcoholysis of the resulting products to achieve *P*-stereogenic phosphonothioates having a range of different types of alkoxy groups.

4.2. 1stStep Alcoholysis

Binaphthyl methylphosphonothioate **2a** and ribose derivative (**3f**) were selected as model substrates for the optimization of 1st-step alcoholysis (Table 1). Alcoholysis was facilitated by using NaHMDS as a base in THF solvent to give the desired product **4f** in 67% isolated yield with >95:5 dr (entry 1). The addition of 1.0 equivalent of 18-crown-6 increased the product yield with lower diastereoselectivity (entry 2). The use of LiHMDS instead of NaHMDS decreased the yield and diastereoselectivity (entry 3). DBU also promoted the alcoholysis of **2a** to give **4f** in comparable yield as the reaction with NaHMDS, but the diastereoselectivity was reduced (entry 5). *tert*-Butylmagnesium chloride, which is used as a phosphorylating reagent for nucleosides in some cases,¹ did not give **4f**, and only the starting material **2a** was recovered (entry 6).

Table 1. Optimization of the reaction condition



entry	base	additive	time (h)	yield (%) ^a	dr ^b
1	NaHMDS	-	1	89 (67)	>95:5
2	NaHMDS	18-crown-6	1	100	82:18
3	LiHMDS	-	1	41	79:21
4	DBU	-	1.5	86 (62)	75:25
5	<i>t</i> BuMgCl	-	1.5	n.r.	-

^a The yields were calculated by ³¹P NMR analysis of the crude reaction mixtures.

Isolated yields are shown in the parentheses. ^b Ratio of diastereomers was determined by

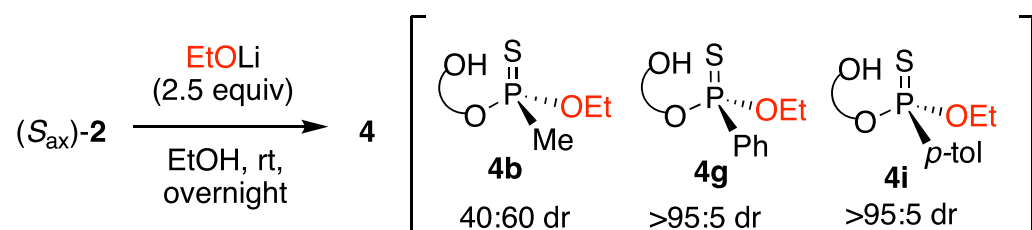
³¹P NMR analysis of the crude reaction mixtures.

The substrate scope of this alcoholysis was examined with the reaction conditions for entry 1 in Table 1 as the optimal conditions (Table 2). In all cases, further alcoholysis of product **4** did not occur under the optimized conditions. The reaction of **2a** with simple alcohols such as methanol (**3a**), ethanol (**3b**) or cyclohexanol (**3c**) proceeded smoothly to give the corresponding products **4a-4c** in moderate to high yields with high diastereoselectivities (entries 1-3). Galactopyranose derivative (**3d**) gave the adducts **4d** in high yield with excellent diastereoselectivity (entry 4). Nucleoside **3e** was tolerated in the presence of a strong base to give the desired product **4e** in 56% yield with >95:5 dr. The carbon substituents in phosphonothioate **2** affected the diastereoselectivities of the products **4**. Lower diastereoselectivity was observed in the ethanolysis of phosphonothioate **2b** having a phenyl group attached to the phosphorus atom, while phosphonothioate **2c** having a mesityl group was converted to **4h** as a single diastereomer (entries 6 and 7). The relationship between the carbon substituents and diastereoselectivities is in sharp contrast to the results as shown in Chapter 3 (Scheme 1). Higher diastereoselectivity was observed in the ethanolysis of phosphothioate **2** having an aromatic group attached to the phosphorus atom with the use of ethanol as a solvent instead of THF. Furthermore, the absolute configuration at the phosphorus atom of the obtained products was different depending on the solvent.

Table 2. Substrate scope

entry	S.M. 2	alcohol 3	product 4	yield (%) ^a	dr ^b
1				63	>95:5
2				85	>95:5
3				66	>95:5
4				84	>95:5
5 ^{c,d}				56	>95:5
6 ^e				76	24:76
7 ^e				70	>95:5

^a Isolated yields are shown. ^b Ratio of diastereomers was determined by ³¹P NMR analysis of the crude reaction mixtures. ^c The reaction was carried out with 1.5 equiv of alcohol **3e** and 3.0 equiv of NaHMDS. ^d T: Thymine. ^e The reaction was carried out with 1.2 equiv of alcohol **3b** and 1.2 equiv of NaHMDS.



Scheme 1. Ethanolysis of phosphonothioate **2b** by the use of ethanol as a solvent

The absolute configuration of the major isomer of **4c** was determined by a single-crystal X-ray diffraction analysis (Figure 1). The phosphorus atom in **4c** exhibited an *S* configuration. The signal of *S* isomer of **4c** in ^{31}P NMR spectra was observed at a higher field than the signal of *R* isomer. In the case of **4i** having a *p*-tolyl group, as shown in the Chapter 3 that the signals of the *S* isomer appeared at a lower field in the ^{31}P NMR spectra. The absolute configurations of products **4** except **4h** were estimated based on a comparison of the chemical shifts of **4c** and **4i** (Table 3).

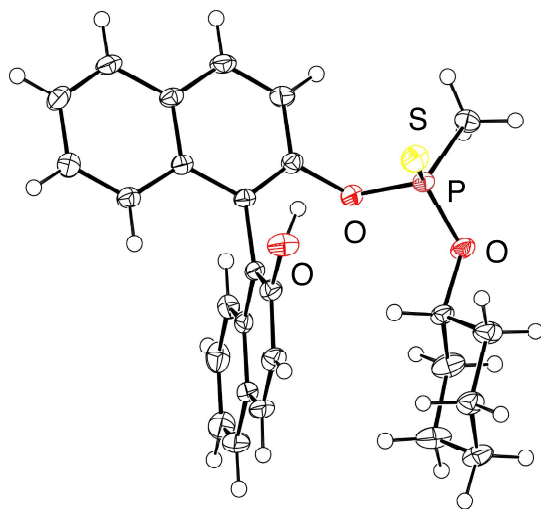
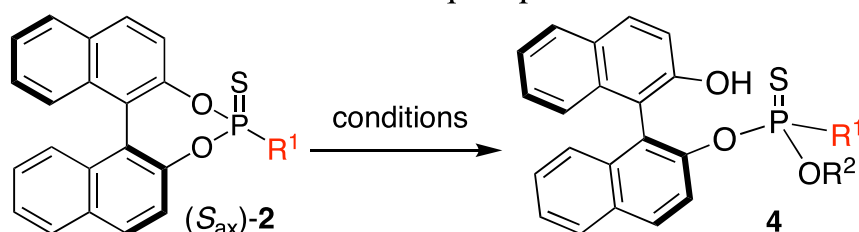


Figure 1. Molecular structure of **4c** with thermal ellipsoids set to 50% probability.

Table 3. ^{31}P NMR chemical shifts of phosphonothioates **4**

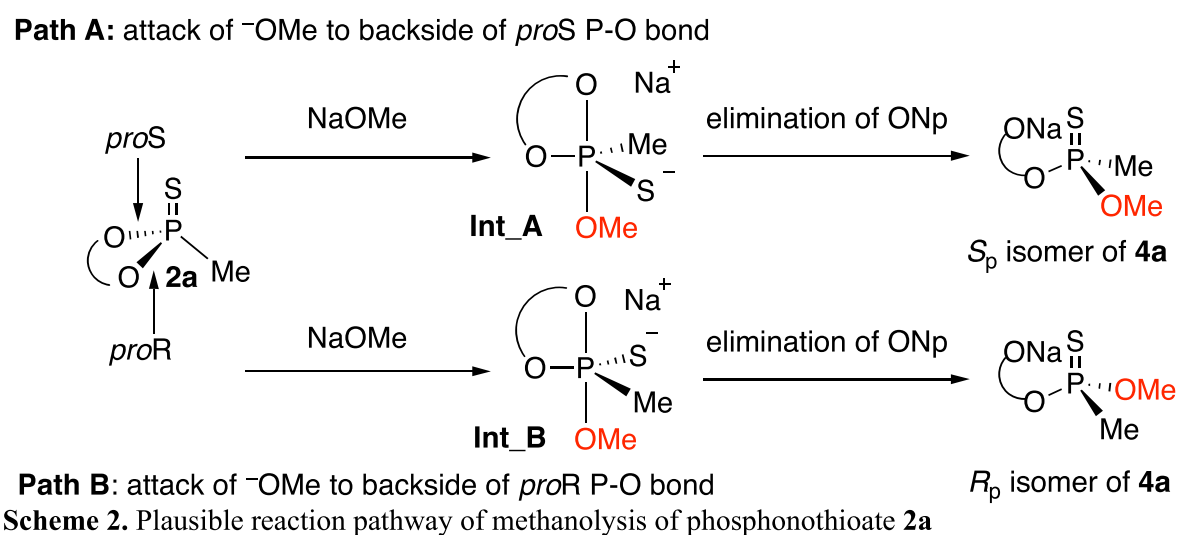


condition1: alcohol **3** (1.0 equiv), NaHMDS (1.0 equiv), THF, rt, 30 min

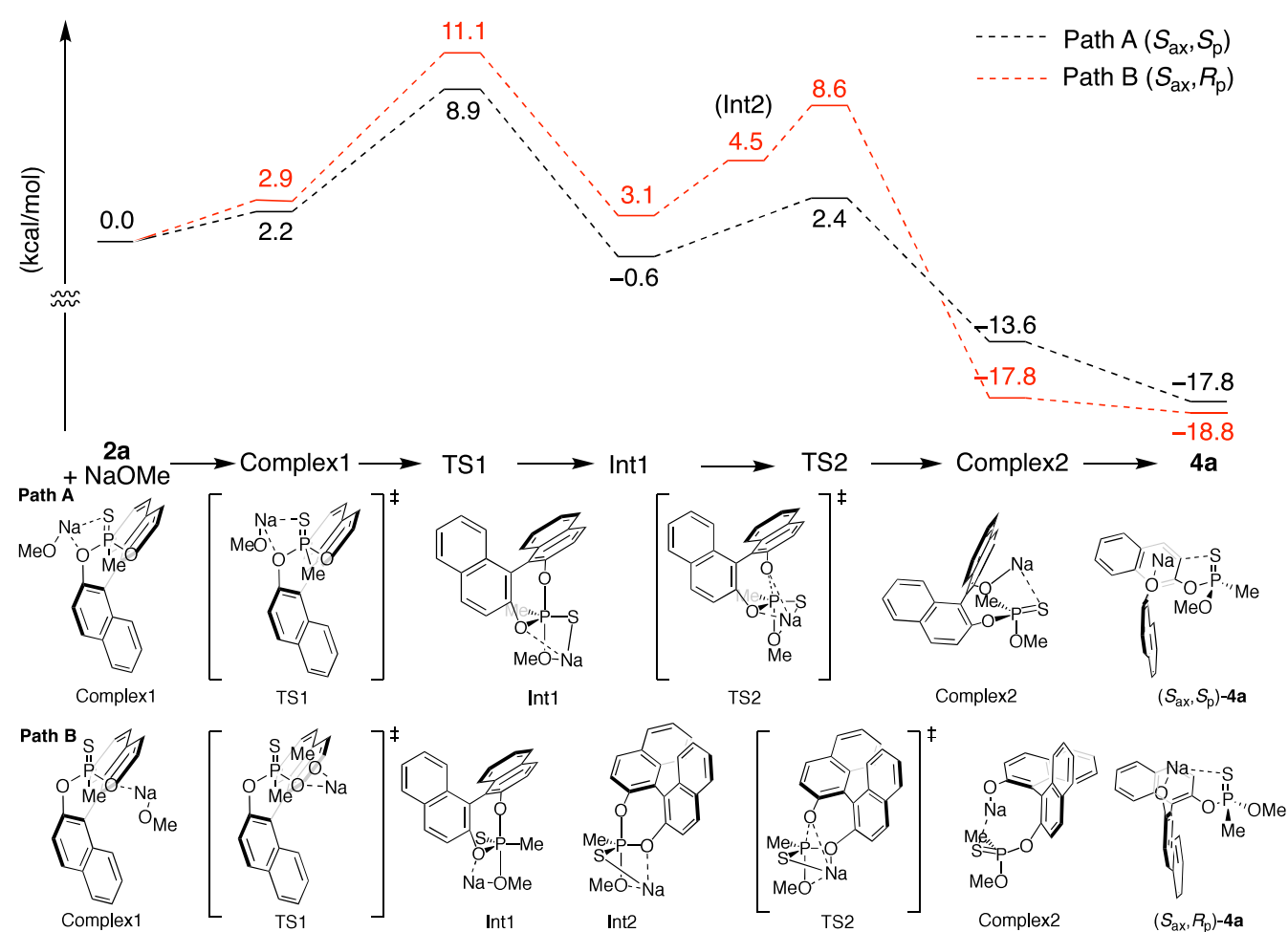
condition2: lithium ethoxide (2.5 equiv), EtOH, 0 °C, 13 h.

Compound (4)	conditions	R ¹	Major (ppm)	Minor (ppm)
4a	1	Me	97.8	98.5
4b	1	Me	95.5	96.2
4b ¹⁴	2	Me	95.5	96.2
4c	1	Me	93.6	95.6
4d	1	Me	96.9	97.8
4e	1	Me	95.2	96.7
4f	1	Me	96.1	97.5
4g	1	Ph	85.9	86.5
4g	2	Ph	85.9	86.5
4h	1	Mesityl	84.3	-
4h ¹⁴	2	Mesityl	84.3	-
4i ¹⁴	2	<i>p</i> -Tolyl	86.5	87.2

The plausible pathway for the methanolysis of phosphonothioates **2a** is shown in Scheme 2.^{2,3} The sodium methoxide attacks to the backside of the P-O bond to generate the trigonal bipyramidal (TBP) intermediate **Int_A** or **B**. Subsequently, naphthyloxy group (ONp) in apical positions is eliminated from the phosphorus atom to give the products **4a**. The diastereoselectivities can be determined by whether the sodium methoxide attacks to the backside of the *proS* P-O bond (**Path A**) or that of the *proR* P-O bond (**Path B**) to give the identical product (*S_P*)-**4a** or (*R_P*)-**4a**, respectively.

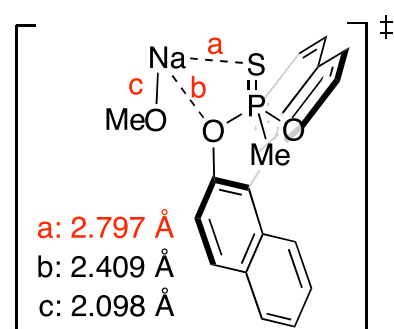


To compare the activation energies of these pathways, theoretical investigations of the detailed transition state (TS) models were conducted using density functional theory (DFT) calculations with the B3LYP functional and the 6-31G(d,p) basis set. The energies are shown in Scheme 3 and Figure 2 including the effects of THF to calculate the single point energy using a PCM model. The reaction coordinate diagrams for the reaction of phosphonothioate **2a** with sodium methoxide were shown in Scheme 3. The structures corresponding to TS1_A and TS1_B are shown in Figure 2, which are highest-energy position in the energy diagrams (for the details of energy diagrams, see the Supporting Information). The Gibbs free energy of TS1_A is 2.2 kcal/mol lower than that of TS1_B. In the geometry of TS1_A, the sulfur atom and two oxygen atoms coordinate to the sodium cation. In contrast, in the geometry of TS1_B, the sodium cation only coordinates to two oxygen atoms (Figure 2, side view). These results indicate that the diastereoselectivity of the chirality transfer reaction could be controlled by the direction of the nucleophilic attack of alkoxides to the phosphorus atom due to the energy differences based on coordination between a sulfur atom and a sodium cation, although we cannot exclude the possibility of isomerization of the TBP intermediates **Int1** Berry's *pseudorotation* process at the present stage.^{3,4} The TBP intermediates **Int1** gave the corresponding isomers **4a** by the elimination of the ONp group in apical positions through the lower energy transition state (TS2) than TS1 (see the Supporting Information). These results are consistent with the experimental results that the methanolysis of **1a** at room temperature gave (*S_P*)-**4a** as a major isomer.

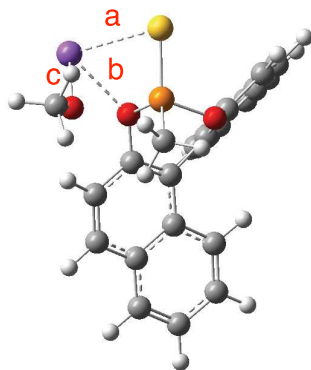


Scheme 3. Reaction coordinate diagrams of the reaction of phosphonothioate **2a** with sodium methoxide, and the corresponding structures

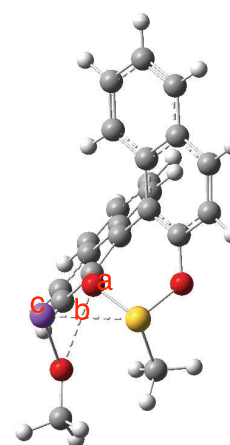
(a) TS1_A: $\Delta\Delta G^\ddagger = 0.0$ kcal/mol



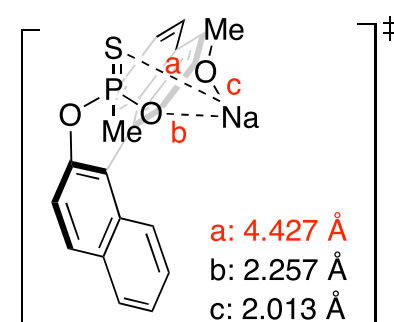
front view



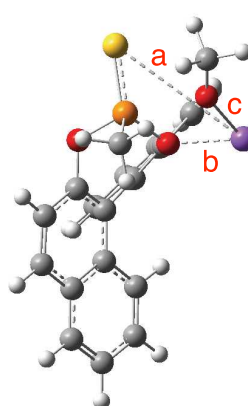
side view



(b) TS1_B: $\Delta\Delta G^\ddagger = +2.2$ kcal/mol



front view



side view

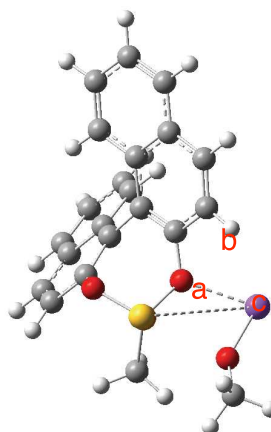
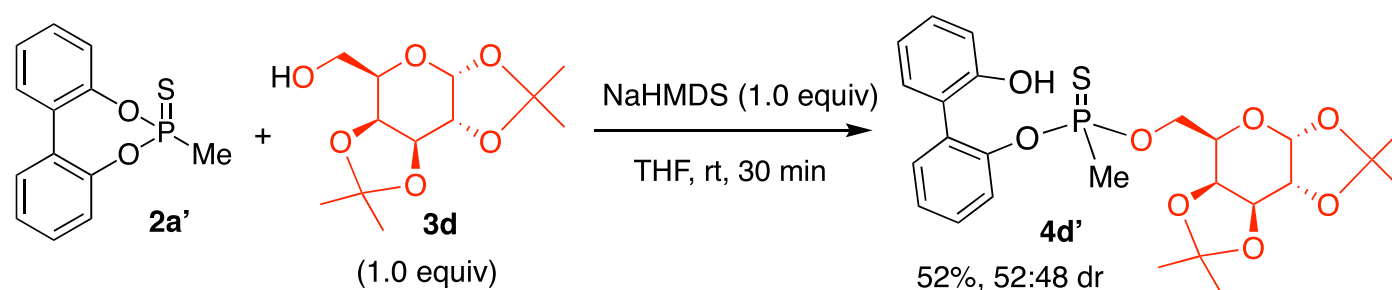


Figure 2. Length of S-Na and O-Na bonds, front and side views of 3D structures, and the relative Gibbs free energies of (a) TS1_A and (b) TS1_B.

The control experiment clearly shows the importance of a chiral binaphthyloxy group for achieving high stereoselectivities in this chirality transfer reaction (Scheme 7). The achiral substrates **2a'** having a biphenyl group showed only moderate diastereoselectivity in alcoholysis with the chiral alcohol **3d**.



Scheme 4. Control experiments by the use of biphenyl derivative **2a'**

In the next stage, further alcoholysis of the obtained products **4h** with benzyl alcohol (**3g**) was examined (Table 4). The phosphonothioate **4h** reacted with sodium benzyl oxide (**6a**) in THF at reflux temperature for 30 min to give the desired product **5hg** in 72% yield with -88% ee (entry 1). The enantioselectivity dropped in the reaction with lithium benzyl oxide (**6b**) instead of **6a** (entry 2). The enantioselectivities were improved by pre-deprotonation of a binaphthyloxy group of **4h** with NaHMDS or *n*-BuLi followed by the reaction with benzyl oxide **6a** or **6b** (entries 3 and 4). DBU did not work well in this 2nd alcoholysis (entry 5). Finally, phosphonothioate **5hg** was obtained in 92% yield with 98% ee by simply reacting **4h** with benzyl alcohol (**2g**) and NaHMDS in THF at room temperature (entry 6). The reaction conditions in entry 6 in Table 3 were selected as optimal conditions for 2nd-step alcoholysis.

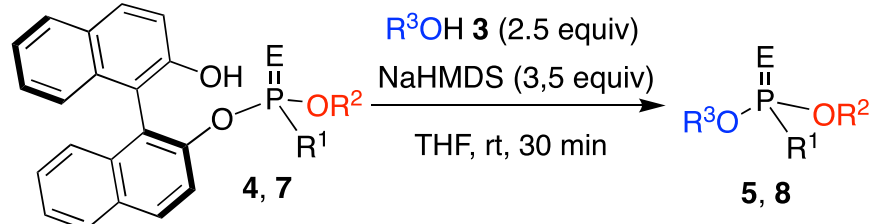
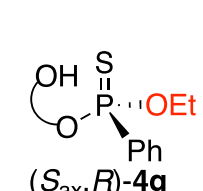
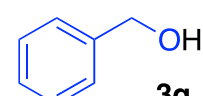
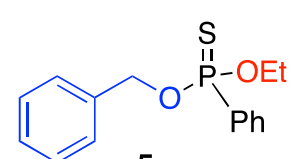
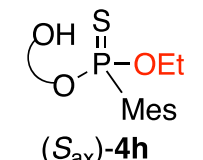
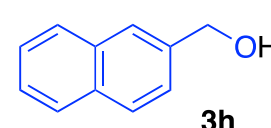
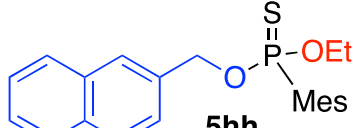
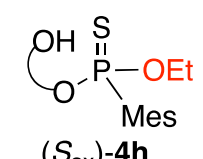
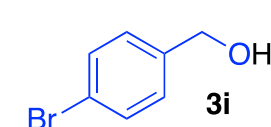
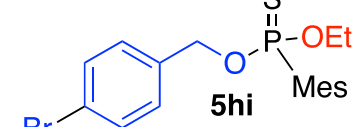
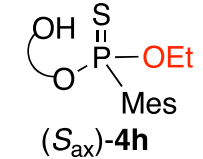
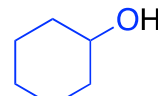
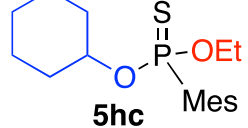
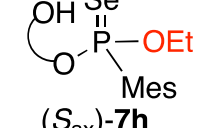
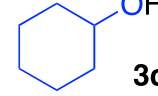
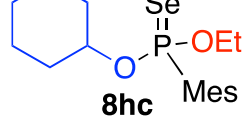
Table 4. Optimization of the reaction condition of 2nd alcoholysis

entry	condition	M	base	3g	temp. (°C)	time (h)	yield (%)	ee (%) ^a
1	BnOM	Na 6a	-	(<i>R</i> _{ax})	65	0.5	72	-88
2	(3.5 equiv)	Li 6b	-	(<i>R</i> _{ax})	65	4	86	-58
3	BnOM (2.5 equiv)	Na 6a	NaHMDS	(<i>S</i> _{ax})	65	0.5	70	98
4	Base (1.0 equiv) ^b	Li 6b	<i>n</i> -BuLi	(<i>R</i> _{ax})	65	4	84	-99
5	BnOH 3g (2.5 equiv)	-	DBU	(<i>S</i> _{ax})	rt	24	15	66
6	base (3.5 equiv)	-	NaHMDS	(<i>S</i> _{ax})	rt	0.5	92	98

Isolated yields are shown. ^aThe enantiometric excess was determined by HPLC analysis using Daicel Chiralpak IA column. ^b*n*-BuLi was added at -78 °C.

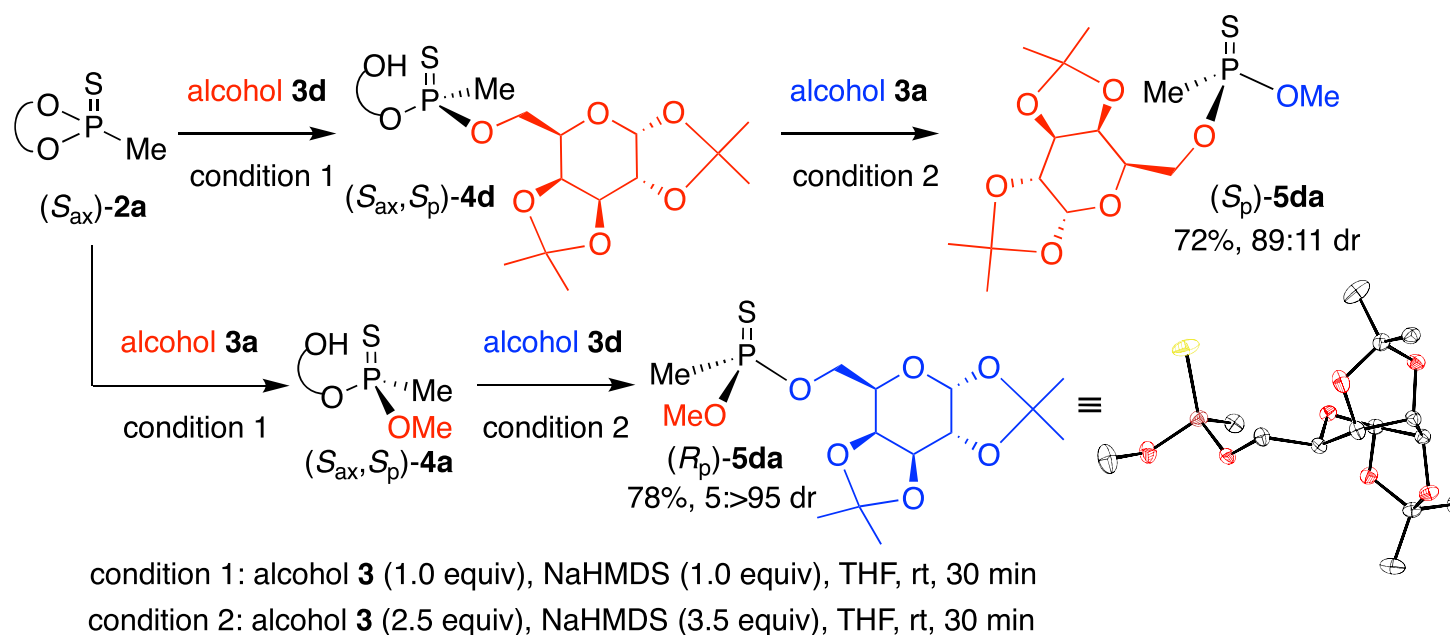
With the optimal conditions in hand, the substrate scope of 2nd-step alcoholysis was elucidated (Table 5). The reaction of phosphonothioates having less sterically hindered carbon substituents at the phosphorus atom (*S*_{ax}, *R*_p)-**4g** with benzyl alcohol (**3g**) proceeded in a stereoselective manner to give the corresponding product **5gg** in high yield with a high enantiomeric excess (entry 1). The reactions with 2-naphthalenemethanol (**3h**) and 4-bromobenzyl alcohol (**3i**) gave the corresponding products **5hh** and **5hi** with excellent enantiomeric excess (entries 2 and 3). The reaction of phosphonothioate **4h** with cyclohexyl alcohol (**3c**) afforded **5hc** in 83% yield with 95%*ee*, but required a longer reaction time (entry 4). This alcoholysis could be applied to the reaction of selenium isologue **7h** to give phosphonoselenoate **8hc** with a high enantiomeric excess (entry 5).

Table 5. Substrate scope of 2nd alcoholysis

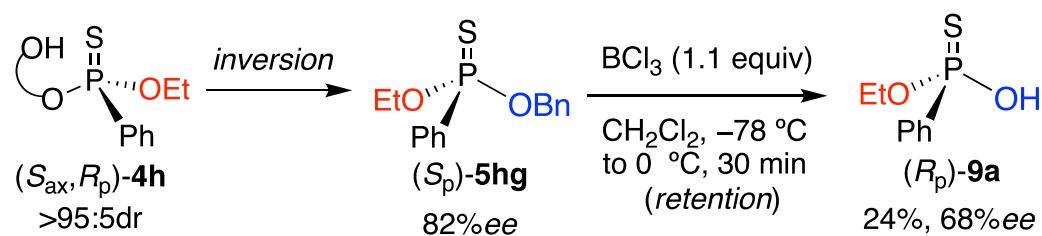
							
entry	S. M.	dr	alcohol 2	product 4	time (h)	yield (%)	<i>ee</i> ^a
1	 (<i>S</i> _{ax} , <i>R</i>)- 4g	>95:5	 3g	 5gg	0.5	99	82
2 ^b	 (<i>S</i> _{ax})- 4h	>95:5	 3h	 5hh	0.5	77	>99
3	 (<i>S</i> _{ax})- 4h	>95:5	 3i	 5hi	0.5	70	90
4	 (<i>S</i> _{ax})- 4h	>95:5	 3c	 5hc	18	83	95
5	 (<i>S</i> _{ax})- 7h	>95:5	 3c	 8hc	11	62	92

^a The enantiomeric excess was determined by HPLC analysis using Daicel Chiralpak AD-H, IA and IB column. ^b *n*-BuLi was used instead of NaHMDS.

This sequential alcoholysis provided access to both stereoisomers of phosphonothioates **5** from the single starting material **2** by simply changing the order of alcohol addition (Scheme 5). Phosphonothioate **5da** was obtained with 89:11 dr by the sequential alcoholysis of phosphonothioate **2a** with galactopyranose (**3d**) and then with methanol (**3a**). On the other hand, **5da** was obtained with 5:>95 dr by a 1st alcoholysis with methanol (**3a**) and a 2nd alcoholysis of the resulting (*S*_{ax},*S*)-**4a** with galactopyranose (**3d**). The X-ray crystal structure analysis of **5da** revealed that the phosphorus atom adopts an *R* configuration. We can estimate that the stereocenter at the phosphorus atom of **5gg** is (*R*) by comparing the optical rotation of the obtained **9a** (68%*ee*, $[\alpha]_D^{20} +2.2$, *c* = 2.2 in MeOH) to the literature value for (*R*)-**9a** (99%*ee*, $[\alpha]_D^{20} -2.2$, *c* = 3.0 in MeOH)⁵ after converting **5gg** to the corresponding phosphonothioic acid **9a** (Scheme 6).⁶ These results clearly suggest that the 2nd alcoholysis proceeds with inversion of the configuration at the phosphorus atom.

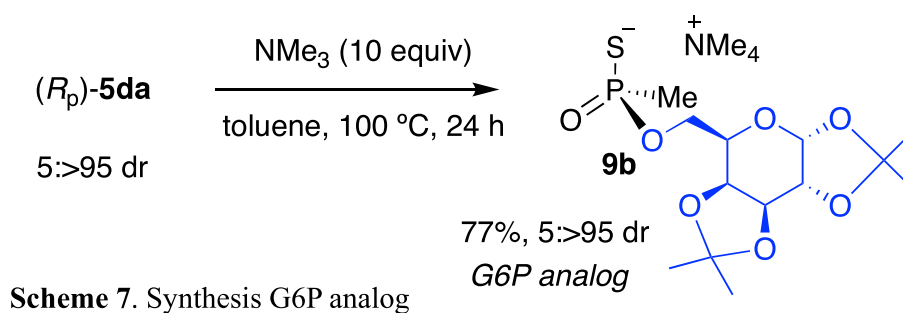


Scheme 5. Synthesis of both stereoisomers **5da** from (*S*_{ax})-**2a**



Scheme 6. Debenzylation of phosphonothioate **5hg** to phosphonothioic acid **9a**

To demonstrate the applicability of the series of alcoholysis via chirality transfer, the obtained phosphonothioate **5** was converted to a biologically relevant phosphonothionyl scaffold (Scheme 7). Demethylation of (*R*)-**5da** with an excess amount of trimethylamine afforded the glucose-6-phosphate (G6P) analog **9b** without a decrease of the diastereomeric ratio.⁷



Scheme 7. Synthesis G6P analog

In summary, the author have described a sequential alcoholysis of phosphonothioates **2** having a binaphthyl group to *P*-stereogenic phosphonothioates **5**. The 1st-step alcoholysis proceeded via the axial chirality transfer of the binaphthyl group to the central chirality of the phosphorus atom to give *P*-stereogenic products **4** having a binaphthyloxy group with moderate to excellent diastereoselectivities. A range of alcohols including a nucleoside participated in the 1st-step alcoholysis. DFT computational analysis suggested two TS models, leading to major and minor isomers. The differences in the coordination of a sulfur atom to a sodium cation on the phosphorus atom in the TS geometries could be caused by a binaphthyl group, and may determine the direction of nucleophilic attack of alkoxides to the phosphorus atom. The 2nd-step alcoholysis of **4** was promoted by the addition of an excess amount of the alcohols and NaHMDS affording *P*-stereogenic phosphonothioates **5** with high enantioselectivities. Pre-deprotonation of the binaphthyloxy group is crucial in improving the product enantioselectivity. Based on X-ray crystal structure analysis of **4** and optical rotation of phosphonothioic acid derivatized from **5**, the author determined that the 2nd-step alcoholysis proceeded by inversion of configuration at the phosphorus atom. The obtained phosphonothioates **5** could be converted to diastereo-enriched biologically relevant phosphonothionylated scaffold.

EXPERIMENTAL SECTION

General Remarks. Unless otherwise noted, materials were purchased from commercial supplies and used as received. Ethanol (Japan Alcohol Corporation) was distilled from magnesium. Toluene (Kanto Chemical Co., Ltd.) was distilled from sodium metal. Phosphonothioate **2a** and **2c**, phosphonothioate **4b**, **4c**, and **4h**, phosphonoselenoates **7g** were previously prepared. Flash column chromatography was run on silica gel 60 N (spherical neutral) 40-50 μm of Kanto Chemical Co., Ltd. All

manipulations were carried out under argon atmosphere.

The ^1H NMR spectra were recorded on JEOL ECX-400P (400 MHz) in CDCl_3 . Chemical shifts of protons are recorded in δ values referred to chloroform as an internal standard in CDCl_3 and dimethyl sulfoxide as an internal standard in $(\text{CD}_3)_2\text{SO}$, and the following abbreviations are used: s: singlet, d: doublet, t: triplet, m: multiplet, br: broad. The ^{13}C NMR spectra were measured on a JEOL ECX-400P (100 MHz) in CDCl_3 . The ^{31}P NMR spectra were measured on a JEOL ECX-400P (162 MHz) in CDCl_3 and with 85% H_3PO_4 as an external standard. The ^{77}Se NMR spectra were measured on a JEOL ECX-400P (76 MHz) in CDCl_3 and with Me_2Se as an external standard. All spectra were acquired in the proton-decoupled mode. Attenuated total reflectance infrared (IR) spectra were obtained as a KBr pellet in the solid state or neat liquid, as indicated. The high-resolution mass spectra (HRMS) were taken on a JMS-700 mass spectrometer. Enantiomeric excesses (*ee*) were determined by normal-phase HPLC analysis with a commercially available chiral stationary phase, using a mixture of hexane–2-propanol as eluent and with UV detector set as 254 nm.

6-Methyldibenzo[d, f][1,3,2]dioxaphosphepine 6-sulfide (2a'). To a 200 mL two-necked flask were added 6-chlorodibenzo[d, f][1,3,2]dioxaphosphepine⁸ (1.0 M toluene solution, 10 mL, 10 mmol) under Ar atmosphere. The solution was heated to 40 °C. Methylmagnesium bromide (1.0 M in Et_2O solution, 10 mL, 10 mmol) was added dropwise for 10 min to the heated solution, and it was stirred at 30 min. Sulfur (0.38 g, 11 mmol) was then added to the solution. After that, the reaction mixture was added to sat. NH_4Cl aq., and it was extracted with Et_2O three times. The combined organic layer was dried over MgSO_4 , filtrate, and concentrated. Purification by column chromatography on silica gel (EtOAc ;hexane = 1:10, R_f = 0.53) gave **2a'** (1.23 g, 47%) as a colorless solid. mp: 152-154 °C; IR (KBr): 2988, 1498, 1433, 1246, 1196, 1093, 935, 805, 638 cm^{-1} ; ^1H NMR (CDCl_3): δ 2.10 (d, J = 14.8 Hz, 3H), 7.26 (d, J = 7.6 Hz, 2H), 7.38 (dd, J = 7.6 Hz, 7.2 Hz, 2H), 7.45 (dd, J = 7.6 Hz, 7.2 Hz, 2H), 7.55 (d, J = 7.2 Hz, 2H); ^{13}C NMR (CDCl_3): δ 19.3 (d, $^1J_{\text{C-P}}$ = 103.4 Hz), 122.0, 126.6, 129.8, 130.0, 130.3, 148.4, 148.5; ^{31}P NMR (CDCl_3): δ 111.3 (s) ; MS (EI) m/z 262 (M^+); HRMS Calcd for $\text{C}_{13}\text{H}_{11}\text{O}_2\text{PS}$: 262.0217, Found: 262.0200.

(S_{ax})-4-Phenylbinaphtho[2,1-d:1',2'-f][1,3,2]dioxaphosphepine 4-sulfide (2b). The following compound was synthesized according to literature procedure,⁹ with (*S_{ax}*)-BINOL (1.44 g, 5.0 mmol), Et_3N (1.4 mL, 10 mmol), dichlorophenylphosphine sulfide (0.8 mL, 5.0 mmol) and CH_2Cl_2 (25 mL) to give (*S_{ax}*)-**2b** (1.69 g, 80%) as a colorless solid. mp: 246-248 °C; IR (KBr): 1588, 1234, 1119, 950, 862, 746 cm^{-1} ; ^1H NMR (CDCl_3): δ 6.91 (d, J = 8.7 Hz, 1H), 7.29-7.40 (m, 5H), 7.47-7.57 (m, 4H), 7.66

(d, $J = 8.7$ Hz, 1H), 7.70-7.76 (m, 2H), 7.79 (d, $J = 8.7$ Hz, 1H), 7.92 (d, $J = 8.2$ Hz, 1H), 7.99 (d $J = 8.2$ Hz, 1H), 8.09 (d, $J = 9.2$ Hz, 1H) ; ^{13}C NMR (CDCl_3): δ 121.2, 122.1, 122.4, 122.8, 125.9, 126.8, 127.2, 127.4, 128.3, 128.4, 128.6, 128.7, 130.0 (d, $^1J_{\text{C-P}} = 141.9$ Hz), 130.6, 131.0, 131.7, 132.0, 132.1, 132.2, 132.6, 132.7, 133.4, 146.0, 146.1, 148.5, 148.6; ^{31}P NMR (CDCl_3): δ 101.2 (s); MS (EI) m/z 424 (M^+); HRMS Calcd for $\text{C}_{26}\text{H}_{17}\text{O}_2\text{PS}$: 424.0687, Found: 424.0663.

General procedure 1 for the preparation of phosphonothioate 4 (GP1)

To a 20 mL Schlenk tube were added phosphonothioate **2** (1.0 equiv), alcohol **3** (1.0-1.5 equiv), and THF (1.0 mL). The reaction mixture was added to NaHMDS (1.0 M THF solution, 1.0-1.5 equiv), and it was stirred at rt for 30 min. After that, the mixture was added to sat. NH_4Cl aq. (2.0 mL), and it was extracted with Et_2O (5 mL \times 3). The combined organic layer was dried over MgSO_4 , filtered, and concentrated. Purification by column chromatography on silica gel provided **4**.

($S_{\text{ax}}, S_{\text{p}}$)-*O*-(2'-Hydroxy-[1,1'-binaphthalen]-2-yl) *O*-methyl methylphosphonothioate (**4a**). The following compound was synthesized via GP1, with (S_{ax})-**2a** (0.189 g, 0.5 mmol), **3a** (0.20 μL , 0.5 mmol) and NaHMDS (0.5 mL, 0.5 mmol). Purification by column chromatography on silica gel (EtOAc :hexane = 1:20, R_f = 0.15) gave **4a** (124 mg, 63%, >95:5 dr) as a colorless solid. mp: 75-80 $^\circ\text{C}$; IR (KBr): 3406, 3057, 2946, 1506, 1211, 1045, 985, 897, 813 cm^{-1} ; ^1H NMR (CDCl_3): δ 1.66 (d, $J = 15.7$ Hz, 3H), 3.18 (d, $J = 14.4$ Hz, 3H), 5.24-5.39 (br, 1H), 7.11 (d, $J = 8.1$ Hz, 1H), 7.26-7.38 (m, 5H), 7.44-7.52 (m, 2H), 7.85-7.87 (m, 1H), 7.92 (d, $J = 9.0$ Hz, 1H), 7.96 (d, $J = 8.1$ Hz, 1H), 8.05 (d, $J = 9.0$ Hz, 1H); ^{13}C NMR (CDCl_3): δ 22.5 (d, $^1J_{\text{C-P}} = 115.6$ Hz), 52.0 (d, $^2J_{\text{C-P}} = 7.5$ Hz), 114.9, 118.5, 121.8, 122.7, 123.8, 125.0, 125.9, 126.2, 127.0, 128.1, 128.4, 129.1, 130.5, 130.8, 131.8, 133.7, 133.8, 148.1, 148.2, 151.7; ^{31}P NMR (CDCl_3): δ 97.8 (s, major), 98.5 (minor); MS (EI) m/z 394 (M^+); HRMS Calcd for $\text{C}_{22}\text{H}_{19}\text{O}_3\text{PS}$: 394.0793, Found: 394.0804.

($S_{\text{ax}}, S_{\text{p}}$)-*O*-(2'-Hydroxy-[1,1'-binaphthalen]-2-yl) *O*-((3a*R*,5*R*,5a*S*,8a*S*,8b*R*)-2,2,7,7-tetramethyltetrahydro-5*H*-bis([1,3]dioxolo)[4,5-*b*:4',5'-*d*]pyran-5-yl)methyl) methylphosphonothioate (**4d**).

The following compound was synthesized via GP1, with (S_{ax})-**2a** (0.90 g, 2.5 mmol), **3d** (0.66 g, 2.5 mmol) and NaHMDS (2.5 mL, 2.5 mmol). Purification by column chromatography on silica gel (EtOAc :hexane = 1:5, R_f = 0.25) gave **4d** (1.31 g, 84%, >95:5 dr) as a colorless solid. mp: 165-167 $^\circ\text{C}$; IR (KBr): 3421, 2987, 1382, 1213, 1071, 989, 903, 815 cm^{-1} ; ^1H NMR (CDCl_3): δ 1.17 (s, 3H), 1.24 (s, 3H), 1.28 (s, 3H), 1.40 (s, 3H), 1.49 (d, $J = 15.3$ Hz, 3H), 3.60-3.67 (m, 1H), 3.75-3.79 (m, 1H), 4.04 (dd, $J = 8.1$ Hz, 2.5 Hz, 1H), 4.10-4.17 (m, 1H), 4.26 (dd, $J = 5.2$ Hz, 2.2 Hz, 1H), 4.53 (dd, $J = 7.9$

Hz, 2.2 Hz, 1H), 5.46 (d, $J = 4.9$ Hz, 1H), 5.54 (br, 1H), 7.07 (d, $J = 8.1$ Hz, 1H), 7.22-7.35 (m, 5H), 7.46-7.50 (m, 1H), 7.71 (d, $J = 9.0$ Hz, 1H), 7.83 (d, $J = 8.1$ Hz, 1H), 7.89 (d, $J = 9.0$ Hz, 1H), 7.95 (d, $J = 8.1$ Hz, 1H), 8.02 (d, $J = 9.0$ Hz, 1H); ^{13}C NMR (CDCl_3): δ 22.7 (d, $^1J_{\text{C-P}} = 114.6$ Hz), 24.6, 25.0, 25.9, 26.0, 65.0, 66.5, 70.5, 70.7, 96.3, 108.9, 109.7, 114.5, 118.3, 121.7, 122.5, 123.7, 125.1, 126.0, 126.1, 126.9, 127.5, 128.0, 128.4, 129.0, 130.5, 130.6, 131.7, 133.7, 148.3, 148.4, 151.8; ^{31}P NMR (CDCl_3): δ 96.9 (s, major), 97.8 (s, minor); MS (EI) m/z 622 (M^+); HRMS Calcd for $\text{C}_{33}\text{H}_{35}\text{O}_8\text{PS}$: 622.1790, Found: 622.1790.

(S_{ax},S_p)-O-((3S)-2-((Bis(4-methoxyphenyl)(phenylmethoxy)methyl)-5-(5-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)tetrahydrofuran-3-yl) O-2'-hydroxy-[1,1'-binaphthalen]-2-yl) methylphosphonothioate (4e).

The following compound was synthesized via GP1, with (*S_{ax}*)-**2a** (112 mg, 0.31 mmol), **3e** (252 mg, 0.46 mmol) and NaHMDS (0.90 mL, 0.90 mmol). Purification by column chromatography on silica gel (CH_2Cl_2 :MeOH = 50:1 with addition of 0.5% of Et_3N , $R_f = 0.25$) gave **4e** (156 mg, 56%, >95:5 dr) as a colorless solid. mp: 156-158 °C; IR (KBr): 3395, 2925, 1508, 1252, 985, 907 cm^{-1} ; ^1H NMR (DMSO): δ 1.22 (d, $J = 15.6$ Hz, 3H), 1.48 (s, 3H), 2.00-2.05 (m, 1H), 2.21-2.28 (m, 1H), 3.15 (dd, $J = 10.5$ Hz, 3.2 Hz, 1H), 3.23 (dd, $J = 10.5$ Hz, 4.1 Hz, 1H), 3.71 (s, 3H), 3.72 (s, 3H), 4.00 (dd, $J = 6.2$ Hz, 3.2 Hz, 1H), 5.24-5.31 (m, 1H), 6.05 (dd, $J = 8.2$ Hz, 6.4 Hz, 1H), 6.86-6.89 (m, 4H), 6.92 (d, $J = 8.2$ Hz, 1H), 7.12 (d, $J = 8.7$ Hz, 1H), 7.17-7.39 (m, 13 H), 7.45-7.50 (m, 2H), 7.57 (d, $J = 8.7$ Hz, 1H), 7.83 (d, $J = 8.7$ Hz, 1H), 7.87 (d, $J = 8.7$ Hz, 1H), 8.03-8.07 (m, 2H), 9.59 (br, 1H), 11.4 (br, 1H); ^{13}C NMR (DMSO): δ 11.7, 21.6 (d, $^1J_{\text{C-P}} = 112.8$ Hz), 37.2, 45.8, 55.0, 55.1, 63.1, 75.9, 83.6, 86.2, 109.9, 113.25, 113.30, 113.6, 118.4, 121.6, 122.6, 124.4, 124.6, 125.3, 125.7, 126.3, 126.7, 126.9, 127.66, 127.74, 127.9, 128.0, 128.1, 128.3, 129.6, 129.7, 130.9, 133.3, 133.7, 135.1, 135.3, 135.5, 144.5, 146.8, 150.3, 153.2, 158.2, 163.6; ^{31}P NMR (CDCl_3): δ 95.2 (s, major), 95.9 (s, minor). Anal. calcd for $(\text{C}_{52}\text{H}_{47}\text{N}_2\text{O}_9\text{PS})_{0.8}(\text{CH}_2\text{Cl}_2)_{0.2}$ (%): C 67.61; H 5.16; N 3.02, found C 67.52; H 5.19; N 3.07.

(S_{ax},S_p)-O-(2'-Hydroxy-[1,1'-binaphthalen]-2-yl) O-(((3aR,4R,6R,6aR)-6-methoxy-2,2-dimethyltetrahydrofuro[3,4-d][1,3]dioxol-4-yl)methyl) methylphosphonothioate (4f).

The following compound was synthesized via GP2, with (*S_{ax}*)-**2a** (109 mg, 0.30 mmol), **3f** (64 mg, 0.30 mmol) and NaHMDS (0.30 mL, 0.30 mmol). Purification by column chromatography on silica gel (EtOAc:hexane = 1:5, $R_f = 0.25$) gave **4f** (114 mg, 67%, >95:5 dr) as a colorless solid. mp: 90-92 °C; IR (KBr): 3433, 2924, 1619, 1213, 984, 814, 734 cm^{-1} ; ^1H NMR (CDCl_3): δ 1.17 (s, 3H), 1.38 (s, 3H), 1.59 (d, $J = 15.3$ Hz, 3H), 3.25 (s, 3H), 3.27-3.34 (m, 1H), 3.80-3.84 (m, 1H), 4.01-4.05 (m, 1H), 4.19 (d, $J = 5.5$

Hz, 1H), 4.42 (d, $J = 5.5$ Hz, 1H), 4.86 (m, 1H), 5.42-5.62 (br, 1H), 7.09 (d, $J = 8.7$ Hz, 1H), 7.24-7.36 (m, 5H), 7.47-7.50 (m, 1H), 7.59 (d, $J = 9.2$ Hz, 1H), 7.85 (d, $J = 7.3$ Hz, 1H), 7.91 (d, $J = 8.7$ Hz, 1H), 7.95 (d, $J = 8.2$ Hz, 1H), 8.04 (d, $J = 8.7$ Hz, 1H); ^{13}C NMR (CDCl_3): δ 23.0 (d, $^1J_{\text{C-P}} = 115.6$ Hz), 25.0, 26.5, 55.2, 66.0 (d, $^2J_{\text{C-P}} = 6.6$ Hz), 81.5, 84.7, 85.0, 109.1, 112.6, 114.6, 118.5, 121.6, 122.8, 123.7, 125.0, 125.9, 126.1, 126.9, 127.7, 128.2, 128.5, 129.0, 130.6, 130.7, 131.8, 133.7, 148.0, 148.1, 151.7; ^{31}P NMR (CDCl_3): δ 96.1 (s, major), 97.5 (s, minor); MS (EI) m/z 566 (M^+); HRMS Calcd for $\text{C}_{30}\text{H}_{31}\text{O}_7\text{PS}$: 566.1528, Found: 566.1530.

(S_{ax},S_p)-O-Ethyl O-(2'-hydroxy-[1,1'-binaphthalen]-2-yl) phenylphosphonothioate (4g). The following compound was synthesized via GP2, with (*S_{ax}*)-**2b** (102 mg, 0.25 mmol), **3b** (18 μL , 0.30 mmol) and NaHMDS (0.30 mL, 0.30 mmol). Purification by column chromatography on silica gel (EtOAc:hexane = 1:10, $R_f = 0.25$) gave **4g** (87 mg, 76%, 24:76 dr) as a colorless solid. mp: 110-112 °C; IR (KBr): 3433, 2924, 1619, 1213, 984, 814, 734 cm^{-1} ; ^1H NMR (CDCl_3): δ 0.87 (t, $J = 7.2$ Hz, 2.4 H), 1.14 (t, $J = 7.2$ Hz, 0.6H), 3.28-3.36 (m, 0.8H), 3.73-3.87 (m, 1H), 3.91-3.99 (m, 0.2H), 5.14 (br, 0.2H), 5.43 (br, 0.8H), 7.08-7.15 (m, 1.6H), 7.20 (d, $J = 9.0$ Hz, 0.8H), 7.22-7.42 (m, 7.6H), 7.45-7.53 (m, 1.8H), 7.58 (d, $J = 9.0$ Hz, 0.2H), 7.69 (d, $J = 9.0$ Hz, 0.2H), 7.73-7.79 (m, 1.6H), 7.85 (d, $J = 8.1$ Hz, 0.8H), 7.88-7.93 (m, 2H), 7.95 (d, $J = 8.1$ Hz, 0.2H), 8.03 (d, $J = 9.0$ Hz, 0.2H); ^{13}C NMR (CDCl_3): δ 15.7 (d, $^3J_{\text{C-P}} = 7.5$ Hz), 16.0 (d, $^3J_{\text{C-P}} = 8.5$ Hz), 62.8 (d, $^2J_{\text{C-P}} = 6.6$ Hz), 63.1 (d, $^2J_{\text{C-P}} = 6.6$ Hz), 114.8, 115.1, 118.4, 118.6, 121.4, 122.0, 122.5, 122.7, 123.5, 123.7, 125.0, 125.8, 125.9, 126.0, 126.1, 126.7, 126.8, 127.6, 127.9, 128.1, 128.3, 128.4, 128.5, 129.1, 129.2, 130.3, 130.35, 130.39, 130.6, 130.7, 131.2, 131.3, 131.6, 131.7, 132.0, 132.6, 132.7, 133.5, 133.7, 133.9, 134.1, 148.46, 148.54, 148.6, 151.7; ^{31}P NMR (CDCl_3): δ 85.9 (s, minor), 86.5 (s, major); MS (EI) m/z 470 (M^+); HRMS Calcd for $\text{C}_{28}\text{H}_{23}\text{O}_3\text{PS}$: 470.1106, Found: 470.1088.

(S_{ax},R_p)-O-Ethyl O-(2'-hydroxy-[1,1'-binaphthalen]-2-yl) phenylphosphonothioate (4g).

To a 20 mL Schlenk tube were added phosphonothioate **2b** (0.84 g, 2.0 mmol) and ethanol (**3b**) (2.0 mL). The reaction mixture was cooled to 0 °C. Then, lithium ethoxide (1.0 M ethanol solution, 5.0 mL, 5.0 mmol) was added to the cooled solution. After that, the mixture was added 1N HCl (3.0 mL), and it was extracted with Et_2O (5 mL \times 3). The combined organic layer was dried over MgSO_4 , filtered, and concentrated. Purification by column chromatography on silica gel (EtOAc:hexane = 1:10, $R_f = 0.20$) provided **3f** (0.84 g, 90%, >95:5 dr) as a colorless solid. mp: 141-143 °C; IR (KBr): 3343, 2980, 1589, 1214, 1023, 983, 818, 744 cm^{-1} ; ^1H NMR (CDCl_3): δ 1.14 (t, $J = 7.2$ Hz, 3H), 3.81-3.87 (m, 1H), 3.91-3.99 (m, 1H), 5.20 (br, 1H), 7.10-7.16 (m, 4H),

7.22-7.39 (m, 7H), 7.46-7.50 (m, 1H), 7.58 (d, $J = 9.0$ Hz, 1H), 7.70 (d, $J = 9.0$ Hz, 1H), 7.75 (d, $J = 8.1$ Hz, 1H), 7.95 (d, $J = 8.1$ Hz, 1H), 8.03 (d, $J = 9.0$ Hz, 1H); ^{13}C NMR (CDCl_3): δ 16.0 (d, $^3J_{\text{C-P}} = 8.5$ Hz), 63.1 (d, $^2J_{\text{C-P}} = 6.9$ Hz), 114.8, 118.4, 122.1, 122.5, 123.5, 125.0, 125.9, 126.1, 126.7, 127.6, 127.9, 128.1, 128.4, 129.1, 130.3, 130.4, 130.6, 131.7, 132.1, 132.7 (d, $^1J_{\text{C-P}} = 123.9$ Hz), 133.5, 133.7, 148.5, 148.6, 151.7; ^{31}P NMR (CDCl_3): δ 85.9 (s, major), 86.5 (s, minor); MS (EI) m/z 470 (M^+); HRMS Calcd for $\text{C}_{28}\text{H}_{23}\text{O}_3\text{PS}$: 470.1106, Found: 470.1084.

O-(2'-Hydroxy-[1,1'-biphenyl]-2-yl)*O*-((3*aR*,5*R*,5*aS*,8*aS*,8*bR*)-2,2,7,7-tetramethylte-trahydro-5*H*-bis([1,3]dioxolo)[4,5-*b*:4',5'-*d*]pyran-5-yl)methyl) methylphosphonothioate (**4d'**).

The following compound was synthesized via GP1, with **2a'** (550 mg, 2.1 mmol), 1,2:3,4-di-*O*- α -D-galactopyranose (**3d**) (581 mg, 2.2 mmol) and NaHMDS (2.2 mL, 2.2 mmol). Purification by column chromatography on silica gel (EtOAc:hexane = 1:5, R_f = 0.25) gave **4d'** (584 mg, 52%, 52:48 dr) as a colorless solid. mp: 50-51 °C; IR (KBr): 3420, 2934, 1384, 1211, 1070, 917, 764 cm^{-1} ; ^1H NMR (CDCl_3): δ 1.32-1.33 (m, 6H), 1.44 (s, 1.5H), 1.45 (s, 1.5H), 1.50 (s, 1.5H), 1.53 (s, 1.5H), 1.59-1.63 (m, 3H), 3.98-4.10 (m, 2.6H), 4.15-4.25 (m, 1.4H), 4.31-4.33 (m, 1H), 4.58 (dd, $J = 7.9$ Hz, 2.5 Hz, 0.5H), 4.62 (dd, $J = 7.9$ Hz, 2.5 Hz, 0.5H), 5.28-5.34 (br, 1H), 5.52-5.53 (m, 1H), 6.96-7.02 (m, 2H), 7.14-7.22 (m, 1H), 7.28-7.42 (m, 5H); ^{13}C NMR (CDCl_3): δ 21.9 (d, $^1J_{\text{C-P}} = 114.6$ Hz), 21.9 (d, $^1J_{\text{C-P}} = 115.6$ Hz), 24.6, 24.7, 25.1, 26.1, 26.2, 65.1, 65.4, 66.8, 67.1, 70.5, 70.6, 70.7, 70.8, 96.4, 109.0, 109.7, 116.8, 120.7, 122.9, 123.0, 124.8, 126.0, 129.5, 129.8, 130.4, 130.5, 131.5, 132.2, 148.8, 148.9, 153.26, 153.31; ^{31}P NMR (CDCl_3): δ 97.1 (s), 97.6 (s); MS (EI) m/z 522 (M^+); HRMS Calcd for $\text{C}_{25}\text{H}_{31}\text{O}_8\text{PS}$: 522.1477, Found: 522.1470.

General procedure 2 for the preparation of phosphonothioate **5** (GP2)

To a 20 mL Schlenk tube were added phosphonothioate **4** (1.0 equiv and THF (1.0 mL). The solution was cooled to -78 °C. *n*-BuLi (1.6 M in hexane, 1.0 equiv) was then added to the cooled solution, and it was stirred for 0.5 h followed by concentrated *in vacuo* at rt. The reaction mixture was added to THF (0.5 mL), and lithium alkoxide (1.0 M in THF, 2.5 equiv), and it was stirred at 65 °C for 4 h. After that, the mixture was added to sat. NH_4Cl aq. (2.0 mL) and it was extracted with Et_2O (3 mL \times 3). The combined organic layer was washed with brine, dried over MgSO_4 , filtered, and concentrated. Purification by column chromatography on silica gel gave **5**.

O-Benzyl *O*-ethyl mesitylphosphonothioate (**5hg**). The following compound was

synthesized via GP2, with (*S*_{ax})-**4h** (255 mg, 0.50 mmol, >95:5 dr), *n*-BuLi (1.6 M in hexane, 0.31 mL, 0.50 mmol), lithium benzyl oxide (**6b**) (1.0 M in THF, 1.3 mL, 1.3 mmol) at 65 °C for 4 h. Purification by column chromatography on silica gel (EtOAc:Hexane = 1:20, R_f = 0.38) gave **5hg** (154 mg, 92%, 98%*ee*) as a colorless liquid. The enantiomeric excess was determined by HPLC analysis using Daicel Chiralpak AD-H column: *i*PrOH:hexane = 0.5:99.5, flow rate 0.3 mL/min, λ = 254 nm, 25 °C, *t*_R = 25.8 min (major), *t*_R = 28.1 min (minor). [α]_D²⁰ −1.5° (*c* = 1.0, THF); IR (neat): 2976, 2360, 1605, 1455, 1030, 686 cm^{−1}; ¹H NMR (CDCl₃): δ 1.23 (t, *J* = 7.2 Hz, 3H), 2.26 (s, 3H), 2.54 (s, 6H), 3.87-3.98 (m, 1H), 4.06-4.17 (m, 1H), 5.09-5.24 (m, 2H), 6.87 (s, 1H), 6.88 (s, 1H), 7.31-7.34 (m, 5H); ¹³C NMR (CDCl₃): δ 16.0 (d, ³*J*_{C-P} = 7.2 Hz), 21.1, 23.6, 62.1 (d, ²*J*_{C-P} = 7.2 Hz), 67.4 (d, ²*J*_{C-P} = 7.2 Hz), 128.3 (d, ¹*J*_{C-P} = 154.8 Hz), 128.4, 128.7, 130.9, 131.0, 136.37, 136.43, 141.3, 141.4; ³¹P NMR (CDCl₃): δ 85.9 (s); MS (EI) *m/z* 334 (M⁺); HRMS Calcd for C₁₈H₂₃O₂PS: 334.1156, Found: 334.1154.

O-Ethyl *O*-(naphthalene-2-ylmethyl) mesitylphosphonothioate (**5hh**). The following compound was synthesized via GP2, with (*S*_{ax})-**4h** (255 mg, 0.50 mmol, >95:5 dr), *n*-BuLi (1.6 M in hexane, 0.31 mL, 0.50 mmol), lithium 2-naphthalenemethyl oxide (1.0 M in THF, 1.3 mL, 1.3 mmol) at 65 °C for 4 h. Purification by column chromatography on silica gel (EtOAc:Hexane = 1:20, R_f = 0.48) gave **5hh** (148 mg, 77%, >99%*ee*) as a colorless solid. The enantiomeric excess was determined by HPLC analysis using Daicel Chiralpak AD-H column: *i*PrOH:hexane = 0.5:99.5, flow rate 0.3 mL/min, λ = 254 nm, 25 °C, *t*_R = 28.5 min (minor), *t*_R = 33.2 min (major). [α]_D²⁰ −3.2° (*c* = 1.0, THF); mp: 61-62 °C; IR (KBr): 2976, 1605, 1450, 1030, 812, 688 cm^{−1}; ¹H NMR (CDCl₃): δ 1.23 (t, *J* = 7.2 Hz, 3H), 2.27 (s, 3H), 2.57 (s, 6H), 3.91-4.00 (m, 1H), 4.09-4.19 (m, 1H), 5.27-5.41 (m, 2H), 6.88 (s, 1H), 6.89 (s, 1H), 7.48-7.55 (m, 3H), 7.83-7.88 (m, 4H); ¹³C NMR (CDCl₃): δ 16.0 (d, ³*J*_{C-P} = 8.5 Hz), 21.1, 23.6, 23.7, 62.2 (d, ²*J*_{C-P} = 6.6 Hz), 67.6 (d, ²*J*_{C-P} = 6.6 Hz), 126.0, 126.5, 127.3, 127.9, 128.2, 128.3 (d, ¹*J*_{C-P} = 155.6 Hz), 128.5, 130.9, 131.1, 133.26, 133.31, 133.8, 133.9, 141.3, 141.4; ³¹P NMR (CDCl₃): δ 86.1 (s); MS (EI) *m/z* 384 (M⁺); HRMS Calcd for C₂₂H₂₅O₂PS: 384.1313, Found: 384.1310.

General procedure 3 for the preparation of phosphonothioate **5** (GP3)

To a 20 mL Schlenk tube were added phosphonothioate **4** (1.0 equiv), alcohol **3** and

THF. The reaction mixture was added to NaHMDS (1.0 M in THF solution, 2.5 equiv), and it was stirred at rt for 0.5-18 h. After that the mixture was added to sat. NH₄Cl aq. (2.0 mL) and it was extracted with Et₂O (3 mL × 3). The combined organic layer was washed with brine, dried over MgSO₄, filtered, and concentrated. Purification by column chromatography on silica gel gave **5**.

O-Benzyl *O*-ethyl phenylphosphonothioate (**5gg**). The following compound was synthesized via GP3, with (*S*_{ax}, *R*)-**4g** (703 mg, 1.5 mmol, >95:5 dr), NaHMDS (1.0 M in THF, 5.3 mL, 5.3 mmol), benzyl alcohol (**3g**) (0.39 mL, 3.8 mmol) and THF (1.5 mL) at rt for 0.5 h. Purification by column chromatography on silica gel (EtOAc:Hexane = 1:10, R_f = 0.50) gave **5gg** (434 mg, 99%, 82%*ee*) as a colorless liquid. The enantiomeric excess was determined by HPLC analysis using Daicel Chiralpak IA column: *i*PrOH:hexane = 0.5:99.5, flow rate 0.3 mL/min, λ = 254 nm, 25 °C, *t*_R = 19.2 min (major), *t*_R = 21.9 min (minor). [α]_D²⁰ 12.3° (*c* = 1.0, THF); IR (neat): 2980, 1439, 1122, 1010, 958, 736, 693 cm⁻¹; ¹H NMR (CDCl₃): δ 1.27 (t, *J* = 7.2 Hz, 3H), 2.39 (s, 3H), 4.05-4.14 (m, 2H), 5.00-5.17 (m, 2H), 7.23-7.38 (m, 7H), 7.78 (d, *J* = 8.1 Hz, 1H), 7.81 (d, *J* = 8.1 Hz, 1H); ¹³C NMR (CDCl₃): δ 16.2 (d, ³*J*_{C-P} = 7.5 Hz), 21.7, 63.0 (d, ²*J*_{C-P} = 5.6 Hz), 68.0 (d, ²*J*_{C-P} = 4.7 Hz), 128.1, 128.3, 128.6, 129.1, 129.2, 131.1, 131.3; ³¹P NMR (CDCl₃): δ 88.3 (s); MS (EI) *m/z* 306 (M⁺); HRMS Calcd for C₁₆H₁₉O₂PS: 306.0843, Found: 306.0834.

O-(4-Bromobenzyl) *O*-ethyl mesitylphosphonothioate (**5hi**). The following compound was synthesized via GP3, with (*S*_{ax})-**4h** (103 mg, 0.20 mmol, >95:5 dr), NaHMDS (1.0 M in THF, 0.7 mL, 0.70 mmol), 4-bromobenzyl alcohol (**3i**) (96 mg, 0.50 mmol) and THF (0.7 mL) at rt for 0.5 h. Purification by column chromatography on silica gel (EtOAc:Hexane = 1:20, R_f = 0.28) gave **5hi** (142 mg, 70%, 89%*ee*) as a colorless solid. The enantiomeric excess was determined by HPLC analysis using Daicel Chiralpak IB column: *i*PrOH:hexane = 0.5:99.5, flow rate 0.3 mL/min, λ = 254 nm, 25 °C, *t*_R = 22.0 min (minor), *t*_R = 24.8 min (major). [α]_D²⁰ -4.9° (*c* = 1.0, THF); mp: 67-68 °C; IR (KBr): 2923, 1605, 1487, 1451, 1038, 999, 784, 681 cm⁻¹; ¹H NMR (CDCl₃): δ 1.26 (t, *J* = 7.2 Hz, 3H), 2.27 (s, 3H), 2.53 (s, 6H), 3.91-4.00 (m, 1H), 4.07-4.17 (m, 1H), 5.04-5.19 (m, 2H), 6.87 (s, 1H), 6.88 (s, 1H), 7.30 (d, *J* = 8.2 Hz, 2H), 7.50 (d, *J* = 8.2 Hz, 2H); ¹³C NMR (CDCl₃): δ 16.2 (d, ³*J*_{C-P} = 7.7 Hz), 21.2, 23.7, 62.3 (d, ²*J*_{C-P} = 7.7 Hz), 66.7 (d, ²*J*_{C-P} = 6.7 Hz), 122.5, 128.1 (d, ¹*J*_{C-P} = 151.4 Hz), 130.0, 130.9, 131.1, 131.9, 135.5, 141.3, 141.4, 141.6; ³¹P NMR (CDCl₃): δ 86.3 (s); MS (EI) *m/z* 412 (M⁺); HRMS Calcd

for C₁₈H₂₂BrO₂PS: 412.0261, Found: 412.0252.

O-Cyclohexyl O-ethyl mesitylphosphonothioate (5hc)

The following compound was synthesized via GP3, with (*S*_{ax})-**4h** (154 mg, 0.30 mmol, >95:5 dr), NaHMDS (1.0 M in THF, 1.1 mL, 1.1 mmol), cyclohexanol (**3c**) (70 μ L, 0.8 mmol) and THF (0.3 mL) at rt for 18 h. Purification by column chromatography on silica gel (EtOAc:Hexane = 1:20, R_f = 0.28) gave **5hc** (83 mg, 83%, 94%*ee*) as a colorless liquid. The enantiomeric excess was determined by HPLC analysis using Daicel Chiralpak IA column: *i*PrOH:hexane = 0.5:99.5, flow rate 0.3 mL/min, λ = 254 nm, 25 °C, *t*_R = 13.9 min (major), *t*_R = 15.3 min (minor). [α]_D²⁰ +3.0° (*c* = 1.0, THF); IR (neat): 2935, 2857, 1606, 1450, 1382, 1045, 985, 793, 687 cm⁻¹; ¹H NMR (CDCl₃): δ 1.19-1.30 (m, 2H), 1.36 (t, *J* = 7.2 Hz, 3H), 1.37-1.43 (m, 2H), 1.49-1.65 (m, 2H), 1.74-1.78 (m, 2H), 1.96-1.99 (m, 1H), 2.09-2.12 (m, 1H), 2.25 (s, 3H), 2.59 (s, 6H), 4.07-4.20 (m, 2H), 4.67-4.76 (m, 1H), 6.87 (s, 1H), 6.88 (s, 1H); ¹³C NMR (CDCl₃): 16.2 (d, ³*J*_{C-P} = 8.4 Hz), 21.1, 23.8, 23.9, 24.2, 25.4, 33.6 (d, ³*J*_{C-P} = 6.0 Hz), 34.1 (d, ³*J*_{C-P} = 2.4 Hz), 62.6 (d, ²*J*_{C-P} = 7.2 Hz), 76.1 (d, ²*J*_{C-P} = 7.2 Hz), 128.7 (d, ¹*J*_{C-P} = 154.8 Hz), 130.9, 131.0, 141.1, 141.2, 141.3; ³¹P NMR (CDCl₃): δ 83.5 (s); MS (EI) *m/z* 326 (M⁺); HRMS Calcd for C₁₇H₂₇O₂PS: 326.1469, Found: 326.1462.

O-Cyclohexyl O-ethyl mesitylphosphonoselenoate (8hc). The following compound was synthesized via GP3, with (*S*_{ax})-**7h** (279 mg, 0.50 mmol, >95:5 dr), NaHMDS (1.0 M in THF, 1.8 mL, 1.8 mmol), cyclohexanol (**3c**) (0.13 mL, 1.3 mmol) and THF (0.5 mL) at rt for 11 h. Purification by column chromatography on silica gel (EtOAc:Hexane = 1:5, R_f = 0.75) gave **8hc** (118 mg, 62%, 91 %*ee*) as a colorless liquid. The enantiomeric excess was determined by HPLC analysis using Daicel Chiralpak IA column: *i*PrOH:hexane = 0.5:99.5, flow rate 0.3 mL/min, λ = 254 nm, 25 °C, *t*_R = 18.1 min (major), *t*_R = 19.0 min (minor). [α]_D²⁰ +1.8° (*c* = 1.0, THF); IR (neat): 2936, 2857, 1605, 1449, 1041, 984, 653 cm⁻¹; ¹H NMR (CDCl₃): δ 1.21-1.29 (m, 1H), 1.37 (t, *J* = 7.2 Hz, 3H), 1.40-1.46 (m, 2H), 1.50-1.67 (m, 3H), 1.73-1.81 (m, 2H), 1.96-2.00 (m, 1H), 2.12-2.16 (m, 1H), 2.26 (s, 3H), 2.57 (s, 6H), 4.12-4.26 (m, 2H), 4.73-4.80 (m, 1H), 6.85 (s, 1H), 6.87 (s, 1H); ¹³C NMR (CDCl₃): δ 16.0 (d, ³*J*_{C-P} = 8.5 Hz), 21.1, 23.7, 24.2, 25.3, 33.4, 34.0, 63.8 (d, ²*J*_{C-P} = 7.7 Hz), 77.3 (d, ²*J*_{C-P} = 8.5 Hz), 129.6 (d, ¹*J*_{C-P} = 140.9 Hz), 131.0, 131.2, 140.8, 140.9, 141.2; ³¹P NMR (CDCl₃): δ 85.4 (d, ¹*J*_{P-Se} = 830.8 Hz); ⁷⁷Se NMR (CDCl₃): δ -215.9 Hz (d, ¹*J*_{P-Se} = 832.3 Hz); MS (EI) *m/z* 374 (M⁺); HRMS Calcd for C₁₇H₂₇O₂PSe: 374.0914, Foud: 374.0917.

(R_p)-O-Methyl O-(((3aR,5R,5aS,8aS,8bR)-2,2,7,7-tetramethyltetrahydro-5H-bis([1,3]dioxolo)[4,5-b:4',5'-d]pyran-5-yl)methyl) (R)-methylphosphonothioate (5da).

The following compound was synthesized via GP3, with (*S_{ax}*, *S_p*)-**4a** (194 mg, 0.50 mmol, >95:5 dr), NaHMDS (1.0 M in THF, 1.8 mL, 1.8 mmol), 1,2:3,4-di-*O*- α -D-galactopyranose (**3d**) (1.0 M in THF, 1.3 mL, 1.3 mmol) and THF (0.5 mL) at rt for 0.5 h. Purification by column chromatography on silica gel (EtOAc:Hexane = 1:5, *R_f* = 0.33) gave (*R_p*)-**5da** (143 mg, 78%, 5:>95 dr) as a colorless solid. mp: 76-78 °C; IR (KBr): 2925, 1383, 1215, 1077, 1030, 1004, 905, 762 cm⁻¹; ¹H NMR (CDCl₃): δ 1.32 (s, 6H), 1.44 (s, 3H), 1.53 (s, 3H), 1.84 (d, *J* = 15.6 Hz, 3H), 3.71 (d, *J* = 13.7 Hz, 3H), 4.02-4.05 (m, 1H), 4.15-4.23 (m, 2H), 4.24 (dd, *J* = 5.0 Hz, 2.3 Hz, 1H), 4.32 (dd, *J* = 5.0 Hz, 2.3 Hz, 1H), 4.61 (dd, *J* = 7.8 Hz, 2.8 Hz, 1H), 5.53 (d, *J* = 5.0 Hz, 1H); ¹³C NMR (CDCl₃): δ 21.2 (d, ¹*J_{C-P}* = 114.6 Hz), 24.6, 25.1, 26.1, 52.6, 65.7, 67.3, 70.6, 70.8, 70.9, 96.4, 108.9, 109.8; ³¹P NMR (CDCl₃): δ 99.1 (s, minor), 100.0 (s, major); MS (EI) *m/z* 355 (M-CH₃)⁺; HRMS Calcd for C₁₃H₂₂O₇PS: 353.0824, Found: 353.0822.

(S_p)-O-Methyl O-(((3aR,5R,5aS,8aS,8bR)-2,2,7,7-tetramethyltetrahydro-5H-bis([1,3]dioxolo)[4,5-b:4',5'-d]pyran-5-yl)methyl) methylphosphonothioate (5da).

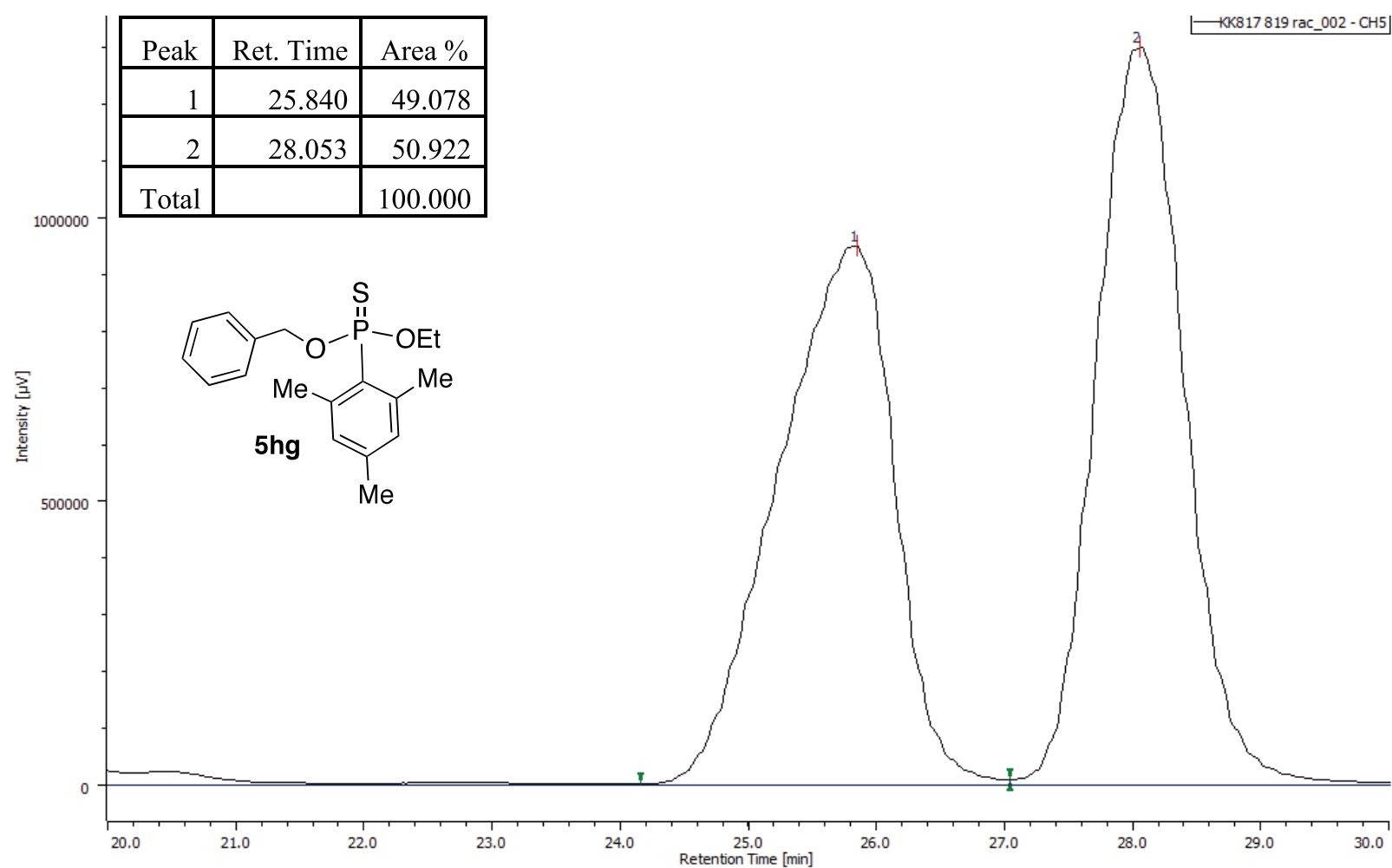
The following compound was synthesized via GP3, with (*S_{ax}*, *S_p*)-**4d** (62 mg, 0.10 mmol, >95:5 dr), NaHMDS (1.0 M in THF, 0.35 mL, 0.35 mmol), methanol (**3a**) (10 μ L, 0.25 mmol) and THF (0.2 mL) at rt for 0.5 h. Purification by column chromatography on silica gel (EtOAc:Hexane = 1:5, *R_f* = 0.38) gave (*S_p*)-**5da** (27 mg, 72%, 89:11 dr) as a colorless oil. IR (neat): 2937, 1382, 1303, 1256, 1212, 1072, 1031, 908, 764 cm⁻¹; ¹H NMR (CDCl₃): δ 1.33 (s, 6H), 1.44 (s, 3H), 1.55 (s, 3H), 1.85 (d, *J* = 15.7 Hz, 3H), 3.70 (d, *J* = 13.9 Hz, 3H), 4.04-4.17 (m, 2H), 4.24 (dd, *J* = 8.8 Hz, 2.2 Hz, 1H), 4.32-4.35 (m, 2H), 4.61 (dd, *J* = 7.7 Hz, 2.4 Hz, 1H), 5.54 (d, *J* = 4.9 Hz, 1H); ¹³C NMR (CDCl₃): δ 21.3 (d, ¹*J_{C-P}* = 116.0 Hz), 24.6, 25.1, 26.1, 52.7, 65.5, 67.3, 70.5, 70.8, 70.9, 96.5, 108.9, 109.8; ³¹P NMR (CDCl₃): δ 99.1 (s, major), 100.0 (s, minor); MS (EI) *m/z* 353 (M-CH₃)⁺; HRMS Calcd for C₁₃H₂₂O₇PS : 353.0824, Found: 353.0836.

(R_p)-Tetramethylammonium O-(((3aR,5R,5aS,8aS,8bR)-2,2,7,7-tetramethyltetrahydro-5H-bis([1,3]dioxolo)[4,5-b:4',5'-d]pyran-5-yl)methyl) methylphosphonothioate (9b)

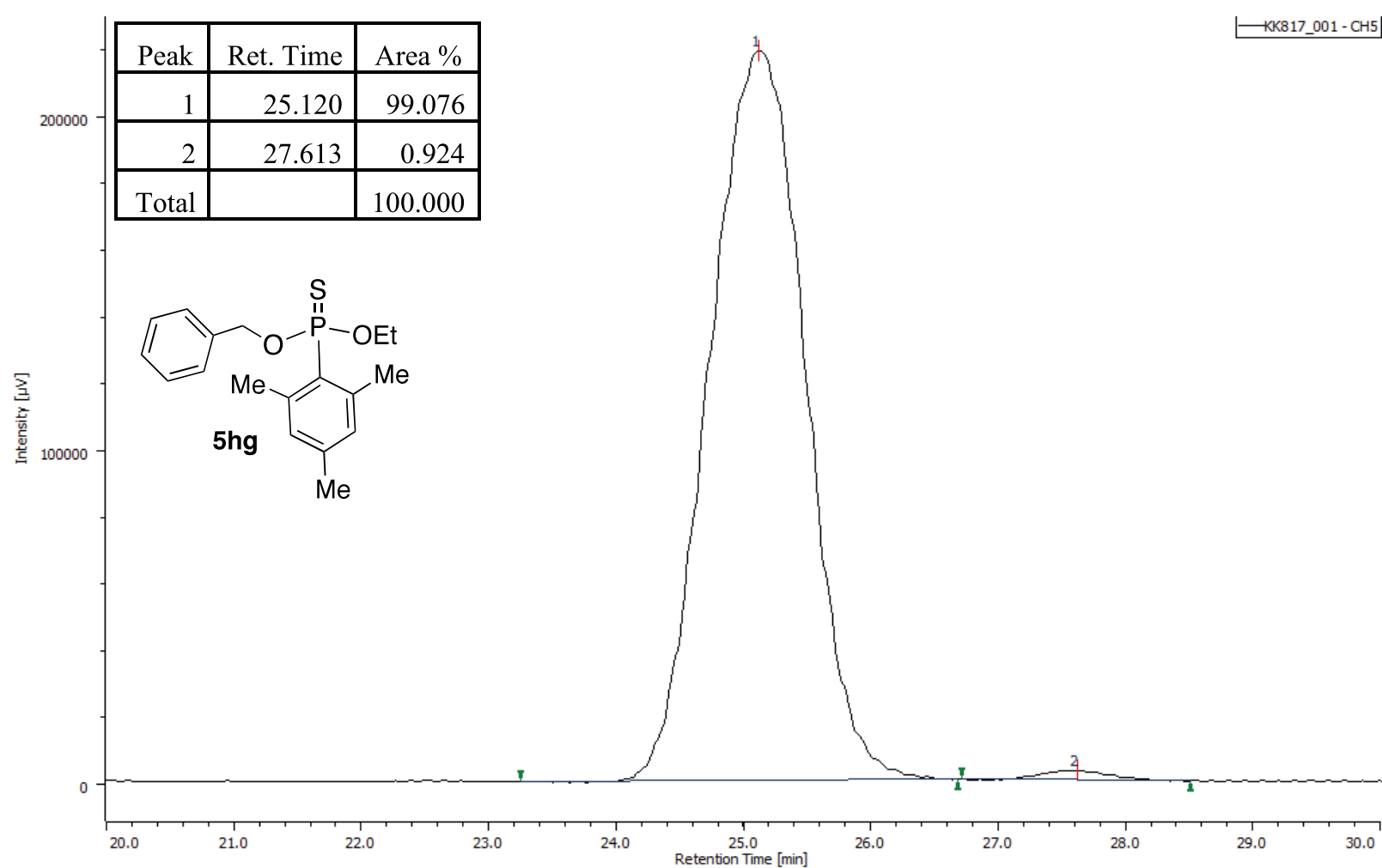
To a vial were added phosphonothioate (*R_p*)-**5da** (26.3 mg, 0.07 mmol) and trimethylamine (1.0 M in toluene solution, 0.7 mL, 0.7 mmol), and sealed. The solution

was heated to 100 °C, and it was stirred for 24 h. After that, the reaction mixture was concentrated *in vacuo*. The residue was washed with cold Et₂O (5 mL), and filtered to give **9b** (23.7 mg, 77%, 5:>95 dr) as a colorless solid. ¹H NMR (CDCl₃): δ 1.30 (s, 6H), 1.41 (s, 3H), 1.51 (s, 3H), 1.67 (d, *J* = 13.9 Hz, 3H), 3.45 (s, 12H), 3.94-3.99 (m, 1H), 4.09-4.16 (m, 2H), 4.27-4.30 (m, 2H), 4.56 (dd, *J* = 7.9 Hz, 2.2 Hz, 1H), 5.51 (d, *J* = 5.4 Hz, 1H); ¹³C NMR (CDCl₃): δ 24.2 (d, ¹*J*_{C-P} = 99.6 Hz), 24.3, 25.1, 26.1, 26.3, 56.0, 63.9, 68.0, 70.5, 70.6, 71.1, 94.5, 108.6, 109.1; ³¹P NMR (CDCl₃): δ 71.8 (s, minor), 72.5 (s, major); MS (EI) *m/z* 353 (M-⁺NMe₄)⁺; HRMS Calcd for C₁₃H₂₂O₇PS: 353.0824, Found: 353.0808.

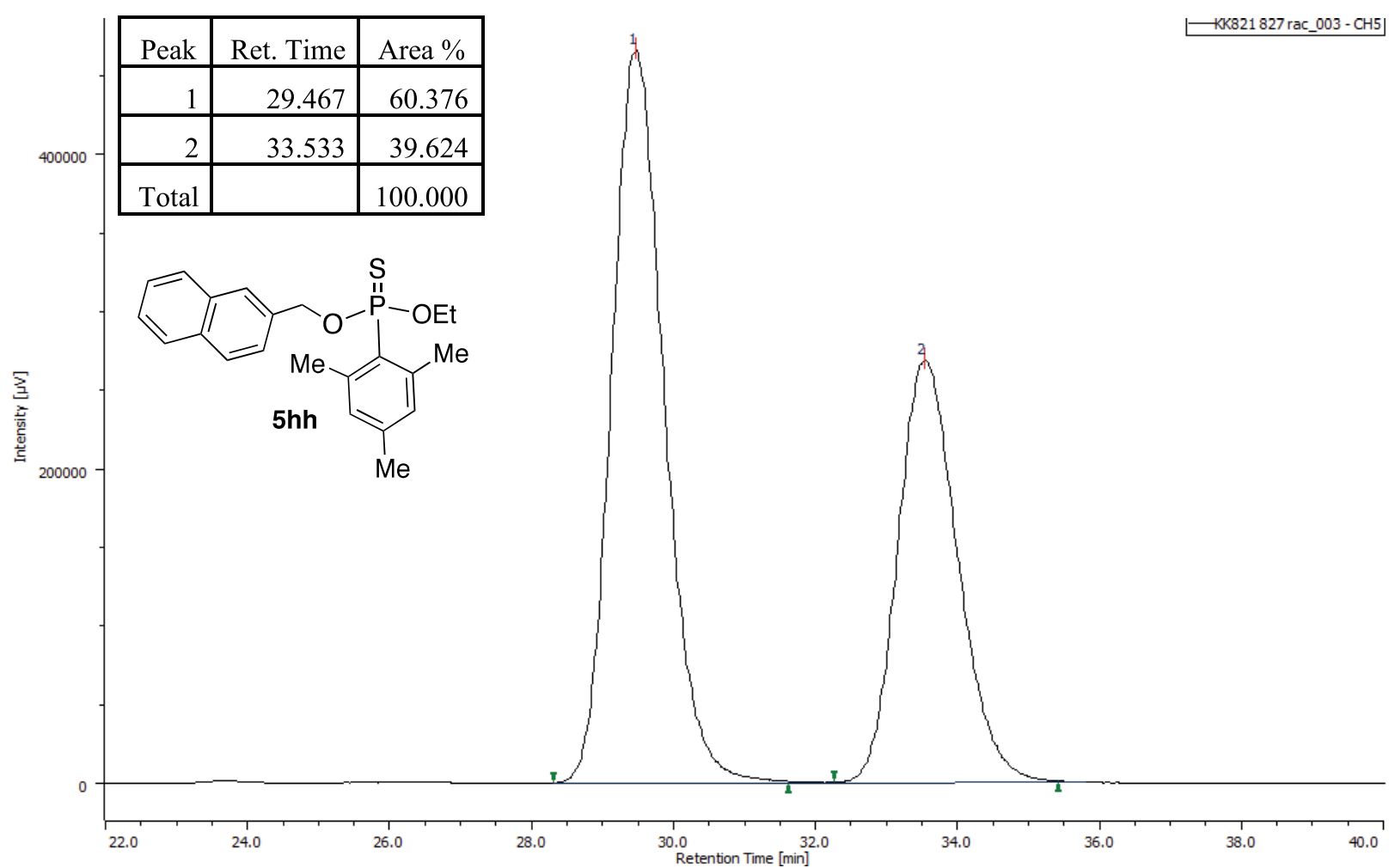
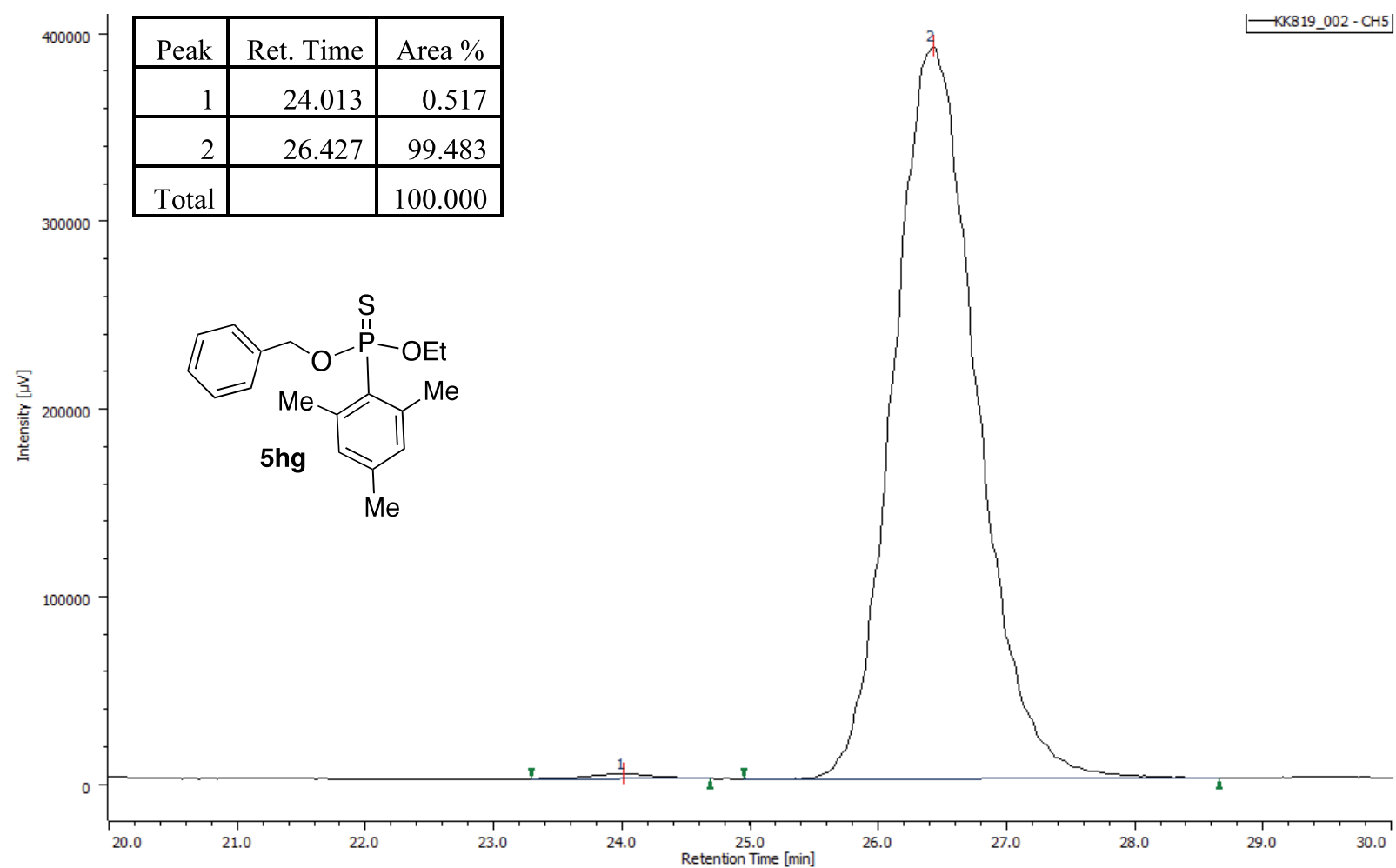
HPLC Chart

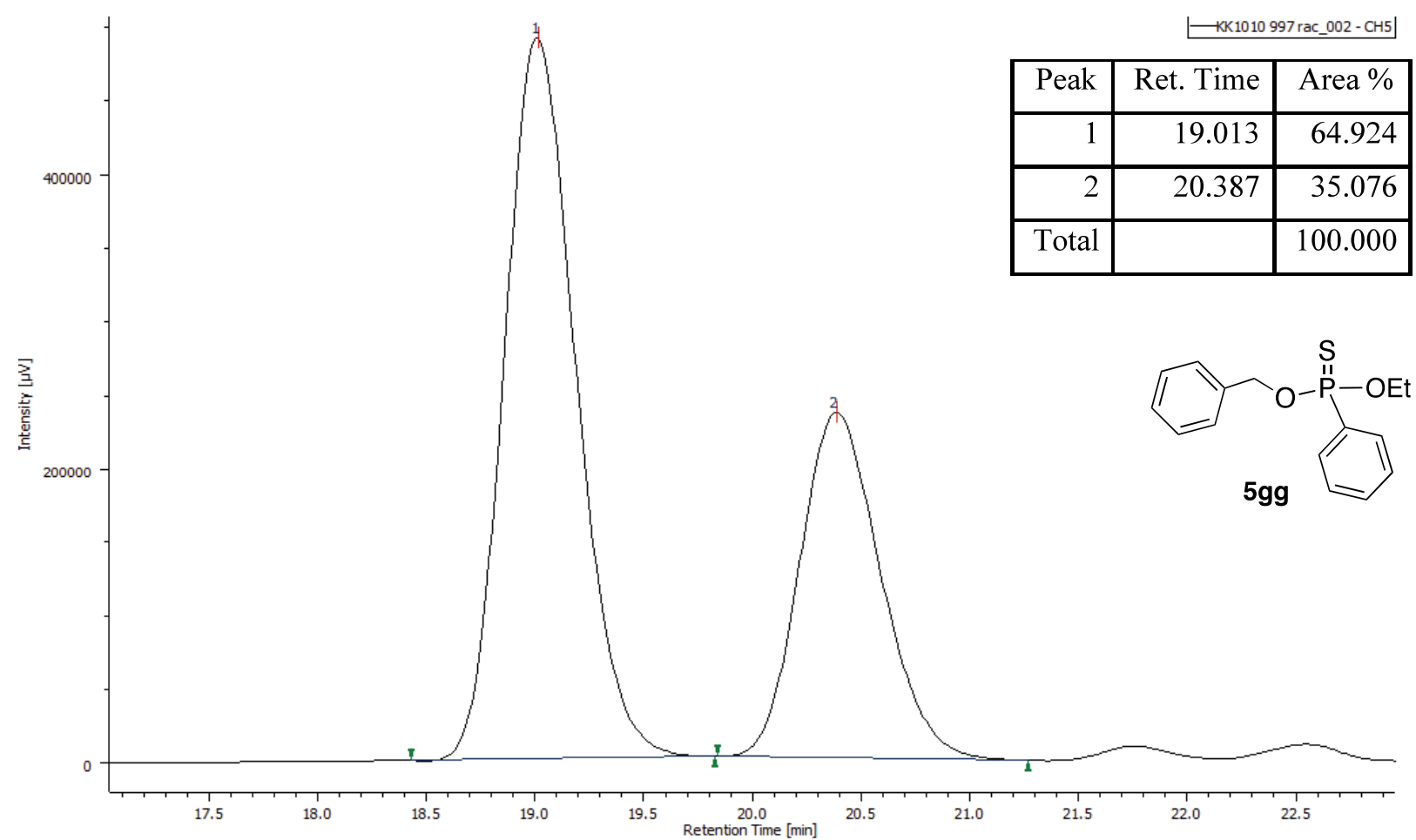
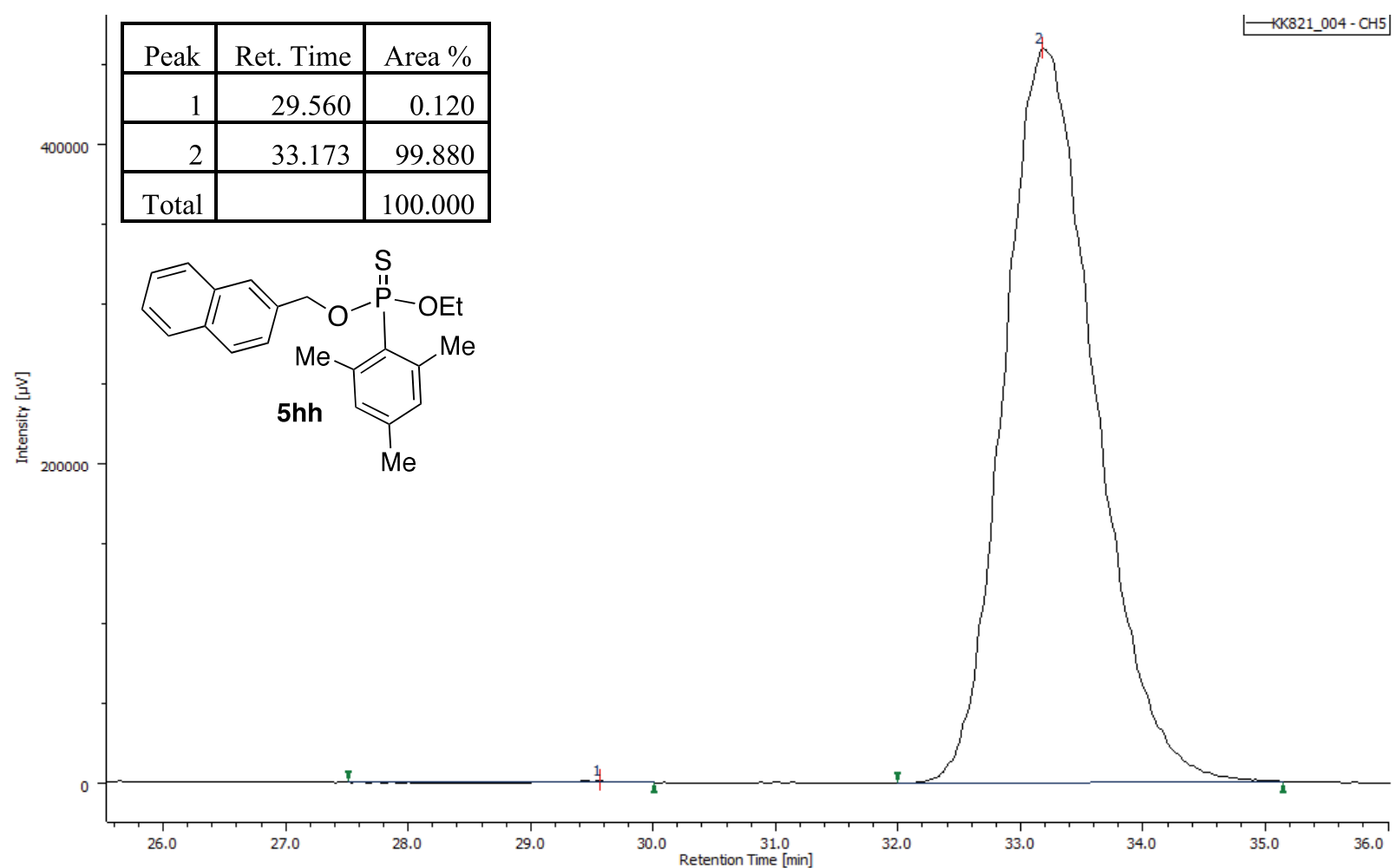


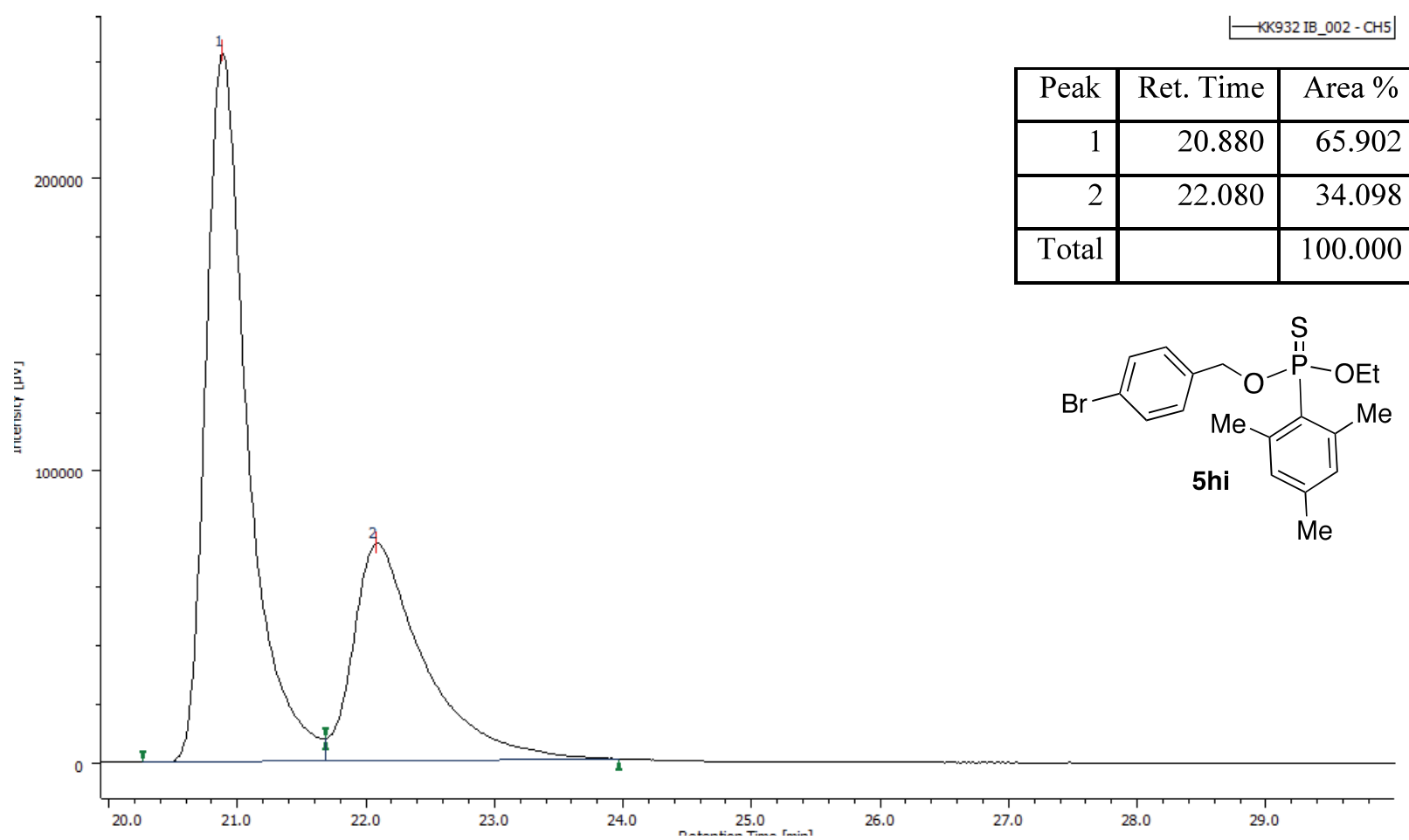
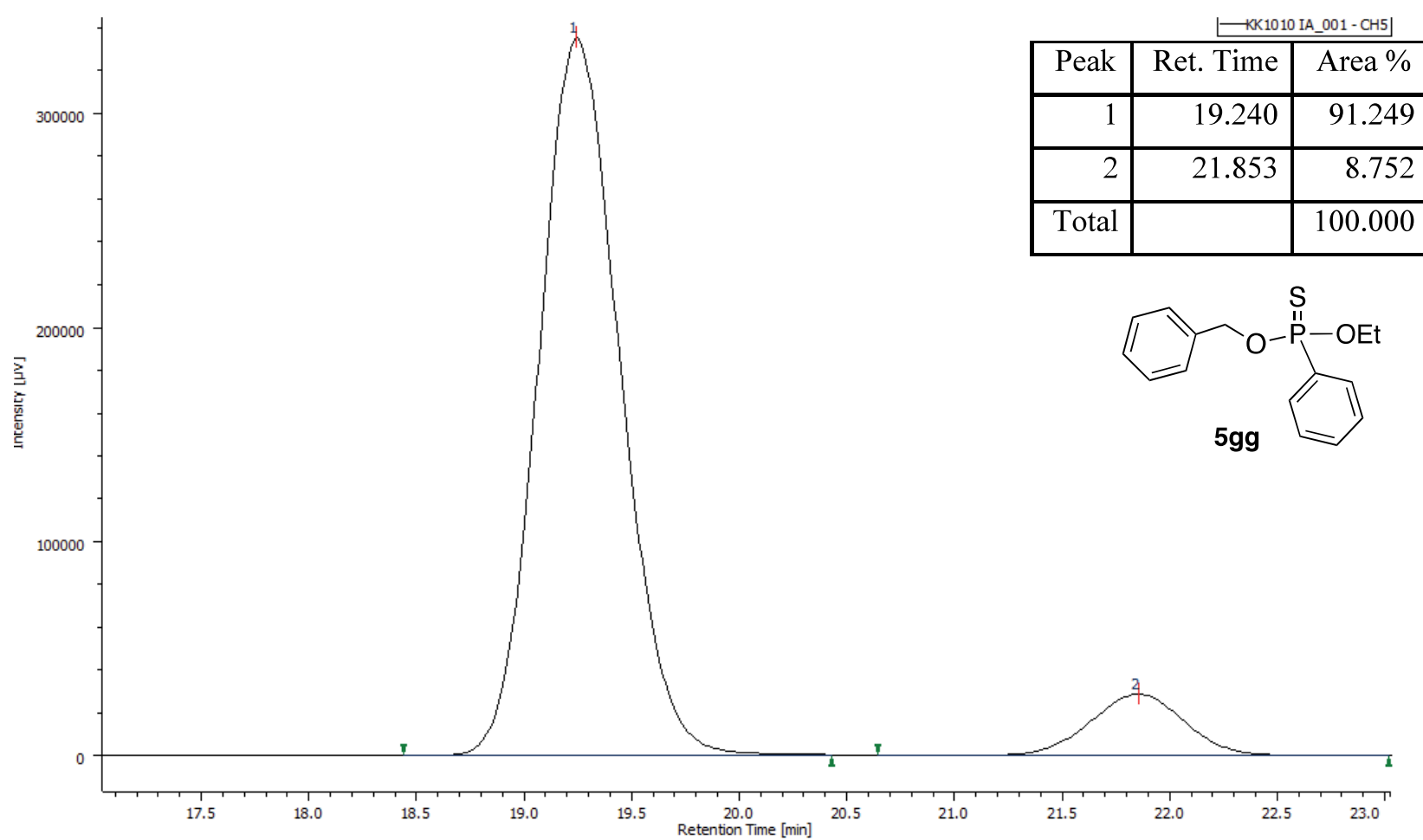
5hg synthesized from (*S*_{ax})-**2c**

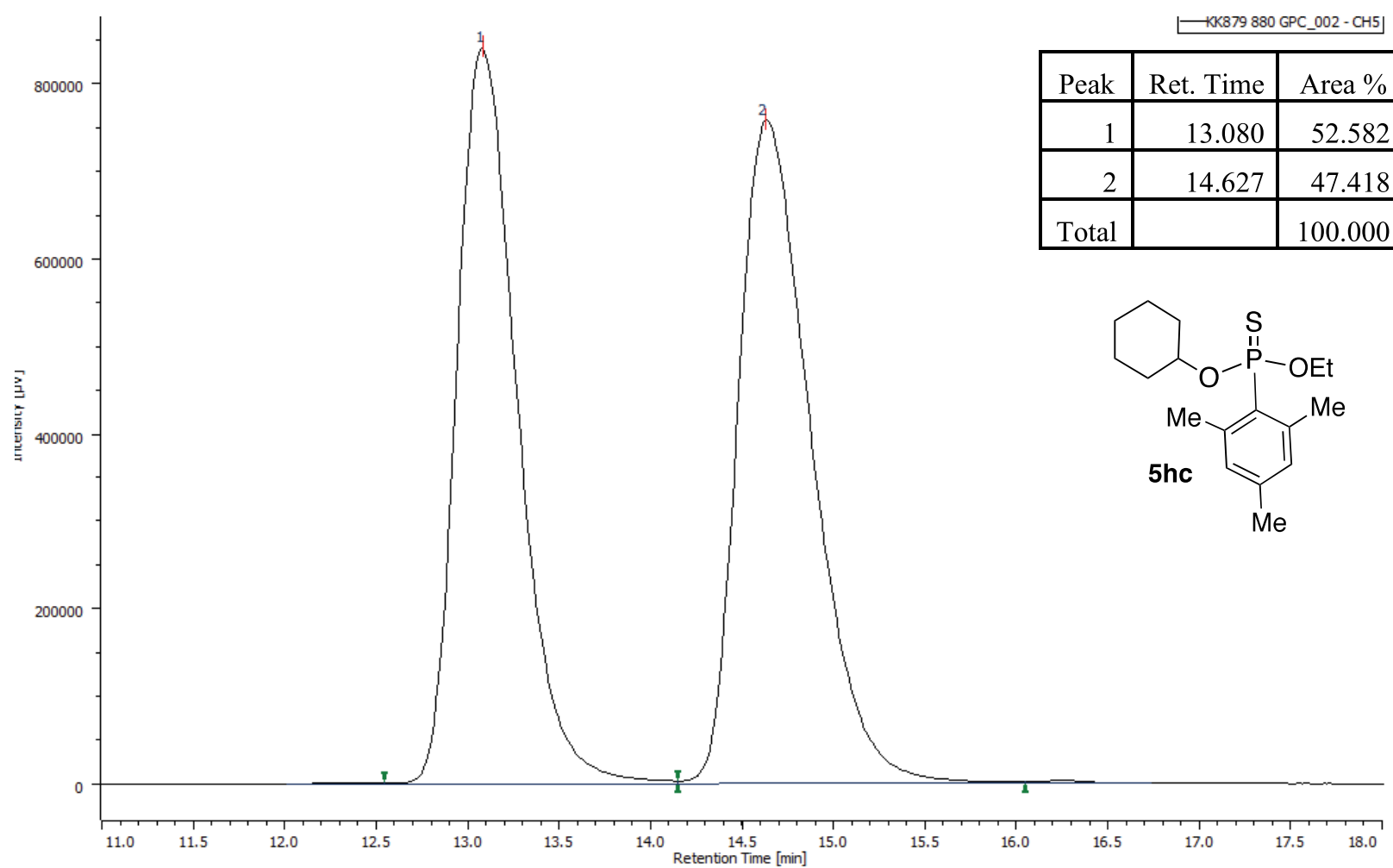
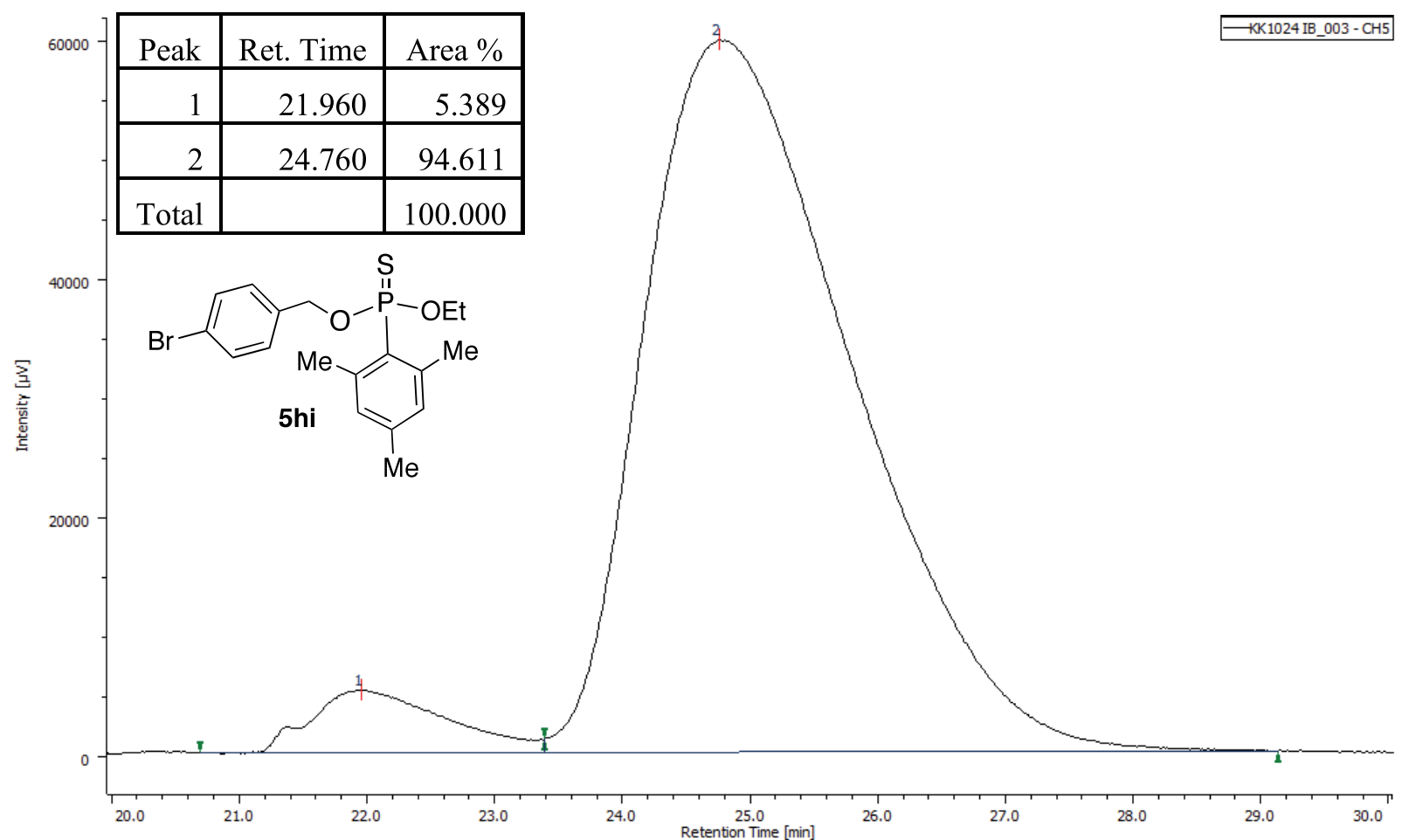


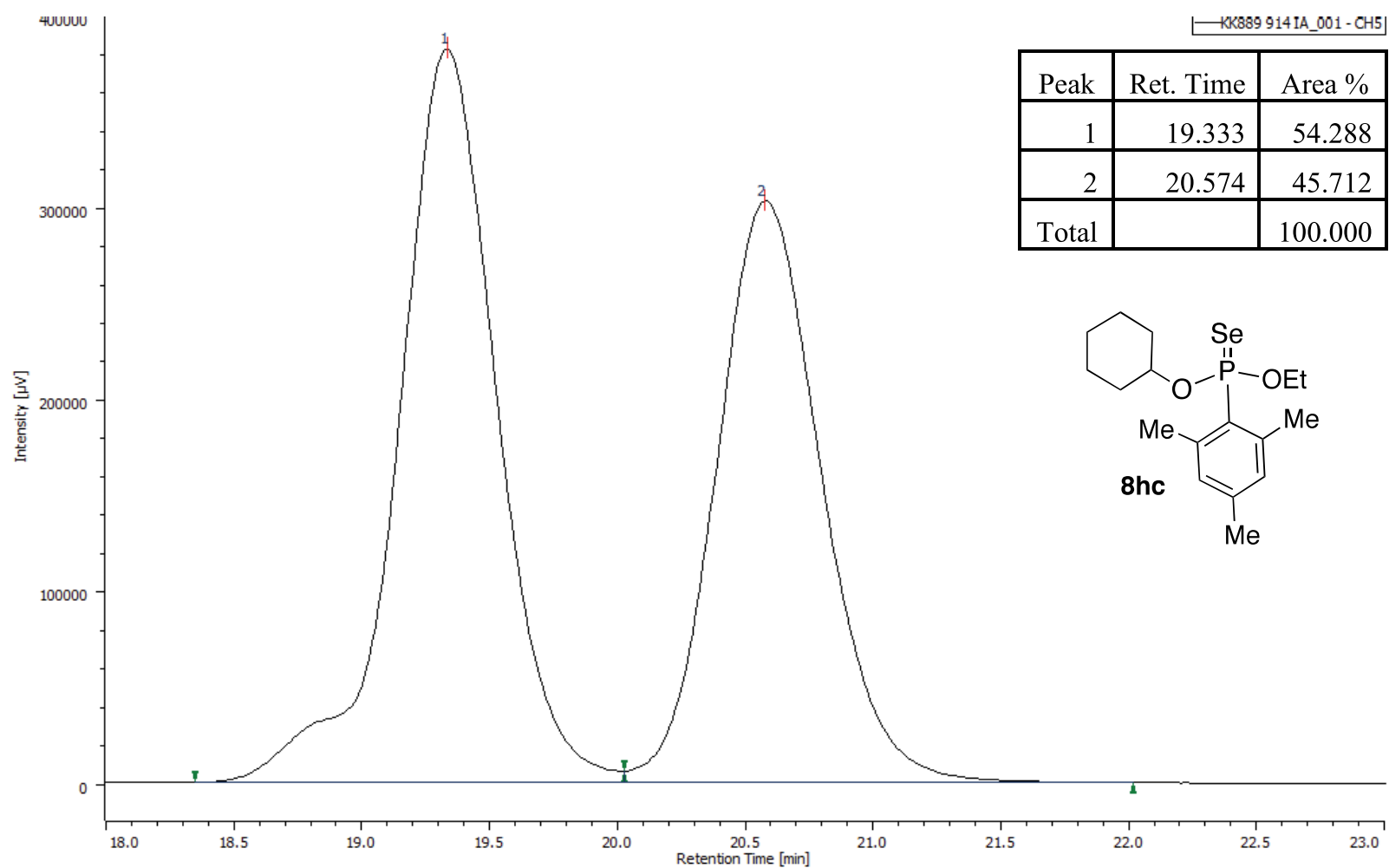
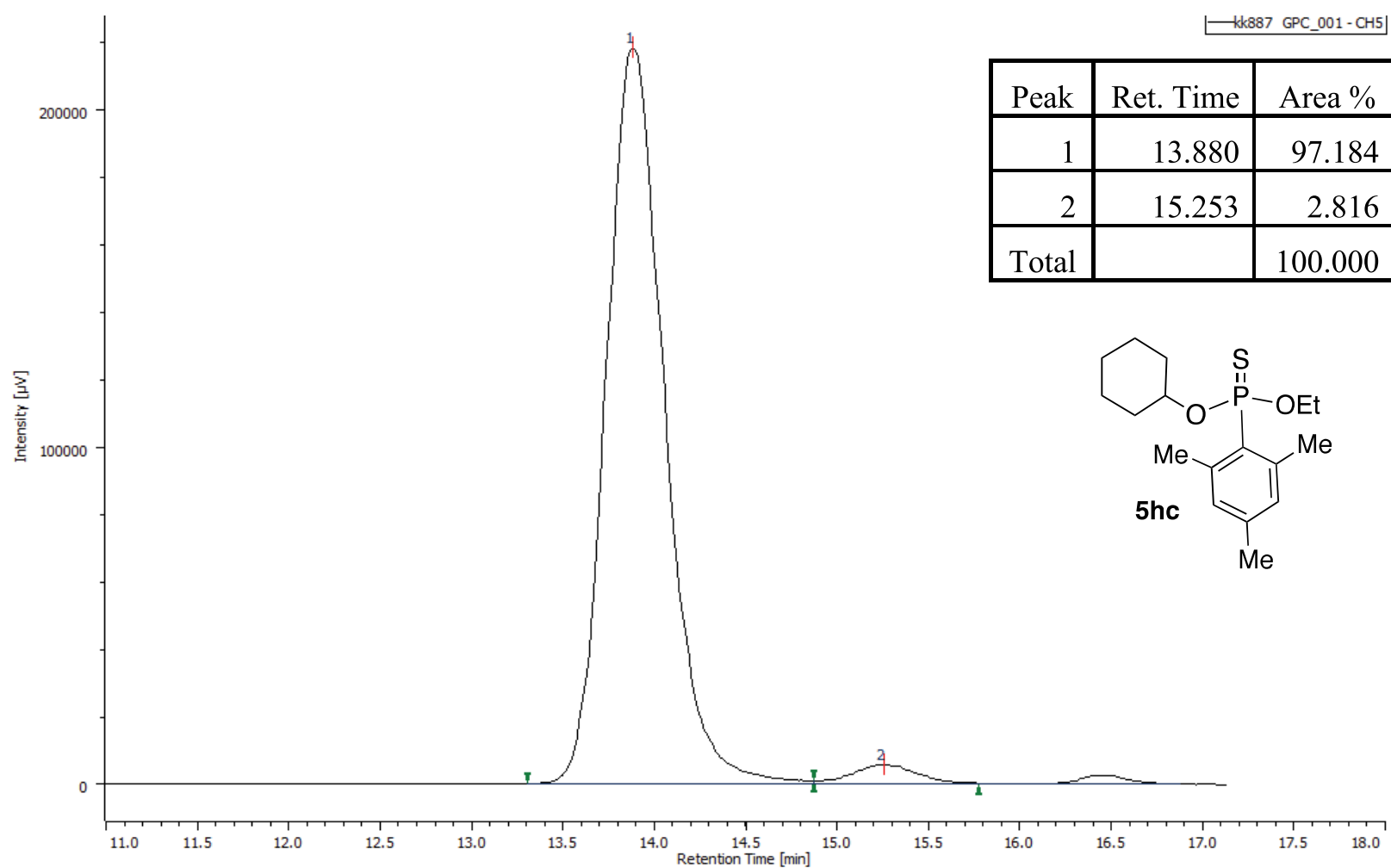
5hg synthesized from (*R*_{ax})-**3c**

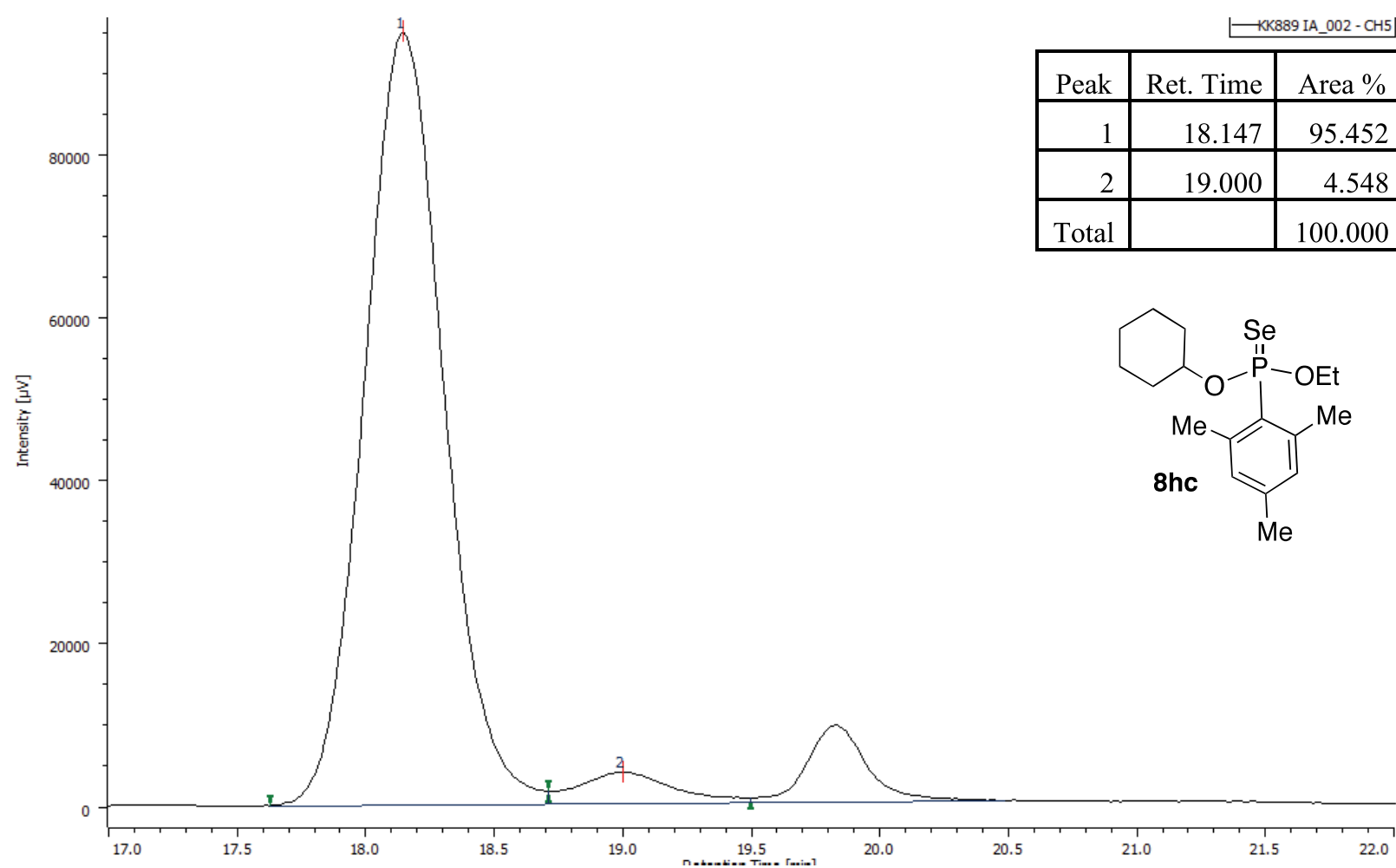












Cartesian Coordinates of Calculated Structures

(S_{ax})-2a

SCF Done: E (RB3LYP) = -1699.36719228 A.U.

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms)		
			X	Y	Z
1	6	0	-0.112003	-1.054732	-3.463574
2	6	0	-0.332886	-1.846300	-2.361234
3	6	0	-1.090723	-1.370123	-1.257859
4	6	0	-1.661812	-0.054039	-1.308741
5	6	0	-1.391107	0.743687	-2.455365
6	6	0	-0.637633	0.257629	-3.500442
7	1	0	-0.846977	-3.165002	-0.069485
8	1	0	0.474117	-1.427586	-4.298016
9	1	0	0.081195	-2.849789	-2.309688
10	6	0	-1.269411	-2.164548	-0.095038
11	6	0	-2.439813	0.426416	-0.195299
12	1	0	-1.776717	1.754837	-2.496448
13	1	0	-0.440513	0.891691	-4.359731
14	6	0	-2.498776	-0.371574	0.937935
15	6	0	-1.940286	-1.667355	0.993613
16	1	0	-2.070346	-2.246850	1.901197
17	6	0	-3.126860	1.749774	-0.209593
18	6	0	-4.094877	2.115819	-1.210323
19	6	0	-2.863061	2.666350	0.795743
20	6	0	-4.563562	1.205715	-2.198245
21	6	0	-4.654372	3.437773	-1.195012
22	6	0	-3.411444	3.964722	0.821963
23	6	0	-5.496357	1.589687	-3.135574
24	1	0	-4.188248	0.189622	-2.200698
25	6	0	-5.602482	3.804991	-2.187328
26	6	0	-4.274799	4.347733	-0.173181
27	1	0	-3.137051	4.627717	1.634221
28	6	0	-6.014362	2.905519	-3.142283
29	1	0	-5.842720	0.871685	-3.873034
30	1	0	-6.008060	4.812996	-2.166534
31	1	0	-4.702137	5.346347	-0.172730
32	1	0	-6.744956	3.196560	-3.890888
33	8	0	-3.173069	0.063482	2.079843
34	8	0	-1.986082	2.318246	1.825298
35	15	0	-2.545095	1.289041	2.989728
36	6	0	-0.951730	0.693778	3.628622
37	1	0	-0.415831	1.537559	4.068156
38	1	0	-1.140171	-0.052621	4.402368
39	1	0	-0.355637	0.260738	2.822066
40	16	0	-3.824820	1.960559	4.268951

NaOMe

SCF Done: E (RB3LYP) = -277.424456095 A.U.

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms)		
			X	Y	Z

1	6	0	-1.767305	-1.088878	0.131462
2	1	0	-1.213368	-1.968104	-0.265276
3	1	0	-1.369300	-0.937015	1.159097
4	1	0	-2.810608	-1.446719	0.276235
5	8	0	-1.671610	0.048324	-0.681379
6	11	0	-1.552155	1.594827	-1.769359

Complex1-Path A

SCF Done: E (RB3LYP) = -1976.83389337 A.U.

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms)		
			X	Y	Z
1	6	0	2.792035	4.249319	-0.863366
2	6	0	1.526158	4.303289	-0.329070
3	6	0	0.777325	3.118789	-0.092785
4	6	0	1.370206	1.844293	-0.389250
5	6	0	2.671321	1.828949	-0.964048
6	6	0	3.361600	2.997935	-1.194661
7	1	0	-0.990994	4.155705	0.603746
8	1	0	3.349982	5.163074	-1.044352
9	1	0	1.068318	5.259334	-0.089730
10	6	0	-0.556269	3.182132	0.394629
11	6	0	0.614401	0.644913	-0.138081
12	1	0	3.118267	0.879665	-1.233647
13	1	0	4.350978	2.958285	-1.640641
14	6	0	-0.694215	0.804511	0.284105
15	6	0	-1.306422	2.043078	0.560261
16	1	0	-2.361780	2.026040	0.854816
17	6	0	1.158933	-0.727155	-0.359533
18	6	0	2.346747	-1.205918	0.298787
19	6	0	0.488591	-1.614570	-1.188679
20	6	0	3.033102	-0.447552	1.288039
21	6	0	2.846396	-2.515855	-0.010228
22	6	0	0.967406	-2.903915	-1.494865
23	6	0	4.163678	-0.936712	1.903216
24	1	0	2.649913	0.526764	1.565501
25	6	0	4.025079	-2.982071	0.631825
26	6	0	2.140824	-3.335704	-0.929469
27	1	0	0.392698	-3.523758	-2.173433
28	6	0	4.676049	-2.210937	1.565559
29	1	0	4.663872	-0.339216	2.659550
30	1	0	4.395472	-3.971502	0.377346
31	1	0	2.528830	-4.323531	-1.160422
32	1	0	5.572450	-2.581122	2.053688
33	8	0	-1.488504	-0.349118	0.468640
34	8	0	-0.707469	-1.221606	-1.806793
35	15	0	-2.062858	-1.089463	-0.895443
36	6	0	-3.053835	0.137092	-1.766317
37	1	0	-3.677458	0.607762	-0.975932
38	1	0	-2.405118	0.880662	-2.234145

39	1	0	-3.671002	-0.356412	-2.518819
40	16	0	-2.965794	-2.726489	-0.309638
41	8	0	-4.247685	1.116182	0.941789
42	11	0	-3.604430	-0.677960	1.707285
43	6	0	-5.215065	2.104221	0.956434
44	1	0	-5.820267	2.129792	1.887436
45	1	0	-4.791881	3.128448	0.858975
46	1	0	-5.952964	2.013802	0.130642

TS1-Path A

SCF Done: E (RB3LYP) = -1976.82357642 A.U.

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms)		
			X	Y	Z
1	6	0	3.003195	4.281268	-0.963729
2	6	0	1.769667	4.427224	-0.373647
3	6	0	0.965743	3.297386	-0.063047
4	6	0	1.468920	1.980471	-0.341458
5	6	0	2.736759	1.870611	-0.977247
6	6	0	3.481829	2.988470	-1.279533
7	1	0	-0.708629	4.459329	0.670610
8	1	0	3.603773	5.154215	-1.201163
9	1	0	1.380312	5.416180	-0.146535
10	6	0	-0.339265	3.455765	0.478111
11	6	0	0.659099	0.835730	-0.016545
12	1	0	3.112366	0.887748	-1.234599
13	1	0	4.443778	2.876041	-1.770853
14	6	0	-0.616255	1.079581	0.463961
15	6	0	-1.138511	2.364799	0.716460
16	1	0	-2.168213	2.423317	1.059509
17	6	0	1.083892	-0.576269	-0.230009
18	6	0	2.276528	-1.133148	0.351583
19	6	0	0.261956	-1.420972	-0.968167
20	6	0	3.104898	-0.408695	1.254506
21	6	0	2.634728	-2.491973	0.058212
22	6	0	0.610022	-2.759905	-1.252508
23	6	0	4.236464	-0.975479	1.797748
24	1	0	2.831906	0.604583	1.523448
25	6	0	3.817764	-3.039542	0.623087
26	6	0	1.784425	-3.275525	-0.765823
27	1	0	-0.071548	-3.349976	-1.854217
28	6	0	4.608450	-2.300167	1.471234
29	1	0	4.846459	-0.399911	2.487879
30	1	0	4.078967	-4.066148	0.379719
31	1	0	2.064957	-4.301936	-0.985123
32	1	0	5.507103	-2.732766	1.900608
33	8	0	-1.449099	-0.012145	0.733328
34	8	0	-0.917916	-0.943880	-1.510814
35	15	0	-2.276575	-0.683008	-0.551285
36	6	0	-3.067075	0.424599	-1.755266
37	1	0	-4.146111	0.328974	-1.675694
38	1	0	-2.780247	1.453043	-1.530761

39	1	0	-2.710859	0.139128	-2.747431
40	16	0	-3.087546	-2.391332	0.021778
41	8	0	-3.917255	0.708525	0.883536
42	11	0	-3.186486	-0.705087	2.251116
43	6	0	-5.235274	0.949121	0.525581
44	1	0	-5.778234	0.038421	0.188430
45	1	0	-5.839115	1.364942	1.356887
46	1	0	-5.338669	1.685940	-0.299242

Int1-Path A

SCF Done: E (RB3LYP) = -1976.83402935 A.U.

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms)		
			X	Y	Z
1	6	0	3.252559	4.234038	-1.058303
2	6	0	2.022570	4.472901	-0.491568
3	6	0	1.147497	3.403492	-0.160745
4	6	0	1.568808	2.050132	-0.389542
5	6	0	2.835074	1.845048	-1.005328
6	6	0	3.652326	2.905005	-1.329525
7	1	0	-0.462390	4.681324	0.525137
8	1	0	3.909326	5.060736	-1.312377
9	1	0	1.691416	5.490319	-0.299619
10	6	0	-0.151545	3.653946	0.356163
11	6	0	0.688193	0.962843	-0.044704
12	1	0	3.151639	0.834307	-1.230617
13	1	0	4.610888	2.717863	-1.804591
14	6	0	-0.584824	1.284247	0.401238
15	6	0	-1.012446	2.616003	0.609943
16	1	0	-2.021312	2.780862	0.973947
17	6	0	1.030905	-0.468100	-0.235320
18	6	0	2.194755	-1.090917	0.336013
19	6	0	0.142503	-1.249324	-0.972974
20	6	0	3.066295	-0.423154	1.242279
21	6	0	2.474971	-2.464819	0.030067
22	6	0	0.430157	-2.605607	-1.273488
23	6	0	4.165836	-1.057519	1.778392
24	1	0	2.852639	0.602850	1.518757
25	6	0	3.625827	-3.082782	0.586594
26	6	0	1.578152	-3.187928	-0.802595
27	1	0	-0.285317	-3.152947	-1.875060
28	6	0	4.460622	-2.398150	1.439966
29	1	0	4.809774	-0.522686	2.470851
30	1	0	3.827995	-4.120414	0.332723
31	1	0	1.803715	-4.224743	-1.038205
32	1	0	5.334217	-2.885716	1.862515
33	8	0	-1.485973	0.278878	0.718726
34	8	0	-0.994777	-0.700495	-1.479429
35	15	0	-2.457359	-0.474327	-0.504883
36	6	0	-3.104437	0.493000	-1.930202
37	1	0	-4.190067	0.443216	-1.972645
38	1	0	-2.802766	1.533901	-1.778642

39	1	0	-2.660062	0.120027	-2.850067
40	16	0	-2.863796	-2.412491	-0.044010
41	8	0	-3.790011	0.234576	0.587984
42	11	0	-2.755969	-0.909965	2.242183
43	6	0	-5.157577	-0.022558	0.306307
44	1	0	-5.313459	-1.039342	-0.077316
45	1	0	-5.731385	0.083224	1.236474
46	1	0	-5.570446	0.700541	-0.410753

TS2-Path A

SCF Done: E (RB3LYP) = -1976.82791026 A.U.

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms)		
			X	Y	Z
1	6	0	-4.399797	-3.068907	-0.605096
2	6	0	-3.308941	-3.632541	0.014491
3	6	0	-2.126976	-2.879421	0.246921
4	6	0	-2.083134	-1.498157	-0.143066
5	6	0	-3.218764	-0.960009	-0.809798
6	6	0	-4.344108	-1.722252	-1.032533
7	1	0	-1.021841	-4.528037	1.115799
8	1	0	-5.295391	-3.657296	-0.781133
9	1	0	-3.328592	-4.673430	0.327085
10	6	0	-0.977710	-3.481697	0.826271
11	6	0	-0.888961	-0.731562	0.104109
12	1	0	-3.187989	0.065601	-1.156143
13	1	0	-5.194452	-1.286024	-1.548489
14	6	0	0.205914	-1.395436	0.633675
15	6	0	0.176826	-2.760822	0.999824
16	1	0	1.074133	-3.198375	1.424539
17	6	0	-0.717346	0.688789	-0.285002
18	6	0	-1.592785	1.747163	0.144739
19	6	0	0.383029	0.995783	-1.097355
20	6	0	-2.620606	1.557019	1.112633
21	6	0	-1.400672	3.071684	-0.374767
22	6	0	0.545727	2.312105	-1.617637
23	6	0	-3.427097	2.599923	1.515784
24	1	0	-2.766833	0.570029	1.537358
25	6	0	-2.260541	4.118564	0.049250
26	6	0	-0.333485	3.309436	-1.285249
27	1	0	1.389010	2.488894	-2.274107
28	6	0	-3.256773	3.894270	0.972836
29	1	0	-4.200908	2.424570	2.257838
30	1	0	-2.107464	5.111945	-0.365281
31	1	0	-0.206706	4.309683	-1.691773
32	1	0	-3.903601	4.706309	1.291338
33	8	0	1.370251	-0.696527	0.905422
34	8	0	1.275980	0.047918	-1.435827
35	15	0	2.631018	-0.467999	-0.283964
36	6	0	2.961856	-1.737593	-1.574070
37	1	0	3.957130	-2.161738	-1.455609
38	1	0	2.217328	-2.528318	-1.440448

39	1	0	2.829507	-1.299403	-2.560865
40	16	0	3.512935	1.373595	-0.150780
41	8	0	3.572803	-1.295774	0.924877
42	11	0	1.922768	1.195859	1.981310
43	6	0	4.989146	-1.327245	0.870205
44	1	0	5.415134	-0.317828	0.891836
45	1	0	5.330856	-1.887556	1.746471
46	1	0	5.370296	-1.840068	-0.025458

Complex2-Path A

SCF Done: E (RB3LYP) = -1976.85599591 A.U.

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms)		
			X	Y	Z
1	6	0	-4.134675	-3.072701	-0.668752
2	6	0	-3.002311	-3.602128	-0.096048
3	6	0	-1.828378	-2.817183	0.060449
4	6	0	-1.829142	-1.449357	-0.371299
5	6	0	-3.016220	-0.940760	-0.968611
6	6	0	-4.134629	-1.730071	-1.114851
7	1	0	-0.653287	-4.386352	0.984506
8	1	0	-5.025757	-3.682436	-0.785851
9	1	0	-2.984941	-4.634749	0.243131
10	6	0	-0.650131	-3.357827	0.634410
11	6	0	-0.649686	-0.633838	-0.219946
12	1	0	-3.022646	0.084402	-1.318417
13	1	0	-5.025783	-1.318853	-1.579961
14	6	0	0.475535	-1.252858	0.294904
15	6	0	0.483767	-2.592846	0.748461
16	1	0	1.386553	-2.998572	1.190681
17	6	0	-0.677397	0.812261	-0.586486
18	6	0	-1.438616	1.732184	0.201987
19	6	0	0.043864	1.254946	-1.724337
20	6	0	-2.105449	1.351783	1.406068
21	6	0	-1.535763	3.114048	-0.186530
22	6	0	-0.128782	2.643710	-2.106268
23	6	0	-2.822468	2.260939	2.151292
24	1	0	-2.036233	0.323521	1.742457
25	6	0	-2.287187	4.022990	0.601723
26	6	0	-0.874050	3.529918	-1.370054
27	1	0	0.313027	2.952583	-3.055616
28	6	0	-2.925594	3.613902	1.750095
29	1	0	-3.314258	1.933495	3.063463
30	1	0	-2.346386	5.059614	0.277273
31	1	0	-0.980625	4.562694	-1.695952
32	1	0	-3.497468	4.318381	2.346412
33	8	0	1.655211	-0.488496	0.441049
34	8	0	0.873685	0.511440	-2.400381
35	15	0	3.074160	-0.950739	-0.210411
36	6	0	2.732915	-1.927003	-1.692413
37	1	0	3.666024	-2.065303	-2.241288
38	1	0	2.315984	-2.896497	-1.414527

39	1	0	2.003514	-1.354841	-2.277059
40	16	0	4.268761	0.621246	-0.407590
41	8	0	3.699123	-2.068090	0.786559
42	11	0	2.506206	1.888245	-2.014725
43	6	0	4.203972	-1.696436	2.086914
44	1	0	5.030019	-0.988532	1.986383
45	1	0	3.408266	-1.255912	2.693986
46	1	0	4.555104	-2.620377	2.546757

(S_{ax},S_p)-**4a**

SCF Done: E (RB3LYP) = -1976.86348065 A.U.

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms)		
			X	Y	Z
1	6	0	2.731704	-5.199823	-0.174263
2	6	0	4.018827	-5.377653	0.312494
3	6	0	4.701622	-4.204673	0.802307
4	6	0	4.050244	-2.925238	0.800806
5	6	0	2.719549	-2.831986	0.312731
6	6	0	2.070130	-3.945531	-0.161840
7	1	0	6.532077	-5.243059	1.284331
8	6	0	6.038224	-4.278362	1.286122
9	6	0	4.748203	-1.786391	1.286547
10	1	0	2.214358	-1.870236	0.326654
11	1	0	1.052474	-3.881369	-0.529407
12	6	0	6.038650	-1.896530	1.750162
13	6	0	6.687582	-3.154674	1.745718
14	1	0	4.240382	-0.825334	1.286421
15	1	0	6.562117	-1.020123	2.120600
16	1	0	7.707041	-3.233582	2.111247
17	6	0	4.851970	-9.163173	3.799941
18	6	0	5.480055	-9.558616	2.637801
19	6	0	5.441380	-8.758289	1.470318
20	6	0	4.735347	-7.507695	1.489038
21	6	0	4.096133	-7.131785	2.706011
22	6	0	4.154032	-7.934637	3.825482
23	1	0	6.630929	-10.096363	0.252777
24	1	0	4.890368	-9.787394	4.687750
25	1	0	6.021125	-10.501684	2.599486
26	6	0	6.089133	-9.152635	0.265177
27	6	0	4.698487	-6.706391	0.308144
28	1	0	3.549617	-6.194468	2.746980
29	1	0	3.654967	-7.618917	4.738017
30	6	0	5.335864	-7.115531	-0.885968
31	6	0	6.041064	-8.372823	-0.857459
32	1	0	6.541804	-8.674115	-1.773628
33	8	0	2.012723	-6.312957	-0.618030
34	8	0	5.298272	-6.419816	-1.988689
35	15	0	1.431408	-6.602863	-2.120235
36	16	0	1.797130	-5.190221	-3.458155
37	8	0	1.913027	-8.081721	-2.495462
38	6	0	3.090378	-8.383040	-3.297053

39	1	0	3.293633	-9.438072	-3.115503
40	1	0	2.848239	-8.221629	-4.350188
41	1	0	3.943853	-7.771164	-2.994348
42	6	0	-0.317449	-6.915334	-1.775042
43	1	0	-0.817856	-7.227549	-2.693245
44	1	0	-0.392564	-7.707005	-1.025675
45	1	0	-0.782749	-6.003923	-1.395311
46	11	0	4.338556	-4.606924	-2.458142

Complex I-Path B

SCF Done: E (RB3LYP) = -1976.81303459 A.U.

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms)		
			X	Y	Z
1	6	0	-0.407992	1.438964	0.075590
2	6	0	0.832353	0.893849	-0.213225
3	6	0	1.950308	1.794900	-0.309702
4	6	0	1.761865	3.184887	-0.002030
5	6	0	0.469319	3.658169	0.344066
6	6	0	-0.607845	2.806528	0.357977
7	1	0	3.391774	0.341482	-1.022490
8	6	0	3.239189	1.376539	-0.742722
9	6	0	2.867481	4.073691	-0.085231
10	1	0	0.335199	4.713726	0.561669
11	1	0	-1.614566	3.162534	0.550578
12	6	0	4.105213	3.628291	-0.484461
13	6	0	4.284935	2.267962	-0.827845
14	1	0	2.709481	5.120489	0.159556
15	1	0	4.940517	4.318498	-0.551747
16	1	0	5.256433	1.924161	-1.169969
17	6	0	3.551975	-3.180581	1.686581
18	6	0	2.812671	-3.661515	0.631638
19	6	0	1.930428	-2.814668	-0.091277
20	6	0	1.833610	-1.427472	0.265611
21	6	0	2.599435	-0.970870	1.374985
22	6	0	3.431746	-1.823504	2.065842
23	1	0	1.214138	-4.369997	-1.417568
24	1	0	4.217207	-3.839722	2.235711
25	1	0	2.880830	-4.706260	0.340657
26	6	0	1.123686	-3.322904	-1.143278
27	6	0	0.941928	-0.569903	-0.470190
28	1	0	2.519461	0.065367	1.681259
29	1	0	3.999806	-1.449764	2.912553
30	6	0	0.122922	-1.152873	-1.427005
31	6	0	0.220305	-2.514795	-1.787049
32	1	0	-0.421393	-2.887882	-2.577636
33	8	0	-1.529073	0.597954	0.128158
34	8	0	-0.809928	-0.381136	-2.114367
35	15	0	-2.200812	0.111891	-1.359951
36	16	0	-3.092031	1.502674	-2.355404
37	6	0	-3.117216	-1.342864	-0.828909
38	1	0	-2.425126	-2.173477	-0.662090

39	1	0	-3.665830	-1.132042	0.131212
40	1	0	-3.820024	-1.600374	-1.623698
41	8	0	-4.227360	-0.851807	1.864960
42	6	0	-5.371964	-1.576104	2.116012
43	1	0	-6.265171	-0.946180	2.313254
44	1	0	-5.661641	-2.232356	1.265290
45	1	0	-5.288827	-2.255382	2.991127
46	11	0	-2.631173	0.310993	2.120847

TS1-Path B

SCF Done: E (RB3LYP) = -1976.80747232 A.U.

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms)		
			X	Y	Z
1	6	0	-0.498964	1.127750	0.495923
2	6	0	0.744937	0.719564	0.043792
3	6	0	1.748603	1.731984	-0.158797
4	6	0	1.464267	3.090825	0.208947
5	6	0	0.178814	3.427545	0.706996
6	6	0	-0.797752	2.469288	0.822860
7	1	0	3.228202	0.448953	-1.087605
8	6	0	3.010189	1.456550	-0.756504
9	6	0	2.460427	4.087680	0.026288
10	1	0	-0.035523	4.462716	0.956818
11	1	0	-1.810913	2.726122	1.118107
12	6	0	3.679964	3.777400	-0.527014
13	6	0	3.947235	2.449573	-0.934117
14	1	0	2.230476	5.108545	0.319531
15	1	0	4.430477	4.549182	-0.668330
16	1	0	4.898809	2.211624	-1.400103
17	6	0	4.100965	-3.146562	1.257077
18	6	0	3.255000	-3.643655	0.293036
19	6	0	2.193648	-2.856781	-0.228068
20	6	0	2.019172	-1.510059	0.236175
21	6	0	2.900266	-1.038301	1.249828
22	6	0	3.909721	-1.833509	1.746028
23	1	0	1.436927	-4.396907	-1.549900
24	1	0	4.905332	-3.760300	1.651057
25	1	0	3.378431	-4.657054	-0.079957
26	6	0	1.286415	-3.384584	-1.184963
27	6	0	0.947149	-0.713113	-0.297316
28	1	0	2.767335	-0.035354	1.638364
29	1	0	4.563875	-1.448424	2.522880
30	6	0	0.033149	-1.318848	-1.153973
31	6	0	0.219645	-2.642034	-1.623403
32	1	0	-0.494753	-3.037579	-2.337238
33	8	0	-1.504039	0.180573	0.706942
34	8	0	-1.054861	-0.620264	-1.626465
35	15	0	-2.418836	-0.323471	-0.648631
36	16	0	-3.485562	0.943617	-1.651136
37	6	0	-2.903029	-2.051287	-0.322178
38	1	0	-2.111027	-2.540041	0.251204

39	1	0	-3.833251	-2.068026	0.234551
40	1	0	-2.991930	-2.544408	-1.293695
41	8	0	-4.089099	-0.178098	1.358383
42	6	0	-5.436296	-0.197165	1.039283
43	1	0	-5.713746	0.586889	0.311574
44	1	0	-5.762803	-1.159221	0.584174
45	1	0	-6.089201	-0.056630	1.923071
46	11	0	-2.637116	0.340765	2.651918

Int1-Path B

SCF Done: E (RB3LYP) = -1976.81403327 A.U.

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms)		
			X	Y	Z
1	6	0	-0.492011	1.106387	0.516560
2	6	0	0.754089	0.687856	0.079753
3	6	0	1.759243	1.696868	-0.144797
4	6	0	1.479371	3.065507	0.188371
5	6	0	0.189881	3.419564	0.662413
6	6	0	-0.786269	2.463349	0.793372
7	1	0	3.234363	0.393133	-1.048830
8	6	0	3.020210	1.407324	-0.737284
9	6	0	2.478866	4.055424	-0.012842
10	1	0	-0.027347	4.462491	0.875361
11	1	0	-1.805449	2.742427	1.051680
12	6	0	3.699160	3.729988	-0.555584
13	6	0	3.961214	2.393052	-0.934760
14	1	0	2.250121	5.083512	0.255846
15	1	0	4.452416	4.496327	-0.712100
16	1	0	4.911591	2.141745	-1.396369
17	6	0	4.140992	-3.194875	1.165838
18	6	0	3.273456	-3.671547	0.209341
19	6	0	2.198062	-2.877874	-0.268019
20	6	0	2.026511	-1.543928	0.230975
21	6	0	2.929578	-1.093909	1.235575
22	6	0	3.954833	-1.895048	1.689657
23	1	0	1.423717	-4.379351	-1.623932
24	1	0	4.956979	-3.814350	1.525926
25	1	0	3.392312	-4.675247	-0.191307
26	6	0	1.270956	-3.381416	-1.220664
27	6	0	0.937249	-0.742446	-0.256528
28	1	0	2.800454	-0.101406	1.652429
29	1	0	4.624829	-1.524487	2.460444
30	6	0	-0.020729	-1.324159	-1.094560
31	6	0	0.187596	-2.637085	-1.607487
32	1	0	-0.533162	-3.020270	-2.321930
33	8	0	-1.485894	0.178553	0.799414
34	8	0	-1.110619	-0.638058	-1.501610
35	15	0	-2.575427	-0.360232	-0.463751
36	16	0	-3.462452	0.908695	-1.690330
37	6	0	-2.859669	-2.180000	-0.391080
38	1	0	-2.078401	-2.626447	0.230624

39	1	0	-3.833738	-2.423505	0.025718
40	1	0	-2.766412	-2.578506	-1.400956
41	8	0	-3.788435	-0.203082	1.012035
42	6	0	-5.180011	-0.303332	0.771038
43	1	0	-5.512965	0.447843	0.047431
44	1	0	-5.469569	-1.293616	0.387764
45	1	0	-5.710398	-0.153625	1.721801
46	11	0	-2.656543	0.641084	2.586355

Int2-Path B

SCF Done: E (RB3LYP) = -1976.81244930 A.U.

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms)		
			X	Y	Z
1	6	0	-0.339858	1.204449	0.200757
2	6	0	0.900448	0.698091	-0.155074
3	6	0	1.962174	1.633972	-0.438123
4	6	0	1.740177	3.040108	-0.252971
5	6	0	0.448131	3.495917	0.109691
6	6	0	-0.573418	2.599672	0.298333
7	1	0	3.407292	0.187297	-1.157170
8	6	0	3.228803	1.233723	-0.949622
9	6	0	2.793131	3.960833	-0.502941
10	1	0	0.265562	4.563938	0.187821
11	1	0	-1.585023	2.976641	0.437897
12	6	0	4.016528	3.529982	-0.957359
13	6	0	4.224409	2.152182	-1.197770
14	1	0	2.603290	5.019273	-0.344450
15	1	0	4.812760	4.242078	-1.152218
16	1	0	5.177636	1.813563	-1.592961
17	6	0	4.096627	-3.294203	1.117649
18	6	0	3.247348	-3.749391	0.134590
19	6	0	2.213788	-2.924722	-0.381229
20	6	0	2.068810	-1.585113	0.108713
21	6	0	2.952409	-1.155314	1.138101
22	6	0	3.936032	-1.985877	1.629277
23	1	0	1.445778	-4.397821	-1.772032
24	1	0	4.879350	-3.937535	1.508416
25	1	0	3.348178	-4.758514	-0.257108
26	6	0	1.306395	-3.398355	-1.367951
27	6	0	1.020512	-0.753476	-0.414097
28	1	0	2.836735	-0.157234	1.546241
29	1	0	4.591239	-1.633641	2.420944
30	6	0	0.062866	-1.312052	-1.266489
31	6	0	0.254547	-2.624755	-1.784570
32	1	0	-0.452045	-2.987886	-2.523103
33	8	0	-1.375335	0.363211	0.587914
34	8	0	-1.015424	-0.597294	-1.669712
35	15	0	-2.451259	-0.368575	-0.582848
36	16	0	-3.455102	0.895567	-1.744590
37	6	0	-2.681425	-2.199001	-0.537569
38	1	0	-1.925738	-2.625987	0.127215

39	1	0	-3.667356	-2.469223	-0.170743
40	1	0	-2.531644	-2.592431	-1.541314
41	8	0	-3.579652	-0.277176	0.933460
42	6	0	-4.948392	-0.624564	0.805662
43	1	0	-5.341586	-0.354031	-0.181650
44	1	0	-5.121103	-1.695484	0.984462
45	1	0	-5.527742	-0.077532	1.563195
46	11	0	-2.884177	1.552376	1.745734

TS2-Path B

SCF Done: E (RB3LYP) = -1976.81387655 A.U.

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms)		
			X	Y	Z
1	6	0	-0.055504	0.277637	0.034198
2	6	0	0.901580	0.008683	-0.938954
3	6	0	1.913319	1.009270	-1.175722
4	6	0	2.005234	2.161095	-0.321291
5	6	0	1.083824	2.304845	0.752291
6	6	0	0.068469	1.385682	0.919116
7	1	0	2.727936	0.089703	-2.955558
8	6	0	2.811280	0.928989	-2.276295
9	6	0	3.012282	3.134381	-0.561805
10	1	0	1.208445	3.126981	1.453293
11	1	0	-0.621139	1.432688	1.760197
12	6	0	3.878089	3.008486	-1.622686
13	6	0	3.762460	1.900470	-2.494486
14	1	0	3.080643	3.987832	0.108211
15	1	0	4.640764	3.760664	-1.800016
16	1	0	4.428285	1.817185	-3.348207
17	6	0	4.024004	-4.085268	-1.985245
18	6	0	2.836361	-4.308652	-2.644083
19	6	0	1.757155	-3.393054	-2.545258
20	6	0	1.908666	-2.194304	-1.771141
21	6	0	3.140115	-2.014392	-1.079649
22	6	0	4.165366	-2.929625	-1.184941
23	1	0	0.407983	-4.557030	-3.776117
24	1	0	4.840571	-4.796622	-2.064492
25	1	0	2.699303	-5.203682	-3.245925
26	6	0	0.510628	-3.655859	-3.176612
27	6	0	0.808968	-1.267658	-1.684125
28	1	0	3.268938	-1.147036	-0.443330
29	1	0	5.089203	-2.763560	-0.637907
30	6	0	-0.426435	-1.612142	-2.246898
31	6	0	-0.550684	-2.806819	-3.016123
32	1	0	-1.510353	-3.004168	-3.482296
33	8	0	-1.105121	-0.567603	0.247626
34	8	0	-1.488658	-0.795865	-2.180980
35	15	0	-2.538628	-0.457165	-0.685079
36	16	0	-3.322113	1.148412	-1.728312
37	6	0	-3.255419	-2.138103	-0.834023
38	1	0	-2.439754	-2.848117	-0.675021

39	1	0	-4.038741	-2.318673	-0.099308
40	1	0	-3.638477	-2.270597	-1.845892
41	8	0	-3.250890	-0.069965	0.851292
42	6	0	-4.651851	0.082762	1.004548
43	1	0	-5.034021	0.942760	0.442818
44	1	0	-5.211850	-0.806480	0.680634
45	1	0	-4.842585	0.227334	2.073130
46	11	0	-1.796747	2.647740	-0.310038

Complex2-Path B

SCF Done: E (RB3LYP) = -1976.86126737 A.U.

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms)		
			X	Y	Z
1	6	0	-0.181452	0.663438	1.020506
2	6	0	0.744435	0.427053	0.013625
3	6	0	1.750604	1.439206	-0.195638
4	6	0	1.796711	2.605521	0.641267
5	6	0	0.836601	2.749374	1.677752
6	6	0	-0.136044	1.797279	1.867594
7	1	0	2.677063	0.443507	-1.873801
8	6	0	2.713081	1.320667	-1.238203
9	6	0	2.800935	3.585781	0.414660
10	1	0	0.882160	3.619466	2.326643
11	1	0	-0.868125	1.891888	2.661063
12	6	0	3.718563	3.434369	-0.598765
13	6	0	3.668408	2.292520	-1.434274
14	1	0	2.830338	4.459287	1.060897
15	1	0	4.482252	4.189244	-0.761077
16	1	0	4.393164	2.181335	-2.235286
17	6	0	3.458134	-4.018658	-0.222457
18	6	0	2.519855	-4.080999	-1.230925
19	6	0	1.598108	-3.027709	-1.445941
20	6	0	1.636071	-1.864612	-0.604001
21	6	0	2.614298	-1.838052	0.432473
22	6	0	3.496700	-2.881685	0.615479
23	1	0	0.593659	-3.964404	-3.120000
24	1	0	4.158216	-4.834422	-0.068395
25	1	0	2.470750	-4.950495	-1.882979
26	6	0	0.619148	-3.085691	-2.478450
27	6	0	0.701527	-0.806125	-0.825544
28	1	0	2.658907	-0.979647	1.095275
29	1	0	4.228789	-2.829378	1.417188
30	6	0	-0.278660	-0.887929	-1.842435
31	6	0	-0.276305	-2.069754	-2.668135
32	1	0	-1.023178	-2.116742	-3.456024
33	8	0	-1.160135	-0.305026	1.264126
34	8	0	-1.171517	0.039908	-2.046528
35	15	0	-2.763258	-0.116562	1.093706
36	16	0	-3.425763	1.686031	0.610041
37	6	0	-3.229808	-1.445432	-0.037037
38	1	0	-2.772289	-2.379439	0.297991

39	1	0	-4.317643	-1.543166	-0.065722
40	1	0	-2.845012	-1.172033	-1.024621
41	8	0	-3.205385	-0.582970	2.581867
42	6	0	-4.572113	-0.493925	3.020016
43	1	0	-4.941695	0.531144	2.930763
44	1	0	-5.213911	-1.170152	2.445232
45	1	0	-4.572374	-0.799806	4.066484
46	11	0	-1.403307	1.978558	-1.275942

(S_{ax},R_p)-**4a**

SCF Done: E (RB3LYP) = -1976.86453038 A.U.

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms)		
			X	Y	Z
1	6	0	2.895564	-5.004052	-0.016383
2	6	0	4.217918	-5.128114	0.388777
3	6	0	4.881252	-3.916260	0.813510
4	6	0	4.186557	-2.660083	0.797354
5	6	0	2.828530	-2.624640	0.379575
6	6	0	2.191821	-3.775991	-0.012972
7	1	0	6.754709	-4.879838	1.279956
8	6	0	6.232654	-3.931176	1.256567
9	6	0	4.866939	-1.481039	1.207637
10	1	0	2.297278	-1.677010	0.380264
11	1	0	1.154712	-3.766411	-0.329470
12	6	0	6.176988	-1.533218	1.623359
13	6	0	6.861527	-2.772027	1.651093
14	1	0	4.327993	-0.537204	1.192408
15	1	0	6.686467	-0.627096	1.937700
16	1	0	7.892701	-2.807365	1.989440
17	6	0	4.065696	-9.578778	3.121078
18	6	0	5.034028	-9.744573	2.153064
19	6	0	5.338019	-8.714401	1.230803
20	6	0	4.627413	-7.467520	1.290916
21	6	0	3.641209	-7.328991	2.310385
22	6	0	3.369579	-8.351882	3.194775
23	1	0	6.889074	-9.816821	0.196312
24	1	0	3.843491	-10.376623	3.823372
25	1	0	5.588898	-10.677861	2.084734
26	6	0	6.348618	-8.872972	0.237895
27	6	0	4.939921	-6.432463	0.353988
28	1	0	3.098984	-6.392938	2.396596
29	1	0	2.611989	-8.209005	3.961068
30	6	0	5.955617	-6.601888	-0.631715
31	6	0	6.647143	-7.872477	-0.644105
32	1	0	7.422144	-7.994301	-1.395619
33	8	0	2.165897	-6.138906	-0.395593
34	8	0	6.258574	-5.698616	-1.507206
35	15	0	2.043799	-6.740849	-1.909645
36	16	0	2.500075	-5.460056	-3.347816
37	6	0	2.905155	-8.326130	-1.898603
38	1	0	2.582518	-8.893313	-1.022705

39	1	0	2.655481	-8.866770	-2.813848	44	1	0	-1.487741	-6.925853	-2.056125
40	1	0	3.981655	-8.158334	-1.840483	45	1	0	-0.624806	-5.801923	-0.969541
41	8	0	0.514379	-7.253900	-1.942718	46	11	0	4.820100	-4.365870	-2.272482
42	6	0	-0.586401	-6.326310	-1.928471	<hr/>					
43	1	0	-0.495902	-5.609310	-2.748901						

REFERENCES

- (1) Ross, B. S.; Ganapati Reddy, P.; Zhang, H.-R.; Rachakonda, S.; Sofia, M. J. Synthesis of Diastereomerically Pure Nucleotide Phosphoramidates. *J. Org. Chem.* **2011**, *76*, 8311–8319.
- (2) Van Bochove, M. A.; Swart, M.; Bickelhaupt, F. M. Stepwise Walden Inversion in Nucleophilic Substitution at Phosphorus. *Phys. Chem. Chem. Phys.* **2009**, *11*, 259–267.
- (3) Kolodiaznyi, O. I.; Kolodiazna, A. Nucleophilic Substitution at Phosphorus: Stereochemistry and Mechanisms. *Tetrahedron Asymmetry* **2017**, *28*, 1651–1674.
- (4) Kolodiaznyi, O. I. Stereoselective Oxidation of *N*-Phosphor (III) Substituted Amino Acids. *Tetrahedron Lett.* **1995**, *36*, 3921–3924.
- (5) Kobayashi, Y.; Morisawa, F.; Saigo, K. A New Hydrogen-Bonding Motif for Chiral Recognition in the Diastereomeric Salts of Racemic 1-Phenylethylamine Derivatives with Enantiopure *O*-Ethyl Phenylphosphonothioic Acid. *Org. Lett.* **2004**, *6*, 4227–4230.
- (6) Williams, D. R.; Brown, D. L.; Benbow, J. W. Studies of Stemonal Alkaloids. Total Synthesis of (+)-Croomine. *J. Am. Chem. Soc.* **1989**, *111*, 1923–1925.
- (7) Ferry, A.; Stemper, J.; Marinetti, A.; Voituriez, A.; Guinchard, X. Thiophostone-Derived Brønsted Acids in the Organocatalyzed Transfer Hydrogenation of Quinolines: Influence of the *P*-Stereogenicity. *Eur. J. Org. Chem.* **2014**, *2014*, 188–193.
- (8) Ferry, A.; Stemper, J.; Marinetti, A.; Voituriez, A.; Guinchard, X. Thiophostone-Derived Brønsted Acids in the Organocatalyzed Transfer Hydrogenation of Quinolines: Influence of the *P*-Stereogenicity. *Eur. J. Org. Chem.* **2014**, *2014*, 188–193.
- (9) Kobayashi, Y.; Morisawa, F.; Saigo, K. Enantiopure *O*-Substituted Phenylphosphonothioic Acids: Chiral Recognition Ability during Salt Crystallization and Chiral Recognition Mechanism. *J. Org. Chem.* **2006**, *71*, 606–615.

List of Publications

1. "Hydrolysis of phosphonothioates with a binaphthyl group: *P*-stereogenic *O*-binaphthyl phosphonothioic acids and their use as optically active ligands and chiral discriminating agents"
Kuwabara, K.; Maekawa, Y.; Minoura, M.; Murai, T. *Org. Lett.* **2018**, *20*, 1375-1379.
2. "Synthesis of *P*-stereogenic phosphonothioates via alcoholysis of phosphonothioates with a binaphthyl group"
Kuwabara, K.; Maekawa, Y.; Ebihara, M.; Maruyama, T.; Murai, T. *Heteroatom Chem.* **2018**, e21448.

Following publications are not included in this thesis.

1. "Phosphonoselenoic acid esters from the reaction between phosphoroselenoyl chlorides and Grignard reagents: synthetic and stereochemical aspects"
Murai, T.; Maekawa, Y.; Hirai, Y.; Kuwabara, K.; Minoura, M. *RSC Adv.* **2016**, *6*, 15180-15183.
2. "Synthesis of *P*-stereogenic phosphinates via an axis-to-center chirality transfer by the reaction of phosphonates having a binaphthyl group with Grignard reagents"
Maekawa, Y.; Kuwabara, K.; Sugiyama, A.; Iwata, K.; Maruyama, T.; Murai, T. *Chem. Lett.* **2017**, *46*, 1068-1071.

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