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Phosphorothioic Acids and Related Compounds as Surrogates for H_2S—Synthesis of Chiral Tetrahydrothiophenes

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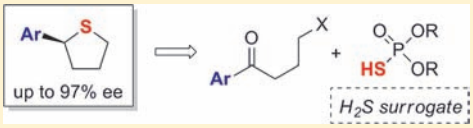
Supporting Information

ABSTRACT: The convenient preparation of chiral tetrahydrothiophenes (THTs) in high enantiopurity via phosphorothioic acids and related compounds is reported. We consider these to be safer alternatives to the use of H_2S which is a highly toxic gas. Each of the THTs is derived from a common intermediate, thereby greatly enhancing the flexibility of the synthesis. The key transformation is a base-promoted, intramolecular, carbon−sulfur bond-forming event. These reactions are highly stereospecific as they operate through a double S_N2 displacement mechanism. The methodology is amenable to a broad array of functional groups and heterocycles. The tetrahydrothiophene motif is important because it is present in a number of bioactive natural products. They have also been utilized to promote various asymmetric transformations including hydrogenation, epoxidation, cyclopropanation, and aziridination reactions.



1. INTRODUCTION

For a number of years now, our laboratories have been developing new methods of incorporating sulfur into compounds through the construction of carbon−sulfur bonds. In particular, we are interested in discovering novel processes for the synthesis of thioethers and saturated sulfur heterocycles. Classical means for the preparation of these compounds nearly always employ nucleophilic or electrophilic sulfur reagents in which one of the carbon−sulfur bonds is already present (Figure 1). For example, the respective reactions of thiols or

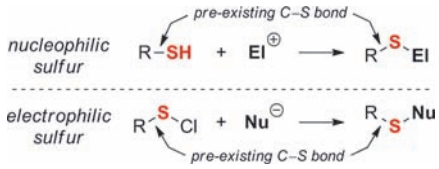
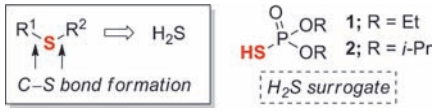


Figure 1. Synthesis of thioethers with sulfur reagents containing pre-existing C−S bonds.

sulfenyl chlorides with electrophiles or nucleophiles are limited by the presence of pre-existing carbon−sulfur bonds (Figure 1).

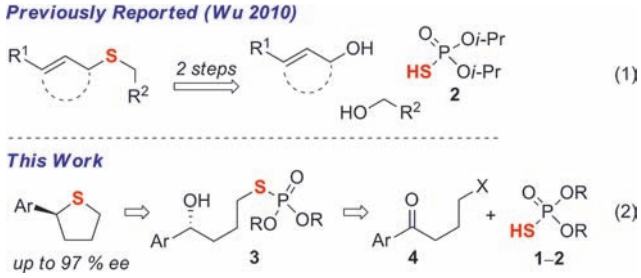
The breadth of the synthesis of thioethers and sulfur heterocycles would be greatly expanded if there were a reagent available in which *both* carbon substituents on either side of sulfur could be independently defined (Scheme 1). One such

Scheme 1. Phosphorothioic Acids as Surrogates for H_2S



reagent is hydrogen sulfide (i.e., H_2S), which is doubly nucleophilic at sulfur. H_2S is quite versatile and can sequentially react with carbon-based electrophiles to form two different carbon−sulfur bonds. However, a major concern with the use of H_2S is that it is a highly toxic gas. Inhalation at concentrations >500 ppm causes pulmonary edema resulting in immediate collapse followed by death.[1] Related compounds such as NaSH or Na_2S (hydrate) are less dangerous since they are solids but their exposure to mild acid will nonetheless generate H_2S. Therefore, while these reagents are quite useful, they are impractical to use on larger scales and in industrial processes.

Our group has been exploring the use of dialkyl phosphorothioic acids **1**−**2** as safer alternatives to H_2S (Scheme 1). These are *odorless* compounds that are resistant to hydrolysis under both acidic and basic conditions. They can be stored at room temperature in air for extended periods of time without any appreciable decomposition. Furthermore, phosphorothioic acids are easily prepared on multigram scale in one pot from the corresponding dialkyl phosphite.



We have previously reported the use of **2** as a surrogate for H_2S in the synthesis of thioethers (eq 1).[2] This is a two-step method in which the first step is either the UV-promoted[3] or

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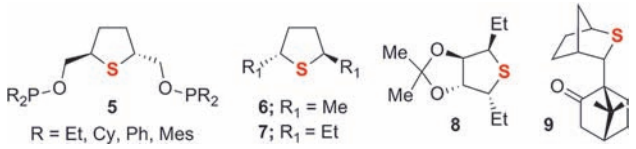
Ga(OTf)-catalyzed[4−6] preparation of the corresponding phosphorothioate esters[7,8] from phosphorothioic acids and either alcohols or ethers. Treatment of the phosphorothioate esters with an exogenous alkoxide completes the synthesis of the thioethers. This methodology is substantially more efficient than other means for obtaining the title compounds. The transformation is stereospecific because it proceeds via a double S_N2 pathway. We reasoned that phosphorothioic acids could also be utilized as H_2S surrogates in *intramolecular* variants. This would provide facile access to chiral tetrahydrothiophenes via enantioenriched chiral alcohol **3** (eq 2). The key step is a base-promoted cyclization event to forge the second carbon−sulfur bond, a reaction that is analogous to what we reported for the intermolecular, one-pot, synthesis of thioethers.[2]

The tetrahydrothiophene[9] moiety is quite important and is found in a number of bioactive natural products. Among these are α-glucosidase inhibitors (i.e., salacinol, kotalanol, salaprinol, and ponkoranol),[10,11] oral hypocholesterolemic agents (i.e., breynin A−B and epibreynin B),[12,13] brain-type cholecystokinin (CCK) receptor antagonists (i.e., tetronothiodin),[14] agonists/antagonists for the human A_3 adenosine receptor,[15] and biotin which is required for gluconeogenesis, fatty acid production/metabolism, and amino acid metabolism.[16] They are also useful as easily displaceable ligands in gold complexes.[17]

Tetrahydrothiophenes have also been utilized as chiral ligands for various enantioselective transformations. Hauptman and co-workers demonstrated that rhodium complexes with chiral bis(phosphinite) ligands **5**[18] are effective in asymmetric hydrogenation reactions. Metzner and co-workers[19] showed that sulfur ylides derived from **6**−**7** can promote enantioselective epoxidation reactions while Huang[20] demonstrated the utility of **8** in aziridinations. Aggarwal's group used sulfur ylides derived from **9** as stereoselective epoxidation,[21] cyclopropanation,[22] and aziridination reagents.[23]



With respect to the synthesis of enantioenriched tetrahydrothiophenes, there have been few precedents. We outline here the more notable reports. Metzner[19] and Huang's[20] preparation of **6**−**8** relied on the double displacement reaction of the corresponding mesylated diol with Na_2S. Wang,[24] Högberg,[25] and Besada[26] have also reported syntheses of chiral tetrahydrothiophenes. These methods were based on conjugate additions, sulfur ylides, or singlet oxygen-mediated rearrangements.

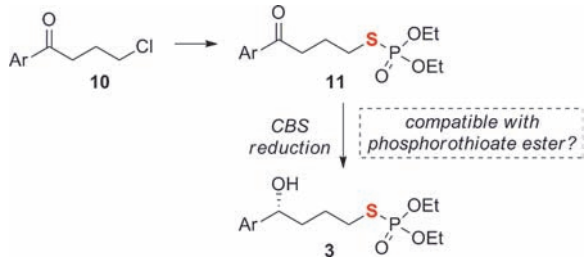
Njardarson and co-workers[27] have developed copper-catalyzed ring expansions of vinyl thiiranes to yield dihydrothiophenes while Maguire and co-workers[28] published an enantioselective C−H insertion approach toward chiral sulfolanes. Block and co-workers reported the [3,3] sigmatropic rearrangement of bispropenyl sulfides to yield thiophenes and dihydrothiophenes.[29] Although the chemistries described in these reports do not provide direct access to tetrahydrothiophenes, they are superb examples of the synthesis of 5-membered sulfur heterocycles.

Herein, we describe an efficient stereospecific synthesis of enantioenriched tetrahydrothiophenes which utilizes phosphorothioic acids and related compounds as H_2S surrogates.

2. RESULTS AND DISCUSSION

We envisioned accessing the obligatory enantioenriched alcohol **3**, and eventually the chiral tetrahydrothiophenes, via asymmetric reduction of the corresponding ketone (Scheme

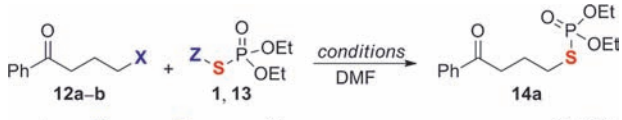
Scheme 2. Proposed Synthesis of Requisite Chiral Alcohol



2). This stereoselective transformation could be accomplished through a number of different methods; but in particular, we elected to focus our attention on the Corey−Bakshi−Shibata (CBS) reduction which makes use of chiral oxazaborolidine (OAB) catalysts.[30] The CBS protocol is effective for ketones flanked by an aromatic group on one side and a linear alkyl chain on the other. There have also been a few instances in which the generation of chiral alcohols in this manner was shown to work well in the presence of sulfides.[31] However, we were uncertain if the phosphorothioate functional group would be compatible with the catalyst or lead to diminished selectivities. As an alternative, if this route should prove unfeasible, we could also explore the use of Noyori's asymmetric transfer hydrogenation protocol, which can also be compatible with sulfur functional groups.[32]

In order to answer these critical questions at the earliest stage possible, we decided to begin our studies with the commercially available chloroketone **12a** (Table 1). Initial alkylation attempts

Table 1. Optimization of 1st C−S Bond Formation



entry	X	Z	conditions	yield (%)
1	**12a**; Cl	**1**; H	NaH (1.4 equiv), rt	trace
2	**12a**; Cl	**1**; H	K_2CO_3 (2.0 equiv), 80 °C	49
3	**12a**; Cl	**1**; H	KHMDS (1.3 equiv), rt	trace
4	**12a**; Cl	**1**; H	$AgNO_3$ (1.0 equiv), rt	trace
5	**12a**; Cl	**1**; H	KI (1.0 equiv), NEt_3 (1.5 equiv), 50 °C	28
6	**12a**; Cl	**13**; Na	no additive, 70 °C	63
7	**12b**; I	**13**; Na	no additive, rt	98

were carried out between **12a** and diethylphosphorothioic acid (**1**) in the presence of various bases or $AgNO_3$ (entries 1−4). These experiments led to uniformly unacceptably low yields. We also examined the use of sodium diethylphosphorothioate **13** which furnished the desired product in 63% yield (entry 6). The use of independently prepared iodide **12b** led to a 98% isolated yield of **14a** (entry 7). Interestingly, substantially lower yields were obtained for the alkylation of iodide **12b** that was prepared in situ with NaI/NEt_3 (entry 5).

With ketophosphorothioate ester **14a** in hand, we proceeded to examine the key enantioselective reduction step (Scheme 3). CBS reduction of ketone **14a** furnished alcohol **16a** in 94%

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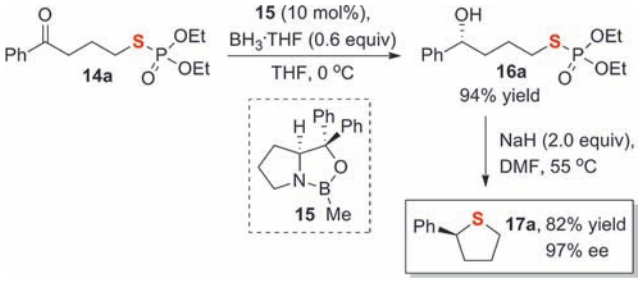
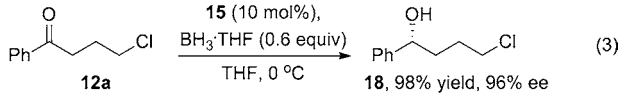
Scheme 3. CBS Reduction and Chiral THT Formation



yield. Unfortunately, attempts to determine the enantiopurity of **16a** at this time was unsuccessful. At issue were difficulties in resolving the enantiomers of the corresponding racemic alcohol using chiral HPLC analysis. Instead, we elected to complete the synthesis of the desired chiral tetrahydrothiophene **17a** by constructing the second carbon–sulfur bond.

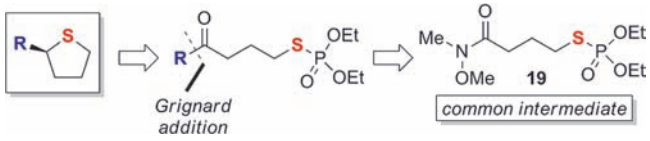
After surveying several different reaction parameters, we settled on the use of NaH in DMF as optimized conditions for the cyclization event (Scheme 3).[33] Tetrahydrothiophene **17a** was isolated in 82% yield. Gratifyingly, the determination of the enantiomeric excess of **17a** was possible at this point and was measured to be 97% ee. As a control, we also carried out the asymmetric reduction of chloroketone **12a** to the alcohol **18** (96% ee, eq 3). The fact that similar levels of enantioinduction was observed for both chloride **18** and tetrahydrothiophene **17a** supports the notions that (1) the initial asymmetric reduction of **12a** occurred at very high levels and that (2) there was little to no loss of enantiopurity in the cyclization event. Having established that phosphorothioate esters are compatible with CBS asymmetric reductions, we proceeded by developing a more streamlined synthesis of the requisite ketones.



(3)

Although chloroketone **12a** and several other substrates were commercially available, we realized that the generality of the described chiral tetrahydrothiophene synthesis would be greatly expanded if all of the ketone precursors could be prepared from a single common intermediate (Scheme 4). In this manner, we

Scheme 4. Streamlined Retrosynthesis of THTs

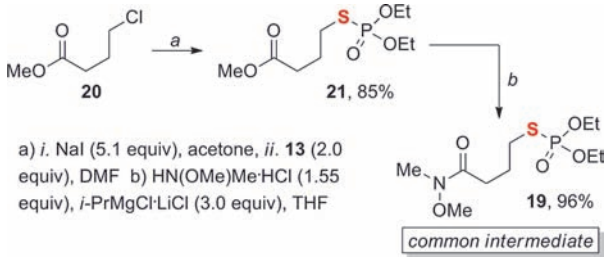


would also gain access to tetrahydrothiophenes whose syntheses would require the use of noncommercially available chloroketones.

We imagined that Weinreb amide **19** could potentially serve as the putative common intermediate (Scheme 4). The reaction between **19** and various functionalized organomagnesium reagents would lead to an array of phosphorothioate ketones that could then be carried forth to the desired chiral tetrahydrothiophenes.

After exploring several unsuccessful routes toward Weinreb amide **19**, we settled on the following two pot procedure as a highly efficient method for its preparation (Scheme 5). The commercially available chloroester **20** (~0.5 US$/gram) was

Scheme 5. Synthesis of Common Intermediate 19

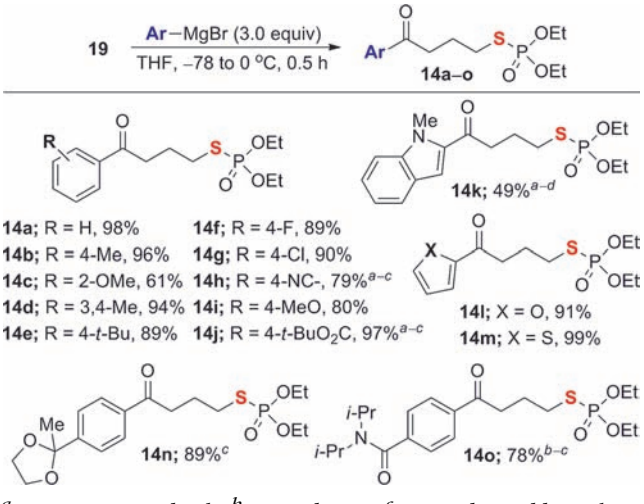


treated with NaI in acetone to generate the corresponding iodide, in situ. The addition of sodium diethylphosphorothioate **13** to the reaction mixture provided **21** in 85% isolated yield. Weinreb amide formation following the Merck protocol gave the desired product **19** in 96% yield.[34]

Having developed an effective synthesis of the common intermediate **19**, we then set out to determine if its reaction with organomagnesium reagents would be compatible with the presence of the phosphorothioate ester moiety at the terminus of the molecule. Previously, our group has demonstrated that *allylic* phosphorothioate esters will undergo transition metal-free[3] or Cu(I)-catalyzed cross-coupling reactions with various Grignard reagents.[7] Our own experiences with this functional group led us to believe that *alkyl* phosphorothioate esters are significantly less reactive than the related allylic systems and would likely not interfere with ketone formation.

Gratifyingly, treatment of **19** with various organomagnesium reagents furnished ketones **14a–o** in very good to excellent yields. The Grignard reagents were prepared from the corresponding aryl halide and magnesium turnings or by halogen-magnesium exchange as described by Knochel and co-workers.[35] As is evident in Table 2, we can access a wide

Table 2. Scope of Ketone Formation



[a]Reaction required 3 h. [b]Warmed to rt. [c]Required an additional 3.0 equiv of Ar-MgBr. [d]Required 12 equiv of LiCl.

assortment of ketones. These include products that contain electron-withdrawing and -donating groups as well as a broad range of functionalities (i.e., halides, esters, nitriles, ketals, and amides) and heterocycles (i.e., indolyl, furanyl, and thienyl).

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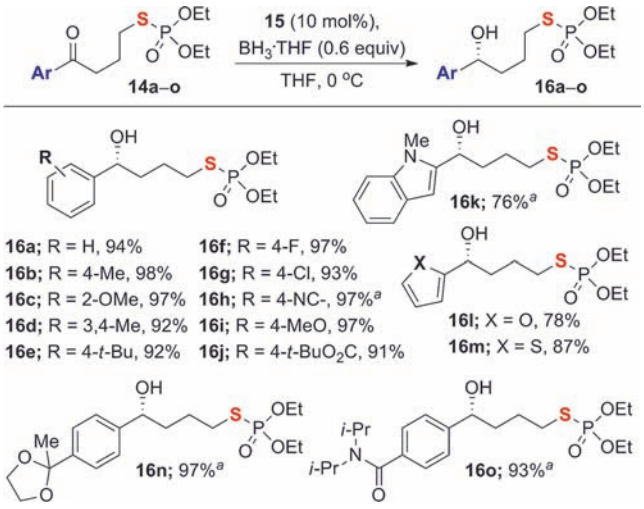
Interestingly, the use of organolithium reagents resulted in significantly lower yields.

Next, we converted ketones **14a–o** to the desired chiral alcohols using the CBS procedure described in Scheme 3 (Table 3). In each case, high yields were achieved for the CBS

Table 3. Asymmetric Ketone Reduction

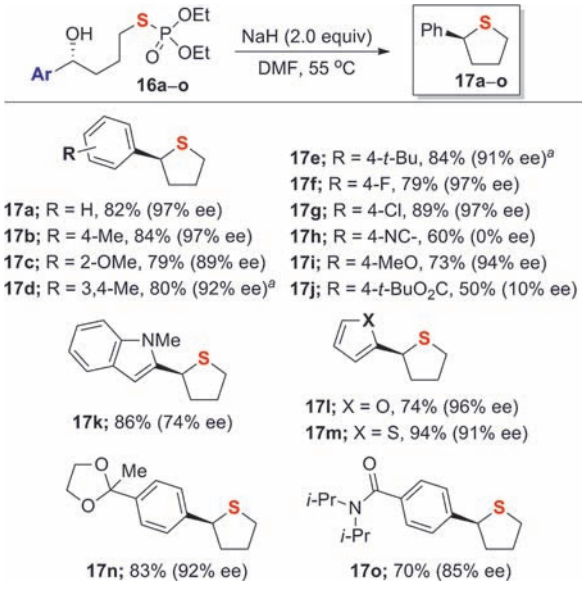


[a]Used 1.2 equiv BH_3 THF.

reduction, but as was the case before, we elected to postpone determination of stereoselectivity levels until after the second carbon–sulfur bond-forming event.

Treatment of the chiral alcohols with NaH in DMF at 55 °C led to efficient ring closure (Table 4). With the exception of a

Table 4. Scope of Chiral Tetrahydrothiophene Formation



[a]The ee was determined on this corresponding sulfone after oxidation with *m*CPBA.

handful of compounds (vide infra), high enantioselectivities were obtained for each of the tetrahydrothiophenes. Again, broad substrate scope and functional group compatibility was demonstrated. We confirmed the absolute stereochemistry of **17e** by oxidation to the corresponding sulfone **22** followed by single crystal X-ray analysis (Figure 2). The stereochemical configurations of the remaining tetrahydrothiophenes were assigned based on analogy.

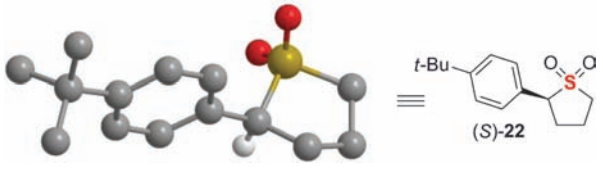
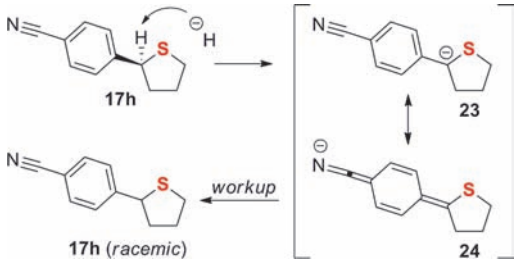


Figure 2. Confirmation of Absolute Stereochemistry via Single Crystal X-ray Analysis of Sulfone (*S*)-**22**.

Curiously, two substrates (i.e., **17h**, **17j**) in Table 4 were isolated in nearly racemic form. We considered the possibility that under the basic reaction conditions (excess NaH), the products were undergoing racemization (Scheme 6). The

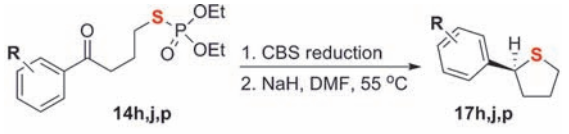
Scheme 6. Proposed Mechanism of Racemization for 17h



conjugated nitrile and ester in the para positions of **17h** and **17j**, respectively, could potentially serve as stabilizing groups for the putative anions resulting from deprotonation with NaH.

To support this conjecture, we prepared ketone **17p** which has a nitrile in the meta position. We reasoned that by moving the nitrile out of conjugation with the benzylic site we would reduce the acidity of the relevant proton, thereby retarding the rate of deprotonation/racemization. Indeed CBS reduction of **17p** followed by tetrahydrothiophene formation generated the expected product in 74% ee (Table 5, entry 1). This is a

Table 5. Improvement of ee for Substrates Possessing EWG's



entry	R	conditions	product	yield (%)	ee (%)
1	3-CN	2.0 equiv NaH	**17p**	70	74
2	3-CN	1.2 equiv NaH	**17p**	81	82
3	4-CN	1.2 equiv NaH	**17h**	82	76
4	4-*t*-BuO_2C	1.2 equiv NaH	**17j**	81	93

substantial improvement to the enantiopurity observed for the 4-CN-substituted tetrahydrothiophene **17h** (cf. Table 4, compound **17h**, 0% ee). We could further improve the ee of tetrahydrothiophene **17p** to 82% ee by reducing the amount of NaH (1.2 equiv) used in the cyclization. A similar reduction in the amount of NaH also improved the enantiopurity of 4-CN- and 4-*t*-BuO_2C-substituted tetrahydrothiophenes (entries 3–4). We also observed a concomitant increase in isolated yield.

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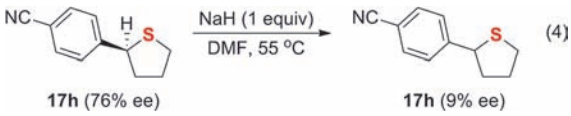
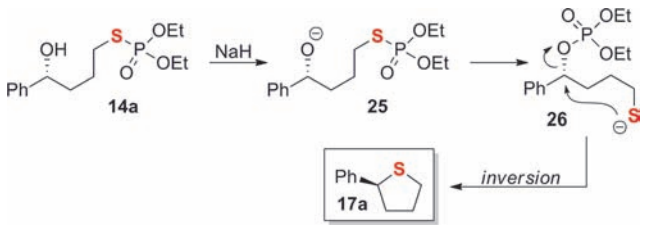
Subjecting enantioenriched **17h** to the typical reaction conditions (NaH/DMF) resulted in nearly complete racemization of the product (eq 4). Taken together, the data described in Table 5 and eq 4, support the notion that the reason tetrahydrothiophenes **17h** and **17j** were isolated in racemic fashion in Table 4 was due to racemization resulting from deprotonation during the course of the reaction.



With respect to the mechanism of tetrahydrothiophene formation, we believe that the chiral alcohol is first deprotonated by NaH to generate a transient alkoxide **25** (Scheme 7). The next step, which is transfer of the phosphate

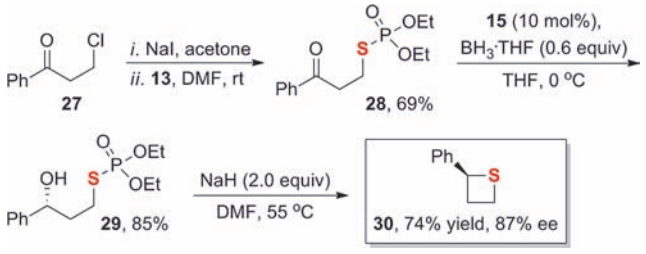
Scheme 7. Proposed Mechanism



group onto oxygen, is driven by the relatively strong phosphorus−oxygen bond that is formed.[8] The resultant thiolate is highly nucleophilic and displaces phosphate to furnish the desired 5-membered ring. The high enantiopurity that we observe in the isolated tetrahydrothiophenes supports the notion that the carbon−sulfur bond-forming event occurs via an S_N2-type pathway at the stereodefining step.

To extend this methodology to other ring sizes, we have applied this chemistry to a representative synthesis of chiral thietanes **30**. Thus, conversion of chloroketone **27** to **28** was accomplished in one-pot transformation. CBS reduction of ketone **28** furnished enantioenriched alcohol **29** which cyclized to the desired thietane **30** (74% yield, 87% ee) upon treatment with NaH. Thietanes are important compounds utilized by certain animals as a means for chemical communication.[36] A limited number of achiral syntheses of thietanes have been reported.[37] Unfortunately, numerous attempts to apply this methodology to the synthesis of chiral thianes, failed.

Scheme 8. Synthesis of Chiral Thietane 30



3. CONCLUSIONS

We have demonstrated a facile synthesis of chiral tetrahydrothiophenes using phosphorothioic acids and related compounds. These are synthetic equivalents to H_2S that are substantially safer to handle. That these important products are all derived from a common intermediate **19** permits the streamlined preparation of various analogs. Each step of the synthesis is tolerant to a broad range of functional groups and the presence of numerous types of heterocycles. Future work in our laboratories will include the exploration of these chiral tetrahydrothiophenes as organocatalysts and as chiral ligands in select asymmetric transformations. The availability of chiral 2-aryl tetrahydrothiophenes also permits further examination of stereochemical issues associated with the alkylation or protonation of the carbanion of the corresponding sulfoxides.[38]

4. EXPERIMENTAL SECTION

General Procedure for Ketone Preparation. To a solution of **19** (0.134 mmol, 40.0 mg) in THF (0.18 mL) at −78 °C was added 1 M PhMgBr (0.401 mmol, 0.401 mL). The reaction mixture was warmed to 0 °C and stirred for 0.5 h. The reaction was quenched with a saturated aqueous NH_4Cl (50 mL), extracted with Et_2O (50 mL), washed with brine (50 mL), dried with $MgSO_4$, and concentrated in vacuo. The residue was purified by silica gel chromatography (50% EtOAc/hexanes) to afford **14a** as a pale yellow oil.

General Procedure for CBS Reduction. To a flame-dried round-bottom flask was added **15** (1.0 M in toluene, 0.029 mmol, 0.029 mL). The toluene was removed in vacuo, BH_3·THF (1.0 M in THF, 0.176 mmol, 0.176 mL) was added, and the solution was cooled to 0 °C. A solution of **14a** (0.293 mmol, 10.0 mg) in THF (0.084 mL) was added to the solution of **15** and borane. After 5 min, the reaction was deemed complete as judged by TLC analysis. The reaction was quenched at 0 °C with MeOH (10 mL) and then the reaction mixture was concentrated in vacuo. The residue was purified by silica gel chromatography (50% EtOAc/hexanes) to afford **16a** as a pale yellow oil.

General Procedure for Tetrahydrothiophene Formation. To a solution of **16a** (0.300 mmol, 95.0 mg) in DMF (6.0 mL) was added NaH (0.600 mmol, 24.0 mg). This solution was placed in a preheated oil bath that was set to 55 °C, and the reaction was stirred overnight. The reaction was diluted with Et_2O (50 mL), washed with a 1:1 H_2O:brine solution (2 × 50 mL), dried with $MgSO_4$, concentrated in vacuo, and the residue was purified by silica gel chromatography (5% EtOAc/hexanes) to afford **17a** as a clear and colorless oil.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental procedures and spectral data (1H NMR, 13C NMR, IR, HRMS, HPLC) for all new compounds and the CIF file for compound (*S*)-22. This material is available free of charge via the Internet at http://pubs.acs.org.

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■ REFERENCES

(1) Reiffenstein, R. J. *Annu. Rev. Pharmacol. Toxicol.* **1992**, 109.
(2) Robertson, F.; Wu, J. *Org. Lett.* **2010**, *12*, 2668.
(3) Han, X.; Zhang, Y.; Wu, J. *J. Am. Chem. Soc.* **2010**, *132*, 4104.
(4) Han, X.; Wu, J. *Org. Lett.* **2010**, *12*, 5780.

(5) Forthe synthesis ofcarbon−sulfur bonds directly from alcohols "on-water",see: Cozzi, P. G.; Zoli, L. *Angew. Chem., Int. Ed.* **2008**, *47*, 4162.
(6) Forsynthesis of carbon−sulfurbonds directly from alcohols catalyzed by stoichiometric In(III),see: Snyder, S. A.; Breazzano, S. P.; Ross, A. G.; Lin, Y.; Zografos, A. L. *J. Am. Chem. Soc.* **2009**, *131*, 1753.
(7) We have also reportedthe use of phosphorothioate esters in Cu(I)-catalyzed C−C bond-formingreactions with organomagnesium reagents, see: Lauer, A. M.; Mahmud, F.; Wu, J. *J. Am. Chem. Soc.* **2011**, *133*, 9119.
(8) For the conversion of α-ketophosphorothioate esters into alkenes, see. (a) Maciągiewicz, I.; Dybowski, P.; Skowronska, A. *Tetrahedron* **2003**, *59*, 6057. (b) Maciagiewicz, I.; Dybowski, P.; Skowronska, A. *Tetrahedron Lett.* **1999**, *40*, 3791. (c) Krawczyk, E. *Synthesis* **2006**, 716. (d) Tanaka, K.; Uneme, H.; Ono, N.; Kaji, A. *Chem. Lett.* **1979**, 1039. (e) Tanaka, K.; Uneme, H.; Ono, N.; Kaji, A. *Synthesis* **1979**, 890.
(9) Rajappa, S.; Deshmukh, A. R. Thiophenes and their Benzo Derivatives: Reactivity. In *Comprehensive Heterocyclic Chemistry III*; Katritzky, A. R.; Ramsden, C. A.; Scriven, E. F. V.; Taylor, R. J. K., Eds.; Elsevier: Amsterdam, 2008; Vol. *3*, pp 793−797.
(10) (a) Yoshikawa, M.; Murakami, T.; Shimada, H.; Matsuda, H.; Yamahara, J.; Tanabe, G.; Muraoka, O. *Tetrahedron Lett.* **1997**, *38*, 8367. (b) Yoshikawa, M.; Murakami, T.; Yashiro, K.; Matsuda, H. *Chem. Pharm. Bull.* **1998**, *46*, 1339. (c) Yoshikawa, M.; Morikawa, T.; Matsuda, H.; Tanabe, G.; Muraoka, O. *Bioorg. Med. Chem.* **2002**, *10*, 1547.
(11) (a) Yoshikawa, M.; Xu, F.; Nakamura, S.; Wang, T.; Matsuda, H.; Tanabe, G.; Muraoka, O. *Heterocycles* **2008**, *75*, 1397. (b) Tanabe, G.; Sakano, M.; Minematsu, T.; Matsuda, H.; Yoshikawa, M.; Muraoka, O. *Tetrahedron* **2008**, *64*, 10080.
(12) Meng, D.; Chen, W.; Zhao, W. *J. Nat. Prod.* **2007**, *70*, 824.
(13) Trost, W. *IRCS Med. Sci.* **1986**, *14*, 905.
(14) Page, P. C. B.; Vahedi, H.; Batchelor, K. J.; Hindley, S. J.; Edgar, M.; Beswick, P. *Synlett* **2003**, *7*, 1022.
(15) Jeong, L. S.; Jin, D. Z.; Kim, H. O.; Shin, D. H.; Moon, H. R.; Gunaga, P.; Chun, M. W.; Kim, Y.-C.; Melman, N.; Gao, Z.-G.; Jacobsen, K. A. *J. Med. Chem.* **2003**, *46*, 3775.
(16) De Clercq, P. J. *Chem. Rev.* **1997**, *97*, 1755.
(17) Uson, R.; Laguna, A.; Laguna, M.; Briggs, D. A.; Murray, H. H.; Fackler, J. P. (Tetrahydrothiophene)Gold(I) or Gold(III) Complexes. In *Inorganic Syntheses*; Kaesz, H. D., Ed.; John Wiley & Sons: New York, 1989; Vol. *26*, pp 85−91.
(18) Hauptman, E.; Shapiro, R.; Marshall, W. *Organometallics* **1998**, *17*, 4976.
(19) (a) Zanardi, J.; Lamazure, D.; Minière, S.; Reboul, V.; Metzner, P. *J. Org. Chem.* **2002**, *67*, 9083. (b) Zanardi, J.; Leriverend, C.; Aubert, D.; Julienne, K.; Metzner, P. *J. Org. Chem.* **2001**, *66*, 5620. (c) Julienne, K.; Metzner, P. *J. Org. Chem.* **1998**, *63*, 4532. (d) Julienne, K.; Metzner, P.; Henryon, V. *J. Chem. Soc., Perkin Trans. 1* **1999**, 731.
(20) Gui, Y.; Shen, S.; Wang, H.-Y.; Li, Z. Y.; Huang, Z.-Z. *Chem. Lett.* **2007**, *36*, 1436.
(21) (a) Aggarwal, V. K.; Alonso, E.; Bae, I.; Hynd, G.; Lydon, K. M.; Palmer, M. J.; Patel, M.; Porcelloni, M.; Richardson, J.; Stenson, R. A.; Studley, J. R.; Vasse, J. L.; Winn, C. L. *J. Am. Chem. Soc.* **2003**, *125*, 10926. (b) Aggarwal, V. K.; Bae, I.; Lee, H.-Y.; Richardson, J.; Williams, D. T. *Angew. Chem., Int. Ed.* **2003**, *42*, 3274.
(22) Riches, S. L.; Saha, C.; Filgueira, N. G.; Grange, E.; McGarrigle, E. M.; Aggarwal, V. K. *J. Am. Chem. Soc.* **2010**, *132*, 7626.
(23) (a) Illa, O.; Arshad, M.; Ros, A.; McGarrigle, E. M.; Aggarwal, V. K. *J. Am. Chem. Soc.* **2010**, *132*, 1828. (b) Aggarwal, V. K.; Alonso, E.; Fang, G.; Ferrara, M.; Hynd, G.; Porcelloni, M. *Angew. Chem., Int. Ed.* **2001**, *40*, 1433.
(24) Luo, G.; Zhang, S.; Duan, W.; Wang, W. *Tetrahedron Lett.* **2009**, *50*, 2946.
(25) Karlsson, S.; Högberg, H. *Org. Lett.* **1999**, *1*, 1667−1669.
(26) Besada, P.; Pérez, M.; Gómez, G.; Fall, Y. *Tetrahedron Lett.* **2009**, *50*, 6941.
(27) Rogers, E.; Araki, H.; Batory, L. A.; McInnis, C. E.; Njardarson, J. T. *J. Am. Chem. Soc.* **2007**, *129*, 2768.
(28) Flynn, C. J.; Elcoate, C. J.; Lawrence, S. E.; Maguire, A. R. J. *Am. Chem. Soc.* **2010**, *132*, 1184.
(29) Block, E.; Zhao, S. H. *Tetrahedron Lett.* **1990**, *31*, 4999.
(30) Corey, E. J.; Helal, C. J. *Angew. Chem., Int. Ed.* **1998**, *37*, 1986.
(31) (a) Cho, B. T.; Choi, O. K.; Kim, D. J. *Tetrahedron: Asymm.* **2002**, *13*, 697. (b) Cho, B. T.; Shin, S. H. *Tetrahedron* **2005**, *61*, 6959.
(32) (a) Kitamura, M.; Ohkuma, O.; Inoue, S.; Sayo, N.; Kumobayashi, H.; Akutagawa, S.; Ohta, T.; Takaya, H.; Noyori, R. *J. Am. Chem. Soc.* **1988**, *110*, 629. (b) Tranchier, J.-P.; Ratovelomanana-Vidal, V.; Genêt, J.-P. *Tetrahedron Lett.* **1997**, *38*, 2951. (c) Gautier, I.; Ratovelomanana-Vidal, V.; Savignac, P.; Genêt, J.-P. *Tetrahedron Lett.* **1996**, *37*, 7721.
(33) For a leading referencefor the related conversion of epoxides to thiiranes, see: Kaboudin, B.; Norouzi, H. *Tetrahedron Lett.* **2004**, *45*, 1283.
(34) Williams, J. M.; Jobson, R. B.; Yasuda, N.; Marchesini, G.; Dolling, U.; Grabowski, E. J. J. *Tetrahedron. Lett.* **1995**, *36*, 5461.
(35) (a) Knochel, P.; Dohle, W.; Gommermann, N.; Kneisel, F. F.; Kopp, F.; Korn, T.; Sapountzis, I.; Vu, V. A. *Angew. Chem., Int. Ed.* **2003**, *42*, 4302. (b) Jensen, A. E.; Dohle, W.; Sapountzis, I.; Lindsay, D. M.; Vu, V. A.; Knochel, P. *Synthesis* **2002**, 565.
(36) (a) Brinck, C.; Erlinge, S.; Sandell, M. *J. Chem. Ecol.* **1983**, *9*, 727. (b) Crump, D. R. *J. Chem. Ecol.* **1980**, *6*, 837. (c) Crump, D. R. *J. Chem. Ecol.* **1980**, *6*, 341. (d) Zhang, J.; Sun, L.; Zhang, Z.; Wang, Z.; Chen, Y.; Wang, R. *J. Chem. Ecol.* **2002**, *28*, 1287.
(37) (a) Ueno, Y.; Yadav, L. D. S.; Okawara, M. *Synthesis* **1981**, 547. (b) Yadav, L. D. S.; Kapoor, R. *Synthesis* **2002**, 1502.
(38) (a) Durst, T.; McClory, M. R. *J. Am. Chem. Soc.* **1971**, *93*, 3077. (b) Bory, S.; Lett, R.; Moreau, B.; Marquet, A. *Tetrahedron Lett.* **1972**, *13*, 4921. (c) Bory, S.; Marquet, A. *Tetrahedron Lett.* **1973**, *14*, 4158. (d) Nishihata, K.; Nishio, M. *Chem. Commun.* **1971**, 958. (e) Brown, T. J.; Chapman, R. F.; Cook, D. C.; Hart, T. W.; McLay, I, M.; Jordan, R.; Mason, J. S.; Palfreyman, M. N.; Walsh, R. J. A.; Withnall, M. T.; Aloup, J.-C.; Cavero, I.; Farge, D.; James, C.; Mondot, S. *J. Med. Chem.* **1992**, *35*, 3613.