Thiophosphonothioates from Oxiranes

Ian P. Shire, Zarko Boskovic*
Department of Medicinal Chemistry, University of Kansas, Lawrence, 66045 KS, United States
*e-mail: zarko@ku.edu

Abstract: Heating oxiranes with Lawesson's reagent in aromatic solvents results in the formation of thiophosphonothioates. The reaction proceeds most efficiently with substrates where elimination is hindered by their geometry. The observed regioselectivity can be explained by cation stabilization in bicyclic systems. In particular, electron-donating groups significantly enhance the stabilization of carbocations at the homobenzylic position in rigid bicyclic frameworks.

Keywords: Lawesson's reagent, thiophosphonothioates, ring expansion, carbocation stabilization.

Certain bicyclic oxiranes can be reliably and selectively converted into thiophosphonothioates (TPTs) upon heating with the Lawesson's reagent.

Lawesson's reagent (LR),[1–3] a dimer of *p*-methoxyphenyl-PS_2 (PMP-PS_2), is widely used to convert ketones to thioketones, and more generally carbonyl compounds to their thio analogs.[4,5] It is readily prepared from anisole and P_2S_5.[6,7] From the modern synthetic strategy vantage point, it can be considered a reagent that accomplishes a molecular O→S edit.[8] When heated in non-polar solvents (typically toluene, benzene, or xylene) the LR dimer dissociates to generate a reactive dithiophosphorus ylide. The resulting monomer exhibits Wittig-like reactivity, exploiting the formation of a strong phosphorus–oxygen bond to produce a four-membered cyclic intermediate, which subsequently undergoes cycloreversion to yield the desired thioketone.

Organophosphorus compounds, in both P(III) and P(V) oxidation states, have many important applications in a diverse array of fields (Figure 1).[9] In agriculture, they are frequently used as pesticides, functioning as cholinesterase inhibitors.[10] In medicinal chemistry, they were shown to have numerous activities, such as anti-cancer, antiviral, and cardioprotective.[11–13] Recently, the Baran lab introduced a thiophospho**r**odithioate-based reagent that enables the controllable, diastereoselective synthesis of phosphodiester bonds in oligonucleotides.[14] In this work, we present a straightforward approach to thiophospho**n**othioates and elucidate certain facets of the reactivity that enabled their formation from oxiranes and Lawesson's reagent.

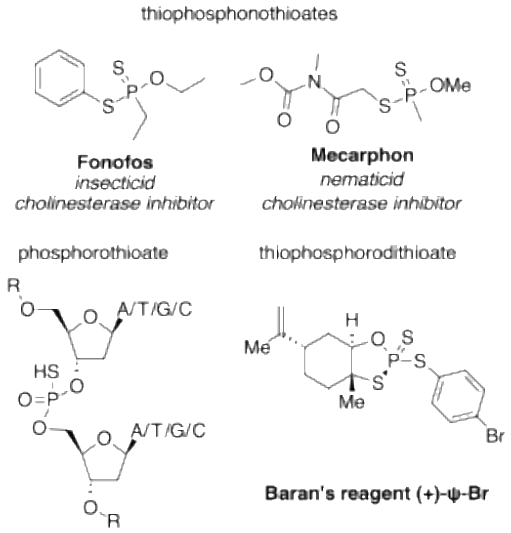

Figure 1 Organophosphorus(V) compounds have numerous uses.

Our investigation into the reactivity of LR (Figure 2A) was motivated by our attempts to synthesize oxetane-3-thione – a molecule expected to exhibit interesting photochemical properties due to a more facile n,π* excitation compared to 3-oxetanone[15] – by heating oxetanone with LR in toluene (Figure 2B). Instead of the thioketone product, we observed the formation of several related compounds, including **1**, which we successfully isolated and characterized. These species appear to arise from ring-opening of the oxetane, likely via reaction with either $ArPS_2$, or ArPOS ylide. Interestingly, the presence of ArPOS ylide implies that oxetane-3-thione may have formed but was too volatile to be retained, possibly escaping the reaction vessel – and our notice.

To rationalize the oxetane ring expansion,[16] we propose that the initial interaction occurs between the basic ether oxygen and the electron-deficient phosphorus center of the LR monomer. This interaction weakens the C–O bond of the highly-strained oxetane ring (strain energy = 25.3 kcal/mol),[17] facilitating partial carbocation formation. The resulting cationic center is subsequently intercepted by a nearby sulfur, yielding the observed ring-expanded products.

The ring strain of oxiranes (26.8 kcal/mol) is only slightly higher than that of oxetanes, prompting us to investigate whether similar reactivity, and perhaps improved yields, could be achieved with this more readily available class of compounds. Surprisingly, the reactions of oxiranes with dithiophosphine ylides have not been investigated in detail. In 1984, El-Barbary reported that styrene oxide, ethylene oxide, and propylene oxide undergo ring expansion upon treatment with LR (Figure 2C).[18] Interestingly, for the latter two substrates, the reported products have three sulfur atoms. The author proposed that, initially, the O→S substitution occurs, which is followed by the ring expansion of the thiirane with another equivalent of the ylide. Notably, this remains the only published account of LR reactivity with epoxides.

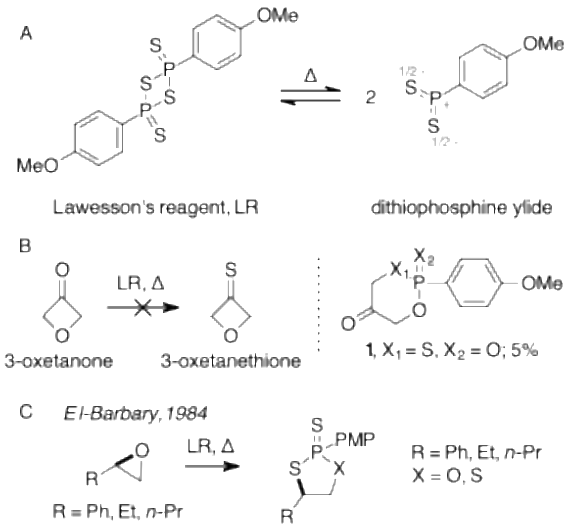

Figure 2 A) Lawesson's reagent de-dimerizes at elevated temperatures. B) Attempt at making thioketone analog of 3-oxetanone; one of the obtained products of oxetane ring expansion. C) El-Barbary's report on the reactivity of three epoxides with LR.

In the coupling of oxiranes with LR, two questions arise: 1) what is the regioselectivity of ring opening, and 2) what is the stereochemistry of the product, given that phosphorus is a stereogenic center? We first examined the reaction of styrene oxide with LR, which could theoretically yield four distinct products (Figure 3A). Heating styrene oxide with LR in xylene at 100 ºC afforded two major products, both featuring sulfur atom at the benzylic position, with the phenyl group oriented either *cis* or *trans* to the PMP substituent on phosphorus. Using 20% ethyl acetate in hexanes, the less polar component (R_f = 0.35) was identified as the *cis* isomer, while the more polar spot (R_f=0.29) corresponded to the *trans* isomer. This assignment was supported by the ^{1}H NMR spectra: in the *cis* isomer, the benzylic methine proton resonates at 5.33 ppm, whereas the diastereotopic methylene protons appear at 4.49 ppm (*cis* to the shielding phenyl group), and at 4.89 ppm (*trans* to the phenyl).

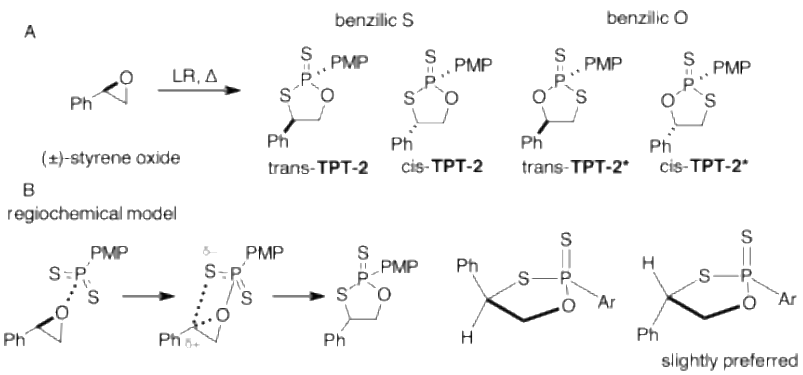

Figure 3 A) The four possible ring expanded products from styrene oxide and LR. B) Model for regioselectivity and for preferred sterechemistry in 1,3-diaryl TPTs.

To more precisely distinguish between the possible isomers, we computed the magnetic shielding tensors of the four potential products (Figure 3 A) at the ωB97X-D/aug-cc-pVDZ level of theory, using a conductor-like polarizable continuum model (CPCM) for chloroform as the solvent. Isotropic shielding values for the protons of interest were referenced to those of tetramethylsilane, calculated with the same parameters. The comparison of predicted and experimental chemical shifts is summarized in Table 1. Among the candidates, the isomer in which sulfur occupies the benzylic position, and the aryl groups are *cis* to each other (cis-**TPT-2**) shows the best agreement with experiment, based on both the summed deviations of predicted versus experimental shifts and the overall correlation between the data.

Table 1 Matching the predicted ^{1}H NMR chemical shifts of four possible products with the experimental data.

Compound	Benzylic methine	Methylene cis to Ph	Methylene trans to Ph	Total difference	Correlation
Trans-TPT-2	5.01	4.45	4.30	0.95	0.766
Cis-TPT2	5.39	4.39	4.81	**0.12**	**0.9979**
Trans-TPT2*	6.25	3.19	3.98	1.29	0.9702
Cis-TPT2*	5.72	3.40	3.59	2	0.9122
Experiment	5.33	4.49	4.89	0	1

In the ^{31}P NMR, TPTs have a signal at around 100 ppm, whereas the corresponding phosphonothioates (P=O analogues) resonate at around 44 ppm.[19] In the infrared spectrum of *cis*-**TPT-2**, a P=S stretching band is observed at 696 cm^{-1}, consistent with the expected range (750 – 580 cm^{-1}).[20] These observations support a mechanism in which the initial coordination between phosphorus and oxygen generates a stabilized benzylic carbocation, which subsequently cyclizes with a thiolate to give a 5-membered ring (Figure 3B).

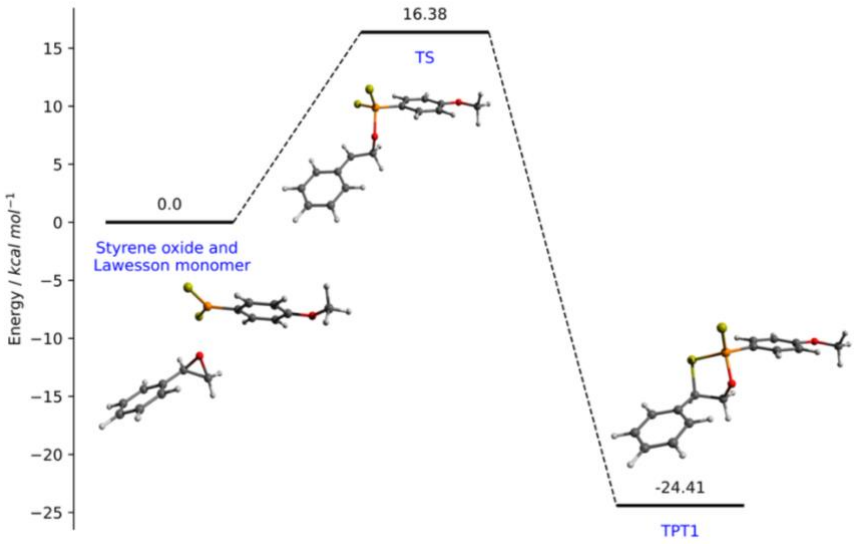

Figure 4 Computed pathway from LR monomer and styrene oxide to TPT-1 using DFT functional B3LYP and 6-31+G(d,p) basis set.

We computationally located a transition state corresponding to cyclization to produce trans-**TPT-2** from styrene oxide (Figure 4). This transition state lies 16.4 kcal/mol above the combined energies of LR monomer and the styrene oxide. Although a discrete minimum corresponding to the carbocation intermediate could not be identified, the potential energy surface near the transition state is relatively flat, consistent with gradual structural reorganization as the sulfur approaches the benzylic center to form the new bond. This computed activation energy suggests that cleavage of the LR is the rate-determining step requiring elevated temperature, and that preactivated ylides should facilitate epoxide opening under milder conditions.

In the five-membered heterocycle, the *cis* aryl groups occupy two pseudo-equatorial in the slightly preferred *cis*-**TPT-2**. This arrangement parallels the greater stability of *cis*-1,3-dimethylcyclopentane relative to its *trans* isomer by 0.53 kcal/mol.[21] Our calculations (B3LYP/6-31+G(d,p)) similarly predict that the *cis* TPT is more stable than the *trans* by 1.18 kcal/mol. Experimental evidence supports for this assignment: no NOESY cross-peak is observed between the benzylic proton and the PMP protons in the NOESY spectrum of *cis*-**TPT2**.

We next examined the reactivity of dihydronaphthalene oxide (**2**) with LR upon heating in xylenes at 100 ºC (Figure 5). Reaction monitoring by ASAP mass spectrometry revealed signals corresponding to the phosphonothioate (**PT-3**, which was isolated) and **TPT-4**, along with a gradual increase in the mass signal of naphthalene over the course of two hours. This suggests a facile elimination pathway, likely proceeding from a carbocation-thiophosphonate intermediate in which the thiolate anion deprotonates the adjacent benzylic position.

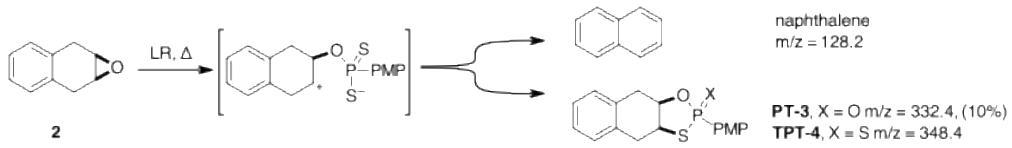

Figure 5 Conformationally flexible oxiranes suffer from facile elimination pathways.

Because the elimination requires precise geometric alignment between the protons and the leaving group, we next investigated substrates in which such an arrangement is sterically inaccessible, namely bicyclic epoxides. Indeed, the *exo*-epoxide of benzo[2.2.2]bicyclooctane (**epo-5)** reacted with LR to afford **TPT-5** in 48% yield (Figure 6). No other isolable products were detected. To further elucidate the structure of **TPT-5**, vapor diffusion crystallization was performed using a pentane/chloroform solvent system. After five days of slow pentane diffusion into chloroform solution, long, clear crystals formed in the inner vial. These were harvested, and single-crystal X-ray diffraction analysis confirmed the molecular structure of the compound (Figure 7).

The crystal structure clearly shows that the TPT ring adopts an *exo* orientations, consistent with the starting epoxide and ruling out an S_N2 mechanism involving nucleophilic attack by sulfur. The PMP substituent on phosphorus occupies a pseudo-equatorial position of the TPT ring, nearly bisecting the bicyclooctane framework, while sulfur is pseudo-axial. The TPT ring adopts an envelope conformation with the S–C–C–O atoms nearly planar (dihedral angle 3º), and the phosphorus atom 0.62 Å above this plane (O–P–S–C dihedral angle -26.9º). Endocyclic P–S bond is slightly longer (2.087 Å) than the exocyclic P=S bond (1.928 Å), consistent with the partial double bond character of the exocyclic bond. For comparison, the average double bond length between a tetrasubstituted P and a monosubstituted S is 1.922 Å when P has two other heteroatomic substituents; data from 26 published crystal structures.[22] Average P–S single bond in a variety of inorganic compounds is 2.01 Å with a third quartile above 2.07 Å, which would put this endocyclic P–S bond among the longest observed.

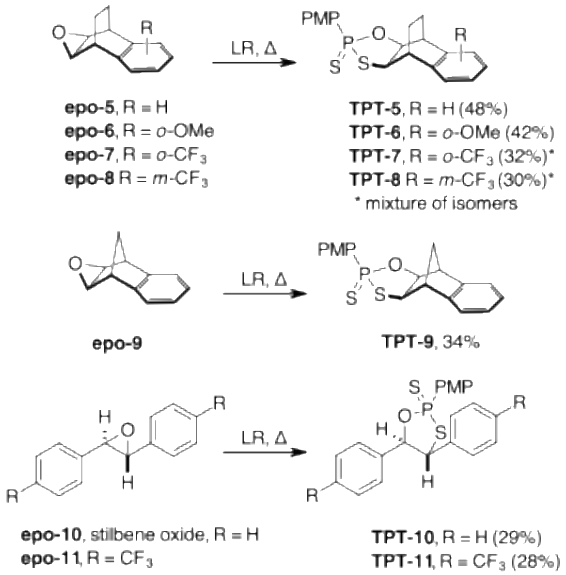

Figure 6 Bicyclic and stilbene-derived oxiranes that reliably produce TPT products.

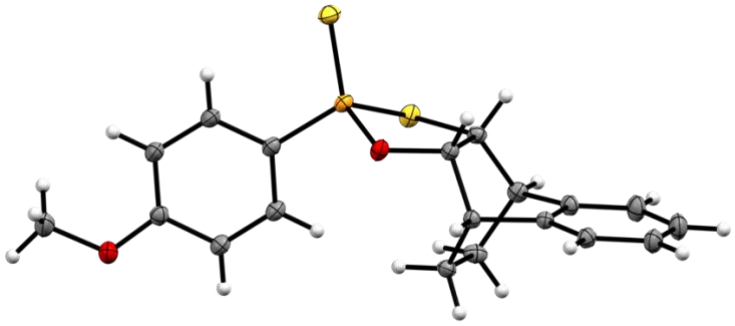

Figure 7 The ORTEP diagram depicts the molecular structure of TPT-6 as determined by single-crystal X-ray diffraction. Thermal ellipsoids are drawn at the 50% probability level to represent atomic displacement parameters, while hydrogen atoms are shown as spheres of arbitrary radius.

Asymmetrically substituted benzo-fused bicyclic structures can, in principle, yield two distinct regioisomeric products. We found that **epo-7** and **epo-8**, containing an electron-withdrawing trifluoromethyl group in the ortho or meta position of the fused benzo ring, gave mixtures of regioisomeric products. **Epo-7** gave a 1.5:1 mixture, with the slight preference for the isomer where the cation forms proximal to the meta position of the CF_3-substituted ring. This regioisomer has, in the ^1H NMR, the bridgehead H at 3.9 ppm, due to cumulative CF_3 and C-O deshielding effects. The other isomer has this H at 3.54 ppm. Trifluoromethyl group is a deactivating, "meta-directing" group, which explains why the meta position better stabilizes the homo-benzylic cation than the ortho position.

Strikingly, the electron-donating methoxy group at the ortho position in **epo-6** leads predominantly to a single regioisomer in a 10:1 ratio. The preferred product, in which sulfur is proximal to the methoxy group, suggests stabilization of the carbocation by the π electrons of the aromatic ring at the homobenzylic position, a remarkable effect enabled by the rigidity of the benzobicyclooctane system (Figure 8A orbital arrangement). This result can also be rationalized by invoking a phenonium cation intermediate.[23]

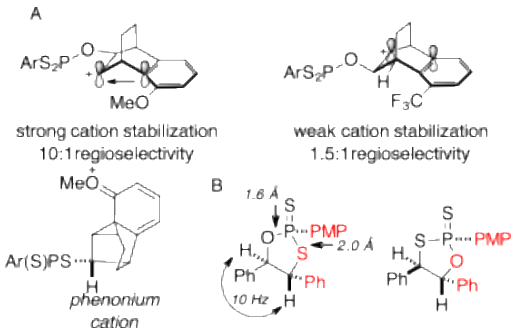

Figure 8 A) Orbital alignment leading to the stabilization of homo-benzylic carbocation formed during the reaction. B) Possible isomerism in stilbene oxides. Only one set of signals is observed in the NMR spectra.

Symmetrically substituted stilbene oxides (**epo-10** and **epo-11**) are also suitable substrates for the ring expansion, yielding desymmetrized products **TPT-10** and **TPT-11**. The stilbene TPTs retain the

trans relationship of the aryl groups of the epoxide, as evidenced by a 10 Hz coupling constant for the relevant protons. According to the Karplus model, a dihedral angle of 174º for the H-C-C-H system of two sp^3-hybridized carbons (bond length 1.543 Å) predicts a coupling of 9.2 Hz.[24] The carbocation is rapidly trapped by the thiolate, preventing rotation around the C–C bond and thus precluding formation of a *cis*-stilbene TPT. However, the PMP group on phosphorus must adopt a position *cis* to either the phenyl group near sulfur or to the phenyl group near oxygen. In NMR spectra, we only observe one set of peaks and we infer that the product in which the PMP group is *cis* to the phenyl group near sulfur would be preferred, because the longer P–S bond allows for less steric crowding (Figure 8B).

Naturally occurring *trans* oxirane found in (–)-caryophyllene oxide also afforded the expected TPT product **TPT-12** in 25% yield (Figure 9). As observed for other TPTs, the regiochemistry of the opening is governed by formation of the stabilized tertiary carbocation, with the PMP substituent on P adopting a pseudo-equatorial position. We observed that introduction of TPT ring into this molecule leads to broadening of ^{13}C NMR signals of carbons in cyclobutane ring suggestive of increased conformational flexibility of the nine-membered ring in caryophyllene TPT compared to caryophyllene oxide that does not show such line broadening.

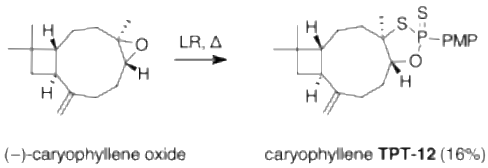

Figure 9 Complex oxiranes like caryophyllene oxide give the predicted TPT adducts.

Dual nature of ylides, functioning as both electrophiles and nucleophiles, combined with the inherent electrophilicity of oxiranes, and the strong oxophilicity of phosphorus(V), enables a predictable ring-expansion reaction. This transformation reliably generates thiophosphonothioates products in which the phosphorus atom is stereogenic, offering a controlled means of introducing chirality into the resulting heterocycle.

Data Statement

The data underlying this study are available in the published article, in its Supporting Information document, and openly available in Boskovic lab GitHub repository at:

https://github.com/boskovicgroup/thiophosphonothioates.

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Author contributions: CRediT

Ian Shire: Conceptualization, Investigation, Methodology, Validation. **Zarko Boskovic:** Conceptualization, Formal analysis, Resources, Supervision, Visualization, Writing.

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