Tetrahedron: *Asymmetry* 20 (2009) 293–297

Contents lists available at ScienceDirect

Tetrahedron: *Asymmetry*

journal homepage: www.elsevier.com/locate/tetasy

Michael addition to a chiral non-racemic 2-phosphono-2,3-didehydrothiolane S-oxide

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ARTICLE INFO

Article history:
Received 17 November 2008
Accepted 12 December 2008
Available online 14 March 2009

ABSTRACT

The Michael addition of selected sulfur and nitrogen nucleophiles to a chiral non-racemic 2-phosphono-2,3-didehydrothiolane S-oxide is fully diastereoselective. The enantiomeric excesses of the adducts obtained could be determined by ^{31}P NMR spectroscopy using (*R*)-(+)-*tert*-butyl(phenyl)phosphinothioic acid as a chiral solvating agent. The addition of thiophenol was monitored by ^{31}P NMR spectroscopy which made it possible to observe the formation and evolution of the kinetic and thermodynamic adducts in the reaction mixture. The structures of both enantiomeric thiophenol adducts have been determined by X-ray analysis.

1. Introduction

Chiral α,β-unsaturated sulfoxides are well known for their applications in asymmetric syntheses as efficient Michael acceptors.[1] Various compounds of this class have been described; however, new structures are still being investigated to access stereoselectively original, highly functionalized products.

Earlier, we reported the synthesis of 2-phosphono-2,3-didehydrothiolane S-oxide **1**,[2] which represents an interesting Michael acceptor, due to the particular geometry of the unsaturated five-membered ring and the double activation of the C–C double bond by both phosphonyl and sulfinyl groups. In a previous communication, we described investigations on the addition of several nucleophiles to the racemic substrate **1**.[3] Herein we report the asymmetric version of these reactions using non-racemic **1** and report a study of the reaction course using ^{31}P NMR spectroscopy.

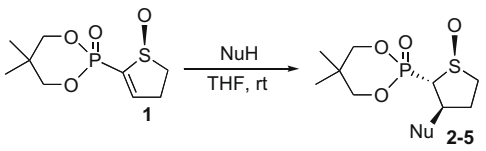
2. Results and discussion

As previously described,[2] 5,5-dimethyl-1,3,2-dioxaphosphorinanyl-2,3-didehydro-thiolane was oxidized by commercially available enantiopure (+)-(2*S*,8a*R*)-8,8-dichloro-camphorsulfonyloxaziridine to give the title sulfoxide **1** with a positive specific rotation value. When an attempt was made to measure the enantiomeric excess of product **1** using (*R*)-(+)-*tert*-butyl(phenyl)-phosphinothioic acid [(+)-TBPPTA] as a chiral solvating agent,[4] only one signal was detected in ^{31}P NMR, which led us to the conclusion that its ee was at least 98%.[2] Control of the enantiomeric excess by chiral HPLC was impossible since no conditions to separate enantiomers could be found. The X-ray analysis of an isolated single crystal of **1** showed that it was a single enantiomer whose absolute configuration at sulfur atom was assigned as (*S*).[2] This was in agreement with other results already obtained in the enantioselective sulfoxidation with the same oxaziridine.[1c,5]

2.1. Asymmetric Michael addition to 1

Having in hand the presumably enantiopure sulfoxide (+)-**1**, we decided to perform the asymmetric version of the Michael additions which had been described previously.[3]

The addition reactions with benzenethiol, *p*-toluenethiol, *tert*-butanethiol, and aniline were performed with the (+)-**1** obtained previously (Scheme 1, Table 1). As already observed in the racemic series under the same conditions (rt, THF, and, in the case of thiols, addition of a catalytic amount of NEt_3), the reactions were fully diastereoselective. Adducts **2**–**5** were obtained in good yields after simple precipitation. All adducts exhibited positive values for their specific rotations (Table 1). However, we were surprized to find that in all cases, the enantiomeric excesses of the resulting adducts **2**, measured by ^{31}P NMR spectroscopy using again (+)-TBPPTA,



Scheme 1.

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doi:10.1016/j.tetasy.2008.12.034

Table 1
Michael additions to (+)-**1**

NuH	Adduct	$[\alpha]_D$[a]	ee[b] (%)	Isolated yield (%)
PhSH	**2**	+13.2	68	98
4-TolSH	**3**	+16.5	70	89
t-BuSH	**4**	+8.5	60	78
$PhNH_2$	**5**	+30.0	70	74

[a] See Section 4 for the measurements conditions.
[b] Measured by ^{31}P NMR spectroscopy using (+)-TBPPTA.

were only ca. 70% (Table 1). As partial racemization under the reaction conditions used is unlikely, the low ees obtained for adducts **2–5** could only be due to the enantiopurity of the starting material, that is, substrate **1** should only be enantioenriched and not enantiopure as supposed. This hypothesis prompted us to re-examine the stereoselectivity of the asymmetric oxidation leading to **1** and to verify the preservation of the integrity of the sulfur configuration during the Michael addition.

We performed a series of reactions starting from various samples of substrate **1** (**1a–c**) using benzenethiol as the nucleophile. Sample **1a** was directly taken from the crude product **1** obtained by oxidation of 5,5-dimethyl-1,3,2-dioxaphosphorinanyl-2,3-didehydrothiolane with (+)-oxaziridine. Samples **1b** and **1c** were obtained from **1** after crystallization from DMSO/Et_2O (1:9) as the precipitate and as the solid resulting from evaporation of the filtrate, respectively. First, we measured the ees [by ^{31}P NMR spectroscopy using (+)-TBPPTA] and the optical rotations $[\alpha]_D$ of substrates **1a–c**, then of the corresponding adducts **2a–c**. The results are shown in Table 2.

Table 2
Michael additions of benzenethiol to various samples of (+)-**1**

	Substrate			Adduct	
(+)-**1**	$[\alpha]_D$ (*c* acetone)	ee[a] (%)	(+)-**2**	$[\alpha]_D$ (*c* acetone)	ee[a] (%)
1a	+59.8 (*c* 0.60)	—[b]	**2a**	+13.2 (*c* 0.25)	68[d]
1b	+27.7 (*c* 0.45)	32[c]	**2b**	+7.5 (*c* 0.30)	36[d]
1c	+77.0 (*c* 0.55)	—[b]	**2c**	+18.6 (*c* 0.55)	90[d]

[a] Measured by ^{31}P NMR spectroscopy using (+)-TBPPTA.
[b] Not determined.
[c] ^{31}P NMR: δ in ppm: 3.14 (minor); 3.21 (major).
[d] ^{31}P NMR: δ in ppm: 12.88 (minor); 12.74 (major).

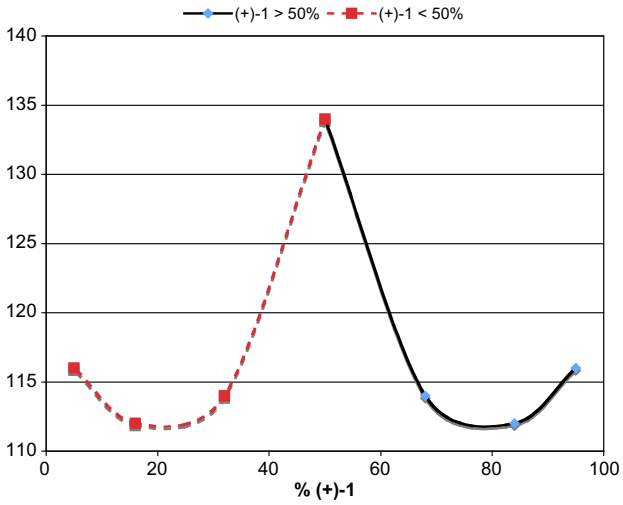
In the substrate series, only the ee of sample **1b** could be measured and was found to be about 32% (Table 2). In all other cases, the two signals overlapped and did not allow ee measurement by ^{31}P NMR spectroscopy.[6] In the Michael adduct series, the ees of samples **2a–c** could be measured and were found to be 68%, 36%, and 90%, respectively (Table 2). The enantiomeric excesses of the substrate **1b** and its adduct **2b** were compared. A good correlation between the enantiopurities of the substrate and product was found (32% and 36% ee, respectively). On this basis, we can assume that the enantiomeric excess of the starting material **1** is identical to that of the corresponding adduct.

The observed influence of the crystallization of **1** on its enantiomeric purity prompted us to check the physical properties of *rac*-**1** and that of samples **1a-c**, for which the ee was considered to be identical to the ee of the corresponding adducts **2a–c** (Table 2). Thus, melting points were measured for each sample as a function of the percentage of (+)-**1** in the mixture of the two enantiomers (Table 3, Graph 1).[7] The highest melting point was measured at 134 °C (for the racemic mixture) and the lowest at 112 °C [for a 84/16 mixture of (+)-**1**/(−)-**1**]. This is typical of the behavior of a true racemate.[8] In our case, the non-racemic mixture of **1** with an enantioselectivity of 68% could be enantioenriched by crystallization.

Table 3
Melting points of various samples of (+)-**1**

Sample	ee (%)	% (+)-**1**[b]	Mp (°C)
rac-**1**	0	50	134
1b	36[a]	68	114
1a	68[a]	84	112
1c	90[a]	95	116

[a] Estimated by correlation with ees of adducts **2a–c** (see Table 2).
[b] Calculated percentage (from ee) of enantiopure (+)-**1** in the mixture.



Graph 1. Melting point diagram of (+)-**1** and (−)-**1** mixture.

2.2. Determination of the stereochemistry of adduct 2

Recrystallization of sample **2c** (obtained from **1c** and having ~90% ee) from Et_2O/AcOEt (9:1) afforded enantiopure (+)-**2**, from which a single crystal could be isolated. The X-ray analysis showed that the absolute configuration at the sulfur atom was (*S*), as expected (Fig. 1). We also prepared compound **2** enantioenriched in the (−)-enantiomer and succeeded in the isolation of a single crys-

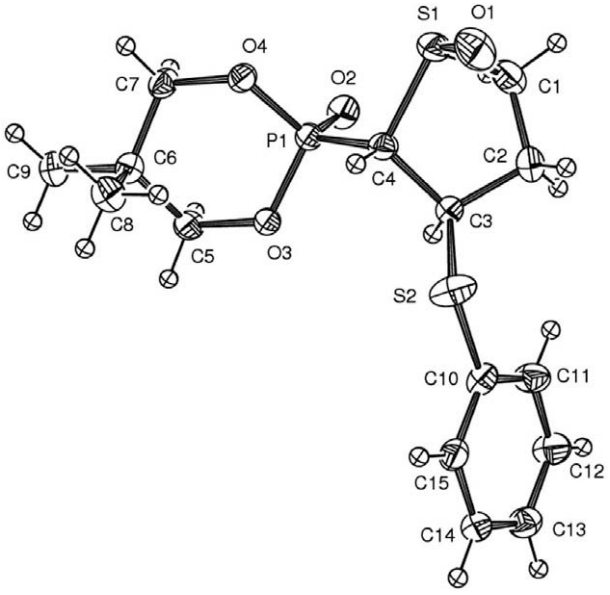


Figure 1. X-ray structure of (+)-**2**.

tal of the opposite enantiomer (−)-**2**,[9] of which the X-ray structure is shown in Figure 2.

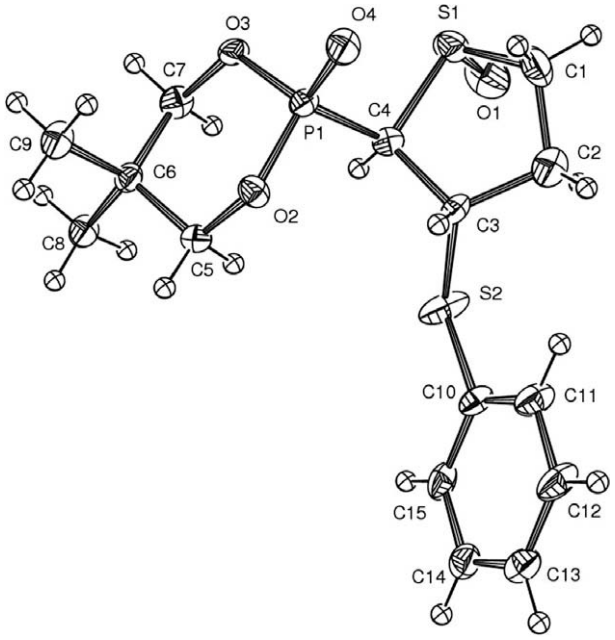
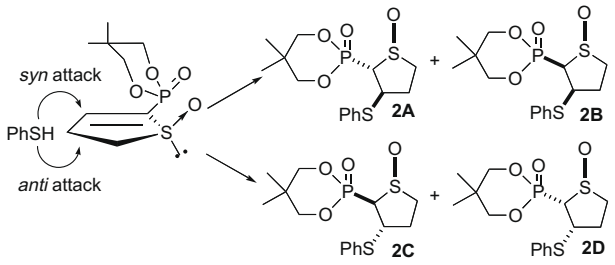


Figure 2. X-ray structure of (−)-**2**.

It is noteworthy that the enantiomeric purity of **1** with $[\alpha]_D$ = +60.5 is about 70% ee, indicating that the enantioselective sulfoxidation of the 5,5-dimethyl-1,3,2-dioxaphosphorinanyl-2,3-didehydro-thiolane with enantiopure 8,8-dichloro-camphorsulfonyl-oxaziridine led to a non-racemic sulfoxide **1** with 70% ee, and not to enantiopure **1** as originally reported.[2] Nevertheless, the originally reported stereochemistry at the sulfur atom determined by X-ray analysis of an isolated single crystal of (+)-**1** was correct.

2.3. Study of benzenethiol addition to 1 by ^{31}P NMR spectroscopy

In our previous study[3] we tried to rationalize the experimental results obtained in the Michael addition using the title thiolane S-oxide as a substrate. The nucleophile can attack either *syn* or *anti* to the S=O group, leading to four possible diastereomers **A**–**D** (addition of benzenethiol is shown in Scheme 2). The relative energies for these diastereomers were estimated by theoretical calculations and found to decrease in the order: **B** > **C** > **D** > **A**.[3] Indeed, in all the cases investigated, the only isolated adduct was **A**, the most stable, resulting from thermodynamic control. We decided to undertake a study by NMR spectroscopy, which could made it possible to observe the formation and evolution of the kinetic and thermodynamic adducts in the reaction mixture.



Scheme 2.

In an NMR tube, benzenethiol and a catalytic amount of triethylamine were added to a solution of racemic **1** in THF at −60 °C and the first spectrum was recorded. The peak corresponding to the substrate (at 3.2 ppm) quickly disappeared, and the spectra revealed three new peaks at 12.5, 10.0, and 7.7 ppm (in a 6:34:60 ratio), which can be attributed to three diastereomers, **d1**, **d2**, and **d3,** respectively (Table 4, entry 1). Temperature was then gradually increased (from −60 to 20 °C) and the ensuing spectra were recorded. Data given in Table 4 and Graph 2 represent the ratio changes of the three products with the temperature. The ratio **d1**:**d2**:**d3** did not substantially change until the temperature reached 0 °C, where the ratio was 17:34:49 (entry 6). Then, a fast increase in the amount of **d1** in the mixture at the expense of **d3** was observed (entries 7–9). At 20 °C, the ratio was 61:34:5 (entry 9), meaning only two diastereomers were still present, **d1** and **d2**. When the temperature was increased to 25 °C, the peak corresponding to **d2** completely disappeared and only **d1** remained (entry 10). The overall time of the experiment was about 2 h.

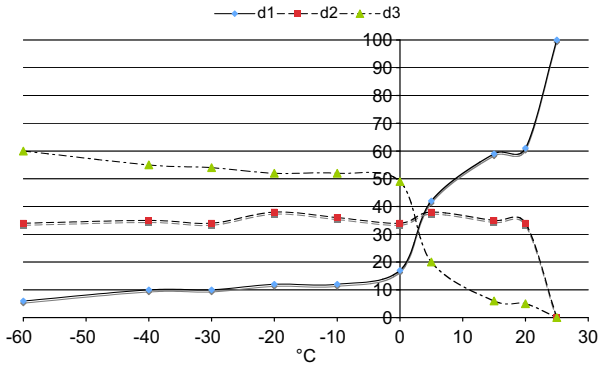
Table 4
^{31}P NMR study of the reaction course

Entry	Temp (°C)	Time[a] (min)	Product content (%)		
			d1[b]	**d2**[c]	**d3**[d]
1	−60	12	6	34	60
2	−40	35	10	35	55
3	−30	40	12	34	54
4	−20	44	12	38	52
5	−10	48	12	36	52
6	0	52	17	34	49
7	+5	74	42	38	20
8	+15	89	59	35	6
9	+20	94	61	34	5
10	+25	130	100	0	0

[a] Cumulated reaction time starting from t_0 = 0 min.
[b] Diastereomer **d1** (δ^{31}P = 12.5 ppm).
[c] Diastereomer **d2** (δ^{31}P = 10 ppm).
[d] Diastereomer **d3** (δ^{31}P = 7.7 ppm).

The ^{1}H NMR spectra showed, as expected, that **d1** corresponds to the structure of the most stable diastereomer **2A**, of which the relative configuration was already demonstrated by NMR spectroscopy in our previous study[3] and by X-ray analysis in the present study. It is very likely that the other diastereomers **d2** and **d3** correspond to two of the structures **2B**, **2C**, or **2D**. They should isomerize via an equilibrium to give the thermodynamically more stable 2**A**.

To gain information on their structures, we attempted to trap **d2** and **d3** before isomerization and to immediately record a ^{1}H NMR spectrum. To this end, the reaction was started at -60 °C, and, after raising the temperature to about −20 °C, the reaction was stopped by pouring the solution in ethyl ether cooled to −60 °C.[10] The small amount of the resulting precipitate was analyzed by NMR spectroscopy. The ^{31}P NMR spectrum showed two peaks at 13.3 and 10.6 ppm in a 10:90 ratio, corresponding to **d1** and **d2**, respectively.[11] It was, however, possible to characterize the major component **d2** by NMR spectroscopy. The coupling constant between H^2 (PCH) and H^3 (PhSCH) in the ^{1}H NMR spectrum of **d2** is similar to that measured in **2A** (7.4 Hz and 7.2 Hz, respectively), indicating a relative *trans* relationship between these two protons, therefore also between the phosphoryl and the phenylsulfanyl groups. Apart from **2A**, the only structure with this stereochemistry is **2C**, of which the difference between **2A** consists of a relative *cis*-arrangement between the phosphoryl group and the oxygen of the sulfinyl group. On this basis, we assume the assignment of the structure **2C** to the diastereoisomer **d2** observed at 10 ppm in ^{31}P NMR. By leaving the sample in a $CDCl_3$ solution at



Graph 2. Graphical presentation of the ^{31}P NMR study.

room temperature overnight, **2C** was completely transformed into **2A**. Unfortunately, our attempts to isolate and characterize the diastereomer **d3** were unsuccessful and therefore its structure, **2B** or **2D**, remains unassigned.

3. Conclusions

The Michael addition of several sulfur and nitrogen nucleophiles to a chiral non-racemic 5,5-dimethyl-1,3,2-dioxaphosphorinanyl-2,3-didehydro-thiolane 1-oxide was fully diastereo- and enantioselective. Although it was not possible to measure the enantiomeric excess of the substrate obtained after the asymmetric oxidation of the thiolane precursor, the enantiomeric excess of the obtained Michael adduct could be determined by ^{31}P NMR spectroscopy using (*R*)-(+)-*tert*-butyl(phenyl)phosphinothioic acid as a chiral solvating agent. This also enabled us to deduce the ee of the starting Michael acceptor. The Michael addition of benzenethiol was monitored by ^{31}P NMR spectroscopy at low temperature and allowed us to follow the formation and evolution of the kinetic and thermodynamic adducts in the reaction mixture. The structures and absolute configurations of both enantiomers of the benzenethiol adduct have been determined by X-ray analysis.

4. Experimental

4.1. General remarks

Most reactions were carried out under nitrogen with magnetic stirring, unless otherwise specified, and monitored by TLC using silica plates. Synthesized products were purified by column chromatography on silica gel or crystallized, if necessary. THF was purified with a PURESOLVTM apparatus developed by Innovative Technology Inc. NMR spectra were recorded on Bruker spectrometers: 250 MHz or 400 MHz (indicated in each case). Chemical shifts (δ) are indicated in ppm using TMS (for ^1H NMR) as an internal standard. Coupling constants *J* were given in hertz (Hz). Mass spectra were obtained on a GC/MS Saturn 2000 or on a Waters QTOF micro. IR spectra were recorded with a Perkin Elmer 16 PC FT-IR instrument. Analytical data were obtained using a THERMOQUEST NA 2500 instrument. Flash chromatography was performed on silica gel columns (40–63 μm) using air pressure. Optical rotation values were measured on a Perkin–Elmer-241 polarimeter for the sodium D line at 20 °C. The infrared spectra were recorded with a spectrometer ATI Mattson Infinity 60 AR FTIR on the liquid film, ν(cm^{-1}) are given. Mass spectra were recorded with a Finnigan MAT 95 Voyager Elite spectrometer in chemical ionization. Enantiomeric excesses of non-racemic compounds were determined by ^{31}P NMR spectroscopy using *R*-(+)-*tert*-butyl(phenyl)phosphinothioic acid as a chiral solvating agent.

Non-racemic **1** (ee = 68–70%), with a positive specific rotation value, was prepared according to the literature from 5,5-dimethyl-1,3,2-dioxaphosphorinanyl-2,3-didehydro-thiolane by oxidation with enantiopure (+)-(2*S*,8a*R*)-8,8-dichloro-camphorsulfonyl-oxaziridine.[2]

The separation of the product from the imine resulting from the oxaziridine was improved by first using pure CH_3CN as the eluent to remove the less polar imine, then a mixture of CH_3CN/DMSO 10/1.

4.2. Michael addition of thiols to non-racemic 2-phosphono-2,3-didehydrothiolane 1-oxide 1. General procedure

To a mixture of thiol (2 mmol) and non-racemic 2-phosphono-2,3-didehydrothiolane 1-oxide **1** (1 mmol) in THF (20 mL) was added NEt_3 (0.1 mmol), at room temperature. The resulting mixture was stirred until the reaction was completed (monitored by TLC). The solvent was evaporated and the product was precipitated from the residue using Et_2O.

4.2.1. 3-Phenylsulfanyl-2-[2′-(5,5-dimethyl-1,3,2-dioxaphosphorinanyl)]thiolane 1-oxide 2

It (diastereomer **2A**) was prepared according to the general procedure from non-racemic 2-phosphono-2,3-didehydrothiolane 1-oxide **1** and benzenethiol.

Yield = 98%; white solid, mp 112 °C; $[\alpha]_D$ = +13.2 (*c* 0.25, acetone); ^{31}P NMR (161.9 MHz, C_6D_6) in the presence of 2 equiv of (+)-*t*BuPhP(O)SH: δ 12.88 minor/12.74 major; ee = 68%. ^{31}P NMR (161.9 MHz, $CDCl_3$) δ 13.2; ^1H NMR (400 MHz, $CDCl_3$) δ 0.99 (s, 3H, CH_3), 1.22 (s, 3H, CH_3), 2.77–2.81 (m, 2H, CH_2), 3.00 (m, 1H, C**H**HSO), 3.20 (m, 1H, CH**H**SO), 3.31 (ddd, $^4J_{HH}$ = 1.1, $^3J_{HH}$ = 7.2, $^2J_{HP}$ = 14.6, 1H, PCH), 3.92–4.01 (m, 3H), 4.11–4.16 (m, 2H), 7.35–7.37 (m, 3H, H^{arom}), 7.54–7.57 (m, 2H, H^{arom}); ^{13}C NMR (100.6 MHz, $CDCl_3$) 20.98 (CH_3), 21.69 (CH_3), 32.43 (d, *J* = 6.8, $(CH_3)_2$**C**), 34.77 (d, *J* = 7.8, CH_2), 48.26 (CHS), 53.29 (d, *J* = 3.4, CH_2SO), 68.52 (d, *J* = 130.8, PCH), 77.05 (d, *J* = 6.6, CH_2O), 77.33 (d, *J* = 6.5, CH_2O), 128.57 (CH^{arom}), 129.37 (2 × CH^{arom}), 133.50 (SC^{arom}), 133.55 (2 × CH^{arom}); IR (neat, cm^{-1}) 2969, 2894, 1582, 1475, 1270, 1055, 1006, 979, 836, 816, 746, 693; MSMS: *m*/*z* (%) 361 (MH^+, 22), 161 (100); HRMS calcd for $C_{15}H_{21}PO_4S_2$: 361.0697. Found: 361.0706.

Enantiopure (+)-**2** and (−)-**2** were prepared according to the general procedure from enantioenriched 2-phosphono-2,3-didehydrothiolane 1-oxide (+)-**1** or (−)-**1** (having ee >90%), respectively, and subsequent recrystallization from Et_2O/AcOEt (9:1).

(1*Ss*,2*R*,3*R*)-(+)-**2**: $[\alpha]_D$ = +19.5 (*c* 1.0, acetone).

(1*Rs*,2*S*,3*S*)-(−)-**2**: $[\alpha]_D$ = −19.1 (*c* 1.1, acetone).

The two crystal structures of (+)-**2** and (−)-**2** have been registered at the Cambridge Crystallographic Data Centre and allocated the deposition numbers **CCDC 610286**, and **CCDC 610285**, respectively:

CCDC 610286: $2(S_2PC_{15}H_{21}O_4)$, M_r = 720.82, monoclinic, $P2_1$, *a* = 16.456(5), *b* = 5.8194(2), *c* = 18.4666(6) Å, β = 108.141(2)°, *V* = 1680.5(5) $Å^3$, *Z* = 2, D_x = 1.424 Mg m^{-3}, λ(Mo Kα) = 0.71073 Å, μ = 4.26 cm^{-1}, *F*(000) = 760, *T* = 120 K.

CCDC 610285: $3(S_2PC_{15}H_{21}O_4)$, M_r = 1081.22, orthorhombic, $P2_12_12_1$, *a* = 5.8692(1), *b* = 29.0024(4), *c* = 29.4854(4) Å, *V* = 5019.03(9) $Å^3$, *Z* = 4, D_x = 1.431 Mg m^{-3}, λ (Mo Kα) = 0.71073 Å, μ = 4.28 cm^{-1}, *F*(0 0 0) = 2280, *T* = 120 K.

4.3. Procedure for the preparation and characterization of diastereomer 2C

To a mixture of benzenethiol (2 equiv, 0.8 mmol) and racemic 2-phosphono-2,3-didehydrothiolane 1-oxide **1** (100 mg, 0.4 mmol)

in THF (15 mL) was added NEt_3 (0.1 equiv, 0.04 mmol), at −60 °C. The dry-ice bath was removed and after ~30 min, when the temperature was −20 °C, the reaction mixture was poured into ethyl ether (50 mL) and cooled to −60 °C. The resulting solution was placed in the freezer (at −4 °C), and, after about 3 h, a precipitate was formed (~15 mg). This precipitate was rapidly filtered, dried under vacuum (0.1 mbar), then dissolved in $CDCl_3$ at −20 °C, and analyzed by NMR spectroscopy. The sample contained product **2C** (90%) together with product **2A** (10%).

Product 2C: ^{31}P NMR (161.9 MHz, $CDCl_3$) δ 10.6; ^1H NMR (400 MHz, $CDCl_3$) δ 1.02 (s, 3H, CH_3), 1.23 (s, 3H, CH_3), 2.35 (m, 1H, C**H**H), 2.80 (m, 1H, CH**H**), 2.90–3.10 (m, 2H, CH_2SO), 3.31 (dd, $^3J_{HH}$ = 7.4 Hz, $^2J_{HP}$ = 20.2 Hz, 1H, PCH), 4.00–4.43 (m, 4H, 2 × CH_2O), 4.48 (m, 1H, C**H**SPh), 7.35–7.37 (m, 3H, H^{arom}), 7.54–7.57 (m, 2H, H^{arom}); ^{13}C NMR (62.9 MHz, $CDCl_3$) 19.18 and 20.11 (($\mathbf{C}H_3)_2C$), 30.71 (d, J = 6.8, $(CH_3)_2\mathbf{C}$), 31.18 (d, J = 7.8, CH_2), 45.59 (CHS), 50.76 (d, J = 3.4, CH_2SO), 63.39 (d, J = 130.8, PCH), 77.05 (d, J = 6.6, CH_2O), 77.33 (d, J = 6.5, CH_2O), 126.54 (CH^{arom}), 127.21 (2 × CH^{arom}), 129.95 (SC^{arom}), 131.99 (2 × CH^{arom}).

4.3.1. 3-*p*-Tolylsulfanyl-2-[2′-(5,5-dimethyl-1,3,2 dioxaphosphorinanyl)]thiolane 1-oxide 3

This compound was prepared according to the general procedure from non-racemic 2-phosphono-2,3-didehydrothiolane 1-oxide **1** and 4-methylbenzenethiol.

Yield = 89%; white solid, mp 125 °C; $[\alpha]_D$ = +16.5 (*c* 1.0, acetone); ^{31}P NMR (161.9 MHz, C_6D_6) in the presence of 2 equiv of (+)-*t*BuPhP(O)SH: δ 13.20 minor/13.05 major; ee = 70%.

^{31}P NMR (101.2 MHz, $CDCl_3$) δ 13.3; ^1H NMR (400 MHz, $CDCl_3$) δ 0.91 (s, 3H, CH_3), 1.14 (s, 3H, CH_3), 2.27 (s, 3H, CH_3), 2.50–2.90 (m, 3H, CH_2 and C**H**HSO), 2.99–3.15 (m, 1H, CH**H**SO), 3.21 (dd, $^3J_{HH}$ = 7.3 Hz, $^2J_{HP}$ = 14.4 Hz, 1H, PCH), 3.60–4.15 (m, 5H, 2 × CH_2O and C**H**STol), 7.09 (d, 2H, J = 7.8 Hz, H^{arom}), 7.36 (d, 2H, J = 8.0 Hz, H^{arom}); ^{13}C NMR (62.9 MHz, $CDCl_3$) 21.37 ($\mathbf{C}H_3$), 21.57 ($\mathbf{C}H_3$), 22.09 ($\mathbf{C}H_3$), 32.79 (d, J = 7.0 Hz, $(CH_3)_2\mathbf{C}$), 35.06 (d, J = 8.2 Hz, CH_2), 48.91 (CHS), 53.68 (CH_2SO), 68.73 (d, J = 131.2 Hz, PCH), 77.05 (d, J = 6.6 Hz, CH_2O), 77.65 (d, J = 6.5 Hz, CH_2O), 129.5 (C^{arom}), 130.53 (2 × CH^{arom}), 134.62 (2 × CH^{arom}), 139.42 (SC^{arom}), 133.55 (2 × CH^{arom}); IR (neat, cm^{-1}) 3360, 2974, 2912, 1603, 1500, 1322, 1258, 1053, 1005, 972, 956, 823, 751, 702; MSMS: *m*/*z* (%) 375 (MH^+, 90); HRMS calcd for $C_{16}H_{24}PO_4S_2$: 375.0854. Found: 375.0848.

4.3.2. 3-*tert*-Butylsulfanyl-2-[2′-(5,5-dimethyl-1,3,2-dioxaphosphorinanyl)]thiolane 1-oxide 4

This compound was prepared according to the general procedure from non-racemic 2-phosphono-2,3-didehydrothiolane 1-oxide **1** and *tert*-butanethiol. Yield = 78%; white solid, mp 116 °C; $[\alpha]_D$ = +8.5 (*c* 1.4, acetone); ^{31}P NMR (161.9 MHz, C_6D_6) in the presence of 2 equiv of (+)-*t*BuPhP(O)SH: δ 14.10 minor/13.91 major; ee = 60%. ^{31}P NMR (81 MHz, $CDCl_3$) δ 13.5; ^1H NMR (200 MHz, $CDCl_3$) δ 0.92 (s, 3H, CH_3), 1.22 (s, 3H, CH_3), 1.31 (s, 9H, 3 × CH_3), 2.60–2.90 (m, 3H), 3.05–3.20 (m, 2H), 3.50 (m, 1H), 3.80–4.30 (m, 4H); ^{13}C NMR (50 MHz, $CDCl_3$) 20.77 ($\mathbf{C}H_3$), 21.95 ($\mathbf{C}H_3$), 31.27 (3 × $\mathbf{C}H_3$), 32.37 (d, J = 6.9 Hz, $(CH_3)_2\mathbf{C}$), 37.59 (d, J = 8.8 Hz, CH_2), 41.95 (($CH_3)_3\mathbf{C}$), 44.81 (CHS), 53.85 (d, J = 3.7 Hz, CH_2SO), 69.68 (d, J = 128.4 Hz, PCH), 77.33 (d, J = 6.3, CH_2O), 77.69 (d, J = 6.5, CH_2O); IR (neat, cm^{-1}) 2965, 1661, 1345, 1267, 1161, 1057, 1005, 838, 815; MSMS: *m*/*z* (%) 341 (MH^+, 20), 285 (100); HRMS calcd for $C_{13}H_{26}PO_4S_2$: 341.1010. Found: 341.0986.

4.4. Michael addition of aniline to 2-phosphono-2,3-didehydrothiolane 1-oxide 1

To the non-racemic 2-phosphono-2,3-didehydrothiolane 1-oxide **1** (1 mmol) dissolved in dry THF (20 mL), aniline (5 mmol) was added at room temperature and the mixture was stirred for 4 h. The resulting adduct, which precipitated from THF, was filtered and dried to give the pure product.

4.4.1. Phenylamino-2-[2′-(5,5-dimethyl-1,3,2-dioxaphosphorinanyl)]thiolane 1-oxide 5

Yield = 74%, white solid, mp 150 °C; $[\alpha]_D$ = +30.0 (*c* 0.5, $CHCl_3$); ^{31}P NMR (161.9 MHz, C_6D_6) in the presence of 2 equiv of (+)-*t*BuPhP(O)SH: δ 12.91 minor/12.82 major; ee = 70%. ^{31}P NMR (101.2 MHz, $CDCl_3$) δ 12.1; ^1H NMR (250 MHz, $CDCl_3$) δ 0.99 (s, 3H, CH_3), 1.22 (s, 3H, CH_3), 2.20–2.85 (m, 2H), 3.10–3.30 (m, 2H), 3.50 (m, 1H), 3.80 (m, 1H), 3.90–4.20 (m, 4H), 4.75 (m, 1H, NH), 6.55–6.75 (m, 2H, H^{arom}), 7.04–7.18 (m, 2H, H^{arom}); ^{13}C NMR (62.9 MHz, $CDCl_3$) 21.51 (CH_3), 21.92 (CH_3), 32.93 (d, J = 6.8, $(CH_3)_2\mathbf{C}$), 33.65 (d, J = 4.1, CH_2), 53.75 (CH_2SO), 59.38 (CHN), 67.27 (d, J = 126.6, PCH),), 77.06 (d, J = 5.5, CH_2O), 77.26 (d, J = 6.5, CH_2O), 114.61 (CH^{arom}), 115.21 (CH^{arom}), 114.94, 119.46, 129.84, 146.35; IR (neat, cm^{-1}) 3360, 2969, 2911, 1604, 1500, 1322, 1258, 1054, 1006, 836, 751; MSMS: *m*/*z* (%) 344 (MH^+, 30), 176 (100), 132 (90); HRMS calcd for $C_{15}H_{23}NPO_4S$: 344.1089. Found: 344.1085.

Acknowledgments

This work was carried out with the support of the French CNRS and the Polish Academy of Sciences (Project No. 19485). Authors thank Dr. Loïc Toupet (University of Rennes) for the X-ray crystal diffraction analysis.

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6. In the presence of (+)-PhtBuP(S)OH, the ^{31}P NMR spectrum of **1** shows two signals for a low ee (0–40%), while in the case of a moderate to high ee (65–95%) the signals overlap. This may explain why only one signal can be observed for some enantiomerically enriched samples of **1**.
7. Three points of the graphic between 0% and 50% on the *x* axis (5%, 16%, and 32%) were obtained by extrapolation (on the *y* axis: 116°, 112°, and 114°, respectively).
8. Jacques, J.; Collet, A.; Wilen, S. H. *Enantiomers, Racemates, and Resolutions*; Wiley: New York, 1981.
9. The same procedure as for the preparation of (*S*)-(+)-**2** was used. The starting phosphonothiolane was oxidized by (−)-8,8-dichloro-camphorsulfonyl-oxaziridine to give a non-racemic mixture of (−)-**1**/(+)-**1** in about an 84:16 ratio. The mixture was enantioenriched in enantiomer (−)-**1** by crystallization and substrate **1** having 90% ee was reacted with benzenethiol. The resulted adduct was recrystallized to afford an enantiopure sample of (*R*)-(−)-**2**.
10. See Section 4.2.1.
11. The slight differences in chemical shifts observed in ^{31}P NMR (13.3 and 10.6 ppm instead of 12.5 and 10.0 ppm) are due to the use of THF as a solvent instead of $CDCl_3$ as normally applied.