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Thiophostone-Derived Brønsted Acids in the Organocatalyzed Transfer Hydrogenation of Quinolines: Influence of the P-Stereogenicity

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A new approach to Brønsted acid organocatalysis is described and is based on the use of thiophosphonic acids possessing both a chiral backbone and a chiral phosphorus function. The influence of the phosphorus stereochemistry on the enantioselectivity proved to be crucial in the hydrogen transfer hydrogenation of 2-phenylquinoline with Hantzsch esters.

Introduction

Over the past few years, catalysis by chiral Brønsted acids has been the subject of much interest.[1] Among this class of organocatalysts, the most used are cyclic phosphoric acids[2] derived from chiral diols such as 1,1′-binaphthol (BINOL),[3] 2,2′-diphenyl-(3,3′-biphenanthrene)-4,4′-diol (VAPOL),[4] tetraaryl-1,3-dioxolane-4,5-dimethanol (TADDOL),[5] 1,1′-spirobiindane-7,7′-diol (SPINOL),[6] and others.[7] Alternatively, acid derivatives with other P^V functions have also been used, such as dithiophosphoric acid or *N*-triflylphosphoramide derivatives (Figure 1a).[8] Although all these catalysts have demonstrated their efficiency in many organocatalytic reactions, to the best of our knowledge, neither phosphonic or thiophosphonic acids nor P-chiral derivatives[9] have been used in Brønsted acid catalysis. This work intends to afford a first insight into this field.

In the course of the synthesis of new glycomimetics, we recently described the synthesis of various P^V phostone[10] derivatives from tri-*O*-benzyl-D-glucal. They display either a phosphonate or thiophosphonate function and a stereogenic phosphorus atom at the pseudoanomeric position.[11] We envisioned that these thiophostone scaffolds might be good precursors for the synthesis of P-chiral, acidic organocatalysts with C_1 symmetry (Figure 1b). In this paper, we wish to report on the synthesis of thiophostone-derived P-chiral thiophosphonic acids, the reactivity of these new species in the transfer hydrogenation of 2-phenylquinoline, and the influence of the stereochemistry of the phosphorus atom on these reactions.

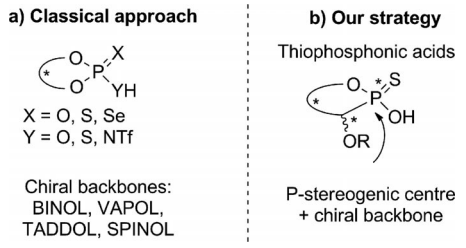

Figure 1. Classical approach (left) and our approach (right) to chiral Brønsted acid catalysts.

Results and Discussion

The synthesis of various stereoisomers of P-chiral thiophosphonic acids with a phostone scaffold is shown in Scheme 1. Four α- or β-configured[12] thiophostones **1a**–**4** in both *gluco* and *manno* series were prepared as previously reported[11] and then converted into the corresponding thiophosphonic acids **5a**–**8**. Initially, classical conditions for the removal of a methyl group from P^V derivatives were applied. These conditions involve the use of bromotrimethylsilane (TMSBr)[10g,10f] or sodium iodide in acetonitrile at reflux[10c,10f] and either left the starting material unchanged or led to degradation. The use of diisopropylamine or, preferably, trimethylamine[13] led to the targeted thiophosphonic acids in excellent yields. Such species can exist in two tautomeric forms, namely, the thiono and thiolo forms; however, this equilibrium usually lies far on the thiono side.[14] In the case of **5a**–**8**, the NMR spectroscopic data are diagnostic of their structures: the ^{31}P NMR shifts in the δ = 69–81 ppm range and the absence of ^{31}P NMR signals in the δ = 45–55 ppm region, characteristic of the thiolo form,[15] confirm the prevalence of the thiono form

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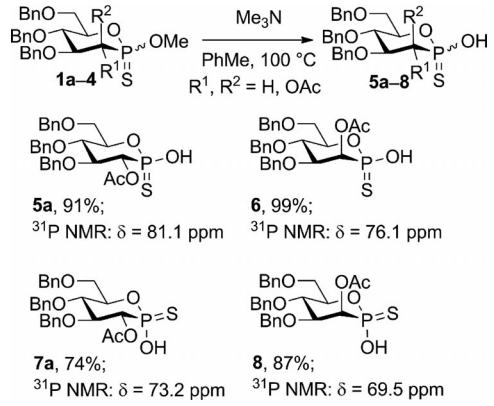
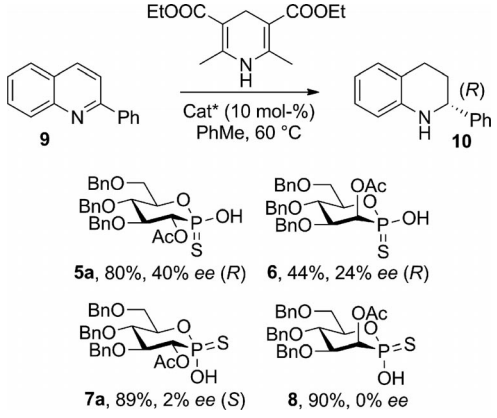
and thereby the presence of an OH function. The chemical shift for the β diastereoisomers is higher than for the corresponding α isomers, in accordance with previous observations.[10f,11] From the above NMR spectroscopic data, the methyl removal was demonstrated to be stereoretentive.



Scheme 1. Preparation of 2-OAc thiophosphonic acids derived from thiophostones.

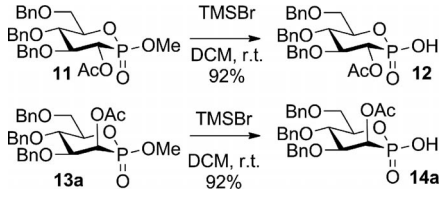
With these new acids in hand, we selected the Brønsted acid catalyzed transfer hydrogenation of quinolines as a benchmark reaction for the evaluation of their reactivity. The reduction of quinolines is a very efficient way to synthesize 1,2,3,4-tetrahydroquinoline derivatives, which are important synthetic intermediates[16] and building blocks for biologically active compounds.[17] For this transformation, the enantioselective metal-catalyzed hydrogenation of 2-substituted quinoline derivatives was initially envisioned.[18] An alternative strategy was then developed in 2006 by Rueping.[19] This strategy is based on the combined use of a chiral Brønsted acid catalyst and Hantzsch esters as the reducing agents.[20] In our work, the reduction of 2-phenylquinoline (**9**) has been undertaken under the conditions developed by Rueping with thiophosphonic acids **5a**–**8** as the catalysts (Scheme 2).



Scheme 2. Preliminary catalytic tests: H-transfer reduction of 2-phenylquinoline.

We were pleased to find that the conversion rates to the desired hydrogenated product **10** were good to excellent, which proves that the thiophosphonic acid function is acidic enough to catalyze the reaction efficiently. Both the glucose- and mannose-derived catalysts **7a** and **8**, which possess α configuration at the phosphorus atom, did not induce any stereoselectivity (0 and 2% *ee*, respectively). On the other hand, both β-configured catalysts **5a** and **6** induced significant stereoselectivities and gave (*R*)-2-phenyltetrahydroquinoline in 40 and 24% *ee*, respectively. The *gluco*-like diastereoisomer **5a** proved superior to the *manno*-like diastereoisomer **6**.

To afford additional evidence for the crucial effect of the P-stereogenicity on the stereochemical outcome of the reaction, we compared the enantioselectivities obtained with thioacids **5**–**8** with those of the two phosphonic acids **12** and **14a**. The *gluco*- and *manno*-type phosphonic acids **12** and **14a** were both obtained in 92% yield from the known phostones **11** and **13a**,[21] respectively, by reaction with bromotrimethylsilane (Scheme 3).[22,10g]



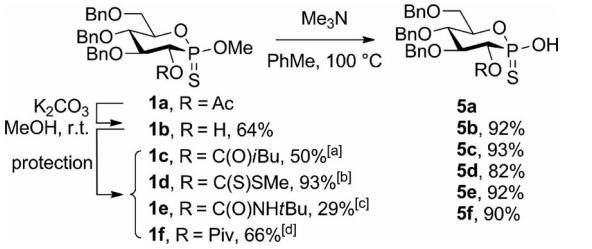
Scheme 3. Preparation of phosphonic acids from phostones.

The H-transfer reduction in Scheme 2 was attempted with phosphonic acids **12** and **14a** as catalysts,[23] and the reactions proceeded in high yields but with low enantioselectivity levels, irrespective of the stereochemistry of the chiral scaffold (*gluco* or *manno*; **12**: 14% *ee*, **14a**: 7% *ee*, see Supporting Information for full experimental data). These preliminary results suggest a key role of the P configuration, that is, the relative configuration of the phosphorus centre with respect to the chiral scaffold, in the stereochemical control of these reactions.

As the β-*gluco* scaffold produced the highest *ee* values, thiophosphonic acids **5** were selected as the best candidates for further studies. Their acetyl function was replaced by various protecting groups to determine the possible influence of the protecting group as well as to optimize the enantioselectivity levels.

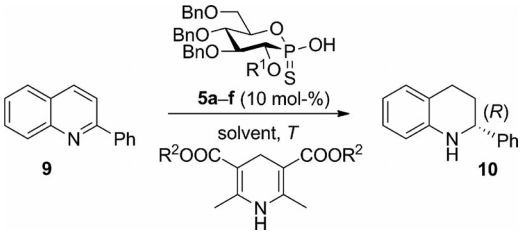
Thiophostone **1a** was deacetylated in 64% yield by MeOH in the presence of K_2CO_3,[25] and the resulting alcohol **1b** was protected with various protecting groups in usually good yields (Scheme 4).[26] The methyl groups of thioesters **1b**–**f** were removed with trimethylamine[13] to provide the requisite β-*gluco*-configured thiophosphonic acids **5b**–**f** in excellent yields. Once again, thioacids **5** were obtained as single diastereomers in their thiono tautomeric forms. These catalysts were evaluated in the test reaction of transfer hydrogenation of **9** (selected results are displayed in Table 1, see Supporting Information for full data).

As mentioned before, thiophosphonic acid **5a** afforded 40% *ee* (Table 1, Entry 1). The reduction of 2-phenylquinoline at 60 °C with the ethyl Hantzsch ester in the presence of the unprotected acid **5b** (R^1 = H) proceeded efficiently but without any enantioselectivity (Table 1, Entry 2). The replacement of the acetate group by a 3-methylbutanoate



Scheme 4. Preparation of various *O*-protected thiophosphonic acids in the *gluco* series. Conditions: [a] ClC(O)*i*Bu, 4-(dimethylamino)pyridine (DMAP), dichloromethane (DCM), room temp., 3 h. [b] Sodium hexamethyldisilazide (NaHMDS), THF, room temp., then CS_2, MeI, room temp., 1 h.[24a] [c] *t*BuNCO, trimethylsilyl chloride (TMSCl), DCM, room temp., 16 h.[24b] [d] Pivalic anhydride (Piv_2O), $Sc(OTf)_3$ (0.5 mol-%), MeCN, room temp., 2.5 h.[24c]

Table 1. Transfer hydrogenation of 2-phenylquinoline.[a]



Entry	Catalyst	R^2	Solvent	*T* [°C]	Yield [%]	*ee* [%]
1	**5a**	Et	PhMe	60	80	40
2	**5b**	Et	PhMe	60	83	1
3	**5c**	Et	PhMe	60	62	38
4	**5d**	Et	PhMe	60	73	40
5	**5e**	Et	PhMe	60	67	41
6	**5f**	Et	PhMe	60	86	52
7	**5f**	Me	PhMe	60	90	45
8	**5f**	*t*Bu	PhMe	60	89	59
9	**5f**	*t*Bu	cC_6H_{12}	60	89	65
10	**5f**	*t*Bu	Et_2O	22	99	66
11	**5f**	*t*Bu	CPME	60	97	55
12	**5f**	*t*Bu	CPME	22	97	67
13	**5f**	*t*Bu	CPME	–4	80	62
14[b]	**5f**	*t*Bu	CPME	22	82	68
15	**7f**	*t*Bu	CPME	22	98	5

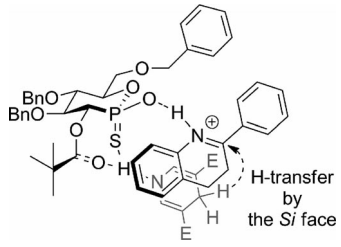
[a] General reaction conditions: 2.4 equiv. Hantzsch ester, 10 mol-% catalyst, 0.05 M. CPME = cyclopentyl methyl ether. [b] 2.0 equiv. Hantzsch ester.

(catalyst **5c**), xanthate (catalyst **5d**), or carbamate group (catalyst **5e**) did not improve the enantioinduction (Table 1, Entries 3–5). However, the pivaloyl (Piv) protecting group (Table 1, Entry 6) resulted in an increase in the *ee* to 52%.

In a second series of experiments, the influence of the ester groups of the Hantzsch reductant[27] was demonstrated by comparing the *ee* values obtained with methyl and *tert*-butyl esters with **5f** as the catalyst (Table 1, Entries 7–8). The product was obtained in 45 and 59% *ee*, respectively.

The effect of the solvent was also evaluated, and cyclohexane and diethyl ether furnish comparable, improved *ee* values of 65–66% (Table 1, Entries 9–10). The best result was then obtained with cyclopentyl methyl ether as the solvent at room temperature with 2.0 equiv. of Hantzsch ester. An 82% yield and a 68% *ee* were obtained (Table 1, Entry 14).[28] Decreasing the temperature to –4 °C did not improve the enantioselectivity (Table 1, Entry 13). Finally, for comparison purposes, the optimized conditions were assayed with catalyst **7f**, which possesses an axial OH function.[29] This experiment resulted in a very low 5% *ee* (Table 1, Entry 15). This last result clearly demonstrates the strong influence of the phosphorus stereochemistry on the enantioselectivity of these reactions.

The (*R*) stereochemistry of the final product **10** suggests the transition state shown in Scheme 5 for these reactions. The stereogenic (*S*)-configured phosphorus atom imposes a *syn* relationship between the P=S bond and the OPiv group. From this arrangement, both the P=S and C=O function might interact with the Hantzsch ester through H bonding.[30] The approach and positioning of 2-phenylquinoline would then be directed by a H bond between the acidic proton and the basic nitrogen centre, which would allow asymmetric hydride transfer from the *Si* face and finally lead to (*R*)-2-phenyltetrahydroquinoline (**10**).



Scheme 5. Proposed transition state.

Conclusions

We have described the stereoselective synthesis of P-chiral thiophosphonic acids with a sugarlike scaffold. We have shown that these acids are good catalysts for the transfer hydrogenation of 2-phenylquinoline. The influence of the P-stereochemistry on the stereochemical outcome of this reaction has been demonstrated. These results open the way to new approaches in the field of organocatalysis with P-chiral Brønsted acids.

Experimental Section

General: Reactions were performed by using oven-dried glassware under argon. All separations were performed under flash-chromatographic conditions on silica gel (Redi Sep prepacked column, 230–400 mesh) at medium pressure (20 psi) with the use of a CombiFlash Companion chromatography system. Reactions were monitored by thin-layer chromatography on Merck silica gel plates (60 F_{254} aluminum sheets), which were rendered visible by ultraviolet light and/or spraying with vanillin (15%) and sulfuric acid (2.5%) in EtOH followed by heating. Tetrahydrofuran (THF), CH_2Cl_2, *N*,*N*-dimethylformamide (DMF), MeOH, and methyl *tert*-butyl ether (MTBE) were purchased from Acros Organics at the highest commercial quality and used without further purification. Reagent-grade chemicals were obtained from diverse commercial

suppliers (Sigma–Aldrich, Acros Organics, TCI, and Alfa-Aesar) and were used as received. ^{1}H (500 or 300 MHz), ^{13}C (125 or 75 MHz), and ^{31}P NMR Spectra (122 or 202 MHz) were recorded with Bruker Avance spectrometers at 298 K. Chemical shifts (δ) are given in ppm and are referenced to the internal solvent signal or to tetramethylsilane (TMS) used as an internal standard. Multiplicities are declared as follow: s (singlet), br. s (broad singlet), d (doublet), t (triplet), q (quadruplet), dd (doublet of doublets), ddd (doublet of doublet of doublets), dt (doublet of triplets), m (multiplet). Coupling constants J are given in Hz. Carbon multiplicities were determined by DEPT-135 experiments. Diagnostic correlations were obtained by two-dimensional COSY and heteronuclear single quantum coherence (HSQC) experiments. Infrared spectra (IR) were recorded with a Perkin–Elmer FTIR system with a diamond window Dura SamplIR II attenuated total reflectance (ATR) accessory, and the data are reported in reciprocal centimeters (cm^{-1}). Optical rotations were measured with an Anton Paar MCP 300 polarimeter at 589 nm. $[\alpha]_D^{T\,°C}$ is expressed in °cm^{3}g^{-1}dm^{-1}, and c is expressed in g/100 cm^3. Melting points were determined in open capillary tubes with a Büchi B-540 apparatus. High-resolution mass spectra (HRMS) were recorded with a Micromass LCT Premier XE instrument (Waters) and were determined by electrospray ionization (ESI).

(2*S*,3*S*,4*S*,5*S*,6*R*)-4,5-Bis(benzyloxy)-6-[(benzyloxy)methyl]-3-hydroxy-2-methoxy-1,2-oxaphosphinane 2-Sulfide (1b): To a solution of **1a** (800 mg, 1.44 mmol) in MeOH (20 mL) was added K_2CO_3 (476 mg, 1.73 mmol, 1.2 equiv.). The resulting mixture was stirred at room temp. for 2 h and then quenched with a saturated solution of NH_4Cl. The two layers were separated, and the aqueous layer was reextracted twice with MTBE. The combined organic layers were dried with $MgSO_4$, filtered, and concentrated. The crude product was purified on silica gel (eluent: EtOAc/heptane, 1:3) to yield **1b** as a colorless oil (470 mg, 0.91 mmol, 64%). $[\alpha]_D^{22}$ = +61.8 (c = 0.8, $CHCl_3$). IR (neat): $\tilde{\nu}_{max}$ = 3443, 3062, 3031, 2916, 2868, 1497, 1454, 1360, 1136, 1107, 1038, 1026, 965, 840, 808, 734, 696 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.38–7.22 (m, 13 H, H_{ar}), 7.19–7.09 (m, 2 H, H_{ar}), 4.92 (d, J = 11.1 Hz, 1 H, CH_2Ph), 4.84 (d, J = 10.7 Hz, 1 H, CH_2Ph), 4.83 (d, J = 10.9 Hz, 1 H, CH_2Ph), 4.61 (d, J = 12.1 Hz, 1 H, CH_2Ph), 4.56 (d, J = 10.7 Hz, 1 H, CH_2Ph), 4.51 (d, J = 12.1 Hz, 1 H, CH_2Ph), 4.34–4.24 (m, 1 H, 5-H), 4.02–3.92 (m, 1 H, 2-H), 3.91–3.78 (m, 3 H, 3-H, 4-H, and 6-H), 3.85 (d, J = 13.9 Hz, 3 H, OMe), 3.73 (dd, J = 11.1 and 2.1 Hz, 1 H, 6-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 138.3 (C_q, C_{ar}), 137.9 (C_q, C_{ar}), 137.8 (C_q, C_{ar}), 128.7 (2 CH, C_{ar}), 128.6 (2 CH, C_{ar}), 128.6 (2 CH, C_{ar}), 128.2 (2 CH, C_{ar}), 128.1 (CH, C_{ar}), 128.0 (4 CH, C_{ar}), 128.0 (2 CH, C_{ar}), 85.4 (d, J = 17.0 Hz, CH, C-3), 77.3 (CH, C-4), 76.4 (CH_2Ph), 75.9 (d, J = 2.2 Hz, CH, C-5), 75.6 (CH_2Ph), 73.7 (CH_2Ph), 72.8 (d, J = 103.2 Hz, CH, C-2), 68.4 (d, J = 11.0 Hz, CH_2, C-6), 54.2 (d, J = 6.6 Hz, CH_3, OMe) ppm. ^{31}P{^{1}H} NMR (122 MHz, $CDCl_3$): δ = 96.2 ppm. HRMS (ESI-TOF): calcd. for $C_{27}H_{32}O_6PS$ [M + H]$^+$ 515.1657; found 515.1685.

(2*R*,3*S*,4*S*,5*S*,6*R*)-4,5-Bis(benzyloxy)-6-[(benzyloxy)methyl]-3-hydroxy-2-methoxy-1,2-oxaphosphinane 2-Sulfide (3b): To a solution of **3a** (60 mg, 0.11 mmol) in MeOH (1 mL) was added K_2CO_3 (60 mg, 0.43 mmol, 4 equiv.). The resulting mixture was stirred at room temp. for 1 h and then quenched with a solution of HCl (2 N in H_2O). The two layers were separated, and the aqueous layer was reextracted twice with EtOAc. The combined organic layers were dried with $MgSO_4$, filtered, and concentrated. The crude mixture was purified on silica gel (eluent: EtOAc/heptane, 1:3) to yield **3b** as a colorless oil (48 mg, 0.093 mmol, 85%). $[\alpha]_D^{22}$ = +55.1 (c = 0.9, $CHCl_3$). IR (neat): $\tilde{\nu}_{max}$ = 3418, 3063, 3031, 2924, 2868, 1497, 1454, 1361, 1136, 1137, 1041, 1026, 967, 796, 736, 697 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.36–7.23 (m, 13 H, H_{ar}), 7.16–7.10 (m, 2 H, H_{ar}), 4.87 (s, 2 H, CH_2Ph), 4.85 (d, J = 10.7 Hz, 1 H, CH_2Ph), 4.61 (d, J = 11.9 Hz, 1 H, CH_2Ph), 4.57 (d, J = 10.5 Hz, 1 H, CH_2Ph), 4.52 (d, J = 11.9 Hz, 1 H, CH_2Ph), 4.18–4.10 (m, 1 H, 5-H), 4.01 (d, J = 9.6 Hz, 1 H, 2-H), 3.90 (dd, J = 9.2 and 2.3 Hz, 1 H, 3-H), 3.88–3.70 (m, 3 H, 4-H and 6-H), 3.82 (d, J = 13.0 Hz, 3 H, OMe) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 138.3 (C_q, C_{ar}), 137.9 (C_q, C_{ar}), 137.8 (C_q, C_{ar}), 128.8 (2 CH, C_{ar}), 128.7 (2 CH, C_{ar}), 128.6 (3 CH, C_{ar}), 128.2 (CH, C_{ar}), 128.1 (CH, C_{ar}), 128.1 (4 CH, C_{ar}), 128.1 (CH, C_{ar}), 128.0 (CH, C_{ar}), 83.8 (d, J = 4.4 Hz, CH, C3), 77.9 (d, J = 8.2 Hz, CH, C5), 77.6 (CH, C-4), 76.4 (CH_2Ph), 75.8 (CH_2Ph), 75.5 (d, J = 111.4 Hz, CH, C-2),73.9 (CH_2Ph), 68.9 (d, J = 9.9 Hz, CH_2, C-6), 54.0 (d, J = 7.7 Hz, CH_3, OMe) ppm. ^{31}P{^{1}H} NMR (122 MHz, $CDCl_3$): δ = 85.7 ppm. HRMS (ESI-TOF): calcd. for $C_{27}H_{32}O_6PS$ [M + H]$^+$ 515.1657; found 515.1649.

(2*S*,3*S*,4*S*,5*S*,6*R*)-4,5-Bis(benzyloxy)-6-[(benzyloxy)methyl]-2-methoxy-2-sulfido-1,2-oxaphosphinan-3-yl Pivalate (1f): To a solution of **1b** (830 mg, 0.16 mmol) in acetonitrile (20 mL) were added pivalic anhydride (1.96 mL, 0.8 mmol, 5 equiv.) and scandium trifluoromethanesulfonate (40 mg, 0.008 mmol, 0.5 mol-%) dissolved in acetonitrile (2 mL). The resulting mixture was stirred at room temp. for 2.5 h. The reaction was then quenched with a saturated solution of $NaHCO_3$. The two layers were separated, and the aqueous layer was reextracted twice with dichloromethane. The combined organic layers were dried, filtered, and concentrated. The crude product was purified on silica gel (eluent: EtOAc/heptane, 1:5) to yield **1f** as a colorless oil (634.5 mg, 0.106 mmol, 66%). R_f = 0.53 (EtOAc/heptane, 1:4). $[\alpha]_D^{20}$ = +79.9 (c = 1.5, $CHCl_3$). IR (neat): $\tilde{\nu}_{max}$ = 3030, 2955, 2930, 2870, 1738, 1454, 1130, 1089, 1043, 1028, 970, 850, 815, 736, 698 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.29–7.10 (m, 13 H, H_{ar}), 7.07–6.98 (m, 2 H, H_{ar}), 5.24 (dd, J = 10.0 and 9.4 Hz, 1 H, 2-H), 4.74 (d, J = 11.1 Hz, 1 H, CH_2Ph), 4.70 (d, J = 10.9 Hz, 1 H, CH_2Ph), 4.68 (d, J = 10.9 Hz, 1 H, CH_2Ph), 4.55 (d, J = 12.1 Hz, 1 H, CH_2Ph), 4.48 (d, J = 10.7 Hz, 1 H, CH_2Ph), 4.44 (d, J = 12.1 Hz, 1 H, CH_2Ph), 4.31–4.20 (m, 1 H, 5-H), 4.02 (td, J = 9.4 and 3.2 Hz, 1 H, 3-H), 3.86 (t, J = 9.4 Hz, 1 H, 4-H), 3.80 (td, J = 11.0 and 3.0 Hz, 1 H, 6-H), 3.72 (d, J = 13.9 Hz, 3 H, OMe), 3.66 (dd, J = 11.3 and 2.1 Hz, 1 H, 6-H), 1.15 (s, 9 H, Piv) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 177.3 (C_q, C=O), 138.1 (C_q, C_{ar}), 137.9 (C_q, C_{ar}), 137.9 (C_q, C_{ar}), 128.6 (2 CH, C_{ar}), 128.6 (2 CH, C_{ar}), 128.6 (2 CH, C_{ar}), 128.0 (4 CH, C_{ar}), 128.0 (2 CH, C_{ar}), 127.9 (CH, C_{ar}), 127.4 (2 CH, C_{ar}), 82.4 (d, J = 13.2 Hz, CH, C-3), 77.9 (CH, C-4), 76.2 (CH_2Ph), 75.7 (CH, C-5), 75.6 (CH_2Ph), 73.7 (CH_2Ph), 72.5 (d, J = 109.2 Hz, CH, C-2), 68.4 (d, J = 11.0 Hz, CH_2, C-6), 54.2 (d, J = 6.0 Hz, CH_3, OMe), 39.0 (C_q, Piv), 27.3 (3 CH_3, Piv) ppm. ^{31}P{^{1}H} NMR (122 MHz, $CDCl_3$): δ = 88.9 ppm. HRMS (ESI-TOF): calcd. for $C_{32}H_{40}O_7PS$ [M + H]$^+$ 599.2232; found 599.2239.

(2*R*,3*S*,4*S*,5*S*,6*R*)-4,5-Bis(benzyloxy)-6-[(benzyloxy)methyl]-2-methoxy-2-sulfido-1,2-oxaphosphinan-3-yl Pivalate (3f): To a solution of **3b** (141 mg, 0.275 mmol) in acetonitrile (2.4 mL) were added pivalic anhydride (0.33 mL, 1.38 mmol, 5 equiv.) and a solution of scandium trifluoromethanesulfonate (6.8 mg, 0.014 mmol, 5 mol-%) in acetonitrile (1 mL). The resulting mixture was stirred at room temp. for 1 h. The reaction was quenched with a saturated solution of $NaHCO_3$. The aqueous layer was reextracted twice with CH_2Cl_2. The combined organic layers were dried, filtered, and concentrated. The crude product was purified on silica gel (eluent: EtOAc/heptane, 20:80) to yield **3f** as a colorless oil (93.5 mg, 0.157 mmol, 57%). R_f = 0.43 (EtOAc/heptane, 1:1). $[\alpha]_D^{23}$ = +59.1 (c = 0.8, $CHCl_3$). IR (neat): $\tilde{\nu}_{max}$ = 3031, 2972, 2933, 2870, 1746, 1455, 1363, 1147, 1124, 1096, 1045, 1028, 987, 973, 806, 737, 698 cm^{-1}. ^{1}H

NMR (300 MHz, $CDCl_3$): δ = 7.38–7.19 (m, 13 H, H_{ar}), 7.13–7.05 (m, 2 H, H_{ar}), 5.61 (dd, J = 10.0 and 2.8 Hz, 1 H, 2-H), 4.80 (d, J = 11.1 Hz, 1 H, CH_2Ph), 4.77 (d, J = 10.5 Hz, 1 H, CH_2Ph), 4.70 (d, J = 11.1 Hz, 1 H, CH_2Ph), 4.64 (d, J = 12.1 Hz, 1 H, CH_2Ph), 4.55 (d, J = 10.5 Hz, 1 H, CH_2Ph), 4.54 (d, J = 12.1 Hz, 1 H, CH_2Ph), 4.24–4.16 (m, 1 H, 5-H), 4.04–3.90 (m, 2 H, 3-H and 4-H), 3.87–3.80 (m, 1 H, 6-H), 3.85 (d, J = 13.4 Hz, 3 H, OMe), 3.76 (dd, J = 11.1 and 1.3 Hz, 1 H, 6-H), 1.22 (s, 9 H, Piv) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 176.5 (d, J = 3.8 Hz, C_q, C=O Piv), 137.9 (C_q, C_{ar}), 137.8 (C_q, C_{ar}), 137.7 (C_q, C_{ar}), 128.6 (3 CH, C_{ar}), 128.6 (2 CH, C_{ar}), 128.1 (4 CH, C_{ar}), 128.1 (2 CH, C_{ar}), 128.0 (CH, C_{ar}), 127.9 (CH, C_{ar}), 127.3 (2 CH, C_{ar}), 82.2 (d, J = 4.9 Hz, CH, C-3), 78.0 (d, J = 8.8 Hz, CH, C-5), 77.9 (CH, C-4), 76.0 (CH_2Ph), 75.8 (CH_2Ph), 73.8 (CH_2Ph), 73.3 (d, J = 113.6 Hz, CH, C-2), 68.8 (d, J = 9.9 Hz, CH_2, C-6), 53.9 (d, J = 6.6 Hz, CH_3, OMe), 39.1 (C_q, Piv), 27.3 (3 CH_3, Piv) ppm. $^{31}P\{^1H\}$ NMR (122 MHz, $CDCl_3$): δ = 80.7 ppm. HRMS (ESI-TOF): calcd. for $C_{32}H_{40}O_7PS$ $[M + H]^+$ 599.2232; found 599.2261.

General Procedure for the Demethylation of Thiophosphonate Esters to Thiophosphonic Acids: To a solution of thiophostone in toluene was added Me_3N at –78 °C. The resulting mixture was stirred at 50 °C for 3 h. The mixture was cooled to room temp. and the reaction quenched with 1 N aqueous HCl. The two layers were separated, and the aqueous layer was reextracted twice with EtOAc. The combined organic layers were dried with $MgSO_4$, filtered, and concentrated to yield the pure thiophosphonic acid.

(2*S*,3*S*,4*S*,5*S*,6*R*)-4,5-Bis(benzyloxy)-6-[(benzyloxy)methyl]-2-hydroxy-2-sulfido-1,2-oxaphosphinan-3-yl Pivalate (5f): Compound **5f** was synthesized according to the general procedure by reaction of **1f** (25 mg, 0.042 mmol) in toluene (0.5 mL) and trimethylamine (0.5 mL). Compound **5f** was obtained as a colorless oil (22 mg, 0.038 mmol, 90%). $[\alpha]_D^{23}$ = +70.2 (c = 0.7, $CHCl_3$). IR (neat): $\tilde{\nu}_{max}$ = 2969, 2922, 2873, 1736, 1497, 1480, 1455, 1363, 1277, 1142, 1058, 989, 829, 742, 699 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 7.28–7.15 (m, 13 H, H_{ar}), 7.07–7.00 (m, 2 H, H_{ar}), 4.91 (dd, J = 9.8 and 7.6 Hz, 1 H, 2-H), 4.75 (s, 2 H, CH_2Ph), 4.72 (d, J = 11.0 Hz, 1 H, CH_2Ph), 4.56 (d, J = 12.0 Hz, 1 H, CH_2Ph), 4.48 (d, J = 11.0 Hz, 1 H, CH_2Ph), 4.43 (d, J = 12.0 Hz, 1 H, CH_2Ph), 4.32–4.16 (br. s, 1 H, OH), 4.29–4.22 (m, 1 H, 5-H), 4.02 (td, J = 9.8 and 2.5 Hz, 1 H, 3-H), 3.85 (t, J = 9.8 Hz, 1 H, 4-H), 3.79 (dt, J = 11.0 and 2.5 Hz, 1 H, 6-H), 3.70 (dd, J = 11.0 and 1.3 Hz, 1 H, 6-H), 1.18 (s, 9 H, Piv) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 179.8 (d, J = 1.8 Hz, C_q, Piv), 138.1 (C_q, C_{ar}), 137.9 (C_q, C_{ar}), 137.6 (C_q, C_{ar}), 128.7 (2 CH, C_{ar}), 128.6 (2 CH, C_{ar}), 128.6 (2 CH, C_{ar}), 128.2 (2 CH, C_{ar}), 128.2 (CH, C_{ar}), 128.1 (CH, C_{ar}), 128.0 (CH, C_{ar}), 127.9 (2 CH, C_{ar}), 127.6 (2 CH, C_{ar}), 82.3 (d, J = 10.1 Hz, CH, C-3), 77.6 (CH, C-4), 76.4 (CH_2Ph), 76.1 (d, J = 98.1 Hz, CH, C-2), 75.6 (CH_2Ph), 75.4 (d, J = 1.8 Hz, CH, C-5), 73.8 (CH_2Ph), 68.4 (d, J = 11.0 Hz, CH_2, C-6), 39.1 (C_q, Piv), 27.4 (3 CH_3, Piv) ppm. $^{31}P\{^1H\}$ NMR (202 MHz, $CDCl_3$): δ = 82.7 ppm. HRMS (ESI-TOF): calcd. for $C_{31}H_{36}O_7PS$ $[M - H]^-$ 583.1919; found 583.1926.

(2*R*,3*S*,4*S*,5*S*,6*R*)-4,5-Bis(benzyloxy)-6-[(benzyloxy)methyl]-2-hydroxy-2-sulfido-1,2-oxaphosphinan-3-yl Pivalate (7f): Compound **7f** was synthesized according to the general procedure by the reaction of **3f** (95 mg, 0.159 mmol), toluene (3 mL), and trimethylamine (1 mL). Compound **7f** was obtained as a colorless oil (82.7 mg, 0.142 mmol, 89%). $[\alpha]_D^{23}$ = +54.7 (c = 0.2, $CHCl_3$). IR (neat): $\tilde{\nu}_{max}$ = 3031, 2970, 2931, 2871, 1744, 1454, 1363, 1274, 1125, 1091, 1048, 1027, 964, 736, 717, 696 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.30–7.11 (m, 13 H, H_{ar}), 7.00–6.93 (m, 2 H, H_{ar}), 5.94–5.70 (br. s, 1 H, OH), 5.47 (dd, J = 10.4 and 3.2 Hz, 1 H, 2-H), 4.71 (d, J = 11.3 Hz, 1 H, CH_2Ph), 4.66 (d, J = 10.9 Hz, 1 H, CH_2Ph), 4.64 (d, J = 11.1 Hz, 1 H, CH_2Ph), 4.63 (d, J = 12.8 Hz, 1 H, CH_2Ph), 4.53 (d, J = 12.4 Hz, 1 H, CH_2Ph), 4.40 (d, J = 10.5 Hz, 1 H, CH_2Ph), 4.30–4.20 (m, 1 H, 5-H), 3.96 (td, J = 10.0 and 2.4 Hz, 1 H, 3-H), 3.76–3.65 (m, 2 H, 4-H and 6-H), 3.64–3.55 (m, 1 H, 6-H), 1.14 (s, 9 H, Piv) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 177.0 (d, J = 3.3 Hz, C_q, C=O Piv), 137.9 (C_q, C_{ar}), 137.3 (C_q, C_{ar}), 137.0 (C_q, C_{ar}), 128.7 (2 CH, C_{ar}), 128.7 (2 CH, C_{ar}), 128.6 (2 CH, C_{ar}), 128.4 (2 CH, C_{ar}), 128.4 (2 CH, C_{ar}), 128.3 (CH, C_{ar}), 128.3 (CH, C_{ar}), 127.9 (CH, C_{ar}), 127.4 (2 CH, C_{ar}), 82.2 (d, J = 4.9 Hz, CH, C-3), 78.2 (CH, C-4), 77.4 (d, J = 8.8 Hz, CH, C-5), 76.0 (CH_2Ph), 75.9 (CH_2Ph), 73.8 (CH_2Ph), 73.0 (d, J = 112.5 Hz, CH, C-2), 69.1 (d, J = 9.9 Hz, CH_2, C-6), 39.1 (C_q, Piv), 27.3 (3 CH_3, Piv) ppm. $^{31}P\{^1H\}$ NMR (122 MHz, $CDCl_3$): δ = 74.3 ppm. HRMS (ESI-TOF): calcd. for $C_{31}H_{41}NO_7PS$ $[M + NH_4]^+$ 602.2341; found 602.2324.

General Procedure for the Asymmetric Hydrogenation of 2-Phenylquinoline: A solution of 2-phenylquinoline (20.5 mg, 0.1 mmol), Hantzsch ester (0.24 mmol, 2.4 equiv.), and the catalyst (0.01 mmol, 10 mol-%) in toluene (2 mL) was stirred at room temp. for 90 min. The solvent was evaporated in vacuo, and the residue was purified on silica gel (eluent: toluene). 2-Phenyl-1,2,3,4-tetrahydroquinoline was obtained as a colorless oil. ^1H NMR (500 MHz, $CDCl_3$): δ = 7.45–7.34 (m, 4 H), 7.31 (t, J = 7.5 Hz, 1 H), 7.07–6.98 (m, 2 H), 6.68 (t, J = 7.5 Hz, 1 H), 6.57 (d, J = 8.0 Hz, 1 H), 4.46 (dd, J = 9.5, 3.3 Hz, 1 H), 4.10 (br. s, 1 H), 3.00–2.88 (m, 1 H), 2.80–2.70 (m, 1 H), 2.21–2.10 (m, 1 H), 2.08–1.95 (m, 1 H) ppm. Chiral HPLC analysis: [CHIRALPAK® IB, 30 °C, 5% *i*PrOH/*n*-heptane, 1 mL/min, 250 nm, retention times: 6.8 min (minor) and 8.6 min (major)]. $[\alpha]_D^{20}$ = +23 (c = 1.8, $CHCl_3$; 68% *ee*) {lit.: $[\alpha]_D^{20}$ = –37.7 (c = 1.1, $CHCl_3$) for (*S*)-2-phenyl-1,2,3,4-tetrahydroquinoline (97% *ee*),[19b] $[\alpha]_D^{20}$ = –34.8 (c = 1.1, $CHCl_3$) for (*S*)-2-phenyl-1,2,3,4-tetrahydroquinoline (96% *ee*)}.[7a]

Supporting Information (see footnote on the first page of this article): Full experimental details and copies of ^1H and ^{13}C NMR spectra.

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