Kinetic Resolution in 1,3-Dipolar Cycloaddition of Tartaric Acid-Derived Nitrones to 2,3-Dihydro-1-phenyl-1*H*-phospholes. An Enantioselective Approach to the 2,2′-Coupled Pyrrolidine–Phospholane Ring System

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Enantiomerically pure five-membered ring nitrones derived from L-tartaric acid via C_2-symmetric *O,O′*-protected 3,4-dihydroxy pyrrolidines undergo highly regio- and stereoselective cycloaddition reactions with racemic 2,3-dihydro-1-phenyl-1*H*-phosphole 1-oxide and 1-sulfide. In all cases formation of only two diastereomeric cycloadducts is observed and their ratio (up to 10:1) is dependent on the size of the protecting groups in the nitrone and on the extent of conversion. The tricyclic cycloadducts feature 2,2′-connection of pyrrolidine and phospholane rings and six contiguous stereogenic centers of which three are created and the one at phosphorus is kinetically resolved during the cycloaddition process. It is established that in the studied kinetic resolutions the stereoselectivity factor $s = k_S/k_R$ exceeds the value of 10 (up to 14) in the most favorable cases. In a properly tuned reaction both the diastereomeric cycloadducts and the enantiomerically enriched dihydrophosphole derivative can be simultaneously obtained in satisfactory chemical and optical yields.

Introduction

The fact that under certain chiral circumstances substrate enantiomers can react at different rates is a basic principle of kinetic resolution of racemic compounds.[1] A typical process of kinetic resolution suffers, however, from the inherent disadvantage that the maximum yield of the recovered unreacted enantiomer is 50%.[1,2] A more advantageous situation develops when the kinetic resolution process is characterized by formation of diastereomeric products,[1a] and both the resolved unreacted substrate and the selectively formed diastereomeric product are desired synthetic targets.

Our interest in the preparation of novel enantiomeric aminophosphine ligands in which the heteroatoms are incorporated in the two 2,2′-connected five-membered rings[3] enabling tricyclic chelate formation has led us to study the possibility of achieving the required 2,2′-connection directly on the two extant heterocycles by means of the 1,3-dipolar cycloaddition of a pyrrolidine-derived nitrone and a simple dihydrophosphole derivative, having in mind that the N–O bond in the expected cycloadduct can be readily cleaved.[4] In this paper we wish to demonstrate that such cycloadditions involving racemic 2,3-dihydro-1-phenyl-1*H*-phosphole 1-oxide (or 1-sulfide) and enantiomerically pure five-membered ring nitrones lead to the highly regio- and stereoselective formation of the desired cycloadducts[5] with concomitant creation of three new carbon stereogenic centers combined with an efficient kinetic resolution of the P center.[6] In a properly tuned reaction both the enantiomerically pure cycloadducts and the enantiomerically enriched dihydrophosphole derivative,[7] also desired as a substrate for single or double asymmetric nitrone cycloadditions, can be simultaneously obtained in satisfactory chemical and optical yields.[8]

Results and Discussion

The cycloadditions of the enantiomeric nitrones **1a–d**, prepared from L-tartaric acid via C_2-symmetric 3,4-

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(1) Reviews: (a) Kagan, H. B.; Fiaud, J. C. *Top. Stereochem.* **1988**, *18*, 249–330. (b) Chen, C.-S.; Sih, C. J. *Angew. Chem., Int. Ed. Engl.* **1989**, *28*, 695–707. (c) Finn, M. G.; Sharpless, K. B. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: New York, 1985; Vol. 5, pp 247–308.

(2) See, however: Kitamura, M.; Tokunaga, M.; Noyori, R. *J. Am. Chem. Soc.* **1993**, *115*, 144–152, and references cited therein, for the most recent discussion on dynamic kinetic resolution.

(3) Symmetrical 2,2′-bipyrrolidine ligands: Oishi, T.; Hirama, M. *J. Org. Chem.* **1989**, *54*, 5384–5385. 2,2′-Biphospholenes and biphospholes: Mercier, F.; Holand, S.; Mathey, F. *J. Organomet. Chem.* **1986**, *316*, 271–279. Deschamp, B.; Mathey, F. *Bull. Soc. Chim. Fr.* **1992**, *129*, 486–489, and references cited therein.

(4) For the most recent review, see: Grünanger, P.; Vita-Finzi, P. Isoxazoles. Part One. In *The Chemistry of Heterocyclic Compounds*; Taylor, E. C., Weissberger, A., Series Eds.; John Wiley & Sons: New York, 1991.

(5) For recent account of studies on regio- and stereoselective cycloadditions of nitrones to phosphinylethenes, see: (a) Brandi, A.; Cicchi, S.; Goti, A.; Pietrusiewicz, K. M. *Gazz. Chim. Ital.* **1991**, *121*, 285–295. (b) Brandi, A.; Cicchi, S.; Goti, A.; Pietrusiewicz, K. M.; Wisniewski, W. *Tetrahedron* **1990**, *46*, 7093-7104. (c) Brandi, A.; Cicchi, S.; Goti, A.; Pietrusiewicz, K. M. *Tetrahedron: Asymmetry* **1991**, *2*, 1063–1074. (d) Reference 6.

(6) Original observation: Goti, A.; Cicchi, S.; Brandi, A.; Pietrusiewicz, K. M. *Tetrahedron: Asymmetry* **1991**, *2*, 1371–1378. Corr. *Tetrahedron: Asymmetry* **1992**, *3*, 671.

(7) Attempted large scale classical resolution of racemic **2a** by fractional crystallization of its diastereomeric complexes with *O,O′*-dibenzoyl-L-tartaric acid from ether or benzene–heptane afforded after several crystallizations only small quantities of (*S*)-(+)-**2a** of ca. 65% enantiomeric purity and was judged to be too inefficient for practical use. Pietrusiewicz, K. M.; Koprowski, M., unpublished results.

(8) To the best of our knowledge no kinetic resolution employing 1,3-dipolar cycloaddition has been reported prior to our work. For a related kinetic resolution in Diels–Alder cycloaddition, see: Wegener, B.; Hansen, M.; Winterfeldt, E. *Tetrahedron: Asymmetry* **1993**, *4*, 345–350. For a precedent of kinetic resolution in phosphorus chemistry, see: Wittig, G.; Cristau, J.-H.; Braun, H. *Angew. Chem., Int. Ed. Engl.* **1967**, *6*, 700–701.

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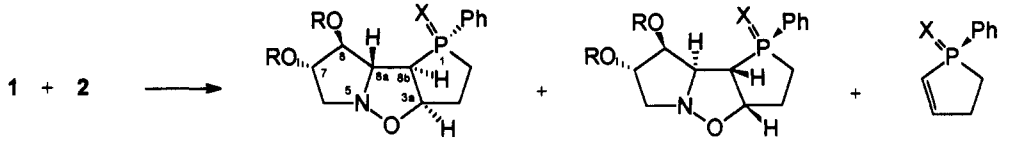
Scheme 1



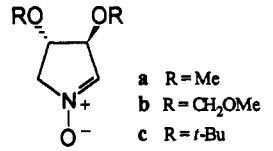
3a-e **4a-e** **(*R*)-2**

a: R=Me, X=O; **b**: R=MOM, X=O; **c**: R=*t*-Bu, X=O
d: R=*t*-Bu, X=S; **e**: R=TBDPS, X=O

Table 1. Cycloadditions of Enantiomerically Pure Nitrones 1 to Racemic 2[a]

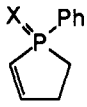
entry	nitrone	phosphole	% yield of 3 and 4[b]	ratio of 3/4	% recov phosphole	$[\alpha]_D$,[c] deg	% ee[d]
1	1a	2a	90	3.3:1	45	−195	61
2[e]	1a	2a	75	4:1	–	–	–
3	1b	2a	65	5:1	45	−132	*f*
4	1c	2a	67	6.4:1	39	−155	49
5	1c	2b	52[g]	8:1[h]	46	−122	*i*
6[j]	1d	2a	60[g]	10:1	39	−188	59
7[k]	1c	2a	91	2.9:1	27	−306	96

[a] Standard reaction conditions 1:1.8 ratio of 1/2, benzene, 60 °C, 8 h. [b] Isolated yield calculated on nitrone. [c] In chloroform, *c* 0.8–1.9. [d] Values based on NMR measurements with chiral shift reagent, see text. [e] Room temperature reaction, 3 d. [f] Not determined. [g] Isolated yield of pure major isomer 3. [h] Minimum ratio, tentative. [i] Signal separation of only 1.5 Hz, insufficient for reliable integration. [j] Four-day reaction. [k] 1:1.5 ratio of 1c/2a, 38 h.



a R = Me
b R = CH_2OMe
c R = *t*-Bu
d R = $SiPh_2$*t*-Bu

1



a X = O
b X = S

2

dihydroxypyrrolidines,[9] with racemic dihydrophosphole oxide **2a**[10] and sulfide **2b**[11] are outlined in Scheme 1, and the results are shown in Table 1.

In order to match as closely as possible conditions of a typical kinetic resolution experiment, usually judged at ca. 50% conversion of the racemic substrate, but to simultaneously have most of the more valuable enantiomerically pure substrate consumed, we decided to run the screening experiments with the initial 1:2 ratio of 1:1.8. The choice of the reaction temperature was restricted by the low reactivity of dihydrophosphole derivative. In fact, the reaction could in some cases also be run with good conversion at room temperature (cf. entry 2), but such a procedure required considerably prolonged reaction times and gave little improvement of stereoselectivity. In the case of sterically more demanding nitrone derivatives it proved, however, impractical.

In all the reactions studied only two diastereomeric products, **3** and **4**, were formed and their ratio was established by integration of ^{31}P and/or ^1H NMR spectra of the crude reaction mixtures. The ratios listed refer to those measured after 8 h (or after the time reported in Table 1). The products and the resolved **2** were typically separated by flash chromatography followed by recrystallization (where possible) and Kugelrohr distillation, respectively. The ee of the recovered **2a** was estimated by means of ^1H NMR using 1 equiv of (*R*)-*N*-(1-phenylethyl)-3,5-dinitrobenzamide (**5**) as a chiral shift reagent[12] affording clearcut (11 Hz) separation of C2-H signals of the two enantiomers. In all the studied reactions the enriched (*R*)-**2** was recovered.[13]

The structural assignment to cycloadducts **3** and **4** was based on the detailed ^1H and ^{13}C NMR analysis including 2D experiments. The ^1H NMR spectra of the major isomers **3** display signals of protons H8a and H8b in the range δ 4.48–4.27 ppm and δ 3.24–2.69 ppm, respectively, in agreement with analogous adducts.[5b,6] The observed relative shielding of H8b and deshielding of H8a attest for the *cis* H8b-Ph relationship. Replacement of oxygen with sulfur in **3d** causes only a slight deshielding (0.2 ppm) of both protons.[5b] *Trans* H8a–H8b relative stereochemistry is easily attributed on the basis of coupling constants *J* in the range 3.2–4.3 Hz, consistent with a *trans* relationship in a five-membered ring. Similarly, *trans* H8–H8a relative stereochemistry is attributed on the observation of coupling constants of ca. 1–4 Hz between the two protons. Indeed, a *cis* H8–H8a coupling of 9 Hz was found in a related compound.[6] An X-ray analysis of an analogous adduct confirms the structural assignment.[14] The minor isomers **4** show similar values, when available, for the chemical shifts of H8a (δ 4.67–4.49 ppm) and H8b (δ 3.30–3.22 ppm) protons and for the coupling constant between them (J = 3 Hz), attesting the same relative stereochemistries at C8b–P and C8a–C8b as the major isomers. On the contrary, the value of ca. 7 Hz for J_{H8-H8a} testifies for a *cis* relationship between the two protons, opposite to that of the major isomers.

The data collected in Table 1 for the reactions studied under the standard conditions indicate that an increase in the size of hydroxyl protecting groups resulted in an increase in the reaction diastereoselectivity and, at the same time, in a noticeable decrease of the overall reaction rate. Conversions dropped gradually from nearly 100% found for the reaction of entry 1 to about 50% for the one of entry 5, after the same 8 h of the reaction time. Nitrone **1d**, possessing the bulkiest *tert*-butyldiphenylsilyl protecting groups, afforded the highest ratio of diastereomeric cycloadducts, but required prolonged heating (4 d, entry 6). The stereoselectivity factor $s = k_S/k_R$[1a] of this remarkably enantioselective reaction was established to

(9) (a) Cicchi, S.; Höld, I.; Brandi, A. *J. Org. Chem.* **1993**, *58*, 5274–5275. (b) Ballini, R.; Marcantoni, E.; Petrini, M. *J. Org. Chem.* **1992**, *57*, 1316–1318.

(10) Quin, L. D.; Gratz, J. P.; Barket, P. T. *J. Org. Chem.* **1968**, *33*, 1034–1041.

(11) Moedritzer, K. *Synth. React. Inorg. Met.-Org. Chem.* **1974**, *4*, 119–132.

(12) Dunach, E.; Kagan, H. B. *Tetrahedron Lett.* **1985**, *26*, 2649–2653.

(13) The assignment of the *R* configuration to the levorotatory **2a** follows from the previous X-ray based assignment of (*S*)-(+)-**2a**.[14] The analogous assignment to (−)-**2b** is based on the addition stereocourse models and should be regarded as tentative.

(14) Pietrusiewicz, K. M.; Wieczorek, W.; Goti, A.; Brandi, A. *Phosphorus, Sulfur, Silicon* **1992**, *70*, 131–137.

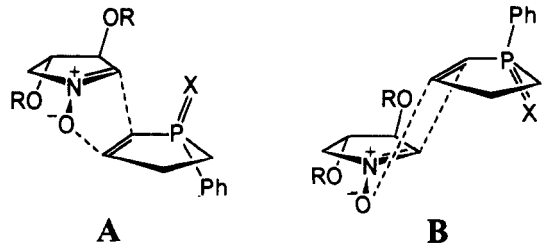


Figure 1. Enantiodifferentiating modes of approach in cycloadditions of 1 to 2.

be $s = 14$.[15] From the point of view of getting the highest possible yield of cycloadducts and, at the same time, also reasonable yield of highly enriched **2a** it was found practical, however, to compromise somewhat on stereoselectivity in order to reach higher conversion. As shown in entry 7, an experiment utilizing **1c** and **2a** in 1:1.5 ratio and driven to a practically complete conversion of **1c** in 38 h afforded the desired cycloadducts in 91% isolated yield and allowed for the recovery of 27%[16] of (*R*)-**2a** of 96% ee.[17]

With the premise that **2** is approached by the nitrone exclusively from the face that bears the P=X substituent and in the exo mode,[18] the nitrone appears more efficiently shielded by the proximal C-3 alkoxy (or silyloxy) group rather than the one at C-4, so that the major, **3**, and the minor, **4**, cycloadducts originate from the **A** and **B** modes of approach, respectively (Figure 1). In the studied reactions in which the *S,S* nitrones were used, the *S* enantiomer of the dihydrophosphole oxide (TS **A**) was indeed preferentially consumed, leaving the excess dihydrophosphole oxide enriched in the *R* enantiomer, in complete accord with the proposed models.

The simple protocol and efficiency of the presented kinetic resolution is noteworthy. With its $s = k_S/k_R = 14$, it joins a limited number of efficient processes of chemical kinetic resolution exhibiting a k_S/k_R ratio exceeding 10 which are known to date.[1,2] Besides providing the optically active dihydrophosphole derivative, it also affords enantiomeric tricyclic adducts featuring 2,2′-connection of pyrrolidine and phospholane rings and six contiguous stereogenic centers of which three have been created with a high degree of stereocontrol, and one of which was efficiently resolved during the process. Since it is possible to use either enantiomer of tartaric acid for the preparation of nitrones **1**, both the dihydrophosphole derivative and the tricyclic adduct can be easily obtained in both enantiomeric forms.[19] Use of the enantiomeric cycloadducts **3** for the synthesis of novel aminophosphine ligands for metal-catalyzed asymmetric reactions as well as the studies on the scope of the developed kinetic resolution are currently underway in our laboratories.

(15) This value was derived from an independent ^{31}P NMR monitored experiment involving **1d** and **2a** in 1:1 ratio and stopped at ca. 53% conversion. The following equation was used for calculation:

$$s = \frac{k_S}{k_R} = \frac{\ln(1 - \text{conv})(1 - \text{ee}_S)}{\ln(1 - \text{conv})(1 + \text{ee}_S)} = \frac{\ln[1 - \text{conv}(1 + \text{ee}_P)]}{\ln[1 - \text{conv}(1 - \text{ee}_P)]}$$

where conv is the extent of substrate conversion, and ee_s and ee_p represent the enantiomeric excess of the recovered substrate and product, respectively.[1a]

(16) To be compared with 33.3% of theoretical yield of recovered **2a** expected in this experiment after virtually complete conversion of the nitrone.

(17) This material was characterized by $[\alpha]_D = -306°$ (*c* 0.8, $CHCl_3$) and was found to contain only 2% of the other enantiomer as determined from its ^1H NMR spectrum recorded with 1 equiv of **5**. It should also be stressed here that, as it now appears, Yb(hfc)$_3$ used in our previous measurement for analogous ^{31}P NMR determination of optical purity of **2a** ($[\alpha]_D = +182°$) gave a highly overestimated value (90% ee), most probably due to line broadening strongly affecting the integration. Use of **5** and ^1H NMR is therefore highly recommended for similar measurements.

(18) In all the previously studied nitrone cycloadditions to **2a** exclusive formation of products arising from the exo attack on the P=O face of dihydrophosphole ring was observed.[6,14]

Experimental Section

All the reactions were run under nitrogen. NMR spectra were recorded in $CDCl_3$ solution on Varian Gemini (^1H, 200 MHz; ^{13}C, 25 MHz) and Varian FT-80A (^{31}P, 32.3 MHz) spectrometers. Notations s, d, t, q, m, and br designate singlet, doublet, triplet, quartet, multiplet, and broad, respectively. Nitrones **1a–c** were prepared according to ref 9a. The new nitrone (3*S*,4*S*)-(+)-3,4-bis[(*tert*-butyldiphenylsilyl)oxy]-3,4-dihydro-2*H*-pyrrole 1-oxide (**1d**) was prepared according to ref 9b: $\{[\alpha]^{25}_D$ +66.5° (*c* 1.45, $CHCl_3$); ^1H NMR δ 7.70–7.25 (m, 20H), 6.34 (q, J = 1.6 Hz, 1H), 4.90 (m, 1H), 4.53 (dt, J = 5.6, 2.7 Hz, 1H), 3.76 (m, 1H), 3.49 (m, 1H), 1.03 (s, 9H), 1.01 (s, 9H); ^{13}C NMR δ 135.6 (d, 8C), 134.2 (d), 132.8 (s), 132.7 (s), 132.3 (s), 132.2 (s), 130.3 (d, 2C), 130.1 (d, 2C), 128.0 (d, 4C), 127.9 (d, 4C), 80.7 (d), 75.9 (d), 65.8 (t), 26.7 (q, 6C), 15.2 (s, 2C). Anal. Calcd for $C_{36}H_{43}NO_3Si_2$: C, 72.80; H, 7.30; N, 2.36. Found: C, 72.68; H, 7.34; N, 2.54. Dihydrophosphole oxide **2a** was synthesized according to ref 10, and the corresponding sulfide **2b** was obtained by reduction of **2a** with $PhSiH_3$ and subsequent oxidation of the intermediate phosphine with S_8: $bp_{0.5}$ 160 °C (Kugelrohr) [lit.[11] $bp_{0.1}$ 135–140 °C].

General Procedure for the Cycloadditions of Nitrones 1 to Dihydrophospholes 2. A 1 M solution of the nitrone **1** and 1.8 equiv of the dihydrophosphole **2** in benzene was heated at 60 °C for the appropriate time. After NMR monitoring, the mixture of adducts was purified by flash chromatography from the unreacted phosphole. Pure enantiomerically enriched dihydrophospholes **2** for $[\alpha]$ measurement were obtained by further Kugelrohr distillation. Major adducts **3** were then obtained pure by fractional crystallization from diisopropyl ether. Minor isomers were obtained by fractional crystallization from the mother liquor in case of **4a** and **4c**; in the other cases they were partially characterized by spectroscopic means in the crude reaction mixture.

(1*S*,3a*R*,7*S*,8*S*,8a*R*,8b*R*)-(+)-7,8-Dimethoxy-1-phenyloctahydro-1*H*-pyrrolo[1,2-*b*]phospholo[2,3-*d*]isoxazole 1-oxide (3a): mp 133–134 °C; R_f = 0.35 (CH_2Cl_2/CH_3OH 10:1); $[\alpha]^{25}_D$ +29.8° (*c* 1.07, $CHCl_3$); ^{31}P NMR δ 57.1; ^1H NMR δ 7.75–7.45 (m, 5H), 4.96 (dm, J_{PH} = 20.9 Hz, 1H), 4.43 (ddd, J = 15.4, 4.3, 1.9 Hz, 1H), 3.80 (m, 2H), 3.64 (dd, J = 12.8, 5.6 Hz, 1H), 3.39 (s, 3H), 3.35 (s, 3H), 3.12 (dd, J = 12.0, 4.3 Hz, 1H), 2.92 (dt, J = 7.6, 4.3 Hz, 1H), 2.45–1.80 (m, 4H); ^{13}C NMR δ 132.7 (s, J_{PC} = 90.8 Hz), 131.9 (d, J_{PC} = 2.6 Hz), 129.4 (d, J_{PC} = 9.3 Hz, 2C), 128.7 (d, J_{PC} = 11.6 Hz, 2C), 89.1 (d, J_{PC} = 6.6 Hz), 84.0 (d), 80.6 (d, J_{PC} = 12.6 Hz), 70.3 (d), 58.1 (t), 57.3 (q), 57.2 (q), 48.3 (d, J_{PC} = 67.0 Hz), 24.9 (t, J_{PC} = 65.2 Hz), 24.6 (t, J_{PC} = 9.0 Hz). Anal. Calcd for $C_{16}H_{22}NO_4P$: C, 59.44; H, 6.86; N, 4.33. Found: C, 59.72; H, 7.18; N, 4.05. **(1*R*,3a*S*,7*S*,8*S*,8a*S*,8b*S*)-(−)-7,8-Dimethoxy-1-phenyloctahydro-1*H*-pyrrolo[1,2-*b*]phospholo[2,3-*d*]isoxazole 1-oxide (4a)**: viscous oil; $[\alpha]^{25}_D$ −3.5° (*c* 0.75, $CHCl_3$); ^{31}P NMR δ 57.2; ^1H NMR δ 7.80–7.65 (m, 2H), 7.60–7.45 (m, 3H), 4.79 (dm, J_{PH} = 19.1 Hz, 1H), 4.67 (ddd, J = 14.3, 6.6, 3.3 Hz, 1H), 3.95 (dt, J = 4.2, 6.4 Hz, 1H), 3.86 (dd, J = 6.6, 4.3 Hz, 1H), 3.38 (s, 3H), 3.37 (s, 3H), 3.31 (dd, J = 15.0, 5.9 Hz, 1H), 3.22 (dt, J = 6.4, 3.4 Hz, 1H), 2.50–1.80 (m, 5H); ^{13}C NMR δ 133.1 (s, J_{PC} = 92.6 Hz), 132.1 (d), 129.8 (d, J_{PC} = 9.3 Hz, 2C), 128.9 (d, J_{PC} = 1.4 Hz, 2C), 84.9 (d, J_{PC} = 6.1 Hz), 83.6 (d), 81.4 (d, J_{PC} = 13.4 Hz), 68.0 (d), 58.4 (q), 57.6 (t), 57.5 (q), 44.2 (d, J_{PC} = 68.6 Hz), 26.3 (t, J_{PC} = 8.9 Hz), 25.2 (t, J_{PC} = 65.8 Hz). Anal. Calcd for $C_{16}H_{22}NO_4P$: C, 59.44; H, 6.86; N, 4.33. Found: C, 59.38; H, 6.97; N, 4.06.

(1*S*,3a*R*,7*S*,8*S*,8a*R*,8b*R*)-(+)-7,8-Bis[(methoxymethyl)oxy]-1-phenyloctahydro-1*H*-pyrrolo[1,2-*b*]phospholo[2,3-

(19) This paper is to be considered Part 17 in the series on Optically Active Phosphine Oxides. For Part 16, see: Pietrusiewicz, K. M.; Wieczorek, W. *Phosphorus, Sulfur, Silicon*, in press.

d]isoxazole 1-oxide (3b): mp 91–93 °C; R_f = 0.35 (ethyl acetate); $[\alpha]^{25}_D$ +26.9° (*c* 0.34, $CHCl_3$); ^{31}P NMR δ 55.9; ^1H NMR δ 7.80–7.40 (m, 5H), 4.97 (dm, J_{PH} = 22.0 Hz, 1H), 4.74–4.62 (m, 4H), 4.32 (ddd, *J* = 14.0, 4.4, 3.4 Hz, 1H), 4.14 (dt, *J* = 4.3, 6.0 Hz, 1H), 4.03 (t, *J* = 4.4 Hz, 1H), 3.66 (dd, *J* = 12.7, 6.3 Hz, 1H), 3.36 (s, 3H), 3.24 (s, 3H), 3.16 (dd, *J* = 12.7, 5.8 Hz, 1H), 3.08 (m, 1H), 2.50–1.80 (m, 4H); ^{13}C NMR: δ 133.1 (s, J_{PC} = 91.2 Hz), 131.9 (d, J_{PC} = 2.6 Hz), 129.5 (d, J_{PC} = 9.3 Hz, 2C), 128.7 (d, J_{PC} = 11.7 Hz, 2C), 96.3 (t), 96.1 (t), 87.2 (d, J_{PC} = 8.3 Hz), 80.6 (d), 79.9 (d, J_{PC} = 11.6 Hz), 70.5 (d), 58.5 (t), 55.5 (q), 55.3 (q), 49.2 (d, J_{PC} = 67.5 Hz), 25.8 (t, J_{PC} = 8.5 Hz), 24.2 (t, J_{PC} = 65.7 Hz). Anal. Calcd for $C_{18}H_{26}NO_6P$: C, 56.39; H, 6.84; N, 3.65. Found: C, 56.60; H, 6.98; N, 3.41. **(1*R*,3a*S*,7*S*,8*S*,8a*S*,8b*S*)-7,8-Bis[(methoxymethyl)oxy]-1-phenyloctahydro-1*H*-pyrrolo[1,2-*b*]phospholo[2,3-*d*]isoxazole 1-oxide (4b)**: ^{31}P NMR δ 56.7; ^1H NMR (only the signals detected) δ 4.84–4.72 (m, 1H), 4.74–4.55 (m, 4H), 3.31 (s, 3H), 3.30–3.10 (m, 1H), 3.20 (s, 3H).

(1*S*,3a*R*,7*S*,8*S*,8a*R*,8b*R*)-(+)-7,8-Di-*tert*-butoxy-1-phenyloctahydro-1*H*-pyrrolo[1,2-*b*]phospholo[2,3-*d*]isoxazole 1-oxide (3c): mp 181–182 °C; R_f = 0.3 (Et_2O/CH_3OH 10:1); $[\alpha]^{25}_D$ +29.2° (*c* 0.53, $CHCl_3$); ^{31}P NMR δ 56.5; ^1H NMR δ 7.75–7.40 (m, 5H), 5.05 (dm, J_{PH} = 23.1 Hz, 1H), 4.27 (ddd, *J* = 16.1, 4.3, 2.8 Hz, 1H), 3.89–3.81 (m, 2H), 3.57 (dd, *J* = 11.2, 5.8 Hz, 1H), 2.98 (dt, *J* = 7.1, 4.3 Hz, 1H), 2.90 (dd, *J* = 11.3, 6.5 Hz, 1H), 2.45–1.60 (m, 4H), 1.18 (s, 9H), 1.14 (s, 9H); ^{13}C NMR δ 133.5 (s, J_{PC} = 90.4 Hz), 131.9 (d, J_{PC} = 2.7 Hz), 129.6 (d, J_{PC} = 9.2 Hz, 2C), 128.8 (d, J_{PC} = 11.4 Hz, 2C), 82.3 (d, J_{PC} = 6.5 Hz), 80.6 (d, J_{PC} = 12.2 Hz), 76.3 (d), 74.1 (s), 74.0 (s), 72.3 (d), 59.7 (t), 49.3 (d, J_{PC} = 66.6 Hz), 28.5 (q, 3C), 28.3 (q, 3C), 25.0 (t, J_{PC} = 65.6 Hz), 24.4 (t, J_{PC} = 10.8 Hz). Anal. Calcd for $C_{22}H_{34}NO_4P$: C, 64.85; H, 8.41; N, 3.44. Found: C, 64.76; H, 8.52; N, 3.30. **(1*R*,3a*S*,7*S*,8*S*,8a*S*,8b*S*)-(+)-7,8-Di-*tert*-butoxy-1-phenyl-octahydro-1*H*-pyrrolo[1,2-*b*]phospholo[2,3-*d*]isoxazole 1-oxide (4c)**: mp 190–191 °C; $[\alpha]^{25}_D$ +38.7° (*c* 1.14, $CHCl_3$); ^{31}P NMR δ 57.0; ^1H NMR δ 7.80–7.48 (m, 5H), 4.71 (dddd, J_{PH} = 21.1 Hz, *J* = 6.9, 4.2, 2.6 Hz, 1H), 4.49 (ddd, *J* = 15.7, 6.9, 3.0 Hz, 1H), 4.01 (t, *J* = 7.0 Hz, 1H), 3.92 (q, *J* = 7.7 Hz, 1H), 3.30 (dt, *J* = 3.0, 6.5 Hz, 1H), 3.27 (dd, *J* = 13.9, 7.0 Hz, 1H), 3.05 (dd, *J* = 13.9, 8.5 Hz, 1H), 2.50–1.80 (m, 4H), 1.14 (s, 9H), 1.06 (s, 9H); ^{13}C NMR δ 133.7 (s, J_{PC} = 92.0 Hz), 131.9 (d), 129.8 (d, J_{PC} = 9.4 Hz, 2C), 128.8 (d, J_{PC} = 10.9 Hz, 2C), 81.7 (d, J_{PC} = 12.3 Hz), 76.7 (d, J_{PC} = 6.2 Hz), 74.9 (d), 74.5 (s), 73.5 (s), 67.5 (d), 60.4 (t), 45.9 (d, J_{PC} = 69.0 Hz), 28.5 (q, 6C), 26.0 (t, J_{PC} = 9.7 Hz), 25.5 (t, J_{PC} = 64.0 Hz). Anal. Calcd for $C_{22}H_{34}NO_4P$: C, 64.85; H, 8.41; N, 3.44. Found: C, 64.62; H, 8.42; N, 3.13.

(1*S*,3a*R*,7*S*,8*S*,8a*R*,8b*R*)-(+)-7,8-Di-*tert*-butoxy-1-phenyloctahydro-1*H*-pyrrolo[1,2-*b*]phospholo[2,3-*d*]isoxazole 1-sulfide (3d): mp 212–213 °C; $[\alpha]^{25}_D$ +75.3° (*c* 0.91, $CHCl_3$); ^{31}P NMR δ 65.0; ^1H NMR δ 8.07–7.92 (m, 2H), 7.53–7.42 (m, 3H), 5.09 (dm, J_{PH} = 24.5 Hz, 1H), 4.48 (dm, J_{PH} = 20.5 Hz, 1H), 3.89 (m, 2H), 3.68 (m, 1H), 3.24 (dt, *J* = 10.6, 3.6 Hz, 1H), 2.91 (m, 1H), 2.54–2.20 (m, 3H), 2.08–1.90 (m, 1H), 1.18 (s, 9H), 1.16 (s, 9H); ^{13}C NMR δ 133.6 (s, J_{PC} = 72.7 Hz), 131.6 (d, J_{PC} = 3.0 Hz), 130.1 (d, J_{PC} = 9.6 Hz, 2C), 128.9 (d, J_{PC} = 11.7 Hz, 2C), 82.5 (d, J_{PC} = 9.5 Hz), 81.8 (d, J_{PC} = 7.6 Hz), 76.5 (d), 74.2 (s), 74.1 (d), 74.1 (s), 61.5 (t), 51.8 (d, J_{PC} = 50.9 Hz), 32.0 (t, J_{PC} = 52.0 Hz), 28.7 (q, 3C), 28.3 (q, 3C), 27.3 (t, J_{PC} = 4.8 Hz). Anal. Calcd for $C_{22}H_{34}NO_3PS$: C, 62.39; H, 8.09; N, 3.31. Found: C, 62.09; H, 8.41; N, 3.11. **(1*R*,3a*S*,7*S*,8*S*,8a*S*,8b*S*)-7,8-Di-*tert*-butoxy-1-phenyloctahydro-1*H*-pyrrolo[1,2-*b*]phospholo[2,3-*d*]isoxazole 1-sulfide (4d)**: ^{31}P NMR δ 64.9; ^1H NMR (only the signals detected) δ 4.80–4.60 (m, 1H), 1.10 (s, 9H), 1.00 (s, 9H).

(1*S*,3a*R*,7*S*,8*S*,8a*R*,8b*R*)-(+)-7,8-Bis[(*tert*-butyldiphenylsilyl)oxy]-1-phenyloctahydro-1*H*-pyrrolo[1,2-*b*]phospholo[2,3-*d*]isoxazole 1-oxide (3e): viscous oil, R_f = 0.45 (Et_2O/CH_3OH 10:1); $[\alpha]^{25}_D$ +24.2° (*c* 3.27, $CHCl_3$); ^{31}P NMR δ 55.1; ^1H NMR δ 7.61–7.11 (m, 25H), 4.94 (dm, J_{PH} = 23.1 Hz, 1H), 4.48 (br dd, *J* = 17.9, 1.9 Hz, 1H), 4.29 (m, 1H), 4.13 (br s, 1H), 3.68 (dd, *J* = 14.4, 4.9 Hz, 1H), 3.12 (d, *J* = 14.3 Hz, 1H), 2.69 (dt, *J* = 6.6, 3.2 Hz, 1H), 2.45–1.60 (m, 4H), 0.94 (s, 9H), 0.92 (s, 9H); ^{13}C NMR aromatic signals not assignable, δ 84.0 (d, J_{PC} = 7.8 Hz), 81.7 (d, J_{PC} = 13.3 Hz), 79.0 (d), 73.6 (d), 63.8 (t), 48.5 (d, J_{PC} = 66.8 Hz), 26.8 (q, 3C), 26.7 (q, 3C), 25.3 (t, J_{PC} = 65.6 Hz), 25.0 (t, J_{PC} = 8.9 Hz), 18.9 (s, 2C). Anal. Calcd for $C_{46}H_{54}NO_4PSi_2$: C, 71.56; H, 7.06; N, 1.81. Found: C, 71.56; H, 7.20; N, 1.88. **(1*R*,3a*S*,7*S*,8*S*,8a*S*,8b*S*)-7,8-Bis[(*tert*-butyldiphenylsilyl)oxy]-1-phenyloctahydro-1*H*-pyrrolo[1,2-*b*]phospholo[2,3-*d*]isoxazole 1-oxide (4e)**: ^{31}P NMR δ 55.5; ^1H NMR (only the signals detected) δ 4.84 (dm, J_{PH} = 23.8 Hz, 1H), 4.65 (dm, J_{PH} = 14.8 Hz, 1H), 4.22 (m, 1H), 3.27 (br d, *J* = 11.7 Hz, 1H), 3.02 (dd, *J* = 11.7, 4.0 Hz, 1H), 0.92 (s, 9H), 0.88 (s, 9H).

Optimization of the Kinetic Resolution of 2a. A solution of 392 mg of nitrone **1c** and 456 mg of phosphole **2a** in 1.5 mL of benzene was heated at 60 °C until no nitrone was detectable at NMR monitoring (38 h). Cycloadducts **3c** and **4c** (630 mg, 91%) and enantiomerically enriched phosphole **2a** (123 mg, 27%) were recovered by flash column chromatography.

(*R*)-2,3-Dihydro-1-phenyl-1*H*-phosphole 1-oxide (2a): $[\alpha]^{25}_D$ −306.0° (*c* 0.80, $CHCl_3$), 96% ee.

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