Desymmetrization Approach to the Synthesis of Optically Active P-Stereogenic Phosphin-2-en-4-ones

Elżbieta Łastawiecka, Sławomir Frynas, and K. Michał Pietrusiewicz*

ABSTRACT: Two synthetic protocols for the conversion of 1-phenylphosphinan-4-ones to novel P-stereogenic 1-phenylphosphin-2-en-4-ones by enantioselective deprotonation followed by oxidation and by asymmetric organocatalytic halogenation accompanied by elimination have been developed. These two-step one-pot transformations provide convenient access to optically active 1-phenylphosphin-2-en-4-one 1-sulphide and 1-phenylphosphin-2-en-4-one 1-oxide of 96 and 55% enantiomeric purities, respectively.

RESULTS AND DISCUSSION

Of the known synthetic methods used frequently for desymmetrization of prochiral ketones,\textsuperscript{10} enantioselective deprotonation,\textsuperscript{10a,10b} and enantioselective α-halogenation,\textsuperscript{10f,10g} seemed to be most suitable for accomplishing our goal. Accordingly, the two alternative paths that we have designed to lead to optically active 4 are based on these two desymmetrization processes (Scheme 1).

The desymmetrization by path A involves asymmetric deprotonation of 1-phenylphosphinan-4-one (1) by a chiral base and conversion of the resulting lithium enolate to the silyl enol ether 2 by quenching with TMSCl.\textsuperscript{10a,10b} The desymmetrization by path B entails transformation of phosphinanone 1 into a chiral α-halogenated derivative 3, which could be achieved by organocatalytic asymmetric α-halogenation.\textsuperscript{10f,10g} Both synthetic procedures make use of the ketone functionality of phosphinanone 1, and both result in the overall asymmetric transformation of the remote prochiral phosphorus center in ketone 1 into a P-stereogenic one in enone 4 via intermediate 2 or 3.

Since the time the enantioselective deprotonation of cyclic ketones by a chiral lithium amide was first demonstrated in 1986,\textsuperscript{10a,10b} the method has been widely utilized in asymmetric synthesis for generating chirality centers in cyclic ketones by...
desymmetrization.\cite{11} Although efficient desymmetrizations of a number of oxa-, aza-, and thia-heterocyclic ketones by chiral lithium amides have been already demonstrated,\cite{10f,10g,10h,10i} the corresponding P-heterocyclic analogs have not been investigated before. Thus, we started with checking the viability of enantioselective deprotonations of 1-phenylphosphinan-4-one 1-oxide (1a), 1-borane (1b), and 1-sulfide (1c) using lithium amide derived from amine (S,S)-5 as the model base premixed with an excess of TMSCl before addition of a ketone (ISQ - in situ quench)\cite{13} (Table 1).

As shown in Table 1 (entries 1−3), phosphinanone oxide 1a failed to provide silyl enol ether 2a, whereas borane 1b and sulfide 1c gave the expected enol ethers 2b and 2c, respectively, albeit in low yields and with very low ee. Subsequent testing of phosphinanone sulfide 1c revealed that addition of 0.5 equiv. of LiCl allowed increasing the yield and ee of silyl enol ether 2c to more acceptable levels (entry 5) and that allowing lithium amide to react with phosphinanone sulfide 1c before TMSCl was introduced (EQ - external quench)\cite{14} gave slightly better results than the ISQ alternative (entries 5 and 6). As checked under these conditions again, the amount of 0.5 equiv. of LiCl was sufficient; increasing its loading to 1 equiv. did not bring about improvement of ee.

---

Figure 1. Reported optically active phosphinanes.

Scheme 1. Designed Desymmetrization Routes to 1-Phenylphosphin-2-en-4-ones 4

---

A. The reported P-stereogenic phosphinanes

B. Ligands

C. This work
Table 1. Enantioselective Deprotonation of 1 Using Lithium Amide Derived from Amine 5

| no. | X     | procedure | additive (equiv.) | yield [%]b | ee [%]c |
|-----|-------|-----------|------------------|------------|--------|
| 1   | O     | ISQ       |                  | traces     | n.d.   |
| 2   | BH₃   | ISQ       |                  | 17         | 7      |
| 3   | S     | ISQ       |                  | 18         | 8      |
| 4   | S     | ISQ       |                  | 19         | 4      |
| 5   | S     | ISQ       |                  | 71         | 53     |
| 6   | S     | EQ        |                  | 76         | 54     |
| 7   | S     | EQ        |                  | 81         | 52     |

aStandard reaction conditions: 1 (0.1 mmol), (S,S)-5 (0.3 mmol, 3 equiv.), n-BuLi (1.6 M solution, 3 equiv.), TMSCl (0.5 mmol, 5 equiv.), in THF for 1 h. bDetermined by ³¹P NMR. cDetermined for the crude reaction mixture by CSP-HPLC.

The details of further optimization of these reaction conditions, which included variations of molarity, stoichiometry, and temperature, are presented in Table 2.

Table 2. Optimization of Conditions of Enantioselective Deprotonation of Phosphinanone Sulfide 1c

| no. | amine (equiv.) | n-BuLi (equiv.) | C₉₆ [mol/dm³] | temp. [°C] | yield [%]b | ee [%]c |
|-----|----------------|----------------|---------------|------------|------------|--------|
| 1   | 1.5            | 1.5            | 0.05          | −78        | 95         | 12     |
| 2   | 1.5            | 1.5            | 0.025         | −78        | 63         | 54     |
| 3   | 1.5            | 1.5            | 0.016         | −78        | 18         | 61     |
| 4   | 2              | 1.5            | 0.025         | −78        | 98         | 67     |
| 5   | 3              | 1.5            | 0.025         | −78        | 85         | 74     |
| 6   | 3              | 3              | 0.025         | −78        | 75         | 59     |
| 7   | 3              | 3              | 0.025         | −20        | 40         | 0      |
| 8   | 3              | 3              | 0.025         | −90        | 77         | 83     |
| 9d  | 3              | 3              | 0.025         | −90        | 87         | 86     |
| 10  | 3              | 1.5            | 0.025         | −90        | 81         | 87     |
| 11d | 3              | 1.5            | 0.025         | −90        | 85         | 86     |
| 12  | 3              | 1.5            | 0.016         | −90        | 51         | 87     |

aStandard reaction conditions: 1 (0.1 mmol), (S,S)-5, n-BuLi (1.6 M solution), LiCl (0.05 mmol), TMSCl (0.5 mmol, 5 equiv.), in THF for 1 h. bDetermined by ³¹P NMR. cDetermined for the crude reaction mixture by CSP-HPLC. dReaction run with 1 equiv. of LiCl.

As shown in Table 2, lowering of concentration led to improvement of enantioselectivity, but unfortunately, it led to a substantial decrease in yield (entries 1–3). The concentration of 0.025 M was deemed a practical compromise and was then used in subsequent trials. A substantial increase of enantioselectivity to 74% ee at 85% conversion was observed when 3 equiv. of amine 5 was used instead of 1.5 equiv. (entries 4 and 5). In addition, lowering of the reaction temperature to −90 °C resulted in further enhancement of enantioselectivity up to 87% ee at 81% conversion (entry 10). Finally, checking the concentration factor once again confirmed that its lowering resulted in a substantial decrease in yield, but this time, it was not even accompanied by an increase of enantioselectivity observed before (cf. entries 10 and 12).

Once the optimization of the reaction conditions was completed, also other amine catalysts were tested for their efficiency in desymmetrization of 1-phenylphosphinan-4-ones 1c and 1b. The results obtained with chiral monoamines 5−13, 15, and 16 and diamines 14 and 17−19 are displayed in Table 3.

Inspection of the results collected in Table 3 reveals that the best enantioselectivities in desymmetrization of phosphinanone sulfide 1c were achieved with C₉-symmetric lithium bis(α-arylethyl)amides derived from amines (S,S)-5 and (S,S)-6, i.e., 87 and 76% ee, respectively. The C₉-symmetric α-phenylethylamidine derived bases 7−12 and 16 were also effective in desymmetrizing phosphinanone sulfide 1c and gave silyl enol ether 2c in good yield and with enantioselectivity reaching 59% ee. Diamines 14 and 17−19 gave slightly lower enantioselectivities than the monoamines. In turn, desymmetrization of phosphinanone borane 1b carried out with lithiated 5−19 under the same conditions gave silyl enol ether 2b in generally better yields but with much lower enantioselectivities than sulfide 2c. For borane 2b, the best ee’s were again achieved with lithium amides derived from (S,S)-5 and (S,S)-6, i.e., 61% ee at 95% conversion and 52% ee at 68% conversion, respectively.

Next, we turned our attention to the oxidation of silyl enol ethers 2b,c required for their conversion into phosphinenones 4b,c. Our initial attempts involved use of the well-known procedures utilizing Pd(OAc)₂ in acetonitrile,¹³ DDQ in benzene, and trityl tetrafluoroborate in dichloromethane as the oxidizing agents, but with these reagents, phosphinenones 4 were produced in very low yields (Table 4, entries 1−3).

Subsequent treatment of silyl enol ethers 2c and 2b with ceric ammonium nitrate (CAN) in DMF led to the formation of phosphinenones 4c and 4a in 69 and 74% yields, respectively (entries 4 and 5). It should be noted, however, that under these conditions, phosphinenone borane 4b could not be obtained due to concurrent oxidation of the P center during the reaction course. Finally, using Nicolau et al.’s procedure for the oxidation of silyl enol ethers to α,β-unsaturated carbonyl compounds utilizing the IBX·MPO complex as the oxidant,¹⁸ phosphinenones 4c and 4a (from 2b) were obtained in high yields, 80 and 73%, respectively (entries 8 and 9).

Encouraged by the latter’s promising results and taking into account the fact that silyl enol ethers 2c and 2b proved to be
highly susceptible to hydrolysis during chromatographic purification, we decided to combine the best desymmetrization and oxidation protocols found for phosphinanone 1c in a one-pot process to avoid substantial loss of the intermediate silyl enol ether during isolation (Scheme 2). As shown in Scheme 2, the two steps carried out in one flask without isolation of the intermediate 2c furnished phosphinenone 4c in overall 49% isolated yield. The determination of enantiomeric excesses of intermediate silyl enol ether 2c and of the obtained phosphinenone 4c (CSP-HPLC) revealed that a slight loss of enantiomeric purity might have taken place during isolation.
Table 5. Preliminary Screening of Reaction Conditions for Conversion of Phosphinanones 1a–c to Phosphinenones 4a–c via Catalytic $\alpha$-Bromination$^a$

| no. | solvent | additive (20 mol %) | Br-source | yield 4a,c [%]$^b$ | ee [%]$^c$ |
|-----|---------|---------------------|-----------|---------------------|----------|
| 1   | O       | DCM                | NBS       | 45                  | 10       |
| 2   | O       | THF                | NBS       | 74                  | 1        |
| 3   | O       | DMF                | NBS       | 61                  | 8        |
| 4   | O       | CH$_3$CN           | NBS       | 41                  | 6        |
| 5   | O       | DCM                | AcOH      | 42                  |          |
| 6   | O       | DCM                | PhCOOH    | 47                  | 32       |
| 7   | O       | DCM                | PhCOOH    | 21                  | 6        |
| 8   | O       | DCM                | PhCOOH    | 76(64)$^d$         |          |
| 9   | O       | DCM                | PhCOOH    | 20                  | 11       |
| 10  | BH$_3$  | DCM                | PhCOOH    | 20 traces           |          |
| 11  | S       | DCM                | PhCOOH    | 20                  | 24       |

$^a$Standard reaction conditions: NBS (0.15 mmol) was added to a mixture of 1 (0.1 mmol), an additive (20 mol %), and amine catalyst (20 mol %) in the indicated solvent (2 mL) and stirred at room temperature for 16 h and at 60°C for 0.5 h. $^b$Determined by GC–MS and $^{31}$P NMR analysis. $^c$Determined for the crude reaction mixture by CSP-HPLC. $^d$Yield of the isolated product in parentheses.

Table 6. Evaluation of Amine Catalysts in Conversion of Phosphinanones 1a,c to Phosphinenones 4a,c via Enantioselective $\alpha$-Bromination under Optimized Conditions$^a$

| Procedure: | To a mixture of 1a or 1c (0.1 mmol), PhCOOH (0.02 mmol), and a catalyst (0.02 mmol) in DCM (2 mL), NBS or 20 (0.15 mmol) was added and the reaction mixture was stirred at room temperature for 16 h and then at 60°C for 0.5 h. $^b$Yields of 4a and 4c determined by GC–MS analysis. $^c$Enantiomeric excess determined for the crude reaction mixture by CSP-HPLC. $^d$Reaction run without PhCOOH.

![Chemical structures and reactions](image-url)
Table 7. Synthesis of Phosphinenones 4a,c via Organocatalytic Enantioselective α-Chlorination of 1a,c

| no. | X   | catalyst | Cl-source | yield 4a,c [%] | ee [%] |
|-----|-----|----------|-----------|---------------|--------|
| 1   | O   | (S)-19   | NCS       | 24            | rac    |
| 2   | O   | (S)-19   | NCS       | 3             | rac    |
| 3   | O   | (S)-19   | PhICl₂    | 26            | rac    |
| 4   | O   | (S)-19   | PhICl₂    | 56            | rac    |
| 5   | O   | (S,S)-25 | NCS       | 34            | 30     |
| 6   | O   | (S,S)-25 | PhICl₂    | 74            | 21     |
| 7   | S   | (S,S)-25 | PhICl₂    | 0             | rac    |
| 8   | O   | (R)-17   | PhICl₂    | 91            | rac    |
| 9   | O   | (S)-21   | PhICl₂    | 87            | rac    |
| 10  | O   | (S)-24   | PhICl₂    | 88            | rac    |

“Standard reaction conditions: NCS or PhICl₂ (0.15 mmol) was added to a mixture of 1 (0.1 mmol), PhCOOH (20 mol %), and amine catalyst (20 mol %) in DCM (2 mL) and stirred at rt for 1 day. DBU (1.5 equiv.) was then added, and the reaction mixture was stirred at rt for an additional 4 h to effect elimination of HCl. Determined by 31P NMR spectroscopy. Enantiomeric excess determined for the crude reaction mixture by CSP-HPLC.

The oxidation step. Importantly, however, recrystallization of the isolated sulfide 4c of 73% ee from hexane/i-PrOH allowed its enantiomeric purity to increase to 96% ee.

In the second part of our study, we turned our attention to another organocatalytic strategy expected to be suitable to achieve our goal. In 2005, Jørgensen et al.10g described the first enantioselective α-bromination of ketones utilizing N-bromo-succinimide (NBS) and 4,4-dibromo-2,6-di-tert-butyl-cyclohexa-2,5-diene (20) as the brominating agents and (S)-proline and a C₂-symmetric imidazolidine as the chiral catalysts. These reagents enabled the formation of stereogenic C–Br centers with up to 94% ee in high yields.10g We decided then to check the viability of this protocol in the asymmetric α-bromination of phosphinanones 1a,c, which, when followed by elimination of HBr, could lead to the target optically active phosphinenones 4a,c.

We started our investigations with a brief screening of solvents and additives in α-bromination of oxide 1a and sulfide 1c, using NBS (or 20) as the brominating agent and (S)-proline as the model chiral catalyst. At the outset, we were pleased to find that elimination of HBr started to occur already under the bromination conditions and that practically quantitative elimination of HBr could be achieved by simply raising the temperature at the end of the reaction to 60 °C for half an hour. We included this maneuver to the screening conditions to make the planned synthesis of phosphinenones 4a,c a one-pot process (Table 5).

As can be seen from the collected data, a change of solvent as well as an added acid10h can strongly influence the outcome of the reaction (Table 5, entries 7–13). With added benzoic acid, the enantiomerically enriched 4a was obtained with 34% ee and in 47% yield, what constituted a significant improvement over the reaction run without this additive in the same solvent (DCM) (cf. entries 7 and 12). In turn, changing the solvent to THF or DMF resulted in a marked increase of the conversion, but the observed enantioselectivity was significantly lowered. Thus, the conditions utilizing DCM and added benzoic acid (entry 12), which best compromised the conversion and induction levels, were selected for screening of a number of other chiral amine catalysts in the next optimization step. The results of this screening are summarized in Table 6. The reactions of all tested amines were performed with and without benzoic acid, but only the better result of these two runs has been listed for clarity.

As can be seen in Table 6, screening of amines 13–17 and 21–24 as the organocatalysts allowed the enantioselectivity of bromination of phosphinanone 1a to increase only up to 55% ee when (S)-proline naphthylamide 24 was used as the catalyst. Interestingly, C₂-symmetric 4,5-diphenyl-imidazolidine (25), the reported most efficient catalyst for enantioselective α-bromination of cyclic ketones,10g afforded enone 4a of only 28% ee. Apparently, pyrrolidine based amines performed somewhat better than other amines tested in the studied α-bromination of phosphinanone 1a. Surprisingly inefficient were C₂-symmetric diamines even though DACH-derived (R,R)-26 afforded enone 4a of 77% ee but, unfortunately, at nearly negligible 3% conversion.

Also listed in Table 6 are the results of desymmetrization of phosphinanone sulfide 1c carried out with compound 20 as the brominating agent under otherwise the same conditions. These reactions proceeded relatively well and afforded enone 4c in good yields (56–84%) but with only moderate enantiomeric enrichment (8–38% ee). Possibly the best match of yield and enantiomeric purity of 4c was achieved with DACH derivative (R,R)-26 (66% and 38% ee, respectively) and with imidazolidine (S,S)-25 (84% and 33% ee, respectively).

Looking for further improvement, we also decided to briefly check the efficiency of analogous enantioselective α-chlorinations, which have been recently demonstrated to be highly efficient in the case of six-membered-ring ketones.10i The results of screening experiments involving chlorination of phosphinanones 1a,c by NCS and PhICl₂ in the presence of (S)-proline and other amine catalysts, followed by DBU-assisted elimination of HCl from intermediate α-chloro ketone 3-Cl to give enone 4a,c, are collected in Table 7.

The collected data reveal that PhICl₂ as the chlorine source gave better conversions than NCS and that addition of benzoic
acid had a beneficial effect on the overall yield of phosphinenone 4a, especially in combination with PhICl. Under these conditions, (S)-proline catalyzed the formation of α-chlorophosphinanone intermediate 3-Cl in moderate yields but, unfortunately, the resulting enone 4a was formed as a racemate (entries 1−4). Similarly, chlorinations of phosphinanone 1a with amines 17, 21, and 24 as the catalysts also led to the formation of racemic enone 4a, although in these cases with remarkably high conversions of 91, 87, and 88%, respectively (entries 8−10). In turn, imidazolidine (S,S)-2S, the reported excellent catalyst for the asymmetric α-chlorination of six-membered-ring ketones,10f afforded enantioenriched enone 4a of only 30 (with PhICl) or 21% ee (with NCS) in moderate 34% and good 74% yields, respectively (entries 5 and 6). It is important to note, however, that in these two cases, as determined by comparison of the pertinent CSP-HPLC chromatograms, the use of (S,S)-2S as the catalyst led to the formation of enone 4a enriched in the enantiomer opposite to that found in predominance in 4a obtained by the α-bromination procedure utilizing the same (S,S)-2S as the catalyst. Interestingly, an attempted reaction of sulfide 1c under exactly the same conditions failed completely (entry 7). At this point, considering that the prospect of getting high enantioselectivity in desymmetrizations of phosphinanones 1a,c by α-chlorination did not look promising, further optimization of this process was discontinued. Nonetheless, despite the fact that the chlorination procedure did not provide the expected improvement of enantioselectivity in the studied syntheses of optically active phosphinenones 4, the developed one-pot chlorination−elimination procedure is likely to find use as an effective method for synthesis of racemic phosphinenone oxide 4a (cf. entries 8−10).

All in all, it is tempting to conclude that enantioselective α-halogenation of phosphinanone 1, a six-membered-ring ketone possessing a phosphorus function in the γ position, is considerably more challenging than the parent cyclohexanone and related six-membered-ring ketones.10h,10i Moreover, a poor result of our attempted organocatalytic desymmetrization of phosphinanone oxide 1a via enamine oxidation under recently reported optimized conditions20 shown to be effective in converting a whole variety of mono and doubly 4-substituted cyclohexanones to the corresponding cyclohexenones of very high enantiomeric purity corroborates this notion further (Scheme 3).

■ CONCLUSIONS

Even though the asymmetric deprotonation and asymmetric halogenation of phosphinanone 4 have turned out to be less efficient than those of carboxyclic ketones, the developed one-pot enolization-oxidation and halogenation-elimination procedures have for the first time provided access to the new P-stereogenic phosphin-2-en-4-one derivatives in nonracemic forms. A good level of asymmetric induction (87% ee at 81% conversion) can be achieved by enantioselective deprotonation of phosphinanone sulfide 1c at −90 °C using 3 equiv. of lithium amide derived from commercially available amine S,S-S, S. Subsequent in situ oxidation of the formed enantiomerically enriched silyl enol ether 2c by IBX-MPO converts it to optically active phosphinenone 4c, the enantiopurity of which can be upgraded to 96% ee by recrystallization. Desymmetrization of phosphinanone oxide 1a can be best achieved by asymmetric α-bromination using (S)-proline amide 24 as the catalyst to provide enriched 3-bromophosphinanone 3, which, in turn, undergoes in situ elimination of HBr to afford phosphinenone 4a of 55% ee in 54% yield. The analogous asymmetric α-chlorination-elimination procedure offers very low or even no enantioselectivity in desymmetrization of phosphinanone 1a. Nevertheless, it allows obtaining phosphinenone oxide 4a in very high yields (cf. Table 7, entries 8−10) and may thus constitute a useful route to rac-4a.

■ EXPERIMENTAL SECTION

General Information. All reactions were performed under an argon atmosphere using Schlenk techniques or in a 10 mL glass reaction tubes with a screw cap. Only dry solvents were used, and the glassware was heated under vacuum prior to use. THF was dried over sodium/benzophenone ketyl. LiCl was dried in a Schlenk tube under vacuum at 150 °C for 5 h. TMSCl, NBS, MPO, DMSO, chiral amines 5, 6, 13, 14, 21, and (S)-proline (19) were purchased from commercial sources and used as received without further purification. Solvents for chromatography and extraction were commercially available and used as received without further purification. Solvents for crystallization and Et3N were distilled once before use. Room temperature (rt) means a range of temperatures from 18 to 22 °C.

The NMR spectra were recorded with a Bruker Ascend (500 MHz) spectrometer in CDCl3 as a solvent at room temperature unless otherwise noted. Chemical shifts (δ) are given in ppm relative to tetramethylsilane (1H), residual CHCl3 (13C), or external 85% H3PO4 (31P) as a reference. The following abbreviations are used in reporting NMR data: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), br (broad). Coupling constants (J) are in Hz. High-resolution mass spectrometry analyses were obtained on a Shimadzu LCMS IT-TOF spectrometer. Elementary analyses were performed on a PerkinElmer CHN 2400 analyzer. Melting points were determined on a Büchi Melting Point M−560 in a capillary tube and are uncorrected. Mass spectra were recorded with a GC−MS spectrometer working in electron ionization (EI) mode. Chiral HPLC analysis was performed on a Shimadzu HPLC using Chiralcel columns. Optical rotations were measured on a PerkinElmer 341LC spectrometer using a 1 mL cell with a 10 mm path length and are reported as follows: [α]D 20 (°c g/100 mL, solvent). Thin layer chromatography (TLC) was performed with precoated silica gel plates and visualized by potassium permanganate (KMnO4) staining or exposing to iodine vapor. The reaction mixtures were purified by column chromatography over silica gel (60−240 mesh). The chiral amines 7−12,15−16,17,18,24,25,26,27,28 and 28−3028 were prepared according to the literature procedures. Analytical data for those amines are in accordance with those previously reported. The reagents IBX24 and 4,4-dibromo-2,6-di-tert-butyl-cyclohexa-2,5-diene (20)25 were synthesized according to reported procedures, and their properties matched those previously reported.
Synthesis of Substrates (1a, 1b, and 1c). 1-Phenylphosphinan-4-one 1a, 1-borane (1b), and 1-sulﬁde (1c) were prepared from the free phosphine (1-phenylphosphinan-4-one) according to the modiﬁed literature procedure. A dry, argon-ﬂushed Schlenk-ﬂask, equipped with a magnetic stirrer and a septum, was charged with 1-phenylphosphinan-4-one (1.92 g, 0.01 mol) and dry solvent (15 mL). The solution was cooled to 0 °C when hydrogen peroxide (0.012 mol, borane-tetrahydrofuran (0.013 mol), or elemental sulfur (0.0105 mol) was slowly added to it. After 45 min at 0 °C, the solution was allowed to warm to room temperature and the solvent was evaporated (during the evaporation, the temperature of the solution should be kept below 25 °C) to give crude silyl enol ether 2c. The silyl enol ether 2c was obtained in 82% yield (determined by 31P NMR spectroscopy) and with an enantiomeric excess of 76% (determined by chiral HPLC analysis using a Chiralcel AS-H column). Then, following the published oxidation protocol,10 equimolar amounts of IBX and MPO (2.06 g of IBX and 0.92 g of MPO, 1.5 equiv.) dissolved in DMSO (5 mL) were added in one portion at room temperature to the crude vacuum-dried silyl enol ether 1c dissolved in 3 mL of DMSO. The solution was stirred vigorously for 2 h at room temperature. After this time, the reaction mixture was diluted with aqueous HCl (5%) and extracted with DCM (ﬁve times). The combined organic phase was dried (MgSO4), and the solvent was removed in vacuum to afford the crude product, which was further puriﬁed by silica gel column chromatography (hexane/TFH = 6:1) to give enone 4c as a light yellow oil in 48% overall yield (two steps) (0.52 g, 2.4 mmol) and with 73% ee (determined by HPLC analysis using a Chiralcel OJ-H column). Repeated recrystallizations (three times) of (−)-4c (73% ee) from a hexane/i-PrOH mixture allowed to increase its enantiopurity of the levorotatory enantiomer of 4c left in the mother liquor up to 96% ee.

Catalytic Desymmetrizing Dehydrogenation of Phenylphosphinin-2-en-4-ones through Enamine Oxidation. Reactions were performed according to the literature procedure20 at room temperature. To a 10 mL ﬂask were added phenylphosphinin-4-one 1a−c (0.041−0.045 g, 0.2 mmol), catalyst (20 mol %, 0.044 mmol), pentanedioic acid (7.3 mg, 0.06 mmol), and diethyl ether (0.1 mL). The reaction system was gently stirred for half an hour. Then IBX (56 mg, 0.2 mmol) was added followed by 0.1 mL of diethyl ether. After 48 h, the reaction system was diluted with ether and immediately passed through a thin layer of silica gel. The remaining organic phase was concentrated in vacuum. Yield was determined by 31P NMR analysis, and enantiomeric excess was determined by CSP-HPLC analysis.

1-Phenylphosphinan-4-one 1-Oxide (1a). This compound was prepared according to the general procedure from 1-phenylphosphinin-4-one (1.92 g, 0.01 mol) and hydrogen peroxide (30% solution in water, 1.36 mL, 0.012 mol), in acetone (15 mL). The reaction gave the corresponding oxide as the crystalline adduct 1a·(H2O)2; Anal. Found: C, 56.8; H, 6.61. The adduct was practically insoluble in common organic solvents such as THF, DCM, and acetone. The formation of this type of adduct of phosphine oxides was previously reported.10 To decompose the adduct and remove H2O from 1a, the formed crystals were melted under vacuum and heated at 180 °C (heating mantle) for 30 min to give 1.85 g (89%) of pure 1a as white crystals, mp = 164.8−166.0 °C (lit. 164−165 °C).14 Rf = 0.16 (DCM/THF = 6:1). 1H NMR (500 MHz, CDCl3): δ 7.83−7.76 (m, 2H), 7.64−7.59 (m, 5H), 7.58−7.52 (m, 2H), 3.24−3.11 (m, 2H), 2.80−2.66 (m, 2H), 2.46−2.31 (m, 4H). 13C{1H} NMR (126 MHz, CDCl3): δ 207.6 (d, J = 8.2 Hz, C=O), 132.6 (d, J = 2.7 Hz, Cpyp), 131.1 (d, J = 99.0 Hz, Cipso), 130.1 (d, J = 91.9 Hz, Cmwh), 129.1 (d, J = 11.8 Hz, Cmwh), 136.4 (d, J = 6.4 Hz, C5,S), 27.2 (d, J = 66.0 Hz, C26,S). 31P{1H} NMR (202 MHz, CDCl3): δ 28.8 ppm. GC−MS (EI, 70 eV) m/z = 208.0 (10), 181.0 (100), 152.0 (46), 151.0 (13), 134.0 (29), 125.0 (80), 124.0 (86), 101.5 (37), 96.0 (13), 91.1 (12). Anal. Calc. for C19H12O3P: C, 64.13; H, 7.83. Found: C, 64.09; H, 7.88.

1-Phenylphosphinan-4-one 1-Borane (1b). This compound was prepared according to the general procedure from 1-phenylphosphinin-4-one (1.92 g, 0.01 mol) and H2B-THF (1.0 M solution in THF, 13 mL, 0.013 mol, 1.3 equiv.) in THF (15 mL) at room temperature for 5 h. Then, after evaporation of solvent, the product was recrystallized from hexane/EtO to yield 1.69 g (82%) of 1b as colorless crystals; mp = 94.1−96.9 °C, Rf = 0.3 (hexane/THF = 8:1). 1H NMR (500 MHz, CDCl3): δ 7.82−7.75 (m, 2H), 7.65−7.51 (m, 5H), 2.93−2.83 (m, 2H), 2.79−2.67 (m, 2H), 2.50−2.38 (m, 2H), 2.37−2.28 (m, 2H), 1.50−0.50 (brm, 3H). 31P{1H} NMR (126 MHz, CDCl3): δ 207.3 (d, J = 6.4 Hz, C=O), 132.0 (d, J = 2.7 Hz, Cyp), 131.2 (d, J = 9.1 Hz, Cmwh), 129.3 (d, J = 10.0 Hz, Cmwh), 127.8 (d, J = 53.6 Hz, Cipso), 36.8
1-Phenylphosphin-2-en-4-one 1-Oxide (rac-4a). This compound was prepared according to the general organocatalytic α-halogenation procedure from 1a (0.1 g, 0.5 mmol) to give 0.78 g (37%) as colorless crystals; (1R,3S)-1-Phenylphosphin-2-en-4-one 1-Oxide (4a) was prepared according to the catalytic desymmetrizing dehydrogenation procedure from 1-phenylphosphinan-4-one 1-Sulfoxide (3a) and 1-phenylphosphinan-4-one 1-Sulfoxide (3a).

31P{1H} NMR (202 MHz, CDCl3): δ 7.08 ppm. GC−MS (EI, 70 eV) m/z = 178.00 (33), 150.00 (19), 132.05 (10), 131.05 (100), 124.00 (24), 103.05 (14). Anal. Calcld for C11H12O2P: C, 64.08; H, 5.38. Found: C, 64.01; H, 5.24.

1-Phenylphosphin-2-en-4-one 1-Oxide (rac-4a). This compound was prepared according to the general one-pot procedure from 1c (0.1 g, 0.2 mmol) to give 0.19 g (86%) as colorless crystals; (1R,3S)-1-Phenylphosphin-2-en-4-one 1-Oxide (4a) was prepared according to the catalytic desymmetrizing dehydrogenation procedure from 1-phenylphosphinan-4-one 1-Sulfoxide (3a).
Table S1 - Complete catalyst screening of enantioselective α-bromination of 1a and 1c; Table S2 - Catalytic desymmetrizing dehydrogenation of 1a−c through examine oxidation; Figure S1 - CSP-HPLC traces of optically active 4c; 1H NMR, 13C[1H] NMR, and 31P[1H] NMR spectra (PDF)

Table S1 - Complete catalyst screening of enantioselective α-bromination of 1a and 1c; Table S2 - Catalytic desymmetrizing dehydrogenation of 1a−c through examine oxidation; Figure S1 - CSP-HPLC traces of optically active 4c; 1H NMR, 13C[1H] NMR, and 31P[1H] NMR spectra (PDF)

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.joc.0c03055.

The Journal of Organic Chemistry pubs.acs.org/joc

Acknowledgments

Financial support from the Ministry of Science and Higher Education (research grant no. N N204 445240) is kindly acknowledged.

References

(1) (a) Phosphorus Ligands in Asymmetric Catalysis; Vol. 1-3; Börner, A., Ed.; Wiley-YCH: Weinheim, 2008. (b) Marinetti, A.; Vottuñiez, A. Enantioselective Phosphate Organocatalysis. Synlett 2010, 2010, 174−194. (c) P3Ph2Stereogenic Ligands in Enantioselective Catalysis; Grabulosa, A. RSC: Cambridge, UK, 2011. (d) Dutartre, M.; Bayardon, J.; Jugé, S. Applications and stereoselective syntheses of P-chirogenic phosphorus compounds. Chem. Soc. Rev. 2016, 45, 5771−5794. (e) Ni, H.; Chan, W.-L.; Lu, Y. Phosphine-Catalyzed Asymmetric Organic Reactions. Chem. Rev. 2018, 118, 9344−9411.

(2) (a) Burk, M. J.; Feaster, J. E.; Harlow, R. L. New Chiral Phospholanes; Synthesis, Characterization, and Use in Asymmetric Hydrogenation Reactions. Tetrahedron: Asymmetry 1991, 2, 569−592. (b) Burk, M. J. Modular Phospholane Ligands in Asymmetric Catalysis. Acc. Chem. Res. 2000, 33, 363−372. (c) Xiao, D.; Zhang, Z.; Zhang, X. Synthesis of a Novel Chiral Binaphthyl Phospholane and its Application in the Highly Enantioselective Hydrogenation of Enamides. Org. Lett. 1999, 1, 1679−1681. (d) Clark, T.; Landis, C. Recent Developments in Chiral Phospholane Chemistry. Tetrahedron: Asymmetry 2004, 15, 2123−2137. (e) Shang, G.; Zhang, X. Phospholes, Phospholanes, and Phosphinanes in ref. 1a, Vol. 1, Ch. 2.2, pp.135−177. (f) Tang, W.; Zhang, X. A Chiral 1,2-Bisphospholane Ligand with a Novel Structural Motif: Applications in Highly Enantioselective Rh-Catalyzed Hydrogenations. Angew. Chem., Int. Ed. 2002, 41, 1612−1614. (g) Pakulski, Z.; Demchuk, O. M.; Frelik, J.; Lubardziki, R.; Pietrusiewicz, K. M. New Monodentate P,C-Stereogenic Bicyclic Phosphanes: 1-Phenyl-1,3a,4,5,6,6a-hexahydrocyclopenta[f]-phosphole and 1-Phenylotrichlorocyclopenta[f]phosphole. Eur. J. Org. Chem. 2004, 3913−3918. (h) Gibbons, S. K.; Xu, Z.; Hughes, R. P.; Gleave, D. S.; Rhieingold, A. L. Chiral Bis(Phospholane) PCP Pincer Complexes: Synthesis, Structure, and Nickel-Catalyzed Asymmetric Phosphorus Allylation. Organometallics 2018, 37, 2159−2166. (i) (3) Marinetti, A.; Carmichael, D. Synthesis and Properties of Phosphetanes. Chem. Rev. 2002, 102, 201−230. (b) Marinetti, A.; Jus, S.; Genêt, J.-P. Investigation into an asymmetric hydrogenation promoted by rhodium-phosphetane complexes. Tetrahedron Lett. 1999, 40, 8365−8368. (c) Tang, W.; Zhang, X. New Chiral Phosphorus Ligands for Enantioselective Hydrogenation. Chem. Rev. 2003, 103, 3029−3070. (d) Immamoto, T.; Oohara, N.; Takahashi, H. Optically Active 1,1′-Di-tert-butyl-2,2′-diphosphanyl and Its Application in Rhodium-Catalyzed Asymmetric Hydrogenations. Synthesis 2004, 2004, 1353−1358. (e) Kollár, L.; Keglevich, G. P-Heterocycles as Ligands in Homogeneous Catalytic Reactions. Chem. Rev. 2010, 110, 4257−4302. (f) (4) Kobayashi, S.; Shiraiishi, N.; Lam, W. W.-L.; Manabe, K. Asymmetric synthesis of proline and proline acid phosphorus analogues using enantioselective deprotonation−carboxylation reactions. Tetrahedron Lett. 2004, 42, 7303−7306. (b) Ostermeier, M.; Prieß, J.; Helmchen, G. Mono- and Bidentate Phosphinanes—New Chiral Ligands and Their Application in Catalytic Asymmetric Hydrogenations. Angew. Chem., Int. Ed. 2002, 41, 612−614. (c) Yan, Y.; Zhang, X. Six-membered bis(azaphosphorinate) readily available ligand for highly enantioselective asymmetric hydrogenations. Tetrahedron Lett. 2006, 47, 1567−1569. (d) Doro, F.; Lutz, M.; Reek, J. N. H.; Spek, A. L.; van Leeuwen, P. W. N. M. P-Chirogenic Benzo-Fused Phenoxaphosphane: Synthesis, Resolution and Study of the Stereochemical Properties of the Corresponding Palladium Complexes. Eur. J. Inorg. Chem. 2008, 1309−1317. (e) Harvey, J. S.; Malcolmson, S. J.; Dunne, K. S.; Meek, S. J.; Thompson, A. L.; Schrock, R. R.; Hoveyda, A. H.; Gouverneur, V. Enantioselective Synthesis of P-Stereogenic Phosphates and Phosphine Oxides by Molybdenum-Catalyzed Asymmetric Ring-Closing Metathesis. Angew. Chem., Int. Ed. 2009, 48, 762−766. (f) Ujji, V.; Kerenyi, A.; Laki, A.; Fogassy, E.; Keglevich, G. Optically Active 6-Membered P-Heterocycles: 1-Phenyln-1,2-Dihydridophosphin oxide and 1-Phenyl-3-Diphenylphosphinyl-1,2,3,6-Tetrahydroporphin oxide. Lett. Org. Chem. 2010, 7, 110−113. (g) Bagi, P.; Laki, A.; Keglevich, G. Preparation of Optically Six-Membered P-Heterocycles: A 3-Phosphabicyclo[3.1.0]hexane 3-oxide, a 1,2-Dihydridophosphin oxide, and a 1,2,3,6-Tetrahydroporphin oxide 1-oxide. Heteroat. Chem. 2013, 24, 179−186. (h) Mohar, B.; Čušak, A.; Modec, B.; Stephan, M. P-Stereogenic Phospholanes or Phosphorinanes from o-Biarylylphosphines: Two Bridges Not Too Far. J. Org. Chem. 2013, 78, 4665−4675. (j) Zheng, Y.; Guo, L.; Zhi, W. Enantioselective and Regioselective Hydroxyferilication of Alkynes by Gold-Catalyzed Desymmetrization of Prochiral Phenols with P-Stereogenic Centers. Org. Lett. 2018, 20, 7039−7043. (5) For bridged six-membered optically active phosphaheterocycles, see: (a) Breit, B.; Fuchs, E. Chiral phosphaborelenie ligands: synthesis and evaluation in rhodium-catalyzed asymmetric hydrogenation. Synthesis 2006, 2006, 2121. (b) Hopewell, J.; Jankowski, P.; McMullin, C. L.; Orpen, A. G.; Pringle, P. G. Subtleties in asymmetric catalyst structure: the resolution of a 6-phospha-2,4,6-trioxad adamantane and its applications in asymmetric hydrogenation catalysis. Chem. Commun. 2010, 46, 100−102. (6) (a) Pietrusiewicz, K. M.; Zablocka, M. Preparation of Scalenal Chiral Phosphines and Their Derivatives. Chem. Rev. 1994, 94, 1375−1411. (b) Gallagher, M. J. Six-membered rings: Phosphinanes, Dihydro- and Tetrahydro-phosphinines. In Phosphorus-Carbon Hetero-
cyclic Chemistry. The rise of New Domain; Matthey, F. Ed., Elsevier, 2001; Ch. S.1, 463–483.

(7) For recent examples, see: (a) de Azambuja, F.; Carmona, R. C.; Chorro, T. H.; Heerd, G.; Correia, C. R. D. Noncovalent Substrate-Directed Enantioselective Heck Reactions: Synthesis of S- and P-Stereogenic Heterocycles. Chem. – Eur. J. 2016, 22, 11205–11209.

(8) Wang, Z.; Hayashi, T. Rhodium-Catalyzed Enantioselective Hydroarylation of Divinylphosphine Oxides with Aryl Boroxines. Angew. Chem. Int. Ed. 2018, 57, 1702–1706. (c) Nishida, G.; Noguchi, K.; Hirano, M.; Tanaka, K. Enantioselective Synthesis of P-Stereogenic Alkynylphosphine Oxides by Rh-Catalyzed 2+2+2 Cycloaddition. Angew. Chem. Int. Ed. 2008, 47, 3410–3413. (d) Jiang, Y.-S.; Woźniak, Ł.; Pedroni, J.; Cramer, N. Access to P- and Axially Chiral Bisaryl Phosphine Oxides by Enantioselective CPBr3-Catalyzed C–H Arylations. Angew. Chem. Int. Ed. 2018, 57, 12901–12905.

(9) Yang, G.-H.; Li, Y.; Li, X.; Cheng, J.-P. Access to P-Chiral Organocatalytic P-Chiral Lithium Amide Bases, In Jørgensen, K. A. Highly Enantioselective Direct Organocatalytic Stereogenic Heterocycles. Ch. 5.1, 463

(10) Yang, G.-H.; Li, Y.; Li, X.; Cheng, J.-P. Access to P-Chiral Phosphine Oxides by Enantioselective Alkyl Alkylation of Bisphensols. Chem. Sci. 2019, 10, 4322–4327. (f) Zhang, Y.; Zhang, F.; Chen, L.; Xu, J.; Liu, X.; Feng, X. Asymmetric Synthesis of P-Stereogenic Compounds via Thulium(III)-Catalyzed Desymmetrization of Dialkynylphosphine Oxides. ACS Catal. 2019, 9, 4834–4840. (g) Fernández-Pérez, H.; Vidal-Ferran, A. Stereoselective Catalytic Synthesis of P-Stereogenic Oxides via Hydrogenative Kinetic Resolution. Org. Lett. 2019, 21, 7019–7023.

(11) Lim, K. M.-H.; Hayashi, T. Dynamic Kinetic Resolution in Rhodium-Catalyzed Asymmetric Arylation of Phosphonate Oxides. J. Am. Chem. Soc. 2017, 139, 8122–8125.

(12) Pietrusiewicz, K. M.; Kroprowski, M.; Pakulski, Z. Enantioselective desymmetrization of a phosphene meso-epoxide. Tetrahedron: Asymmetry 2002, 13, 1017–1019. (b) Pakulski, Z.; Kroprowski, M.; Pietrusiewicz, K. M. Chiral Base Promoted Enantioselective Rearrangement of Organophosphorus Epoxides. Tetrahedron 2003, 59, 8219–8226. (c) Pakulski, Z.; Pietrusiewicz, K. M. Enantioselective desymmetrization of phosphene meso-epoxide by nuclophilic opening of the epoxide. Tetrahedron: Asymmetry 2004, 15, 41–45.
(31) (a) Snider, T. E.; Morris, D. L.; Srivastava, K. C.; Berlin, K. D. 1-Phenyl-4-Phosphorinanone. Org. Synth. 1973, 53, 98. (b) Pietrusiewicz, K. M. $^{13}$C and $^{31}$P NMR studies of configurational and conformational effects in 1-Phenyl-4-phosphorinanones and their 1-selenides. Org. Magn. Reson. 1983, 21, 345–351.

(32) Meeuwissen, H. J.; Sirks, G.; Bickelhaupt, F.; Stam, C. H.; Spek, A. L. Synthesis and structure of 6-exo-hydroxy-1,2-diphenyl-1-phosphoniatricyclo [3.3.1.1]decane iodide, a derivative of 1-phosphaadamantane. J. R. Neth. Chem. Soc. 1982, 101, 443–450.

(33) Hilliard, C. R.; Bhuvanesh, N.; Gladysz, J. A.; Blümel, J. Synthesis, purification, and characterization of phosphate oxides and their hydrogen peroxide adducts. Dalton Trans. 2012, 41, 1742–1754.

(34) Venkataramu, S. D.; Berlin, K. D.; Ealick, S. E.; Baker, J. R.; Nichols, S.; Van Der Helm, D. V. Carbon-13 NMR studies of 1-phenyl-4-phosphorinanone and derivatives. Single crystal X-ray diffraction analysis of 1-phenyl-4-phosphorinanone 1-oxide and 1-sulfide. Phosphorus Sulfur Relat. Elem. 1979, 7, 133–141.

(35) Märkl, G.; Olbrich, H. 4-Methylene phospho-2,5-cyclohexadienes. Angew. Chem., Int. Ed. 1966, 5, 589–590.