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P-Chiral phosphine oxide catalysed reduction of prochiral ketimines using trichlorosilane

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ABSTRACT

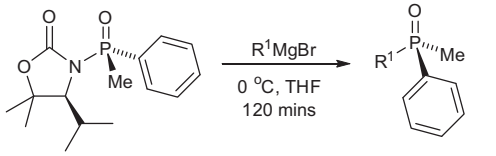
Twelve *P*-chiral phosphine oxides were screened for their ability to act as a chiral Lewis base catalyst for the asymmetric hydrosilylation of ketimines, providing chiral amines in good conversion and yield, but relatively poor enantioselectivity (ee <30%). Mechanistic studies paralleling work on chiral sulfinamides have shown a non-linear relationship of catalyst enantioselectivity and the chiral amine product.

1. Introduction

The synthesis of enantiomerically enriched amines is an area of great interest, the longstanding importance stemming from the widespread presence of this functional group in a wide variety of natural products and pharmaceutically active compounds.[1,2] Amongst methodologies developed to reduce ketimines, the use of trichlorosilane as a reductant has received growing interest in recent years.[3,4] Trichlorosilane needs to be activated by coordination with a Lewis base, such as DMF, to generate a hexa-coordinate hydridosilicate complex, which is believed to be the active reducing species. In 2001, Matsamura reported the first enantioselective reduction of a ketimine using *N*-formyl proline as a chiral Lewis base, giving enantiomerically enriched amines in moderate yields with up to 66% ee.[5] Several other *N*-formyl derived organocatalysts then followed, including those developed by Malkov and Kočovský,[6–8] Matsumura,[9] and Sun,[10–14] in addition to imidazole[15–17] and picolinoyl amides.[18] Other than amides, only a small selection of other Lewis base catalysts have been evaluated, the most successful being *S*-chiral sulfinamides developed by Sun[19–21] In contrast, phosphorus derived reagents have received much less attention. Sugiura et al. identified BINAPO as an effective organocatalyst for the synthesis of enantioenriched 4*H*-1,3-oxazines via a trichlorosilane mediated reductive cyclisation of *N*-acylated-β-amino enones.[22] Benaglia et al. reported the potential of a range of chiral phosphinamides derived from proline to promote the hydrosilylation of β-enamino esters.[23] However, neither of these cases involve direct 1,2-reduction of a non-conjugated C=N bond catalysed by a *P*-chiral phosphine oxides. Herein describes preliminary investigations in this area.

2. Results and discussion

Our previously published work has detailed a new route for the efficient preparation of *P*-chiral phosphine oxides in an enantioselective manner via reaction of a *P*-chiral *N*-phosphinoyl oxazolidinone **1** with a Grignard reagent.[24] Several of the phosphine oxides **2**–**7** from this work were utilised, and a further subset **8**–**12** prepared by use of the appropriate Grignard reagent, all with excellent enantioselectivity, as determined by chiral phase HPLC (Scheme 1).



(see Table 1 for a complete list of R^1)

R^1 = (2-iPrC$_6$H$_4$), **8**, 91%
(2,4,6-MeOC$_6$H$_2$), **9**, 53%
(2-Me-4-FC$_6$H$_3$), **10**, 80%
(4-MeOC$_6$H$_4$), **11**, 25%
(2-Me-4-MeOC$_6$H$_3$), **12**, 78%

Scheme 1. Synthesis of phosphine oxides **8**–**12**.

These compounds were then screened as potential catalysts in the trichlorosilane mediated reduction of the benchmark *N*-PMP ketimine **13** at both 10 mol % and 1 mol % loading (Scheme 2, Table 1).

In every case, the phosphine oxides demonstrated excellent reactivity at 10 mol % loading, with each catalyst enabling complete conversion to the *N*-PMP amine **14** after 4 h. The catalyst loading was also reduced to 1 mol %, but this lowered the reactivity

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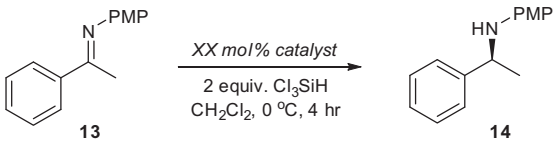
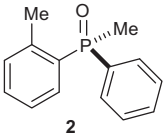
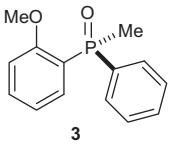
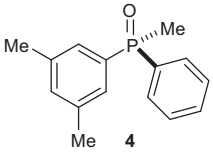
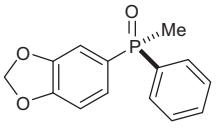
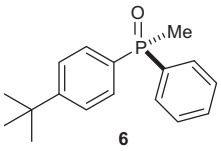
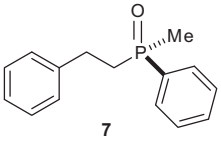
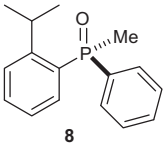
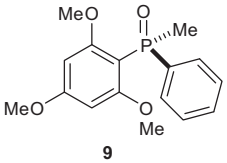
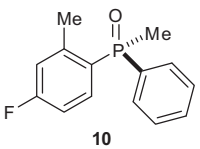


Scheme 2. Asymmetric reduction of ketimine **13**.

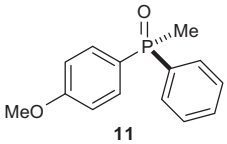
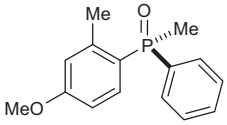
and resulted in amine **13** being isolated in a lower yield, albeit with similar selectivity. Although the reactivities were good, the enantioselectivities were poor in comparison to other reported catalysts. Species containing an *ortho*-methoxy displayed the highest selectivity (Table 1, entries 2 and 8), but incorporation of an isopropyl group at this position was less well-tolerated resulting in a decrease in enantioselectivity to 16% ee (Table 1, entry 7). The

Table 1
Evaluation of *P*-chiral catalysts as described in Scheme 2[a]

Entry	Catalyst	10 mol % loading			1 mol % loading		
		Conversion[b] (%)	Yield[c] (%)	ee[d] (%)	Conversion[b] (%)	Yield[c] (%)	ee[d] (%)
1	 **2**	100	91	22	73	41	21
2	 **3**	100	90	29	78	43	28
3	 **4**	100	81	12	68	39	10
4	 **5**	100	85	11	79	41	10
5	 **6**	100	88	10	77	39	11
6	 **7**	100	90	19	75	41	19
7	 **8**	100	87	16	64	39	17
8	 **9**	100	94	28	81	48	27
9	 **10**	100	88	20	72	41	18

(*continued on next page*)

Table 1 (*continued*)

Entry	Catalyst	10 mol % loading			1 mol % loading		
		Conversion[b] (%)	Yield[c] (%)	ee[d] (%)	Conversion[b] (%)	Yield[c] (%)	ee[d] (%)
10	 **11**	100	92	7	77	37	7
11	 **12**	100	91	23	74	35	21

[a] All reactions performed on 1 mmol scale using 1 mL of CH_2Cl_2 with either 1 or 10 mol % loading of catalyst.
[b] Refers to amine **14**, determined by comparison of appropriate integrals in the ^1H NMR spectrum of the crude reaction mixture.
[c] Refers to yield of isolated product **14**.
[d] Determined by chiral phase HPLC analysis of amine **14**.

use of an *o*-tolyl group also reduced the enantioselectivity to 22% ee (entry 1). The crucial requirement of an *o*-methoxy group is also exemplified by the other methoxy-aryl catalysts (Table 1, entries 4, 10 and 11), all of which are significantly less selective.

Of the successful *S*-chiral sulfinamide catalysts developed by Sun, only two **15** and **17** have been evaluated in the reduction of PMP-ketimine **13** (Fig. 1).

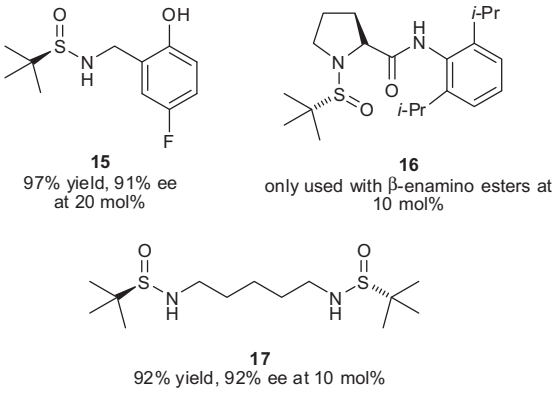
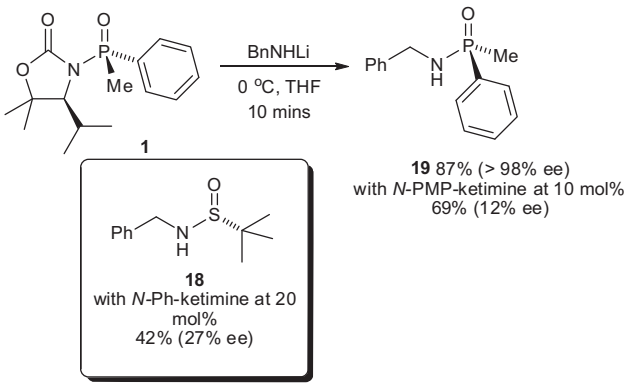


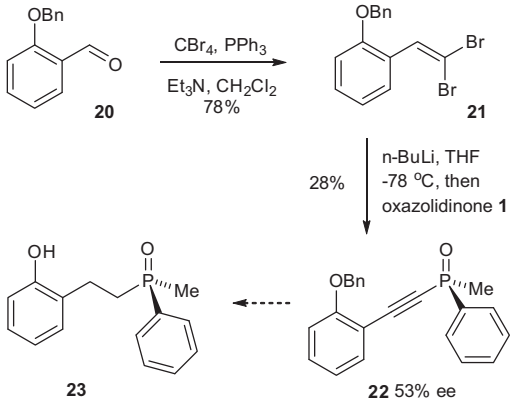
Figure 1. Activity and selectivity of Sun's sulfinamide catalysts **15** and **17** with imine **13**.

In general, the catalytic activities of the phosphine oxides were comparable to the sulfinamides, however the enantioselectivities were significantly lower. The two sulfinamide catalysts **15** and **17** used to reduce acetophenone derived ketimines differ from the phosphine oxides in several ways, primarily as a consequence of using the Ellman chiral sulfinamide to construct these species.[25] The combined stereo-discriminatory effect of the *t*-butyl group, the lone pair and the oxygen atom is apparently sufficient to induce excellent levels of enantioselectivity. Each also bears an acidic NH group adjacent to the stereogenic sulfur atom and is benzylic. Sun's closest analogue to those evaluated herein is benzyl sulfinamide **18**, which although evaluated with the *N*-Ph ketimine, gave the amine product in 42% yield and with 27% ee using 20 mol % loading of catalyst. In an attempt to directly compare the sulfur and phosphorus variants, phosphonamide **19** was prepared by the careful addition of lithium benzylamide to oxazolidinone **1** (Scheme 3). The product phosphinamide was isolated in 87% yield and with excellent enantioselectivity (>98% ee). However, when evaluated under standard reaction conditions (Scheme 2), the product amine was only obtained in 69% conversion and with 12% ee using 10 mol % catalyst. Although there are slight differences in substrate and the amount of catalyst used, this is reasonably in-line with the data obtained with Sun's sulfinimide. When further comparison is made with the analogue missing the NH group (Table 1, entry 6), there does not appear to be any particular need for this functional group, and in some ways it might even be considered detrimental.



Scheme 3. Asymmetric synthesis of phosphinamide **19** and comparison of its activity to sulfinamide **18**.

In comparing these data, it does highlight the crucial need for an oxygen substituent on the aromatic ring, correctly spaced relative to the stereogenic centre. Since the NH group was not deemed to be important, an attempt was made to access catalyst **23** containing the key structural elements found in Sun's catalyst (Scheme 4). Thus, 2-benzyloxybenzaldehyde **20** was converted into *gem*-dibromoalkene **21** and this was treated with *n*-BuLi to generate the lithio-alkyne in situ, which was immediately reacted with oxazolidinone **1**. However, alkyne **22** was only isolated in a disappointingly low 28% yield and with 53% ee. This low ee usually results from a slow reaction rate of the organometallic with the *N*-phosphinoyl oxazolidinone **1**, leading to an in situ racemisation pathway.[24,26] Despite numerous attempts, the enantioselectivity of the phosphine oxide **22** could not be improved, and further development of this chemistry was abandoned.



Scheme 4. Attempted synthesis of phosphine oxide **23**.

The low enantioselectivity, coupled with Sun's observations of a non-linear effect with sulfinamide catalysts[20] prompted an evaluation of this effect for these systems. The relationship between the enantioselectivity of the *o*-anisyl catalyst (Table 1, entry 2) and that of product amine **14** was plotted (Fig. 2), exhibiting a negative [ML_2] non-linear system in which two ligands were required in the stereoselective step of the reduction.[27,28]

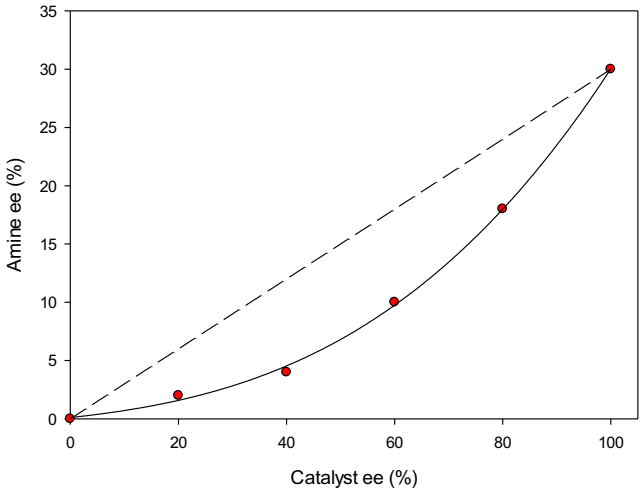


Figure 2. The non-linear relationship of the ee of *P*-chiral phosphine oxide (Table 1, entry 2) and amine **14**.

3. Conclusion

In conclusion, *P*-chiral phosphine oxides can act as catalysts and offer some degree of stereocontrol for the Lewis base mediated reaction of trichlorosilane with ketimines. However, crucial to the development of a catalyst capable of delivering high levels of enantioselectivity with *P*-chiral stereocontrol elements is judicious design of the supporting scaffold; work is currently underway to develop such systems.

4. Experimental

4.1. General

Dry solvents were obtained either from the Grubbs dry solvent system or by distillation. All other reagents were used as supplied without purification, unless specified. Glassware was flame dried and cooled under vacuum before use. Thin layer chromatography was performed on aluminium backed plates pre-coated with silica (0.2 mm, Merck DC-alufolien Kieselgel 60 F_{254}). Plates were visualised using UV light or by dipping in $KMnO_4$ solution, followed by exposure to heat. Flash column chromatography was performed on silica gel (Merck Kieselgel 60 F_{254} 230–400 mesh), unless otherwise stated. ^1H and ^{13}C NMR spectra were measured using $CDCl_3$ as solvent unless otherwise stated, on a Bruker AV-250 or AV-400 MHz machine with an automated sample changer. Chemical shifts for carbon and hydrogen are given on the δ scale. Coupling constants were measured in Hertz (Hz). ^{13}C NMR spectra were recorded using the JMOD method. Specific rotations were performed on an Optical Activity Ltd. AA-10 automatic polarimeter at 589 nm (Na line). $[\alpha]_D$ values are given in 10^{-1} deg cm^2 g^{-1}. Infrared spectra were recorded on a Perkin–Elmer 100 FT-IR machine using attenuated total reflectance (ATR). Peaks between 1600 and 4000 cm^{-1} with an absorbance of >10% are quoted. Mass spectra were either recorded on a micromass autospec (EI^+) or Waters LCT Classic (TOF ES^+). HPLC was carried out on a Gilson analytical system using chiral phase analytical columns (4.8 mm × 250 mm). Melting points (mp) were measured on a Gallenkamp melting point apparatus and are uncorrected.

Experimental details and general procedures for the synthesis of *P*-chiral phosphine oxides **2** to **7** have been previously reported.[24]

4.2. General procedure A for the preparation of diaryl methyl *P*-chiral phosphine oxides from the *N*-phosphinoyl oxazolidinone 1

N-Phosphinoyl oxazolidinone **1** (297 mg, 1 mmol) was dissolved in anhydrous THF (5 mL) and the solution cooled to 0 °C. The Grignard reagent (2 mmol) in THF (concentration indicated in individual experiments) was then added dropwise, after which the reaction mixture was warmed to room temperature and stirred for 45 min. Next, 1 M HCl solution (5 mL) was added drop-wise and the aqueous phase was extracted with CH_2Cl_2 (3 × 10 mL). The organic phases were combined, washed with brine (10 mL) and dried over $MgSO_4$. After filtration and removal of the solvent in vacuo, the crude phosphine oxide was purified as described in the individual experimental details. Racemic samples of the phosphine oxide for HPLC analysis were prepared in the same way but substituting methylphenyl phosphinic chloride for the *N*-phosphinoyl oxazolidinone.

4.2.1. (S_P)-(2-Isopropylphenyl)methylphenylphosphine oxide 8[29]

Prepared according to the general procedure using isopropylphenylmagnesium bromide (2 mL, 1 M in THF, 2 mmol), followed by purification by flash column chromatography using a gradient eluent of 75% EtOAc/petroleum ether 40–60 to 5% MeOH/CH_2Cl_2 giving recovered oxazolidinone **1** as a yellow crystalline material (143 mg, 91%) and the phosphine oxide **8** as a white solid (108 mg, 42%); mp 140–141 °C; $[\alpha]_D^{25} = -34.0$ (*c* 1.0, $CHCl_3$) >99% ee; δ_H (250 MHz, $CDCl_3$) 0.85 [3H, d, *J* 6.8, 1 × CH(CH_3)$_2$), 1.14 [3H, d, *J* 6.8, 1 × CH(CH_3)$_2$], 2.06 (3H, d, J_{P-H} 13.0, PCH_3), 3.48 [1H, heptet, *J* 6.8, CH(CH$_3$)$_2$], 7.27–7.76 (9H, m, ArCH); δ_P (121 MHz, $CDCl_3$) 31.2; Chiral phase HPLC (CHIRALPAK-AS, 95:5 hexane/propan-2-ol at 1.0 mL min^{-1}, 210 nm) t_R 29.8 (minor isomer) and 40.2 (major isomer). No melting point or specific rotation data are reported in the literature, otherwise all is in accordance.

4.2.2. (S_P)-Methylphenyl(2,4,6-trimethoxyphenyl)phosphine oxide 9

Prepared according to the general procedure using 2,4,6-trimethoxyphenylmagnesium bromide (4 mL, 0.5 M in THF, 2 mmol), followed by purification by flash column chromatography on silica gel using a gradient eluent of 75% EtOAc/petroleum ether

40–60 to 5% MeOH/CH_2Cl_2 affording the recovered oxazolidinone **1** as a yellow crystalline material (133 mg, 86%) and the phosphine oxide **9** as a white solid (162 mg, 53%); mp 133–134 °C; $[\alpha]_D^{25}$ = −28.1 (*c* 1.0, $CHCl_3$) >99% ee; ν_{max} (ATR)/cm^{-1} 2360, 1599, 1577; δ_H (400 MHz, $CDCl_3$) 1.98 (3H, d, J_{P-H} 14.0, PC*H*$_3$), 3.58 (6H, s, 2 × OC*H*$_3$), 3.82 (3H, s, OC*H*$_3$), 6.06 (2H, d, *J* 3.6, 2 × ArC*H*), 7.35–7.41 (3H, m, ArC*H*), 7.64–7.67 (2H, m, ArC*H*); δ_C (101 MHz, $CDCl_3$) 21.8 (d, J_{C-P} 76.0, PCH_3), 55.4 (OCH_3), 55.5 (2 × OCH_3), 91.0 (ArCH), 91.1 (ArCH), 103.0 (d, J_{C-P} 108.0, ArC), 127.8 (d, J_{C-P} 13.0, 2 × ArCH), 129.2 (d, J_{C-P} 10.0, 2 × ArCH), 130.0 (d, J_{C-P} 3.0, ArCH), 138.9 (d, J_{C-P} 107.0, ArC), 164.0 (2 × ArC), 165.0 (ArC); δ_P (101 MHz, $CDCl_3$) 27.1; *m*/*z* (TOF ES$^+$) 307.1105 (MH^+, 100%. $C_{16}H_{20}O_4P$ requires 307.1099); Chiral phase HPLC (Celluose-1, 90:10 hexane/propan-2-ol at 1 ml min^{-1}, 210 nm) t_R 35.5 (minor isomer) and 38.5 (major isomer).

4.2.3. (S_P)-(2-Methyl-4-fluorophenyl)methylphenylphosphine oxide 10[30]

Prepared according to the general procedure from 2-methyl-4-fluorophenylmagnesium bromide (1.7 mL, 1.4 M in THF, 2 mmol), followed by purification by flash column chromatography on silica gel using a gradient eluent of 75% EtOAc/petroleum ether 40–60 to 5% MeOH/CH_2Cl_2, affording the recovered oxazolidinone **1** (150 mg, 97%) as a white solid and the phosphine oxide **10** as a white solid (200 mg, 80%); mp 134–135 °C (lit.[30] 98–102 °C for racemate); $[\alpha]_D^{24}$ = −24.2 (*c* 1.0, $CHCl_3$) 99% ee; δ_H (250 MHz, $CDCl_3$) 2.04 (3H, d, J_{P-H} 13.1, PC*H*$_3$), 2.38 (3H, s, C*H*$_3$), 6.91–7.05 (2H, m, ArC*H*), 7.42–7.75 (6H, m, ArC*H*); δ_P (101 MHz, $CDCl_3$) 30.6; δ_F (235 MHz, $CDCl_3$) −107.9; Chiral phase HPLC (Cellulose 1, 96:4 hexane/propan-2-ol at 1.0 mL min^{-1}, 210 nm) t_R 30.9 (minor isomer) and 32.8 (major isomer). No specific rotation value is reported in the literature, otherwise all data are in accordance.

4.2.4. (S_P)-(−)-(4-Methoxyphenyl)methylphenylphosphine oxide 11[31]

Prepared according to the general procedure from 4-anisylmagnesium bromide (3 mL, 1 M in PhMe, 3 mmol), followed by purification by flash column chromatography on silica gel using an eluent of 5% MeOH/CH_2Cl_2 to afford the title compound **11** as a white crystalline solid (62 mg, 25%); mp 119–120 °C (lit.[31] 120–121 °C); $[\alpha]_D^{25}$ = −8.1 (*c* 1.0 in MeOH) >99% ee, lit.[31] = b+7.0 (*c* 0.99, MeOH) for the (R_S)-enantiomer, >95% ee); δ_H (250 MHz, $CDCl_3$) 1.94 (3H, d, J_{P-H} 13.2, PC*H*$_3$), 3.79 (3H, s, OC*H*$_3$), 6.90–6.96 (2H, m, ArC*H*), 7.37–7.47 (3H, m, ArC*H*), 7.57–7.66 (4H, m, ArC*H*); δ_P (121 MHz, $CDCl_3$) 29.7; Chiral phase HPLC (Cellulose 1, 90:10 hexane/propan-2-ol at 1.0 mL min^{-1}, 210 nm) t_R 21.7 (major isomer) and 24.1 (minor isomer). Data are in accordance with the literature.

4.2.5. (S_P)-(2-Methyl-4-methoxyphenyl)methylphenylphosphine oxide 12[31]

Prepared according to the general procedure from 2-methyl-4-methoxyphenylmagnesium bromide (2 mL, 1 M in THF, 2 mmol), followed by purification by flash column chromatography on silica gel using a gradient eluent of 75% EtOAc/petroleum ether 40–60 to 5% MeOH/CH_2Cl_2 afforded the recovered oxazolidinone **1** (148 mg, 94%) and the phosphine oxide **12** as a white solid (203 mg, 78%); mp 135–137 °C (lit.[31]140.0–140.5 °C for racemate); $[\alpha]_D^{25}$ = −21.6 (*c* 0.95, $CHCl_3$) >99% ee, lit.[31] $[\alpha]_D^{26}$ = +1.75 (*c* 0.92, MeOH) for 23% ee for the (R_p)-enantiomer); ν_{max} (ATR)/cm^{-1} 2973, 2907, 2839, 1601, 1566; δ_H (400 MHz, $CDCl_3$) 2.00 (3H, d, J_{P-H} 13.1, PC*H*$_3$), 2.32 (3H, s, C*H*$_3$), 3.81 (3H, s, OC*H*$_3$), 6.72–6.82 (2H, m, ArC*H*), 7.39–7.51 (3H, m, ArC*H*), 7.57–7.67 (3H, m, ArC*H*); δ_C (100 MHz, $CDCl_3$) 17.4 (d, J_{C-P} 74.0, PCH_3), 21.5 (d, J_{C-P} 4.0, CH_3), 55.2 (OCH_3), 110.5 (d, J_{C-P} 13.1, ArCH), 117.4 (d, J_{C-P} 11.0, ArCH), 123.0 (d, J_{C-P} 105.0, ArC), 128.5 (d, J_{C-P} 11.8, 2 × ArCH), 130.3 (d, J_{C-P} 9.9, 2 × ArCH), 131.3 (d, J_{C-P} 2.3, ArCH), 133.4 (d, J_{C-P} 12.7, ArCH), 135.2 (d, J_{C-P} 99.7, ArC), 144.2 (d, J_{C-P} 9.4, ArC), 162.3 (d, J_{C-P} 3.0, ArC); δ_P (101 MHz, $CDCl_3$) 30.9; *m*/*z* (TOF ES$^+$) 261.1036 (MH^+, 100%, $C_{15}H_{18}O_2P$ requires 261.1039); Chiral phase HPLC (Celluose-1, 90:10 hexane/propan-2-ol at 1 mL min^{-1}, 210 nm) t_R 17.3 (minor isomer) and 19.9 (major isomer).

4.3. General procedure B for the asymmetric reduction of the PMP-ketimine 13

The PMP-ketimine **13** (225 mg, 1.00 mmol) and catalyst (0.1 mmol) were dissolved in CH_2Cl_2 (1 mL) and the solution cooled to 0 °C. Trichlorosilane (0.20 mL, 2.0 mmol) was then added dropwise and the reaction mixture stirred for 4 h. The reaction solution was quenched via the addition of 1 M aqueous HCl solution (1 mL), diluted with CH_2Cl_2 (5 mL) and basified with a 1 M aqueous NaOH solution (10 mL). The organic phase was separated, and the aqueous phase extracted with CH_2Cl_2 (3 × 5 mL). The combined organics were washed with brine (10 mL), before being dried over $MgSO_4$, filtered and concentrated in vacuo to yield the crude material. Purification of the crude product by flash column chromatography eluting on silica gel with 10% EtOAc/petroleum ether afforded the desired amine **14** as a golden yellow solid.

4.3.1. (S_P)-*N*-Benzyl-methylphenyl-phosphinic amide 19[32]

A solution of benzylamine (0.25 mL, 2.3 mmol) in dry THF (5 mL) at −78 °C was treated with a solution of *n*-BuLi (1.15 mL, 2.00 M in hexanes, 2.30 mmol) and stirred at −78 °C for 40 min and then for a further 10 min at 0 °C. A solution of phosphinoyloxazolidinone **1** (0.223 g, 0.755 mmol) in dry THF (5 mL) was added to the solution of the lithium amide over a period of 10 min at 0 °C. The reaction mixture was stirred for a further 45 min at this temperature before being quenched with a saturated aqueous solution of NH_4Cl (2 mL). This mixture was diluted with CH_2Cl_2 (25 mL) and the layers were separated and the aqueous portion was extracted with CH_2Cl_2 (2 × 15 mL). The combined organic layers were washed with a saturated aqueous solution of NH_4Cl (2 × 10 mL) and brine (10 mL), before being dried over $MgSO_4$, filtered and concentrated in vacuo to give the crude material as a yellow oil. Purification by chromatography eluting on basic alumina with 10% propan-2-ol/CH_2Cl_2 afforded the title compound **19** as a white waxy solid (0.102 g, 87%); mp 76–77 °C (lit.[32] 73–74 °C); $[\alpha]_D^{25}$ = −6.1 (*c* 0.9, $CHCl_3$) 98% ee; ν_{max} (ATR)/cm^{-1} 3167, 3055, 2888, 1629, 1569; δ_H (400 MHz, $CDCl_3$) 1.64 (3H, d, J_{P-H} 14, PC*H*$_3$), 3.03–3.10 (1H, m, N*H*), 3.91 (1H, ddd, J_{P-H} 14.2, *J* 8.3, 7.7, C*H*H), 4.10 (1H, ddd, J_{P-H} 14.2, *J* 7.7, 6.5, CH*H*), 7.18–7.27 (5H, m, ArC*H*), 7.41–7.52 (3H, m, ArC*H*), 7.81–7.86 (2H, m, ArC*H*); δ_C (100 MHz, $CDCl_3$) 16.3 (d, J_{C-P} 93.1, PCH_3), 44.4 (NCH_2), 127.4 (ArCH), 127.7 (2 × ArCH), 128.5 (ArCH), 128.6 (2 × ArCH), 128.7 (ArCH), 131.7 (ArCH), 131.8 (ArCH), 131.9 (d, J_{C-P} 2.3, ArCH), 133.2 (ArC), 139.6 (d, J_{C-P} 8.1, ArC); δ_P (162 MHz, $CDCl_3$) 31.1; *m*/*z* (TOF ES+) 246.1047 (100%, MH^+, $C_{14}H_{17}NOP$ requires 246.1048); Chiral phase HPLC (Celluose-1, 90:10 hexane/propan-2-ol at 1 mL min^{-1}, 254 nm) t_R 13.9 (major isomer) and 16.8 (minor isomer).

4.3.2. 1-(2,2-Dibromoethenyl)-2-(phenylmethoxy)benzene 21

Triphenylphosphine (3.51 g, 13.4 mmol) was added portionwise to a solution of carbon tetrabromide (2.22 g, 6.69 mmol) in dry CH_2Cl_2 (30 mL) at 0 °C and then stirred for a further 20 min at this temperature. 2-Benzyloxybenzaldehyde **20** (709 mg, 3.34 mmol) was then added to the mixture followed immediately by triethylamine (0.47 mL, 3.34 mmol). The reaction was stirred for 30 min at 0 °C before being poured onto a saturated aqueous solution of $NaHCO_3$ (15 mL). The subsequent layers were separated and the aqueous phase was extracted with CH_2Cl_2 (2 × 30 mL). The combined organic layers were sequentially washed with a saturated aqueous solution of $NaHCO_3$ (10 mL), a saturated aqueous solution

of NH_4Cl (2 × 10 mL), and brine (10 mL), before being dried over $MgSO_4$, filtered and concentrated in vacuo to give a crude material as a yellow oil. Purification by flash column chromatography eluting on silica gel with 5% EtOAc/petroleum ether afforded the title compound **21** as a colourless oil (959 mg, 78%); ν_{max} (ATR)/cm^{-1}) 3065, 3029, 2868, 1597; δ_H (400 MHz, $CDCl_3$) 5.18 (2H, s, C*H*$_2$Ph), 7.00 (1H, dd, *J* 8.3, 0.7, ArC*H*), 7.08 (1H, td, *J* 7.6, 0.8, ArC*H*), 7.35–7.52 (6H, m, ArC*H*), 7.79 (1H, s, *H*C=CBr$_2$), 7.83 (1H, dd, *J* 7.7, 1.4, ArC*H*); δ_C (100 MHz, $CDCl_3$) 70.4 (*C*H$_2$Ph), 90.0 (Ar*C*O), 112.4 (*C*HCBr$_2$), 120.7 (ArCH), 125.0 (2 × Ar*C*), 127.2 (Ar*C*H), 128.1 (2 × ArCH), 128.8 (ArCH), 129.4 (ArCH), 130.0 (ArCH), 133.1 (ArCH), 136.8 (Ar*C*), 155.8 (*C*Br$_2$); *m*/*z* (EI$^+$) 367.9235 (5%, M$^+$, $C_{15}H_{12}^{79}Br_2O$ requires 367.9230), 287 (5), 196 (20), 169 (28), 91 (100).

4.3.3. (S_P)-[2-(2-Benzyloxyphenyl)ethynyl]methylphenylphosphine oxide 22

A solution of 1-(2,2-dibromoethenyl)-2-(phenylmethoxy)benzene **21** (0.13 g, 0.71 mmol) in dry THF (2 mL) at −78 °C was treated with a solution of *n*-BuLi (0.32 mL, 2.2 M in hexanes, 0.70 mmol) and stirred at −78 °C for 5 min. The flask was then removed from the cold bath and stirred for a further 30 min before being re-cooled to −78 °C. A solution of phosphinoyloxazolidinone **1** (0.10 g, 0.35 mmol) in dry THF (1.5 mL) was then added at −78 °C over a period of 15 min. The reaction was stirred at −78 °C for 5 h before being quenched with a saturated aqueous solution of NH_4Cl (2 mL). This mixture was diluted with CH_2Cl_2 (25 mL) and the layers were separated and the aqueous portion was extracted with more CH_2Cl_2 (2 × 15 mL). The combined organic layers were washed with brine (10 mL), before being dried over $MgSO_4$, filtered and concentrated in vacuo to give the crude material as an orange oil. Purification by flash column chromatography eluting on silica gel with 20% petroleum ether/EtOAc afforded the title compound **22** as white waxy solid (34 mg, 28%); mp 93–94 °C; $[\alpha]_D^{24} = -1.6$ (*c* 0.6, $CHCl_3$) 53% ee; ν_{max} (ATR)/cm^{-1} 3058, 3031, 2907, 1599, 1589; δ_H (400 MHz, $CDCl_3$) 1.93 (3H, d, J_{P-H} 14.4, PC*H*$_3$), 5.15 (2H, s, C*H*$_2$Ph), 6.94–7.00 (2H, m, ArC*H*), 7.30–7.48 (8H, m, ArC*H*), 7.49–7.57 (2H, m ArC*H*), 7.86–7.94 (2H, m, ArC*H*); δ_C (100 MHz, $CDCl_3$) 20.9 (d, J_{C-P} 85.4, P*C*H$_3$), 70.5 (*C*H$_2$Ph), 87.7 (d, J_{C-P} 164.8, P*C*≡C), 100.4 (d, J_{C-P} 30.8, Ar*C*), 110.0 (d, J_{C-P} 3.4, Ar*C*≡C), 112.4 (ArCH), 120.9 (ArCH), 127.2 (2 × ArCH), 128.1 (ArCH), 128.5 (ArCH), 128.6 (2 × ArCH), 128.7 (ArCH), 130.0 (ArCH), 130.1 (Ar*C*H), 132.0 (d, J_{C-P} 3.0, ArCH), 132.1 (ArCH), 133.0 (Ar*C*), 134.2 (Ar*C*H), 136.3 (Ar*C*), 160.5 (Ar*C*); δ_P (162 MHz, $CDCl_3$) 11.1; *m*/*z* (TOF ES$^+$) 693 (35%), 347.1198 (100, MH$^+$, $C_{22}H_{20}O_2P$ requires 347.1195); Chiral phase HPLC (Celluose-1, 90:10 hexane/propan-2-ol at 1 mL min^{-1}, 254 nm) t_R 21.8 (minor isomer) and 25.0 (major isomer).

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Supplementary data

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