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. Amongst methodologies developed to reduce ketimines, the use of trichlorosilane as a reductant has received growing interest in recent years. 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. Several other N-formyl derived organocatalysts then followed, including those developed by Malkov and Ko˘c´ov´sky, Matsumura, and Sun in addition to imidazole and picolinoyl amides. 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. In contrast, phosphorus derived reagents have received much less attention. Sugiu et al. identified BINAPO as an effective organocatalyst for the synthesis of enantioenriched 4H-1,3-oxazines via a trichlorosilane mediated reductive cyclisation of N-acylated-β-amino enones. Benaglia et al. reported the potential of a range of chiral phosphinamides derived from proline to promote the hydrosilylation of β-enamino esters. 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. Several of the phosphine oxides from this work were utilised, and a further subset prepared by use of the appropriate Grignard reagent, all with excellent enantioselectivity, as determined by chiral phase HPLC (Scheme 1).

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.
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 2a

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<th>Entry</th>
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<th>10 mol % loading</th>
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(continued on next page)
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](image)

**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 acetoephone derived ketimines differ from the phosphine oxides in several ways, primarily as a consequence of using the Ellman chiral sulfinamide to construct these species. 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 which although evaluated with the o-tolyl group also reduced the enantioselectivity to 22% 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.

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 an oxygen substituent on the aromatic ring, correctly spaced relative to the stereogenic centre. Since the NH group was not deemed necessary for this functional group, and in some ways it might even be considered detrimental.

![Scheme 3](image)

**Scheme 3.** Asymmetric synthesis of phosphinamide 19 and comparison of its activity to sulfinamide 18.
The non-linear effect, coupled with Sun's observations of a non-linear system in which two ligands were used, 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 [ML2] non-linear system in which two ligands were required in the stereoselective step of the reduction.27,28

4. 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 CH2Cl2 (3 × 10 mL). The organic phases were combined, washed with brine (10 mL) and dried over MgSO4. 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. (S)-{2-Isopropylphenyl)methylphenylphosphine oxide 8

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/CH2Cl2, 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; [α]D 3.0 (c 1.0, CHCl3) >99% ee; δH (250 MHz, CDCl3) 0.85 [3H, d, J = 6.8, 1 × CH(Me)2]; 1.14 [3H, d, J = 6.8, 1 × CH(CH3)2]; 2.06 [3H, d, J = 6.8, 13.0, PCH2]; 3.48 [1H, hept, J = 6.8, CH(CH3)2]; 7.27–7.76 (9H, m, ArCH); δP (121 MHz, CDCl3) 31.2; Chiral phase HPLC (CHIRALPAK-AS, 95:5 hexane/propan-2-ol at 1.0 mL min−1, 210 nm) tR 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)-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/CH2Cl2 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; [α]D = −28.1 (c 1.0, CHCl3) >99% ee; vmax (ATR)/cm−1 2360, 1599, 1577; δH (400 MHz, CDCl3) 1.98 (3H, d, JHH = 14.0, PCH); 3.58 (6H, s, 2 × OCH3) 3.82 (3H, s, OCH3); 6.06 (2H, d, J = 3.6, 2 × ArCH); 7.35–7.41 (3H, m, ArCH), 7.64–7.67 (2H, m, ArCH); δC (101 MHz, CDCl3) 21.8 (d, JCP = 76.0, PCH); 55.4 (OCH3) (5 × OCH3), 91.0 (ArCH), 91.1 (ArCH), 102.0 (d, JCP = 108.0, ArCH), 127.8 (d, JCP = 13.0, 2 × ArCH), 129.2 (d, JCP = 10.0, 2 × ArCH), 130.0 (d, JCP = 3.0, ArCH), 138.9 (d, JCP = 107.0, ArC), 164.0 (2 × ArC), 165.0 (ArCH); δP (101 MHz, CDCl3) 271.1: m/z (TOF ES+) 307.1105 (MH+1, 100%). C16H22O4P requires 307.1099; Chiral phase HPLC (Cellulose-1, 90:10 hexane/propan-2-ol at 1 mL min−1, 210 nm) tR 35.5 (minor isomer) and 38.5 (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 CH2Cl2 (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 CH2Cl2 (5 mL) and basified with a 1 M aqueous NaOH solution (10 mL). The organic phase was separated, and the aqueous phase extracted with CH2Cl2 (3 × 5 mL). The combined organic layers were washed with brine (10 mL), before being dried over MgSO4, 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. (Sd)-N-Benzyl-methylphenyl-phosphinic amide 19

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 phosphinoylloxazolidinone 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 NH4Cl (2 mL). This mixture was diluted with CH2Cl2 (25 mL) and the layers were separated and the aqueous portion was extracted with CH2Cl2 (2 × 15 mL). The combined organic layers were washed with a saturated aqueous solution of NH4Cl (2 × 10 mL) and brine (10 mL), before being dried over MgSO4, 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/CH2Cl2 afforded the title compound 19 as a white xerogel solid (0.102 g, 87%); mp 76–77 °C (lit.32 73–74 °C); [α]D = −6.1 (c 0.99, CHCl3) 98% ee; vmax (ATR)/cm−1 3167, 3055, 2888, 1629, 1599; δH (400 MHz, CDCl3) 1.64 (3H, d, JHH = 13.14, PCH3), 3.03–3.10 (1H, m, NH), 3.91 (1H, ddd, JHH = 14.2, JHP = 8.3, 7.7, CH3), 4.10 (1H, ddd, JHH = 14.2, JHP = 7.7, 6.5, CH3), 7.18–7.27 (5H, m, ArCH); 7.41–7.52 (2H, m, ArCH), 7.81–7.86 (2H, m, ArCH); δP (100 MHz, CDCl3) 163.3 (3H, d, JCP = 91.3, PCH3), 44.4 (NCH3), 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, JCP = 2.3, ArCH), 133.2 (ArCH), 139.6 (d, JCP = 8.1, ArC); δP (162 MHz, CDCl3) 31.1; m/z (TOF ES+) 246.1047 (100%, MH+1, C16H17NOP requires 246.1048). Chiral phase HPLC (Cellulose-1, 90:10 hexane/propan-2-ol at 1 mL min−1, 254 nm) tR 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 CH2Cl2 (30 mL) at 0 °C and then stirred for a further 20 min at this temperature. 2-Benzoylbenzaldehyde 20 (709 mg, 3.34 mmol) was then added to the mixture followed immediately by triethylaniline (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 NaHCO3 (15 mL). The subsequent layers were separated and the aqueous phase was extracted with CH2Cl2 (2 × 30 mL). The combined organic layers were sequentially washed with a saturated aqueous solution of NaHCO3 (10 mL) a saturated aqueous solution...
of NH₄Cl (2 × 10 mL), and brine (10 mL), before being dried over MgSO₄, 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%); v_max (ATR)/cm⁻¹ 3065, 3029, 2868, 1597; δH (400 MHz, CDCl₃) 5.18 (2H, s, CH₂Ph), 7.00 (1H, dd, J 8.3, 0.7, ArCH), 7.08 (1H, td, J 7.6, 0.8, ArCH), 7.35–7.52 (6H, m, ArCH), 7.79 (1H, s, H-C=CB₂), 7.83 (1H, dd, J 7.7, 1.4, ArCH); δC (100 MHz, CDCl₃) 120.7 (ArCH₂), 125.0 (2 × ArCH₂), 127.2 (ArCH), 128.1 (2 × ArCH), 128.8 (ArCH₂), 130.0 (ArCH), 133.1 (ArCH), 136.8 (ArC), 155.8 (CBr₂); m/z (EI⁺) 367.9235 (5%, M⁺, C₁₈H₁₂O₂P requires 367.1195); Chiral HPLC (Celluose-1, 90:10 hexane/propan-2-ol at 1 mL min⁻¹, 254 nm) r_t 21.8 (minor isomer) and 25.0 (major isomer).

**Supplementary data**

Supplementary data associated with this article can be found, in the online version, at [http://dx.doi.org/10.1016/j.tetasy.2016.01.001](http://dx.doi.org/10.1016/j.tetasy.2016.01.001).

**References**