SYNTHESIS OF SEVERAL CHIRAL PHOSPHINAMIDES AND THEIR APPLICATION IN THE ASYMMETRIC BORANE REDUCTION OF PROCHIRAL KETONES

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ABSTRACT

Several chiral phosphinamide catalysts were prepared from (S)-(+)-Betti Base, (D)-1R,2R-(-)-threo-1-(p-Nitrophenyl)-2-amino-3-triphenyl-methoxypropanol-1 and L-Serine respectively. Their application in the asymmetric borane reduction of prochiral ketones was examined. The chiral secondary alcohols were obtained in excellent chemical yields with moderate enantioselective excesses.

INTRODUCTION

The enantioselective reduction of prochiral ketones is an important route for the synthesis of optically active secondary alcohols^[1] which were widely used in the preparation of bioactive substances^[2]. The enantioselective borane reduction catalyzed by oxazaborolidine prepared from chiral amino alcohols is one of the most efficient method^[3] which give excellent ee values and often have wide substrate scope. Other catalysts such as chiral sulfur reagents^[4, 5] and chiral phosphorous reagents^[5] were also used in this reaction. In recent years, great progress was achieved using chiral phosphorous reagents as catalysts for the reduction of prochiral ketones. In this paper, we reported several chiral phosphinamides compounds **I**, **II** and **III** prepared from (S)-(+)-Betti Base, (D)-1R,2R-(-)-threo-1-(p-Nitrophenyl)-2-amino-3-triphenylmethoxypropanol-1 and L-Serine respectively. Their application as ligand catalysts in the asymmetric borane reduction of prochiral ketones were investigated.

MATERIALS AND METHODS

¹H NMR and ³¹P NMR were recorded in CDCl₃ as solvent on an AC-P200 instrument using TMS as internal standard and 85% H₃PO₄ as external standard, respectively. Elemental analyses were done on an MF-3 automatic analyzer. Melting points were determined on an MP-500 melting point apparatus. Optical rotations were measured on a Perkin-Elmer 241MC polarimeter. All temperatures were uncorrected.

Preparation of 1-(α-N-diphenylphosphinylaminobenzyl)-2-naphthol **I** (Scheme 1)

Scheme 1

0.757g (3.2 mmol) diphenylphosphinyl chloride in 5ml dry CH₂Cl₂ was added to the solution of 0.747g (3 mmol) (S)-(+)-Betti Base **1**, which was prepared according to the reference method^[6], 0.303g (3 mmol) triethylamine and 15ml CH₂Cl₂ at -10°C. The resulting mixture was stirred overnight and washed successively with water and saturated NaCl solution. The organic layer was separated and dried over anhydrous Na₂SO₄. After removal of the solvent the crude product was purified by column chromatography on silica gel (200-300 mesh, petroleum ether/EtOAc as eluent) to afford 0.47g product as a white solid. Yield 35.0%, m.p. 142~144°C, [α]_D²⁵ = +57.0 (c 0.56, CH₂Cl₂). ³¹P NMR 26.37 ppm (s), ¹H NMR 2.15 (s, H, CH), 5.90 (bs, H, OH), 6.15 (s, 1H, NH), 7.08~7.82 (m, 21H, Ar-H). Anal. Calcd for C₂₉H₂₄NO₂P : C, 77.49; H, 5.38; N, 3.12. Found: C, 77.54; H, 5.29; N, 3.13.

Preparation of (D)-1R,2R-(-)-threo-1-(p-Nitrophenyl)-2-(N-diphenylphosphinyl)amino-3-triphenyl-methoxypropanol-1 **II** (Scheme 2)

To a solution of 1.14g (2.5 mmol) (D)-1R,2R-(-)-threo-1-(p-Nitrophenyl)-2-amino-3-triphenylmethoxypropanol-1 **2**, which was prepared according to the reference method^[7], and 0.51g (5 mmol) triethylamine in 20ml dry CH₂Cl₂ was added 0.71g (3 mmol) diphenylphosphinyl chloride in 10ml CH₂Cl₂ under -10°C. The

resulting mixture was warmed to room temperature and stirred overnight, and then washed successively with water and saturated NaCl solution. The organic layer was separated and dried over anhydrous Na_2SO_4 .

Scheme 2

After removal of the solvent the crude product was purified by column chromatography on silica gel (200–300 mesh, petroleum ether/EtOAc as eluent) to give 0.5g light yellow solid. Yield 30.7%, m.p. $204\sim 206^\circ\text{C}$, $[\alpha]_{\text{D}}^{20} -43.7$ (c 1.0, CH_2Cl_2), ^{31}P NMR 26.79 ppm (s), ^1H NMR 1.81–1.47 (m, 2H, CH_2), 1.89–2.15 (m, 2H, CH_2), 1.81–1.47 (d, 6H, 2 CH_3), 2.41–3.04 (m, 2H, CH_2), 4.68–4.80 (m, 1H, CH), 5.60 (bs, 1H, OH), 7.03–7.70 (m, 18H, Ph-H). Anal. Calcd for $\text{C}_{40}\text{H}_{35}\text{N}_3\text{O}_5\text{P}$: C, 73.38; H, 5.39; N, 4.28. Found: C, 73.19; H, 5.20; N, 4.17.

Preparation of N-Triphenylmethyl-O-para-toluenesulphonyl-(2S)-serine methyl ester 4 and (-)-(2S)-Methyl-1-tritylaziridine-2-carboxylate 5: (Scheme 3)

These two compounds were prepared according to the procedures reported before^[8].

i) Ph_3CCl , Et_3N , CH_2Cl_2 ; ii) TsCl , Pyridine; iii) Et_3N , THF, reflux; iv) RMgBr , THF; v) MeOH/THF , 35% KOH ; vi) $\text{Ph}_2\text{P}(\text{O})\text{Cl}$, Et_3N , CH_2Cl_2 .

Preparation of (-)-(2S)-1-aziridin-2-yl(diaryl)methanol 6: according to the modified procedures reported by Zwanenburg^[9].

(-)-(2S)-1-aziridin-2-yl(diphenyl)methanol 6a:

white solid, m.p. $158\sim 160^\circ\text{C}$, $[\alpha]_{\text{D}}^{20} -18.3$ (c 0.875, CH_2Cl_2), ^1H NMR 1.47–1.49 (d, 2H, CH_2), 2.72 (s, 1H, NH), 3.32 (s, 1H, OH), 5.20 (s, 1H, CH), 7.18–7.47 (m, 10H, Ph-H). Anal. Calcd for $\text{C}_{15}\text{H}_{13}\text{NO}$: C, 79.97; H, 6.71; N, 6.22. Found: C, 79.82; H, 7.05; N, 6.15.

(-)-(2S)-1-aziridin-2-yl[di(p-methyl)-phenyl]methanol 6b:

white solid, m.p. $140\sim 141^\circ\text{C}$, $[\alpha]_{\text{D}}^{20} -15.2$ (c 1.05, CHCl_3), ^1H NMR 1.25–1.27 (m, 2H, CH_2), 2.31 (s, 6H, 2 CH_3), 3.70–3.85 (m, 2H, NH, OH), 4.85 (s, 1H, CH), 7.07–7.80 (m, 8H, Ph-H). Anal. Calcd for $\text{C}_{17}\text{H}_{19}\text{NO}$: C, 80.59; H, 7.56; N, 5.53. Found: C, 80.46; H, 7.42; N, 5.43.

(-)-(2S)-1-aziridin-2-yl[di(p-fluoro)-phenyl]methanol 6c:

light yellow solid, m.p. $92\sim 94^\circ\text{C}$, $[\alpha]_{\text{D}}^{20} -18.5$ (c 1.08, CHCl_3), ^1H NMR 2.99–2.10 (m, 2H, CH_2), 3.02–4.95 (m, 3H, NH, OH, CH), 7.18–7.47 (m, 8H, Ph-H). Anal. Calcd for $\text{C}_{15}\text{H}_{13}\text{F}_2\text{NO}$: C, 68.96; H, 5.02; N, 5.36. Found: C, 69.13; H, 5.42; N, 5.10.

Typical procedure for preparation of compound IIIa~c:

To a mixture of 2.3mmol 6, 3mmol (0.303g) Et_3N and 15ml CH_2Cl_2 was added a solution of 2.5mmol (0.591g) $\text{Ph}_2\text{P}(\text{O})\text{Cl}$ in 5ml CH_2Cl_2 under ice-salt bath. White precipitate was formed quickly, and the

reaction was complete after the addition (monitored by TLC). The solid was collected by filtration and washed with CH_2Cl_2 thoroughly to afford the pure product.

(-)-(2S)-1-(N-diphenylphosphinyl)aziridin-2-yl(diphenyl)methanol IIIa:

white solid m.p. >240°C, $[\alpha]_{\text{D}}^{20}$ -26.0 (c 0.27, DMF), ^{31}P NMR 32.72ppm, ^1H NMR 2.40~2.80 (m, 2H, CH_2), 3.10 (bs, 1H, OH), 3.85~3.90 (m, 1H, CH), 6.95~7.95 (m, 20H, Ph-H). Anal. Calcd for $\text{C}_{27}\text{H}_{22}\text{NO}_2\text{P}$: C, 76.22; H, 5.69; N, 3.29. Found: C, 76.10; H, 5.50; N, 3.35.

(-)-(2S)-1-(N-diphenylphosphinyl)aziridin-2-yl[di(p-methyl)-phenyl]methanol IIIb:

white solid m.p. >240°C, $[\alpha]_{\text{D}}^{20}$ +4.0 (c 3.10, CHCl_3), ^{31}P NMR 26.98ppm, ^1H NMR 2.25~2.31 (d, 6H, 2CH_3), 3.10~3.32 (m, 3H, CH_2 , OH), 5.05~5.10 (t, 1H, CH), 7.06~7.85 (m, 18H, Ph-H). Anal. Calcd for $\text{C}_{29}\text{H}_{28}\text{NO}_2\text{P}$: C, 76.80; H, 6.22; N, 3.09. Found: C, 76.62; H, 6.16; N, 3.21.

(-)-(2S)-1-(N-diphenylphosphinyl)aziridin-2-yl[di(p-fluoro)-phenyl]methanol IIIc:

white solid m.p. >240°C, $[\alpha]_{\text{D}}^{20}$ -17.8 (c 0.90, CHCl_3), ^{31}P NMR 32.85ppm, ^1H NMR 2.40~2.60 (m, 1H, H), 3.50~3.80 (m, 2H, H, OH), 6.57~6.60 (t, 1H, CH), 6.93~7.48 (m, 18H, Ph-H). Anal. Calcd for $\text{C}_{27}\text{H}_{22}\text{F}_2\text{NO}_2\text{P}$: C, 70.28; H, 4.81; N, 3.04. Found: C, 69.98; H, 4.76; N, 3.15.

Typical procedure for the asymmetric reduction of prochiral ketones catalyzed by I~III:

To a solution of 2ml toluene and 10mol% I~III, was added 1.2eq $\text{BH}_3\text{Me}_2\text{S}$ under nitrogen atmosphere. The mixture was stirred for 20min, then a solution of 1mmol prochiral ketone in 4ml dry toluene was added in 30mins. The reaction was complete (monitored by TLC) after the addition. 10ml saturated NH_4Cl solution was added and the resulting mixture was stirred for another 10mins. The organic phase was separated and the water layer was extracted with 210ml EtOAc. The combined organic layer was washed with saturated NaCl solution and dried over anhydrous Na_2SO_4 .

Scheme 4

Table I Asymmetric borane reduction of prochiral ketones catalyzed by I~III

Cat.	X	Y	Temp./°C	Yield/% ^a	$[\alpha]_{\text{D}}^{25}$ ° ^c	e.e./% ^d (ee/% ^e)	Config.
I	Cl	H	-20~rt	88.7	-30.0	63.8(62.4)	S
I	Cl	H	30~40	95.2	-26.0	55.5(54.2)	S
I	Cl	H	60~70	93.5	-24.3	51.7(49.8)	S
I	Cl	H	Reflux	92.7	-	11.1	S
I	Br	H	30~40	94.3	-28.3	50.7	S
I	H	H	-20~rt	91.7	-21.5	45.8	S
II	Cl	H	30~40	96.8	+20.0	46.5	R
II	H	H	30~40	83.0	+15.0	33.3	R
II	H	o-Cl	30~40	88.7	+10.1	15.4	R
II	H	p-Me	30~40	93.5	+29.0	50.3	R
II	H	p-MeO	30~40	91.7	+17.5	54.2	R
IIIa	Cl	H	Reflux	92.7	+23.9	54.5	R
IIIa	H	p-MeO	Reflux	92.0	+14.5	44.9	R
IIIa	H	p-Me	Reflux	92.0	+5.0	8.7	R
IIIa	H	o-Cl	Reflux	90.0	0	0	-
IIIb	Cl	H	Reflux	92.5	+4.3	10.0	R
IIIb	H	p-MeO	Reflux	95.8	+17.0	52.6	R
IIIb	H	p-Me	Reflux	84.0	+6.6	11.4	R
IIIb	H	o-Cl	Reflux	92.7	+4.3	6.6	R
IIIc	Cl	H	Reflux	88.3	+7.0	16.0	R
IIIc	H	p-MeO	Reflux	96.7	+2.0	6.0	R

a. isolated yield; b. c=1.0; c. determined by specific rotation, for (S)-1-phenylethanol $[\alpha]_{\text{D}}^{20}$ = -45.5 (c 2.0, MeOH)^[5d], for (R)-2-Chloro-1-phenylethanol $[\alpha]_{\text{D}}^{20}$ = +47 (c 1.84, cyclohexane)^[1v], for (R)-1-(2-Chlorophenyl)ethanol $[\alpha]_{\text{D}}^{20}$ = +65.7 (c 0.625, CHCl_3)^[11], for (R)-1-(2-Bromophenyl)ethanol $[\alpha]_{\text{D}}^{20}$ = +58.8 (c 0.57, CH_2Cl_2)^[12], for (R)-1-(4-Methoxyphenyl)ethanol $[\alpha]_{\text{D}}^{20}$ = +32.3 (c 2.0, CHCl_3)^[13], for 1-(4-Methylphenyl)ethanol $[\alpha]_{\text{D}}^{20}$ = +57.5 (c 0.36, CHCl_3)^[14]; d. determined Chiral HPLC analysis.

After removal of the solvent the crude product was purified by column chromatography on silica gel. The catalyst could be recycled and reused. The enantioselective excess of the product could be determined by the comparison the specific rotation with literature or by chiral HPLC analysis.

RESULTS AND DISCUSSION

The prepared chiral phosphinamides **I–III** were used as catalysts in the borane reduction of prochiral ketones. (Scheme 4). The results are summarized in Table 1.

As shown in Table 1, in all cases, the chiral secondary alcohols were obtained with excellent chemical yields and moderate enantiomeric excesses. The reaction temperature had a marked influence on the enantioselectivity in the reduction of 2-chloro-1-phenylethanone catalyzed by **I**. In general, lower temperature was beneficial for the improvement of the enantioselectivity. For example, carrying out the reaction at -20°C provided the optical product with 63.8% ee value which was much higher than the results obtained at $30\sim 40^{\circ}\text{C}$ (55.5% ee) and $60\sim 70^{\circ}\text{C}$ (51.7% ee), respectively. The ee value dramatically decreased to 11.1% at reflux temperature. To the other two substrates, 2-bromo-1-phenylethanone and acetophenone, only moderate ee were also obtained at definite condition. For catalyst **II**, the nature of the substrates was found to be an essential factor to the asymmetric induction. Compared with acetophenone (33.3% ee), much higher catalytic activities (50.3% ee and 54.2% ee respectively) were observed when there was electron-donor group (Me-, MeO-) substituted at the *para*-position of the benzene ring in acetophenone. On the contrary, the enantiomeric excess decreased rapidly (15.4% ee) when electron-withdrawing group, such as Cl, was present instead. Our further study demonstrated that only low enantiomeric excesses (0–54.5% ee) were obtained when **IIIa–c** were employed in the reduction of a series of prochiral ketones. A possible interpretation is that the large strain of the three-membered ring in catalysts **IIIa–c** led to the low catalytic activities but it still needs to be proved with more experimental data.

In conclusion, a new class of chiral phosphinamide catalysts was synthesized and their application as catalyst in the reduction of prochiral ketone were investigated. The corresponding alcohols were obtained in excellent chemical yields with moderate ee-values. The impact factors on the selectivities were also studied. These findings will give us very useful information for the design and synthesis of the new types of chiral catalysts in our ongoing research program.

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