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C_2-Symmetric diphenylphosphoramide and diphenylthiophosphoramide derived from (1*R*,2*R*)-1,2-diaminocyclohexane as ligands for the titanium(IV) alkoxide-promoted addition of diethylzinc to aldehydes

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Abstract

Chiral C_2-symmetric diphenylphosphoramide **4** and diphenylthiophosphoramide **5** were prepared from the reaction of diphenylphosphinic chloride and diphenylthiophosphinic chloride with (1*R*,2*R*)-(−)-1,2-diaminocyclohexane in the presence of diisopropylethylamine in high yields. They were used as chiral ligands in the catalytic asymmetric addition reaction of diethylzinc to aldehydes in the presence of titanium(IV) isopropoxide to give the corresponding *sec*-alcohols in 70–83% ee with an (*R*)-configuration and in 40–50% ee with an (*S*)-configuration, respectively.

1. Introduction

Catalytic asymmetric synthesis is a valuable method for preparing optically active substances.[1] Concerning this subject, the stereoselective addition of organometallics to one of the two heterotopic faces of a carbonyl group has been extensively studied: in particular, the addition of diethylzinc to arylaldehydes has become a prototype in the evaluation of new chiral catalysts. So far, it is well known that dialkylzinc is activated to react with aldehydes by the addition of a catalytic amount of chiral 1,2-, 1,3- and 1,4-diols, aminoalcohols and diamines.[2] In addition, in the presence of titanium(IV) alkoxide [$Ti(OPr^i)_4$], chiral bidentate ligands such as the diol **1**,[3] ditriflamide **2**[4] and tetradentate ligand **3**[5] have also been extensively and successfully used in the catalytic enantioselective addition of dialkylzinc to aldehydes (Fig. 1). Ditriflamide **2** especially is an excellent chiral ligand for this asymmetric addition reaction and its mechanistic detail has recently been disclosed by Walsh et al. through the crystal structure

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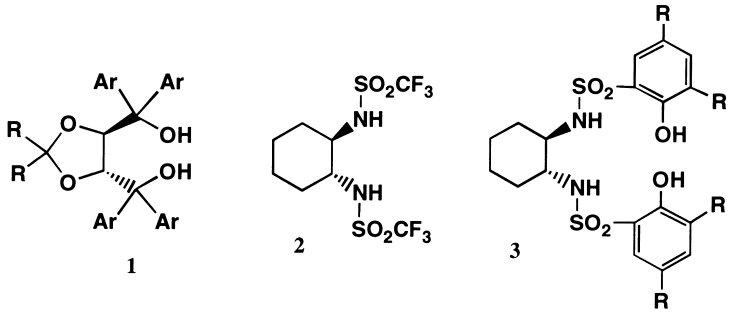
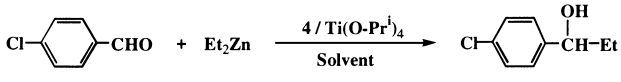


Figure 1.

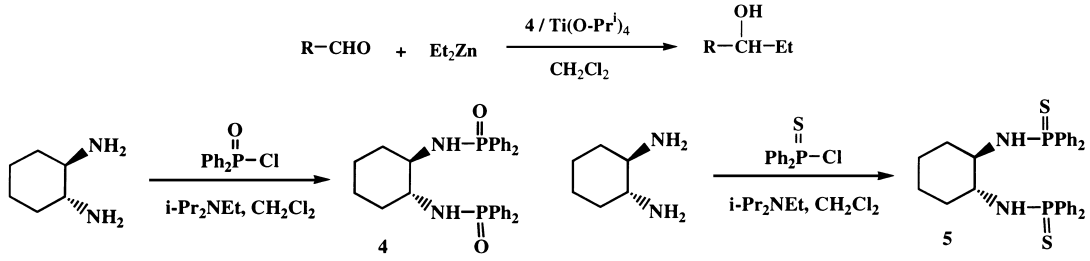
of bis(sulfonamido) titanium bis(alkoxide) complexes.[6] They found that sulfonyl oxygens are actually bonded to the titanium center with Ti–O distances ranging from 2.249(3) to 2.390(3) Å combined with the Ti–N bond. The coordination of the titanium–sulfonyl oxygens maintains a rigid C_2-symmetric environment and is an important factor in the transfer of the chirality. This result stimulated us to study the chiral C_2-symmetric phosphoramide and C_2-symmetric thiophosphoramide for this asymmetric addition reaction simply because it is conceivable that phosphoryl oxygen atoms and sulfur atoms could coordinate to the titanium metal center as well and these novel chiral ligands could promote a high chiral induction. Based on this concept, we started to prepare the chiral C_2-symmetric phosphoramide **4** and chiral C_2-symmetric thiophosphoramide **5** and used them as catalytic chiral ligands for titanium(IV) alkoxide-promoted asymmetric addition reaction of diethylzinc to aldehydes.

2. Results and discussion



Diphenylphosphoramide **4** and diphenylthiophosphoramide **5** were synthesized from the reaction of diphenylphosphinic chloride and diphenylthiophosphinic chloride with (1*R*,2*R*)-(−)-1,2-diaminocyclohexane in the presence of diisopropylethylamine in dichloromethane, respectively (Scheme 1). After usual workup and purification by silica gel column chromatography, compounds **4** and **5** were obtained as colorless solids in over 90% yields. Those C_2-symmetric chiral ligands were used in the addition reaction of diethylzinc to *p*-chlorophenylaldehyde in the presence of titanium(IV) isopropoxide [RCHO:Ti(OPr^i)$_4$:Et$_2$Zn=1:1.4:1.8]. In fact, the addition product, *sec*-alcohol, was obtained in 92% yield and 22% ee (enantiomeric excess) in the presence of 4 mol% of **4** (0.04 equiv.) in toluene (Table 1, entry 1). The ees of the product were determined by HPLC analysis using chiral stationary-phase columns (Chiralcel OD and OJ) and the absolute configuration of the major enantiomer was assigned according to the sign of the specific rotation. The ee of *sec*-alcohol could be improved by increasing the amount of chiral ligand **4**. The better result was obtained by using 20 mol% of **4** in toluene with 40% ee (Table 1, entry 4). From Table 1, it is very clear that the chiral C_2-symmetric phosphoramide **4** must have a so-called 'ligand acceleration effect',[7] i.e. the reactivity of the active species bearing the chiral ligand was enhanced. That is why the ee of the product could be increased with the increase of the amount of chiral ligand. In the meantime, we found that the solvent drastically affected the ee of this asymmetric addition reaction. Toluene and dichloromethane are good solvents for achieving higher ees (40 and 50%) and the lowest ee of *sec*-alcohol was obtained in tetrahydrofuran (THF), although the yields of the reaction products are very similar. The addition of molecular sieve 4A did not improve

the enantioselectivity (Table 1, entry 3). Moreover, although it is convenient if this asymmetric addition reaction is carried out at 0°C because the reaction is very sluggish at very low temperature (−50°C), we found that the reaction temperature drastically affects the ee of the reaction product. For example, the ee decreased to 22% at 7°C, but could reach 66% at −5°C and 81% at −20°C (Table 1, entries 7, 8, 9). The best result was obtained in Table 1, entry 9. By means of this optimized reaction condition, various aldehydes were used as substrates for this addition reaction and the corresponding *sec*-alcohol could be obtained in 80–99% yield and 70–83% ee with *R*-configuration. The results are summarized in Table 2. It should be emphasized that the chiral C_2-symmetric ligand phosphoramide **4** could be recovered from the reaction mixture in 90% after usual workup and can be used again in the asymmetric reaction without loss of enantioselectivity. Thus, the chiral C_2-symmetric phosphoramide is a quite effective chiral ligand. We suggest that the phosphoryl oxygen atoms can coordinate to the titanium center as well as maintain a rigid chiral C_2-symmetric environment and thus achieve a high enantioselectivity. In order to verify this coordination, we tried to isolate the active complex from the reaction of **4** with the mixed amide alkoxide complex $Ti(NMe)_2(OPr^i)_2$,[6] but despite extensive efforts, we did not obtain a single crystal which could be subjected to X-ray crystal analysis.



Scheme 1.

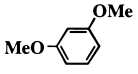
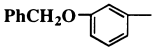
On the other hand, it is well known that the sulfur-containing compounds such as substituted β-aminothiols[8] and β-hydroxysulfides derived from D-camphor[9] are very effective chiral ligands for the

Table 1
Asymmetric addition reaction of diethylzinc to *p*-chlorobenzaldehyde in the presence of chiral ligand **4** under different reaction conditions

entry	Solvent	Ligand equiv.	$Ti(O\text{-}Pr^i)_4$ equiv.	Et_2Zn equiv.	Temp. [°C]	Time [h]	Yield[a] [%]	ee[b] [%]	Config.
1	Toluene	0.04	1.4	1.8	-20 - 0 °C	20	92	22	R
2	Toluene	0.1	1.4	1.8	-50 - 0 °C	26	92	32	R
3	Toluene	0.1/MS 4A	1.4	1.8	-50 - 0 °C	25	79	32	R
4	Toluene	0.20	1.4	1.8	-50 - 0 °C	25	97	40	R
5	CH_2Cl_2	0.20	1.4	1.8	-50 - 0 °C	36	90	50	R
6	THF	0.20	1.4	1.8	-50 - 0 °C	36	80	9	R
7	CH_2Cl_2	0.20	1.4	1.8	-50 - 7 °C	36	94	22	R
8	CH_2Cl_2	0.20	1.4	1.8	-50 - -5 °C	36	92	66	R
9	CH_2Cl_2	0.20	1.4	1.8	-50 - -20 °C	48	95	81	R

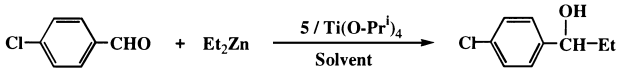
[a] Isolated yields. [b] Determined by chiral HPLC.

Table 2
Asymmetric addition reaction of diethylzinc to arylaldehydes in the presence of a catalytic amount of chiral ligand **4** [**4**:RCHO:Ti(OPr^i)$_4$:Et$_2$Zn=0.2:1:1.4:1.8]

R	Temp. [°C]	Time [h]	Yield[a] [%]	ee[b] [%]	$[\alpha]_D^{20}$	Config.[d]
Ph	-50 - -20	48	82	81	+38.1 (c 4.6, $CHCl_3$)	R
p-MePh	-50 - -20	60	80	76	+31.3 (c 4.1, C_6H_6)	R
p-MeOPh	-50 - -20	60	92	80	+13.9 (c 4.3, C_6H_6)	R
	-50 - -20	60	99	82	+22.6 (c 4.5, $CHCl_3$)	R
	-50 - -20	48	82	74	+17.7 (c 4.0, $CHCl_3$)	R
1-Naphthyl	-50 - -20	60	90	83	+46.6 (c 4.3, $CHCl_3$)	R
Ph-CH=CH−	-50 - -20	60	94	70	+5.9 (c 4.4, $CHCl_3$)	R
n-C_4H_9	-50 - -20	60	92	62[c]	-4.2 (neat)	R

[a] Isolated yield. [b] Determined by chiral HPLC. [c] Determined by chiral GC.
[d] Determined by the sign of the specific rotation.

enantioselective addition reaction of aldehydes and reduction of imides. Thus, we prepared chiral C_2-symmetric diphenylthiophosphoramide **5** and used it as chiral ligand in the same asymmetric addition reaction. The reaction was carried out in the same manner as when using chiral ligand **4**. Surprisingly, we found that the *sec*-alcohol was obtained preferentially with the *S*-configuration, i.e. inversion of enantioselectivity was observed compared to when using the chiral ligand **4**, although the ee was not as high (31% at −5°C and 40% at −20°C) (Table 3). The best result was obtained in toluene at −20°C. The chiral ligand **5** can also be recovered from the reaction mixture in 60% after usual workup and can be used again without loss of enantioselectivity. At present the mechanistic detail of this interesting inversion phenomenon remains obscure and work to elucidate this is in progress. As one explanation, we think that the different electron withdrawing ability of the P=S and P=O bonds may play an important role in this interesting inversion of enantioselectivity. The higher electron withdrawing ability of the P=O bond (atomic electronegativity: O: 3.52, S: 2.52, P: 2.11) causes the higher acidity of NH proton in **4**. Thus it can readily exchange the ligand with Ti(OPr^i)$_4$ to give the complex A, just like ditriflamide **2** (Fig. 2).[6] However, for diphenylthiophosphoramide **5**, due to the lower acidity of NH proton in **5**, no ligand exchange could take place and complex B may be the active chiral Lewis acid for its enantioselective addition reaction (Fig. 2). Namely, the structural difference of the active species might cause the inversion of the enantioselectivity between chiral ligands **4** and **5**.



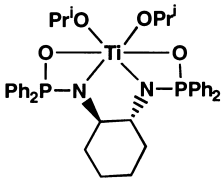
By means of the optimized reaction conditions, various aldehydes were used as substrates for the same addition reaction using **5** as a catalytic ligand and the corresponding *sec*-alcohol could be obtained in 80–99% yield and 40–50% ee with the *S*-configuration. The results are summarized in Table 4.

In conclusion, the chiral bidentate C_2-symmetric phosphoramide **4** and thiophosphoramide **5** were found to be a new class of effective chiral ligands for the titanium-promoted enantioselective addition

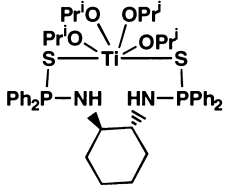
Table 3
Asymmetric addition reaction of diethylzinc to *p*-chlorobenzaldehyde in the presence of chiral ligand **5** under different reaction conditions

entry	Solvent	Ligand equiv.	$Ti(O\text{-}Pr^i)_4$ equiv.	Et_2Zn equiv.	Temp. [°C]	Time [h]	Yield[a] [%]	ee[b] [%]	Config.
1	CH_2Cl_2	0.20	1.4	1.8	-50 - 0 °C	36	80	8	S
2	Toluene	0.20	1.4	1.8	-50 - 0 °C	25	97	22	S
3	Toluene	0.20	1.4	1.8	-50 - -5 °C	36	90	31	S
4	Toluene	0.20	1.4	1.8	-50 - -20 °C	36	90	40	S

[a] Isolated yields. [b] Determined by chiral HPLC.



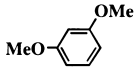
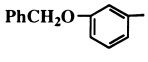
complex A



complex B

Figure 2.

Table 4
Asymmetric addition reaction of diethylzinc to arylaldehydes in the presence of a catalytic amount of chiral ligand **5** [**5**:RCHO:$Ti(OPr^i)_4$:Et_2Zn=0.2:1:1.4:1.8] in dichloromethane

R	Temp. [°C]	Time [h]	Yield[a] [%]	ee[b] [%]	$[\alpha]_D^{20}$	Config.[d]
Ph	-50 - -20	48	80	40	-18.3 (c 3.6, $CHCl_3$)	S
p-MePh	-50 - -20	60	84	43	-17.2 (c 4.0, C_6H_6)	S
p-MeOPh	-50 - -20	60	96	40	-7.1 (c 4.6, C_6H_6)	S
	-50 - -20	60	90	46	-12.8 (c 4.5, $CHCl_3$)	S
	-50 - -20	48	88	50	-11.5 (c 4.2, $CHCl_3$)	S
1-Naphthyl	-50 - -20	60	94	48	-25.9 (c 3.6, $CHCl_3$)	S
Ph–CH=CH–	-50 - -20	60	91	41	-3.2 (c 3.5, $CHCl_3$)	S
n-C_4H_9	-50 - -20	60	92	32[c]	+2.2 (neat)	S

[a] Isolated yield. [b] Determined by chiral HPLC.
[c] Determined by chiral GC. [d] Determined by the sign of the specific rotation.

reaction of dialkylzinc reagents to aldehydes although they are not as effective as ditriflamide **2**.[4] These results should lead to the design and synthesis of new chiral ligands. Efforts are underway to elucidate the mechanistic details of this addition reaction and to disclose the exact structure of the active species. Moreover, we are planning to synthesize other similar bidentate C_2-symmetric chiral phosphoramides in order to seek out more effective and stereoselective chiral ligands and to utilize these novel chiral ligands to the other catalytic asymmetric reactions.

3. Experimental

3.1. General

Mps were obtained with a Yanagimoto micro melting point apparatus and are uncorrected. Optical rotations were determined in a solution of $CHCl_3$ at 20°C by using a Perkin–Elmer 241 MC polarimeter; $[\alpha]_D$ values are given in units of 10^{-1} deg cm^2 g^{-1}. ^{1}H NMR spectra were recorded on a Bruker AM-300 spectrometer for solution in $CDCl_3$ with tetramethylsilane (TMS) as internal standard; *J* values are in hertz. Mass spectra were recorded with an HP-5989 instrument and HRMS was measured by a Finnigan MA+ mass spectrometer. Organic solvents used were dried by standard methods when necessary. All solid compounds reported in this paper gave satisfactory CHN microanalyses with an Italian Carlo–Erba 1106 analyzer. Commercially obtained reagents were used without further purification. All reactions were monitored by TLC with Huanghai $60F_{254}$ silica gel coated plates. Flash column chromatography was carried out using 300–400 mesh silica gel at increased pressure. All ethylation experiments were performed under argon using standard Schlenk techniques. The optical purities of *sec*-alcohols were determined by HPLC analysis using a chiral stationary phase column (column, Daicel Co. Chiralcel OD and OJ; eluent, 100:0.5–2 hexane–2-propanol mixture; flow rate, 1.0 ml min^{-1}; detection, 254 nm light) and absolute configuration of the major enantiomer was assigned according to the sign of the specific rotation.

3.2. Preparation of chiral phosphoramide *4*

To a solution of (1*R*,2*R*)-(−)-1,2-diaminocyclohexane (182 mg, 1.60 mmol) and diisopropylethylamine (724 mg, 5.60 mmol) in dichloromethane was added diphenylphosphinic chloride (757 mg, 3.20 mmol) at −30°C. After stirring of the mixture for 6 h, the reaction mixture was washed with 3% aq. HCl, water, 10% Na_2CO_3 and brine and the product was extracted with ether. The extract was dried over $MgSO_4$, and then evaporated under reduced pressure. The residue was purified by silica gel column chromatography to give the compound **4** (740 mg, 90%). Mp 196–198°C; $[\alpha]_D$ +40.5 (*c* 1, $CHCl_3$); δ_H ($CDCl_3$) 1.0–1.20 (2H, m, CH_2), 1.22–1.49 (2H, m, CH_2), 1.50–1.72 (2H, m, CH_2), 1.80–2.10 (2H, m), 2.90–3.10 (2H, m), 4.40–4.60 (2H, m), 7.30–7.40 (4H, m, Ar), 7.40–7.60 (8H, m, Ar), 7.70–7.90 (4H, m, Ar), 7.95–8.12 (4H, m, Ar); MS (EI) *m/z* (%): 514 (M^+, 5.4), 313 (50), 297 (40), 270 (45), 201 (100). Found: C, 70.17; H, 6.30; N, 5.40%. HRMS (EI) *m/z*: 514.1961 (M^+); $C_{30}H_{32}N_2O_2P_2$ requires: C, 70.03; H, 6.27; N, 5.44%; M, 514.1939.

3.3. Preparation of chiral thiophosphoramide *5*

This compound was prepared in the same manner as that described above. To a solution of (1*R*,2*R*)-(−)-1,2-diaminocyclohexane (158 mg, 1.38 mmol) and diisopropylethylamine (536 mg, 4.15 mmol) in

dichloromethane was added diphenylthiophosphinic chloride (702 mg, 2.78 mmol) to give **5** as a colorless solid (693 mg, 92%). Mp 84–85°C; $[\alpha]_D$ +18.9 (*c* 1.3, $CHCl_3$); δ_H ($CDCl_3$) 0.80–1.72 (6H, m, CH_2), 1.80–2.00 (2H, m), 3.20–3.45 (2H, m), 3.90–4.20 (2H, m), 7.20–7.60 (12H, m, Ar), 7.70–7.90 (4H, m, Ar), 7.95–8.12 (4H, m, Ar); MS (EI) *m/z* (%): 547 (MH^+, 5.4), 513 (5.4), 328 (59.7), 313 (90.3), 217 (100). Found: C, 65.87; H, 5.81; N, 5.20%. HRMS (EI) *m/z*: 546.1499 (M^+). $C_{30}H_{32}N_2S_2P_2$ requires: C, 65.91; H, 5.90; N, 5.12%; 546.1482.

3.4. Typical reaction procedure

To a solution of phosphoramide **4** (103 mg, 0.2 mmol) in dichloromethane was added titanium(IV) isopropoxide (398 mg, 1.4 mmol) at room temperature. After stirring of the mixture for 0.5 h, *p*-chlorobenzaldehyde (140 mg, 1.0 mmol) was added into the reaction solution and the reaction mixture was cooled to −50°C. Then diethylzinc (1.80 ml, 1.80 mmol, 1 M solution in hexane) was added into the solution and the reaction mixture was stirred for 48 h at −20°C. The reaction was quenched by 5% aq. HCl and the product was extracted with ether. The organic layer was washed with brine and dried over $MgSO_4$, and then evaporated under reduced pressure. The residue was purified by silica gel TLC to give the optically active 1-(*p*-chlorophenyl)propan-1-ol (162 mg, 95%).

Acknowledgements

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