Pergamon

Tetrahedron 54 (1998) 10295–10307

TETRAHEDRON

An External Chiral Amidophosphine Ligand for Asymmetric Conjugate Addition of Organocopper

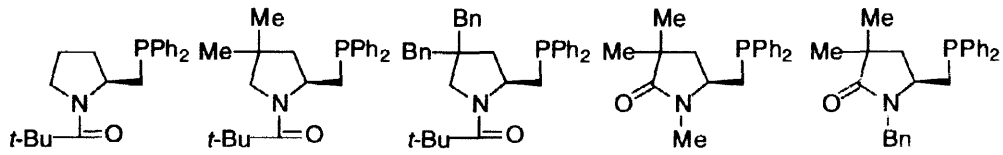
Yuichi Nakagawa, Motomu Kanai,† Yasuo Nagaoka, and Kiyoshi Tomioka*

Graduate School of Pharmaceutical Sciences, Kyoto University, Sakyo, Kyoto 606-8501, Japan
† Graduate School of Pharmaceutical Sciences, University of Tokyo, Bunkyo-ku, Tokyo 113, Japan

Received 5 January 1998; revised 17 January 1998; accepted 2 February 1998

Abstract: Two types of external, chiral amidophosphine ligands, **1-5**, were prepared. Examination of their behavior in an asymmetric conjugate addition reaction of organocuprate revealed the possibility for steric tuning to realize high selectivity.

We have been involved in the development of external, chiral ligands for asymmetric reaction of organometallics[1] and succeeded in the development of highly efficient chiral ether or amino ether ligands for organolithium,[2] lithium ester enolate,[3] lithium phosphonate,[4] and lithium thiophenolate.[5] A chiral amidophosphine **1** was developed for organocuprate to provide an efficient asymmetric carbon-carbon bond-forming reaction with α,β-unsaturated carbonyl compounds.[6] In contrast to chirally modified heterocuprates,[7] metal-selective coordination is essential for the design of external chiral ligands for organocopper.[8] Powerful external ligands bearing chiral phosphorus have been reported.[9] Other than phosphorus,[10] sulfur is a known coordinating atom to copper, and sulfur-based ligands have been used for the efficient reaction of organocopper.[11] The amidophosphine **1** was designed by us based on the concept of metal-differentiating coordination, whose phosphorus and carbonyl oxygen atoms selectively coordinate to copper and lithium or magnesium of the organocopper species, respectively. The ligand **1** was improved to the dimethyl version **2** based on the coordination model to give the conjugate addition product in up to 90% ee.[6] We describe herein the synthesis and reaction of the dibenzyl amidophosphine **3** together with the lactam ligands **4** and **5**.



1 **2** **3** **4** **5**

SYNTHESIS OF AMIDOPHOSPHINE LIGANDS 2 AND 3

We designed **2** based on the metal-selective coordination model shown in the figure **1**. The dimethyl substituent in **2** blocks the bottom face of the dimer structure of lithium dimethylcuprate and improved the

E-mail: tomioka@pharm.kyoto-u.ac.jp; Fax: 81 75 753 4604

0040-4020/98/$ - see front matter
PII: S0040-4020(98)00485-2

enantioselectivity in up to 90% (Figure 1).[6] Therefore we examined the more bulky dibenzyl version **3**. The synthesis of **3** was carried out using the similar way as that of **2** as shown in the scheme **1**. The ligands **4** and **5** were also prepared from L-Glu as shown in Scheme **2**.

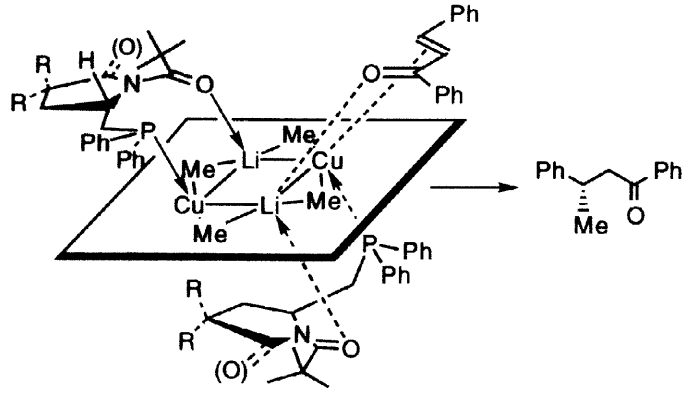
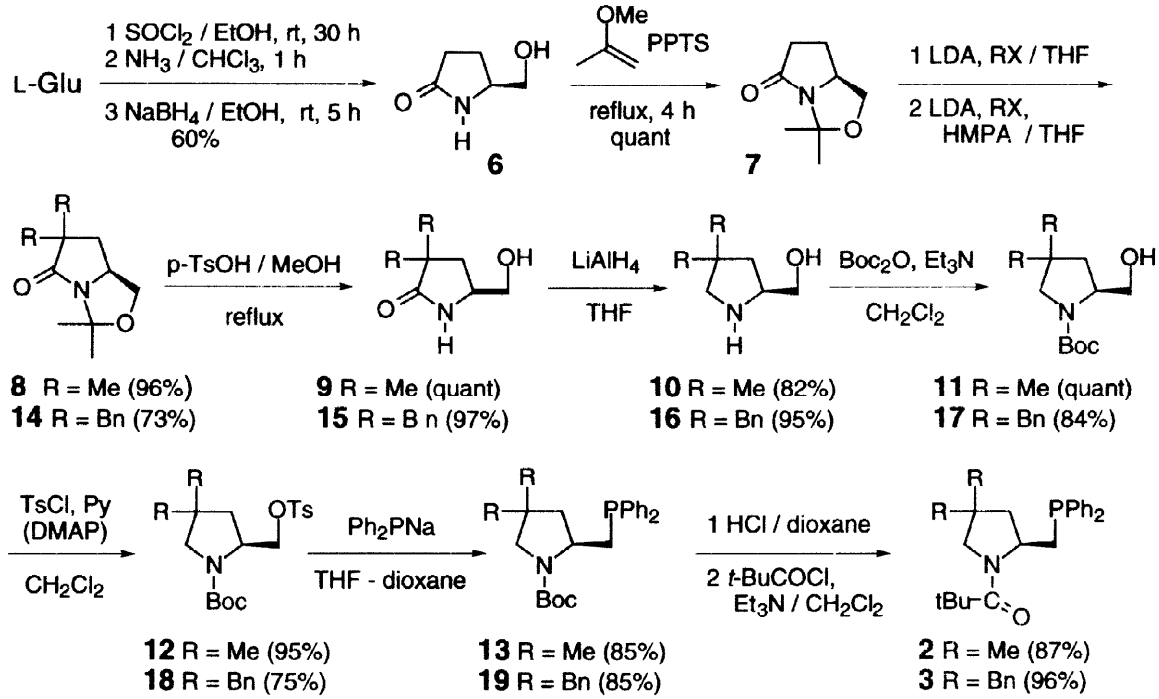


Figure 1. The metal selective coordination model for ligand-organocuprate.

The dimethyllactam **9** was prepared from L-glutamic acid according to the reported procedure.[12] Reduction to pyrrolidine, protection of amine, and diphenylphosphination of the tosylate gave the dimethylamidophosphine **2**. Application of the same sequence as **2** from **7** gave without event the dibenzyl-amidophosphine **3**.



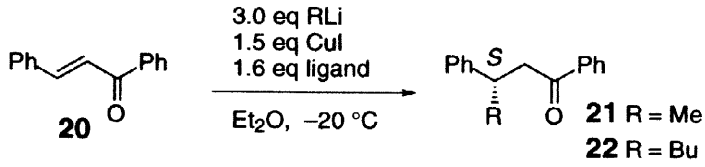
Scheme 1. Synthesis of **2** and **3** from L-Glutamic acid.

REACTION MEDIATED BY CHIRAL AMIDOPHOSPHINES 2 AND 3

The most effective ligand among **1-3** was **2** in the reaction of lithium dimethylcuprate, prepared from CuI and low halide methyllithium, with chalcone **20** to give (+)-*S*-**21** in 90% ee as show in Table 1.[13] The ligand **3** bearing the most bulky dibenzyl-pyrrolidine moiety was not so beneficial and mediated the reaction

to give the selectivity of 72%. These ligands were not effective for the reaction with dibutylcuprate to give the rather poor selectivity of 11-24%.

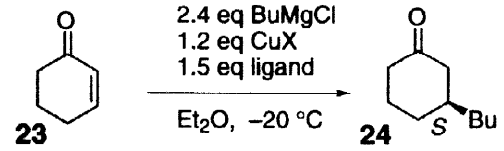
Table 1. Asymmetric Reaction of R_2CuLi with Chalcone **20** Mediated by **1-3**



run	ligand	R	yield/%	ee/%	*R/S*
1	**1**	Me	79	84	*S*
2	**2**	Me	99	90	*S*
3	**3**	Me	97	72	*S*
4	**1**	Bu	97	24	*S*
5	**2**	Bu	95	11	*S*
6	**3**	Bu	99	23	*S*

The reaction of butylmagnesium chloride with cyclohexenone **23** giving **24**[14] was dependent on the combination of the ligands **1-3** and copper source (Table 2). Generally, the bulky amidophosphines **2** and **3** gave the higher enantioselectivity of over 80% with CuI than CuCN. The highest enantioselectivity of 96% was realized with **2** and CuI.

Table 2. Asymmetric Reaction of $R_2CuMgCl$ with Cyclohexenone **23** Mediated by **1-3**



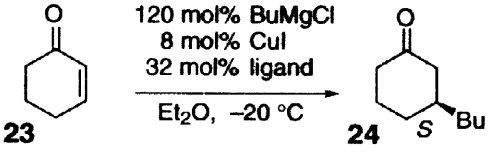
run	ligand	X	yield/ %	ee/ %	*R/S*
1	**1**	CN	94	89	*S*
2	**1**	I	91	86	*S*
3	**2**	CN	51	51	*S*
4	**2**	I	96	96	*S*
5	**3**	CN	62	31	*S*
6	**3**	I	94	80	*S*

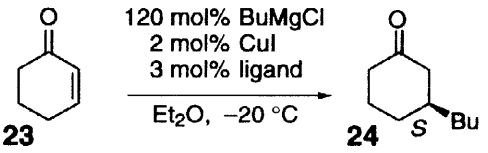
The catalytic reaction with 8 mol% of CuI and 32 mol% of the ligands proceeded smoothly at –78 °C to give 3-butylcyclohexanone (Table 3). The efficiency of **2** (32 mol%) is the best to give *S*-**24** in 92% ee (run 2). However, 2 mol% of CuI and 3 mol% of the ligands gave the poorer enantioselectivity, 40, 27, and 12% ees with **2**, **1**, and **3**, respectively (run 4-6).

The degree of enantioselectivity demonstrated by the ligands is presumably attributable to the efficiency in blocking the down face of the chelate shown in Figure 1. The dibenzyl group of **3** would destabilize the chelation due to too much bulkiness. The ligand **1** would form chelation, which needs much more bulkiness to block the down face attack. The dimethyl group of **2** would best meet such circumstances.

The poorer selectivity demonstrated by 3 mol% of the ligands is probably due to the kick out of the ligands from coordination to copper, and the reaction takes place with copper species free from the ligands.

Table 3 Asymmetric Reaction of Butylmagnesium Chloride Catalyzed by Ligands **1-3**



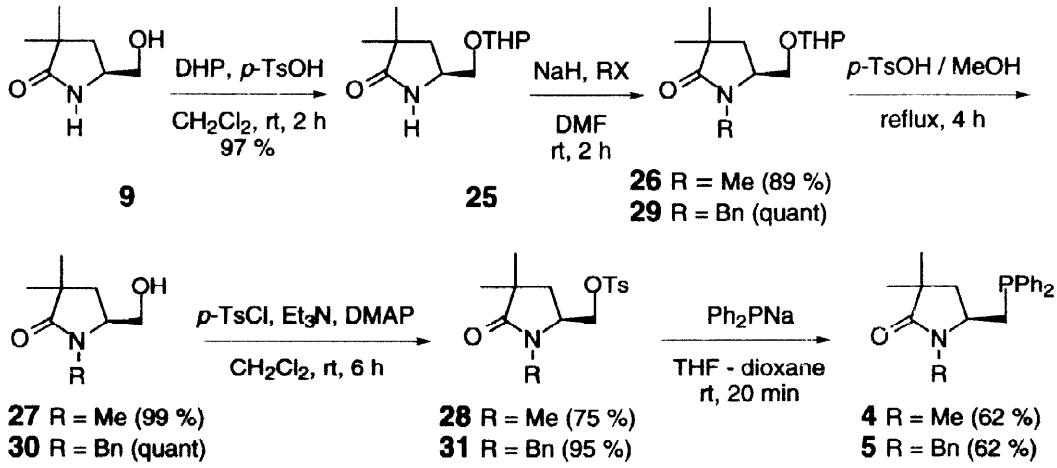


run	ligand	yield/ %	ee/ %	*R/S*
1	**1**	87	80	*S*
2	**2**	82	92	*S*
3	**3**	80	75	*S*

run	ligand	yield/ %	ee/ %	*R/S*
4	**1**	83	27	*S*
5	**2**	60	40	*S*
6	**3**	72	12	*S*

SYNTHESIS OF LACTAMPHOSPHINE LIGANDS 4 AND 5

The synthesis of lactam version with *N*-methyl and *N*-benzyl groups was carried out starting from **9** as shown in the scheme 2.



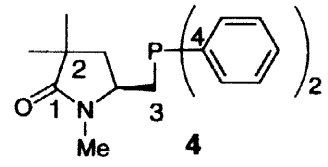
Scheme 2. Synthesis of **4** and **5**.

REACTION MEDIATED BY CHIRAL LACTAMPHOSPHINES 4 AND 5

The direction of the carbonyl oxygen affects enantioselectivity, and the ligand **4** gave the product in marginal ee as shown in Table 5 (run 3, 4). However, as shown in Table 4, ^{13}C-NMR large chemical shift changes of **4** in toluene-ether (0.1 M) were observed at the carbonyl and its adjacent carbons upon addition of 1 eq $LiClO_4$, and at the carbons bonded to phosphorus upon addition of 1 eq CuBr, indicating that **4** maintains metal-selective coordination. The more bulky *N*-substituent of **5** may cause failure in the carbonyl oxygen coordination to lithium as has been shown in the reaction of **1** in THF solvent which gives the opposite enantiofacial selection (Table 5, run 1, 2).

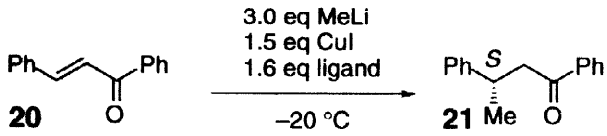
The N-benzyl amidophosphine **5** showed enantioselection of 34% ee in toluene solvent as shown in Table 5. It is indicative that the absolute configuration of the addition product **21** is the same *R* as that of the product **21** obtained with **1** in THF solvent. In THF solvent, coordination of lithium cation to the carbonyl oxygen of **1** was shown to be absent by NMR study.[6]

Table 4 CMR Chemical shift change of **4**



	δ (ppm)	+ $LiClO_4$ Δδ (ppm)	+$CuBr{\bullet}SMe_2$ Δδ (ppm)
C-1	178.3	+ 2.3	+ 0.1
C-2	40.0	+1.0	+ 0.3
C-3	34.7	- 0.7	- 1.6
C-4	138.4	+ 0.3	- 5.8
	139.3	+ 0.2	- 4.7

Table 5. Asymmetric Reaction of Me_2CuLi with Chalcone **20** Mediated by **1**, **4**, and **5**

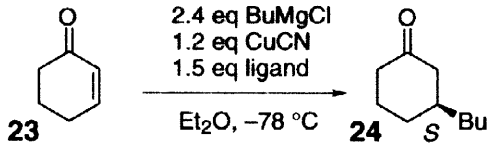


20 **21**

run	ligand	solvent	yield/ %	ee/ %	*R/S*
1	**1**	Et_2O	79	84	*S*
2	**1**	THF	72	50	*R*
3	**4**	Et_2O	90	1	*R*
4	**4**	THF	98	1	-
5	**5**	toluene	86	34	*R*
6	**5**	THF	99	0	-

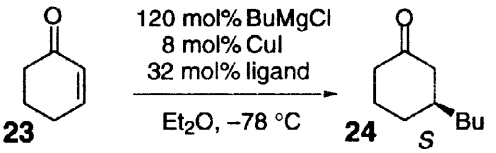
The reaction of butylmagnesium chloride with cyclohexenone was catalyzed by **4** and **5** as shown in Table 6. The *N*-methyl version **4** gave the product in 38% ee. It is interesting that catalytic reaction with **4** gave the higher ee of 48%, though the yield was not so high. The *N*-benzyl ligand **5** was not effective.

Table 6 Asymmetric Reaction of Butylmagnesium Chloride Catalyzed by Ligands **1**, **4**, and **5**



23 **24**

run	ligand	yield/ %	ee/ %	*R/S*
1	**1**	94	89	*S*
2	**4**	83	38	*S*
3	**5**	84	9	*R*



23 **24**

run	ligand	yield/ %	ee/ %	*R/S*
4	**1**	87	80	*S*
5	**4**	52	48	*S*
6	**5**	67	6	*R*

Thus, appropriate steric tuning of the amidophosphine is a promising guide for the design of external, chiral ligands for an organocopper reagent.

Acknowledgment: We gratefully acknowledge financial support from Japan Society for Promotion of Science (RFTF-96P00302), the Ministry of Education, Science, Sports and Culture, and the Science and Technology Agency, Japan, and SUNBOR.

EXPERIMENTAL[15]

(*S*)-(+)-(4,4-dimethylpyrrolidin-2-yl)methan-1-ol 10

A suspension of $LiAlH_4$ (798 mg, 21 mmol) and lactam **9** (500 mg, 3.5 mmol) in 30 mL of THF was stirred under reflux for 8 h. After successive addition of 0.8 mL of water, 0.8 mL of 10% aq NaOH, and 2.4 mL of water, and filtration, the filtrate was concentrated to give a yellow oil (384 mg). Distillation at 10 mmHg and 99 °C gave **10** (82%) as a colorless oil of $[\alpha]^{20}_D$ +29.5 (c 2.46, toluene).

PMR δ: 1.04 and 1.08 (each 3H, s, CH_3), 1.24 (1H, dd, J = 6.8, 12.5 Hz, CH_2), 1.61 (1H, dd, J = 7.0, 12.5 Hz, CH_2), 2.64 (2H, s, CH_2N), 3.35-3.62 (3H, m, CH_2O, CH), 4.2 (2H, brs, OH, NH). CMR δ: 27.1, 27.2, 39.4, 42.4, 59.5, 60.0, 64.8. IR (nujol): 3300, 1080 cm^{-1}. Rf 0.24 (MeOH + 5% Et_3N). MS *m/z*: 129 (M^+). Anal: Calcd. for $C_7H_{15}NO$: C, 65.07; H, 11.70; N, 10.84. Found: C, 64.74; H, 12.03; N, 10.62.

(*S*)-(–)-*tert*-butyl 2-(hydroxymethyl)-4,4-dimethylpyrrolidinecarboxylate 11

A solution of **10** (200 mg, 1.6 mmol), Boc_2O (340 mg, 1.6 mmol), and Et_3N (0.22 mL, 1.6 mmol) in CH_2Cl_2 (4 mL) was stirred at rt for 2 h. After addition of 2 mL of water, the mixture was extracted with CH_2Cl_2 (10 mL x 3). The extract was washed with 10 mL of satd $NaHCO_3$, and 10 mL of brine, and then dried over Na_2SO_4. Concentration and silica gel column chromatography (PhH/AcOEt = 2/1) followed by distillation (0.3 mmHg, 102 °C) gave **11** (388 mg, quant) as a colorless oil of $[\alpha]^{25}_D$ –28.9 (c 1.48, $CHCl_3$).

PMR δ: 1.01 and 1.07 (each 3H, s, CH_3), 1.27 (1H, dd, J = 10.2, 12.5 Hz, CH_2), 1.47 (9H, s, *t*-Bu), 1.78 (1H, dd, J = 7.3, 12.5 Hz, CH_2), 2.98 and 3.29 (each 1H, d, J = 10.8 Hz, CH_2N), 3.60-3.62 (2H, m, CH_2O), 3.96-4.02 (1H, m, CH), 5.21 (1H, brs, OH). CMR δ: 25.9, 26.1, 28.4, 36.6, 42.6, 60.1, 60.4, 67.8, 80.3, 157.4. IR (nujol): 3400, 1680 cm^{-1}. Rf 0.72 (PhH/AcOEt = 1/1). MS *m/z*: 229 (M^+). Anal: Calcd. for $C_{12}H_{23}NO_3$: C, 62.85; H, 10.11; N, 6.11. Found: C, 62.70; H, 10.31; N, 5.91.

(*S*)-(–)-*tert*-butyl 4,4-dimethyl-2-[((4-methylphenyl)sulfonyloxy)methyl]pyrrolidinecarboxylate 12

A solution of **11** (380 mg, 1.7 mmol), *p*-TsCl (382 mg, 2.0 mmol) in a mixture of CH_2Cl_2 (1 mL) and pyridine (2 mL) was stirred at –2 °C for 16 h. After addition of 2 mL of brine, the mixture was extracted with CH_2Cl_2 (10 mL x 4). The extract was washed with 10 mL of 10% $CuSO_4$, 10 mL of satd $NaHCO_3$, 10 mL of water, and 10 mL of brine, and then dried over Na_2SO_4. Concentration and silica gel column chromatography (PhH/AcOEt = 2/1) gave **12** (620 mg, 95%) as a colorless solid of mp 85 °C (ether) and $[\alpha]^{20}_D$ –43.9 (c 1.04, $CHCl_3$).

PMR δ: 0.90 and 1.02 (each 3H, s, CH_3), 1.33, 1.40 (9H, s, *t*-Bu), 1.70 (m, 2H, CH_2), 2.41 (3H, s, Ar CH_3), 2.82 (1H, d, J = 9.0 Hz CH_2N), 3.30 (1H, brd, J = 9.0 Hz, CH_2N), 3.73-4.30 (3H, m, CH_2O, CH), 7.27 and 7.70 (each 2H, d, J = 8.2 Hz, Ar). CMR δ: 21.5, 25.6, 28.2, 26.2, 36.8, 37.2, 41.4, 42.8, 55.3, 58.9, 59.7, 70.0, 70.7, 79.4, 79.7, 127.8, 129.7, 132.7, 144.6, 154.2. IR (nujol): 1680 1170 cm^{-1}. Rf 0.72 (PhH/AcOEt = 1/1). MS *m/z*: 383 (M^+). Anal: Calcd. for $C_{19}H_{29}NO_5S$: C, 59.51; H, 7.62; N, 3.65. Found: C, 59.52; H, 7.48; N, 3.48.

(*S*)-(–)-*tert*-butyl 2-[(diphenylphosphino)methyl]-4,4-dimethylpyrrolidinecarboxylate 13

Small pieces of sodium (200 mg, 8.8 mmol) were added at 0 °C over 5 min to a solution of Ph_2PCl (380 μL, 2.1 mmol) in 2 mL of 1,4-dioxane and stirred under reflux for 6 h. A solution of the tosylate **12** (540 mg, 1.4 mmol) in 2 mL of THF was added at 0 °C. After stirring for 20 min, the mixture was filtered through celite to afford a yellow oil (734 mg). Silica gel column chromatography (PhH/ether = 100/1) gave **13** (471 mg, 85%) as colorless plates of mp 156 °C ($CHCl_3$) and $[\alpha]^{25}_D$ –21.2 (c 0.95, $CHCl_3$).

PMR δ: 0.9 and 1.06 (each 3H, s, CH_3), 1.42 (9H, s, *t*-Bu), 1.63 (1H, dd, *J* = 4.0, 7.8 Hz, CH_2), 1.92-2.20 (2H, m, CH_2, CH_2O), 2.90-2.94 (1H, m, CH_2O), 3.25 and 3.42 (each 1H, d, *J* = 6.9 Hz, CH_2N), 3.87-3.91 (1H, m, CH), 7.20-7.65 (10H, m, Ar). CMR δ: 26.0, 26.2, 28.6, 34.0 (d, *J* = 14.3 Hz), 35.7, 37.3 (d, *J* = 12.2 Hz), 46.6, 47.5 (d, *J* = 9.8 Hz), 55.1 (d, *J* = 22.2 Hz), 58.6, 59.7, 78.9, 79.4, 128.5, 128.7, 132.2, 133.5, 134.5, 135.6, 138.3, 139.2, 139.4, 154.8. IR (nujol): 1680 cm^{-1}. Rf 0.48 (hex/AcOEt = 19/1). MS *m/z*: 397 (M^+). Anal: Calcd. for $C_{24}H_{32}NO_2P$: C, 72.52; H, 8.11; N, 3.52. Found: C, 72.32; H, 7.91; N, 3.32.

(*S*)-(–)-1-[2-((diphenylphosphino)methyl)-4,4-dimethylpyrrolidinyl]-2,2-dimethylpropan-1-one 2

A 5.1 N HCl in 1,4-dioxane (50 mL, 256 mmol) was added at 0 °C over 20 min to a solution of **13** (2.1 g, 13 mmol) in 1,4-dioxane (50 mL). The mixture was stirred at rt for 1.5 h and then concentrated. The mixture was treated three times with PhH and concentrated to afford white solid (5.5 g).

A solution of the above solid, Et_3N (2.1 mL, 56 mmol), and pivaloylchloride (7.7 mL, 17 mmol) in 20 mL of CH_2Cl_2 was stirred at 0 °C for 20 min. After addition of 10 mL of 10% Na_2CO_3, the mixture was extracted with CH_2Cl_2 (10 mL x 4). The extract was washed with 10 mL of 10% HCl, 10 mL of satd $NaHCO_3$, 10 mL of water, and 10 mL of brine, and then dried over Na_2SO_4. Concentration and silica gel column chromatography (Hex/AcOEt = 9/1) followed by distillation (0.2 mmHg, 200 °C) gave **2** (4.3 g, 87%) as a colorless gum of $[\alpha]^{25}_D$ +59.8 (c 0.95, $CHCl_3$).

PMR δ: 0.90 and 1.11 (each 3H, s, CH_3), 1.16 (9H, s, *t*-Bu), 1.67 (1H, dd, *J* = 9.6, 12.5 Hz, CH_2), 1.91 (1H, dd, *J* = 7.6, 12.5 Hz, CH_2), 2.09 (1H, dd, *J* = 9.8, 12.7 Hz, CH_2P), 3.35 (1H, ddd, *J* = 3.2, 6.0, 12.7 Hz, CH_2P), 3.15 (1H, d, *J* = 10.2 Hz, CH_2N), 3.55 (1H, d, *J* = 10.2 Hz, CH_2N), 4.25-4.48 (1H, m, CH), 7.20-7.65 (10H, m, Ar). CMR δ: 25.5, 25.6, 27.5, 33.6 (d, *J* = 12.2 Hz), 38.6, 38.7, 44.6 (d, *J* = 9.8 Hz), 56.3 (d, *J* = 17.1 Hz), 60.6, 128.2, 128.3, 128.4, 128.5, 132.5, 132.8, 133.1, 137.3, 137.4, 139.2, 139.3, 176.6. IR (neat): 1640 cm^{-1}. Rf 0.60 (PhH/ether = 20/1). MS *m/z*: 381 (M^+). Anal: Calcd. for $C_{24}H_{32}NOP$: C, 75.56; H, 8.45; N, 3.67. Found: C, 75.36; H, 8.43; N, 3.68.

(*S*)-(+)-1-aza-3,3-bisbenzyl-8,8-dimethyl-7-oxabicyclo[3.3.0]octan-2-one 14

A solution of **7** (4.0 g, 26 mmol) in 20 mL of THF was added at –78 °C over 20 min to a solution of LDA (31 mmol) in THF (30 mL) and stirred for 0.5 h. After addition of benzylbromide (3.7 mL, 31 mmol), the mixture was stirred at –78 °C for 1 h. A mixture of LDA (34 mmol) and HMPA (6.0 mL, 34 mmol) in THF (32 mL) was added. After stirring for 40 min, the whole was treated with benzylbromide (4.0 mL, 34 mmol) and stirred at –78 °C for 3 h. After addition of satd NH_4Cl (30 mL), the mixture was extracted with benzene. The extract was washed successively with 30 mL of 10% HCl, 30 mL of $NaHSO_3$, and 40 mL of brine, and then dried over Na_2SO_4. Concentration and silica gel column chromatography (Hex/AcOEt = 10/1) gave **14** (6.4 g, 73%) as colorless needles of mp 89 °C (ether) and $[\alpha]^{25}_D$ +75.9 (c 1.05, $CHCl_3$).

PMR δ: 1.19 and 1.45 (each 3H, s, CH_3), 1.70 (1H, dd, *J* = 7.6, 13.1 Hz, CH_2) 1.88 (1H, dd, *J* = 6.8, 13.1 Hz, CH_2), 2.55-2.71 (4H, m, CH_2Ph, CH_2O, CH), 3.12 (1H, d, *J* = 13.2 Hz, CH_2Ph), 3.33 (1H, d, *J* = 13.2 Hz, CH_2Ph), 3.57 (1H, dd, *J* = 4.9, 7.3 Hz, CH_2O), 7.25 (10H, s, ArH). CMR δ: 23.7, 26.0, 29.5, 43.6, 44.8, 57.2, 58.3, 70.0, 90.7, 126.6, 126.8, 128.1, 130.0, 130.6, 137.1, 137.6, 172.4. IR (nujol): 1690 cm^{-1}. Rf 0.80 (Hex/AcOEt = 1/1). MS *m/z*: 335 (M^+). Anal: Calcd. for $C_{22}H_{25}NO_2$: C, 78.80; H, 7.51; N, 4.18. Found: C, 79.0; H, 7.56; N, 3.98.

(*S*)-(+)-3,3-bisbenzyl-5-(hydroxymethyl)pyrrolidin-2-one 15

A solution of **14** (1.0 g, 3.0 mmol) and *p*-TsOH (6.0 mg, 0.03 mmol) in MeOH (20 mL) was stirred

under reflux for 1 h, and then concentrated. Silica gel column chromatography ($CHCl_3$/MeOH = 40/1) gave **15** (857 mg, 97%) as colorless prisms (AcOEt) of mp 136 °C and $[\alpha]^{25}_D$ +34.5 (c 1.0, $CHCl_3$).

PMR δ: 1.63 (1H, dd, *J* = 6.8, 13.6 Hz, CH_2), 1.98 (1H, dd, *J* = 7.3, 13.6 Hz, CH_2), 2.58-2.68 (4H, m, $PhCH_2$, CH_2O), 3.05 (1H, d, *J* = 12.9 Hz, $PhCH_2$), 3.14 (1H, d, *J* = 13.5 Hz, $PhCH_2$), 3.18-3.26 (1H, m, CH), 3.72 (1H, brs, OH), 3.96 (1H, brs, NH), 7.16-7.28 (10H, m, Ar). CMR δ: 29.5, 43.3, 44.2, 51.0, 53.0, 66.1, 126.6, 126.8, 128.2, 130.0, 130.4, 137.0, 137.4, 180.7. IR (nujol): 3450, 3250, 1675 cm^{-1}. Rf 0.12 (hex/AcOEt = 1/1). MS *m/z*: 295 (M^+). Anal: Calcd. for $C_{19}H_{21}NO_2$: C, 77.26; H, 7.17; N, 4.74. Found: C, 77.12; H, 7.24; N, 4.73.

(*S*)-(+)-(4,4-dibenzylpyrrolidin-2-yl)methan-1-ol 16

A solution of **15** (30 g, 0.102 mol) in 200 mL of THF was added at 0 °C over 3 h to a suspension of $LiAlH_4$ (23 g, 0.612 mol) in 200 mL of THF and stirred at rt for 4 d. Usual workup and alumina gel column chromatography ($CHCl_3$/MeOH = 9/1) gave **16** (27.1 g, 95%) as colorless gum of $[\alpha]^{25}_D$ +34.5 (c 1.15, $CHCl_3$).

PMR δ: 1.61 (1H, dd, *J* = 6.9 Hz, 13.8 Hz, CH_2), 1.95 (1H, dd, *J* = 8.3, 13.8 Hz, CH_2), 2.56-2.67 (6H, m, CH_2Ph, CH_2O, CH_2N), 3.07 (1H, d, *J* = 12.9 Hz, CH_2Ph), 3.16 (1H, d, *J* = 12.9 Hz, CH_2Ph), 3.18-3.25 (1H, m, CH), 3.99 (1H, brs, OH), 7.07 (1H, brs, NH), 7.18-7.32 (10H, m, Ar). IR (nujol): 3300 cm^{-1}. Rf 0.44 (MeOH + 1% Et_3N). MS *m/z*: 281 (M^+). Anal: Calcd. for $C_{19}H_{23}NO$: C, 81.10; H, 8.24; N, 4.98. Found: C, 81.11; H, 8.27; N, 4.73.

(*S*)-(–)-*tert*- butyl 4,4-bisbenzyl-2-(hydroxymethyl)pyrrolidinecarboxylate 17

Prepared as a pale yellow gum of $[\alpha]^{25}_D$ +20.5 (c 2.40, $CHCl_3$) in 84% yield from **16** by the same procedure for **11**.

PMR δ: 1.39 and 1.49 (9H, s, *t*-Bu), 1.34-1.42 (1H, m, CH_2), 1.83 (1H, dd, *J* = 8.3, 12.6 Hz, CH_2), 2.62-2.72 (4H, m, CH_2N, $PhCH_2$), 3.41-3.55 (4H, m, CH_2O, $PhCH_2$), 3.83-3.86 (1H, m, CH), 50.8 (1H, brs, OH), 7.14-7.32 (10H, m, Ar). CMR δ: 27.2, 28.3, 37.0, 37.8, 41.8, 42.9, 44.7, 53.9, 54.2, 59.3, 67.5, 80.2, 126.3, 126.4, 127.9, 128.0, 130.2, 130.4, 137.1, 137.6, 156.7. IR (nujol): 3300, 1680 cm^{-1}. Rf 0.52 (PhH/AcOEt = 4/1). MS *m/z*: 381 (M^+). Anal: Calcd. for $C_{24}H_{31}NO_3$: C, 75.56; H, 8.19; N, 3.67. Found: C, 75.42; H, 8.25; N, 3.66.

(*S*)-(–)-*tert*-butyl 4,4-bisbenzyl-2-[((4-methylphenyl)sulfonyloxy)methyl]pyrrolidinecarboxylate 18

Prepared as colorless crystals of mp 97 °C (ether) and $[\alpha]^{25}_D$ –21.2 (c 5.0, $CHCl_3$) in 75% yield from **17** by the same procedure for **12**.

PMR δ: 1.29 and 1.43 (9H, s, *t*-Bu), 1.76-2.04 (2H, m, CH_2), 2.43 and 2.56 (3H, s, CH_3), 2.70 (2H, s, CH_2N), 2.98 (1H, dd, *J* = 7.9, 11.0 Hz, CH_2O), 3.40-3.52 (2H, m, $PhCH_2$, CH_2O), 3.62-3.73 (1H, m, $PhCH_2$), 3.81-4.22 (3H, m, $PhCH_2$, CH), 7.10-7.28 (12H, m, Ar), 7.68 (2H, brd, *J* = 5.6 Hz, Ar). CMR δ: 21.5, 28.2, 28.4, 36.9, 38.3, 42.6, 43.1, 43.9, 45.1, 45.5, 54.6, 54.8, 69.9, 70.7, 79.6, 79.8, 126.4-130.4, 132.8, 137.4, 137.7, 144.5, 144.6, 153.4, 153.6. IR (nujol): 1690, 1410 cm^{-1}. Rf 0.84 (PhH/AcOEt = 4/1). MS *m/z*: 535 (M^+). Anal: Calcd. for $C_{33}H_{37}NO_5S$: C, 69.51; H, 6.96; N, 2.61. Found: C, 69.52; H, 6.94; N, 2.41.

(*S*)-(–)-*tert*-butyl 4,4-bisbenzyl-2-[(diphenylphosphino)methyl]pyrrolidinecarboxylate 19

Prepared as white powder of $[\alpha]^{25}_D$ –52.6 (c 1.20, $CHCl_3$) in 85% yield from **18** by the same procedure for **13**.

PMR δ: 1.37 and 1.39 (9H, s, *t*-Bu), 1.68-2.06 (3H, m, CH_2, CH_2P), 2.16 (2H, s, CH_2N), 2.77-2.80

(1H, m, CH_2P), 2.99 (1H, d, J = 10.0 Hz, CH_2Ph), 3.12 (1H, d, J = 11.2 Hz, CH_2Ph), 3.47 (1H, d,J = 10.0 Hz, CH_2Ph), 3.67 (1H, d, J = 11.2 Hz, CH_2Ph), 3.83-3.95 (1H, m, CH), 7.07-7.50 (20H, m, Ar). CMR δ: 28.5, 33.8 (d, J = 13.4 Hz), 35.4 (d, J = 13.5 Hz), 41.7, 42.8, 45.2, 53.6, 54.3 (d, J = 19.6 Hz), 79.1126.2, 128.0, 128.2, 128.3, 128.4, 128.7, 130.0, 132.2, 132.5, 132.8, 133.0, 133.2, 132.5, 132.8, 133.0, 133.2, 137.6, 137.8, 137.9, 154.1. IR (nujol): 1680 cm^{-1}. Rf 0.3 (hex/AcOEt = 9/1). MS *m/z*: 549 (M^+). Anal: Calcd. for $C_{36}H_{40}NO_2P$: C, 78.66; H, 7.33; N, 2.55. Found: C, 78.67; H, 7.36; N, 2.39.

(*S*)-(–)-1-[4,4-bisbenzyl-2-((diphenylphosphino)methyl)pyrrolidinyl]-2,2-dimethylpropan-1-one 3

Prepared as colorless prisms of mp 135 °C (ether) and $[\alpha]^{25}_D$ +73.7 (c 1.15, $CHCl_3$) in 96% yield from **19** by the same procedure for **2**.

PMR δ: 1.18 (9H, s, *t*-Bu), 1.34 (1H, dd, J = 10.2, 12.5 Hz, CH_2), 1.82-1.96 (2H, m, CH_2, CH_2P), 2.53 (2H, s, CH_2N), 2.69 (1H, d, J = 10.2 Hz, CH_2Ph), 2.73 (1H, d, J = 10.6 Hz, CH_2Ph), 3.04 (1H, ddd, J = 3.2, 4.3, 12.8 Hz, CH_2P), 3.35 (1H, d, J = 10.2 Hz, CH_2Ph), 3.37 (1H, d, J = 10.6 Hz, CH_2Ph), 4.22-4.36 (1H, m, CH), 7.0-7.59 (20H, m, Ar). CMR δ: 27.7, 37.2 (d, J = 12.3 Hz), 38.9 (d, J = 8.2 Hz), 40.9 (d, J = 20.8 Hz), 46.6, 56.9, 60.3, 65.8, 126.5, 127.8, 128.2, 128.7, 130.0, 133.0, 133.2, 134.0, 134.9, 137.3, 137.5, 139.1, 139.3, 177.0. IR (nujol): 1590 cm^{-1}. Rf 0.50 (PhH/AcOEt = 9/1). MS *m/z*: 533 (M^+). Anal: Calcd. for $C_{36}H_{40}NOP$: C, 81.02; H, 7.55; N, 2.62. Found: C, 81.19; H, 7.54; N, 2.54.

3,3-dimethyl-5-(2-oxanyloxymethyl)pyrrolidin-2-one 25

A solution of **9** (1.0 g, 7.0 mmol), dihydropyrane (0.71 mL, 7.7 mmol), and *p*-TsOH (12 mg, 0.07 mmol) in CH_2Cl_2 (35 mL) was stirred at rt for 2 h. After addition of ether (20 mL), the mixture was washed with satd $NaHCO_3$ (10 mL) and brine (10 mL), and then dried over Na_2SO_4. Concentration and silica gel column chromatography ($CHCl_3$/MeOH = 9/1) gave **25** (1.53 g, 97%) as white powders of mp 55-62 °C.

PMR δ: 1.19 (6H, s, CH_3), 1.40-2.19 (8H, m, CH_2), 3.41-3.91 (3H, m, CH_2O, CH), 3.85-4.03 (2H, m, OCH_2), 4.53-4.66 (1H, m, OCH), 6.40 (1H, brs, NH). CMR δ: 19.2, 19.3, 25.0, 25.1, 25.3, 30.3, 30.4, 38.9, 40.0, 40.1, 50.4, 62.2, 62.3, 71.9, 99.0, 99.3, 182.2. IR (nujol): 3200, 1700, 1260, 1040 cm^{-1}. Rf 0.48 ($CHCl_3$/MeOH = 9/1). MS *m/z*: 227 (M^+). Anal: Calcd. for $C_{12}H_{21}NO_3$: C, 63.41; H, 9.31; N, 6.16. Found: C, 63.32; H, 9.38; N, 5.98.

1,3,3-trimethyl-5-(2-oxanyloxymethyl)pyrrolidin-2-one 26

Prepared as a colorless oil of bp 110 °C at 2 mmHg in 89% yield using methyliodide from **25** by the same procedure for **29**.

PMR δ: 1.13 and 1.20 (each 3H, s, CH_3), 1.56-2.01 (8H, m, CH_2), 2.89 (3H, s, NCH_3), 3.38-3.75 (3H, m, CH_2O, CH), 3.80-3.96 (2H, m, OCH_2), 4.60-4.64 (1H, m, OCH); CMR δ: 19.1, 25.2, 25.3, 25.7, 28.4, 30.2, 34.1, 39.8, 56.1, 62.0, 68.5, 98.7, 98.9, 179.8. IR (neat): 1680, 1280, 1050 cm^{-1}. Rf 0.32 (PhH/AcOEt = 1/1). MS *m/z*: 241 (M^+). Anal: Calcd. for $C_{13}H_{23}NO_3$: C, 64.70; H, 9.61; N, 5.80. Found: C, 63.86; H, 9.75; N, 6.06.

3,3-dimethyl-5-(2-oxanyloxymethyl)-1-benzylpyrrolidin-2-one 29

A solution of **25** (16.0 g, 70.8 mmol) in 80 mL of DMF was added dropwise at 0 °C to a suspension of NaH (4.25 g, 106 mmol) in 160 mL of DMF and the mixture was stirred at rt for 2 h. After addition of benzylbromide (10.1 mL, 85 mmol), the whole was stirred at rt for 2h, and then quenched with 40 mL of satd NH_4Cl. The mixture was extracted with $CHCl_3$ (100 mL x 3), which was washed with 10 mL of satd $NaHCO_3$ and 100 mL of brine, and then dried over Na_2SO_4. Concentration and silica gel column

chromatography (PhH/AcOEt = 9/1) followed by distillation (0.05 mmHg, 220 °C) gave **29** (24 g, quant) as a colorless oil.

PMR δ: 1.17 and 1.28 (each 3H, s, CH_3), 1.39-2.0 (8H, m, CH_2), 3.19-3.89 (5H, m, OCH_2, CH_2O, CH), 4.08-4.50 (2H, m, $PhCH_2$), 4.98-5.10 (1H, m, CH), 7.08-7.33 (5H, m, ArH). CMR δ: 18.5, 18.7, 24.7, 24.9, 25.1, 29.8, 36.4, 36.6, 39.3, 44.1, 52.7, 53.0, 61.3, 67.6, 68.2, 98.2, 126.6, 127.2, 127.3, 127.8,136.6, 179.4. IR (neat): 1680, 1260, 1040 cm^{-1}. Rf 0.60 (PhH/AcOEt = 2/1). MS *m/z*: 317 (M^+). Anal: Calcd. for $C_{19}H_{27}NO_3$: C, 71.89; H, 8.57; N, 4.41. Found: C, 71.72; H, 8.42; N, 4.53.

(*S*)-(+)-5-(hydroxymethyl)-1,3,3-trimethylpyrrolidin-2-one 27

Prepared as a colorless oil of bp 150 °C at 2 mmHg and $[\alpha]^{25}_D$ +6.2 (c 1.70, $CHCl_3$) in 99% yield from **26** by the same procedure for **30**.

PMR δ: 1.12 and 1.18 (each 3H, s, CH_3), 1.77 (1H, dd, *J* = 7.1, 12.9 Hz, CH_2), 1.91 (1H, dd, *J* = 7.9, 12.9 Hz, CH_2), 2.88 (3H, s, N-CH_3), 3.54 (1H, dddd, *J* = 4.0, 4.0, 7.1, 7.9 Hz, CH), 3.62 (1H, dd, *J* = 4.0, 11.6 Hz, CH_2O), 3.71 (1H, brs, OH), 3.82 (1H, dd, *J* = 4.0, 11.6 Hz, CH_2O). CMR & 25.5, 25.6, 28.3, 36.4, 40.1, 58.0, 62.7, 180.6. IR (nujol):3350, 1660, 1410, 1050 cm^{-1}. Rf 0.20 (AcOEt). MS *m/z*: 157 (M^+). Anal: Calcd. for $C_8H_{15}NO_2$: C, 61.12; H, 9.62; N, 8.91. Found: C, 60.98; H, 9.57; N, 8.95.

(*S*)-(+)-(5-hydroxymethyl)-3,3-dimethyl-1-benzylpyrrolidin-2-one 30

A solution of **26** (1.90 g, 6.0 mmol) and *p*-TsOH (10 mg, 0.06 mmol) in 20 mL of MeOH was stirred under reflux for 4 h, and then concentrated. Silica gel column chromatography (CH_3Cl/MeOH = 9/1) gave **30** (1.43 g, quant) as white powder of mp 79.0 °C ($CHCl_3$) and $[\alpha]^{25}_D$ +78.3 (c 1.0, $CHCl_3$).

PMR δ: 1.14 and 1.24 (each 3H, s, CH_3), 1.81 (2H, m, CH_2), 3.39-3.78 (3H, m, CH_2O, CH), 4.17 (1H, d, *J* = 12.8 Hz, CH_2Ph), 4.73 (1H, d, *J* = 12.8 Hz, CH_2Ph), 7.08-7.39 (5H, m, PhH). CMR δ: 25.3, 36.3, 40.1, 44.4, 55.2, 62.0, 127.3, 127.7, 128.5, 136.8, 180.8. IR (nujol):3350, 1660, 1080, 690 cm^{-1}. Rf 0.28 ($CHCl_3$/MeOH = 9/1). MS *m/z*: 233 (M^+). Anal: Calcd. for $C_{14}H_{19}NO_2$: C, 72.07; H, 8.21; N, 6.00. Found: C, 71.89; H, 8.19; N, 5.85.

(*S*)-(+)-1,3,3-trimethyl-5-[((4-methylphenyl)sulfonyloxy)methyl]pyrrolidine-2-one 28

Prepared as colorless needles of mp 102 °C (ether-$CHCl_3$) and $[\alpha]^{25}_D$ +13.7 (c 1.30, $CHCl_3$) in 75% yield from **27** by the same procedure for **12**.

PMR δ: 1.06 and 1.10 (3H, s, CH_3), 1.56 (1H, dd, *J* = 7.3, 12.8 Hz, CH_2), 1.90 (1H, dd, *J* = 7.9, 12.8 Hz, CH_2), 2.43 (3H, s, $ArCH_3$), 2.70 (3H, s, NCH_3), 3.40-3.60 (1H, m, CH), 3.91 (1H, dd, *J* = 7.0, 12.0 Hz, CH_2O), 4.08 (1H, dd, *J* = 6.4, 12.0 Hz, CH_2O), 7.34 (2H, d, *J* = 8.1 Hz, Ar), 7.73 (2H, d, *J* = 8.1 Hz, Ar). CMR δ: 21.6, 25.4, 25.6, 28.3, 36.8, 39.7, 55.1, 69.6, 127.8, 130.0, 132.2, 145.3, 179.7. IR (nujol):1660, 1170 cm^{-1}. Rf 0.12 (hex/AcOEt = 1/1). MS *m/z*: 311 (M^+). Anal: Calcd. for $C_{15}H_{21}NO_4S$: C, 57.86; H, 6.80; N, 4.50. Found: C, 57.75; H, 6.89; N, 4.39.

(*S*)-(+)-3,3-dimethyl-5-[((4-methylphenyl)sulfonyloxy)methyl]-1-benzylpyrrolidine-2-one 31

Prepared as a pale yellow oil of $[\alpha]^{25}_D$ +39.3 (c 1.0, $CHCl_3$) in 95% yield from **30** by the same procedure for **12**.

PMR δ: 1.14 and 1.22 (3H, s, CH_3), 1.64 (1H, dd, *J* = 6.0 13.5 Hz, CH_2), 1.88 (1H, dd, *J* = 9.0, 13.5 Hz, CH_2), 2.44 (3H, s, $ArCH_3$), 3.44-3.58 (1H, m, CH), 3.60 (1H, d, *J* = 12.8 Hz, CH_2Ph), 3.92 (1H, dd, *J* = 5.3, 9.5 Hz, CH_2O), 4.10 (1H, dd, *J* = 3.6, 9.5 Hz, CH_2O), 4.98 (1H, d, *J* = 12.8 Hz, CH_2Ph), 7.03-7.35 (5H, m, PhH), 7.33 (2h, d, *J* = 7.5 Hz, Ar), 7.69 (2H, d, *J* = 7.5 Hz, Ar). CMR δ: 21.5, 25.3, 36.2, 39.7, 44.4,

52.1, 69.0, 127.5, 127.8, 128.6, 129.9, 132.3, 136.0, 145.2, 179.8. IR (nujol): 1680, 1355, 1170 cm^{-1}. Rf 0.62 (hex/AcOEt = 1/1). MS *m/z*: 387 (M^+). Anal: Calcd. for $C_{21}H_{25}NO_4S$: C, 65.09; H, 6.50; N, 3.61. Found: C, 64.82; H, 6.39; N, 3.65.

(*S*)-(–)-5-[(diphenylphosphino)methyl]-1,3,3-trimethylpyrrolidin-2-one 4

Prepared as colorless needles of mp 71 °C (ether) and $[\alpha]^{25}_D$ –67.4 (c 1.0, $CHCl_3$) in 62% yield from **28** by the same procedure for **13**.

PMR δ: 1.05 and 1.18 (3H, s, CH_3), 1.68 (1H, dd, *J* = 7.6, 12.9 Hz, CH_2), 1.97 (1H, ddd, *J* = 3.1, 9.0, 13.2 Hz, CH_2P), 2.12 (1H, dd, *J* = 6.9, 12.9 Hz, CH_2), 2.74 (1H, ddd, *J* = 3.1, 3.1, 13.2 Hz, CH_2P), 2.77 (3H, s, NCH_3), 3.32-3.50 (1H, m, CH), 7.26-7.50 (10H, m, Ar-H). CMR δ: 25.0, 25.8, 27.8, 34.1 (d, *J* = 14.7 Hz), 40.3, 41.9 (d, *J* = 8.5 Hz), 54.5 (d, *J* = 21.9 Hz), 128.5, 128.7, 128.8, 130.4, 130.5, 132.3, 132.5, 132.8, 132.9, 136.2, 136.3, 136.5, 136.8, 179.6. IR (nujol): 1680 cm^{-1}. Rf 0.20 (hex/AcOEt = 1/1). MS *m/z*: 325 (M^+). Anal: Calcd. for $C_{20}H_{24}NOP$: C, 73.83; H, 7.43; N, 4.30. Found: C, 73.80; H, 7.46; N, 4.26.

(*S*)-(–)-5-[(diphenylphosphino)methyl]-3,3-dimethyl-1-benzylpyrrolidin-2-one 5

Prepared as colorless plates of mp 156 °C ($CHCl_3$) and $[\alpha]^{25}_D$ –50.5 (c 1.05, $CHCl_3$) in 62% yield from **31** by the same procedure for **13**.

PMR δ: 1.08 and 1.25 (3H, s, CH_3), 1.68 (1H, dd, *J* = 6.3, 12.5 Hz, CH_2), 1.82 (1H, ddd, *J* = 3.1, 6.2, 12.7 Hz, CH_2P), 2.11 (1H, dd, *J* = 5.2, 12.5 Hz, CH_2), 2.72 (1H, ddd, *J* = 3.1, 3.1, 12.7 Hz, CH_2P), 3.22-3.39 (1H, m, CH), 3.90 (1H, d, *J* = 12.4 Hz, $PhCH_2$), 5.07 (1H, d, *J* = 12.4 Hz, $PhCH_2$), 7.06-7.36 (15H, m, PhH x 3). CMR δ: 24.9, 25.5, 33.6 (d, *J* = 14.6 Hz), 40.3, 41.8 (d, *J* = 9.8 Hz), 43.9, 51.2 (d, *J* = 22.0 Hz), 127.9, 128.4, 128.5, 128.6, 128.9, 132.1, 132.4, 132.7, 136.3, 136.4, 136.5, 138.3, 179.7. IR (nujol): 1660 cm^{-1}. Rf 0.72 (hex/AcOEt = 1/1). MS *m/z*: 401 (M^+). Anal: Calcd. for $C_{26}H_{28}NOP$: C, 77.78; H, 7.03; N, 3.49. Found: C, 77.54; H, 6.78; N, 3.50.

Conjugate addition of lithium dimethylcuprate to chalcone controlled by 2 in ether solvent (*S*-(+)-1,3-diphenylbutan-1-one 21) (Table 1, run 2).

A solution of methyllithium in ether (2.8 mL, low halide, 1.14 mmol) was added to a suspension of CuI (109 mg, 0.57 mmol) in ether (5 mL) and the whole was stirred at –20 °C for 20 min. A solution of **2** (230 mg, 0.60 mmol) in ether (2 mL) was added at –78 °C and the whole was stirred for 20 min. A solution of chalcone (79.0 mg, 0.38 mmol) in ether (3 mL) was added dropwise over 5 min and the whole was stirred at –20 °C for 1 h. A mixture of 10 mL of satd aq NH_4Cl and 10 mL of 23% NH_4OH was added and the mixture was stirred for 30 min. After extraction with ether (20 mL x 3), the extracts were washed successively with 10 mL of 10% HCl, 10 mL of satd $NaHCO_3$, 10 mL of water, and 10 mL of brine, and then dried over $MgSO_4$. Concentration and following silica gel column chromatography (PhH/hex = 2/1) of the residue (400 mg) gave (+)-**21** (88 mg, quant) as a colorless oil of $[\alpha]^{25}_D$ +13.6 (c 2.25, CCl_4) *S* 93 % ($[\alpha]^{25}_D$ +12.6 (c 2.62, CCl_4).[13] PMR δ: 1.2 (3H, d, J=6.4 Hz, CH_3), 3.0-3.5 (3H, m, CHPh, CH_2CO), 7.0-7.8 (10H, m, ArH). IR (neat): 1690 cm^{-1}. Rf 0.46 (PhH/hex = 4/1). MS *m/z* 224 (M^+). HPLC: Daicel ChiralPak AD, Hex/iPrOH = 30/1, 0.5 mL/min, 250 nm, rt (min), con (%): 17.1, 94.8; 21.3, 5.20, *S*-90% ee.

The ligand **2** (209 mg) was recovered in 91% yield.

Catalytic conjugate addition of lithium butylmagnesium chloride to cyclohexenone controlled by 2 in ether solvent (*S*-(–)-3-butylcyclohexan-1-one 24) (Table 3, run 2).

A suspension of CuI (90 mg, 0.08 mmol) and **2** (115 mg, 0.32 mmol) was stirred in ether (8 mL) at rt

for 20 min. The suspension was cooled to –78 °C and BuMgCl (0.59 mL, 1.13 mmol) in ether was added. After 20 min stirring, a solution of 2-cyclohexenone (0.94 mmol) in ether (2 mL) was added dropwise. The reaction mixture was stirred for 1 h at –78 °C. Usual workup and purification by column chromatography (SiO_2, hexane/EtOAc = 4/1) followed by distillation afforded (–)-**24** ($[\alpha]^{25}_{405}$ –74.8 (c 1.30, $CHCl_3$)) in 92% ee and 82% yield.

Ee was determined by ^{13}C-NMR analysis of the corresponding diastereomeric ketals prepared with (*R,R*)-2,3-butanediol. The absolute configuration was determined by specific rotation.[14]

References and Notes

1. Tomioka, K. *Synthesis* **1990**, 541-549; Noyori, R. *Asymmetric Catalysis in Organic Synthesis* John Wiley and Sons, Inc. New York, 1994; Denmark, S. E.; Nicaise, O. J.-C. *J. Chem. Soc., Chem.Commun.* **1996**, 999-1004.
2. Shindo, M.; Koga, K.; Tomioka, K. *J. Am. Chem. Soc.* **1992**, *114*, 8732-8733; Mizuno, M.; Kanai, M.; Iida, A.; Tomioka, K. *Tetrahedron* **1997**, *53*, 10699-10708; Taniyama, D.; Kanai, M.; Iida, A.; Tomioka, K. *Chem. Pharm.Bull.* **1997**, *4*, 1705-1707; Asano, Y.; Iida, A.; Tomioka, K. *Tetrahedron Lett.* **1997**, *38*, 8973-8976.
3. Fujieda, H.; Kanai, M.; Kambara, T.; Iida, A.; Tomioka, K. *J. Am. Chem. Soc.* **1997**, *119*, 2060-2061.
4. Mizuno, M.; Fujii, K.; Tomioka, K. *Angew. Chem.* in press.
5. Nishimura, K.; Ono, M.; Nagaoka, Y.; Tomioka, K. *J. Am. Chem. Soc.* in press.
6. Kanai, M.; Koga, K.; Tomioka, K. *Tetrahedron Lett.* **1992**, *33*, 7193-7196; *Idem, J. Chem. Soc., Chem. Commun.* **1993**, 1248-1249; Kanai, M.; Tomioka, K. *Tetrahedron Lett.* **1994**, *35*, 895-898; *Idem, ibid.* **1995**, *36*, 4273-4274; *Idem, ibid.* **1995**, *36*, 4275-4278; Nakagawa, Y.; Kanai, M.; Nagaoka, Y.; Tomioka, K. *ibid.* **1996**, *37*, 7805-7808.
   Other ligands: Nakano, H.; Iwasa, K.; Okuyama, Y.; Hongo, H. presented at the 117th Annual Meeting of the Pharmaceutical Society of Japan, Tokyo, March 1997, Abstract Paper 2, p. 79.
7. Chirally modified heterocuprate in stoichiometric conjugate addition reaction: Zweig, J. S.; Luche, J. L.; Barreiro, E.; Crabbé, P. *Tetrahedron Lett.* **1975**, 2355-2358; Mukaiyama, T.; Imamoto, T. *Chem. Lett.* **1980**, 45-46; Huché, M.; Berlan, J.; Pourcelot, G.; Cresson, P. *Tetrahedron Lett.* **1981**, *22*, 1329-1332; Bertz, S. H.; Dabbagh, G.; Sundararajan, G. *J. Org. Chem.* **1986**, *51*, 4953-4959; Corey, E. J.; Naef, R.; Hannon, F. J. *J. Am. Chem. Soc.* **1986**, *108*, 7114-7116; Tanaka, K.; Ushio, H; Suzuki, H. *J. Chem. Soc., Chem. Commun.* **1990**, 795-797; Dieter, R. K.; Lagu, B.; Deo, N.; Dieter, J. W. *Tetrahedron Lett.* **1990**, *31*, 4105-4108; Quinkert, G.; Müller, T.; Königer, A.; Schrtheis, O.; Sickenberger, B.; Düner, G. *Tetrahedron Lett.* **1992**, *33*, 3469-3472; Rossiter, B. E.; Eguchi, M.; Miao, G.; Swingle, N. M.; Hernandez, A. E.; Vickers, D.; Fluckiger, E.; Patterson, R. G.; Reddy, K. V. *Tetrahedron* **1993**, *49*, 965-986; Swingle, N. M.; Reddy, K. V.; Rossiter, B. E. *Tetrahedron* **1994**, *50*, 4455-4466.
   Chirally modified heterocuprate in catalytic conjugate addition reaction: Villacorta, G. M.; Rao, C. P.; Lippard, S. J. *J. Am. Chem. Soc.* **1988**, *110*, 3175-3182; Ahn, K.-H.; Klassen, R. B.; Lippard, S. J. *Organometallics* **1990**, *9*, 3178-3181; Lambert, F.; Knotter, D. M.; Janssen, M. D.; van Klaveren, M.; Boersma, J.; van Koten, G. *Tetrahedron: Asymmetry* **1991**, *2*, 1097-1100; Knotter, D. M.; Grove, D. M.; Smeets, W. J. J.; Spek, A. L.; van Koten, G. *J. Am. Chem. Soc.* **1992**, *114*, 3400-3410; Spescha, M.; Rihs, G. *Helv. Chim. Acta* **1993**, *76*, 1219-1230; Zhou, Q.-L.; Pfaltz, A *Tetrahedron Lett.* **1993**, *34*,

7725-7728; *Idem, Tetrahedron* **1994**, *50*, 4467-4478; van Klaveren, M.; Lambert, F.; Eijkelkamp, D. J. F. M.; Grove, D. M.; van Koten, G. *Tetrahedron Lett.* **1994**, *35*, 6135-6138; Wendisch, V.; Sewald, N. *Tetrahedron Asymmetry* **1997**, *8*, 1253-1257; de Vries, A. H. M.; Hof, R. P.; Staal, D.; Kellogg, R. M.; Feringa, B. L. *ibid.* **1997**, *8*, 1539-1543.

8. Review for asymmetric reaction of organocopper: Rossiter, B. E.; Swingle, N. M. *Chem. Rev.* **1992**, *92*, 771-806; Kanai, M.; Nakagawa, Y.; Tomioka, K. *J. Syn. Org. Chem. Jpn.* **1996**, *54*, 474-480.
9. Alexakis, A.; Mutti, S.; Normant, J. F. *J. Am. Chem. Soc.* **1991**, *113*, 6332-6334; Alexakis, A.; Frutos, J.; Mangeney, P. *Tetrahedron: Asymmetry* **1993**, *4*, 2427-2430; de Vries, A. H.; Meestsma, A.; Feringa, B. L. *Angew. Chem. Int. Ed. Engl.* **1996**, 35, 2374-2376; Alexakis, A.; Vastra, J.; Burton, J.; Mangeney, P. *Tetrahedron Asymmetry* **1997**, *8*, 3193-3196; Stangeland, E. L.; Sammakia, T. *Tetrahedron* **1997**, *53*, 16503-16510.
10. External, chiral diamine ligand: Kretchmer, R. A. *J. Org. Chem.* **1972**, *37*, 2744-2747.
11. Leyendecker, F.; Laucher, D. *Tetrahedron Lett.* **1983**, *24*, 3517-3520; *Idem, Nouv. J. Chim.* **1985**, *9*, 13-19.
12. Davies, S. G.; Doisneau, G. J.-M.; Prodger, J. C.; Sanganee, H. J. *Tetrahedron Lett.* **1994**, *35*, 2369-2372.
13. Ee was determined by HPLC analysis (Daicel ChiralPak AD, *i*-PrOH/hexane 1/30, 0.5 mL/min, (*S*) 14 min, (*R*) 17 min). The absolute configuration was determined by specific rotation. R=Me: Leitereg, T. J.; Cram, D. J. *J. Am. Chem. Soc.* **1968**, *90*, 4011-4018; R=Bu: Ahllerecht, H.; Sommer, H. *Chem. Ber.* **1990**, *123*, 829.
14. Corey, E. J.; Naef, R.; Hannon, F. J. *J. Am. Chem. Soc.* **1986**, *108*, 7114-7116.
15. Melting points were measured using a Yamato MODEL MP-21 melting point apparatus and are not corrected. Optical rotations were taken with a Jasco DIP-370 polarimeter. IR spectra were taken with a HITACHI infrared spectrometer model 260-10. 1H-NMR spectra were taken with a JEOL GX-270 spectrometer at 270 MHz, a HITACHI R-90H spectrometer at 90 MHz, in CDCl3 unless otherwise noted. 13C-NMR spectra were taken with a JEOL GX-270 spectrometer at 67 Mhz in CDCl3 unless otherwise noted Chemical shift values are expressed in ppm relative to internal tetramethylsilane. Abbreviations are as follows: s, singlet; d, doublet; t, triplet; m, multiplet. MS were taken with a JEOL-01, SG-2 mass spectrometer or a JEOL DX-300 mass spectrometer.