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Approach to Enantioselective Conjugate Addition of Organocopper Reagents to Cycloalkenones by the Aid of Chiral Lactam Bearing Phosphine Group

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Abstract—The chiral lactam-phosphine ligand and copper salt mediated asymmetric conjugate addition reaction of butylmagnesium chloride and diethylzinc with cycloalkenones afforded the addition products in moderate selectivity. Among phosphines examined, 5-[(diphenylphosphino)methyl]-3,3-dimethylpyrrolidin-2-one **5** gave rise to moderate enantioselectivity and high yield.

Introduction

Organocopper reagent has been established as an excellent reagent for conjugate addition reaction and is readily available by treatment of copper(I) salt with organometallics such as Grignard reagent, organolithium or organozinc.[1] The reagent involves two different metals as constituents in the cluster. A chiral modification of the reagent needs a chiral bidentate ligand of which heteroatoms coordinate selectively to copper and other metals. Since nitrogen, sulfur, and phosphorus atoms are known to coordinate with copper, chiral ligands bearing these atoms in a coordinating site have been examined in an asymmetric conjugate addition reaction. Kretchmer was the first who applied chiral diamine (−)-sparteine as a ligand for methylcopper.[2] The breakthrough in the stoichiometric reaction was brought by Leyendecker who used hydroxyprolinol-derived sulfide bearing three coordinating sites.[3] Alexakis introduced chiral phosphorus ligand in the reaction of medium order cuprate with cycloalkenones in the presence of lithium bromide to afford the conjugate addition product in high ee.[4] Unfortunately, the catalytic process with the reagent derived from organolithium was unsuccessful. Asymmetric conjugate additions of organozincs to enones in the presence of a chiral ligand are a rapidly developing and exciting area. Alexakis discovered the copper-catalyzed asymmetric conjugate addition of diethylzinc to cyclohexenone. Binaphthol-based phosphorus amidite was developed by Feringa to afford the cyclohexenone ethyl adduct in an extremely high ee.[5,6] The success is laid on the use of copper triflate as a copper source. The ligand–copper complex catalyzes not only the reaction of cycloalkenone but also that of acyclic enone. Chiral thiazolidinone was also developed as a chiral ligand to afford the product in good ee.[7] Since the diphosphine or monophosphine greatly accelerates the copper catalyzed reaction,[8] a survey of the known diphosphine was carried out to find that 0.5 mol% of copper(II) triflate and 0.5 mol% of phosphine are sufficient, though enantioselectivity was moderate.[9] Chiral phosphite ligand-based on tartrate also showed the same ligand acceleration,[10] although the ee was not so satisfactory.[11] Chiral ferrocenylphosphine–oxazoline was also introduced as a catalytic amount of chiral ligand (12 mol%) in the reaction of Grignard reagents and 10 mol% of copper iodide with cyclohexenone to afford the product in good ee.[12] Chiral sulfonamide was also examined by Sewald to find that both catalytic amount of sulfonamide and copper(I) are necessarily to catalyze the reaction, while the ee was not satisfactory.[13]

We have been involved in this exciting field and have developed proline-derived bidentate amidophosphines **1**, **2** based on the concept 'metal differentiating coordination' (Fig. 1). The carbonyl oxygen and phosphorus atoms of the ligand selectively coordinate to copper and other metal of organocopper species **3** that discriminates the enantioface of alkenone. The metal differentiating coordination was supported by NMR studies.[14] The reaction of lithium dimethylcuprate with chalcone gave an adduct in 90% ee.[15] The reaction of lithium cyanocuprate with cycloalkenone was also highly efficient to give the adducts in up to 95% ee.[16] However, the catalytic version of lithium cyanocuprate was unsuccessful. On the other hand, magnesium cyanocuprate prepared from Grignard reagent was highly effective to afford the products in up to 98% ee. It is

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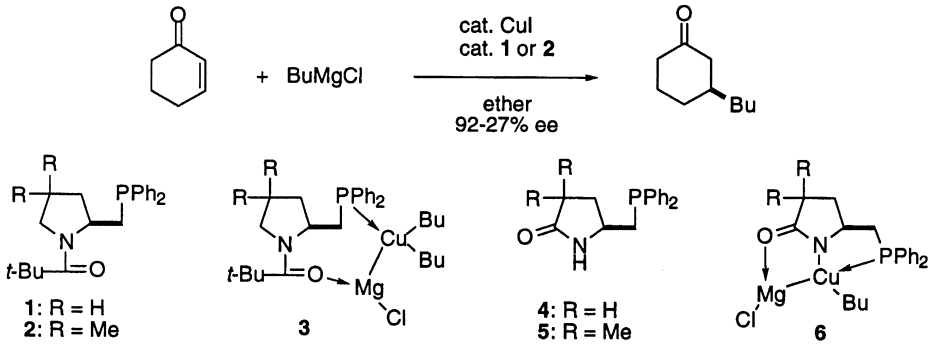


Figure 1. Conjugate addition of butylmagnesium chloride with aid of chiral phosphines **1**, **2**, **4,** and **5**.

noteworthy that the same chiral ligand gave the products with the reversed absolute configuration by changing lithium to magnesium.[17] Catalytic asymmetric conjugate addition was realized by using 8 mol% of copper iodide and 32 mol% of the chiral amidophosphine to afford the products in 72–94% ee.[18] There is a drawback, however, that use of 2 mol% of copper iodide and 3 mol% of the amidophosphine gave rather poor enantioselectivity of 27–40%. Dissociation of chiral phosphine from a copper–ligand complex **3** is attributable to these disappointing results. Use of less reactive organozinc as an organometallics is one of the possible methodologies for avoiding dissociation.[19] Another possibility is use of copper amide that contains a covalent copper–nitrogen bond.[20] It may be reasonably expected that chiral lactams **4** and **5** bearing a phosphine appendage should form a stable amidocopper species whose copper is intramolecularly coordinated by the phosphorus atom as shown in **6**. We describe herein that the asymmetric conjugate addition reaction of butylmagnesium chloride and diethylzinc[21] was catalyzed by the lactam-phosphine ligands **4** and **5** in the presence of copper salt to give the corresponding addition product in up to 64% ee.

Synthesis of Lactam-Phosphines 4, 5, and 12

Chiral lactam-phosphines **4**, **5**, **12** were prepared by diphenylphosphination[22] of tosylates **8** and **10** or fluoride **11** derived from L-glutamic acid applying the previously reported procedure (Fig. 2).[15c] Dicyclohexylphosphine **12** was prepared from the expectation that alkylphosphine coordinates to copper atom more strongly than arylphosphine. As a reference lactam, trityl-lactam **14** was prepared from **9**.

Examination of Procedure for Conjugate Addition of Butylmagnesium Chloride to Cyclohexenone

We examined three types of reaction procedure for forming reactive copper complex. At first, stoichiometric amount of **5** was lithiated with butyllithium in THF and then treated with stoichiometric amount of butylcopper, prepared from CuI and butyllithium, at −30°C for 0.5 h.[23] The mixture was then treated with cyclohexenone at −20°C for 0.5 h to afford (*S*)-3-butylcyclohexanone in 65% ee.[24] However, the yield was not high, 29%. Next, 15 mol% of **5** was treated at 0°C for 1 h in ether or THF with butylcopper, preformed by 1.2 equiv. of butylmagnesium chloride and 10 mol% of CuI or CuBr at 0°C for 0.5 h. Then, treatment with cyclohexenone at −78°C for 1 h gave the product in 60–90% yield, but in poor ee of 0–11%.[25] Finally, 15 mol% of lithiated **5** was treated with 10 mol% of CuI in ether at 0°C for 1 h and then with butylmagnesium chloride at −78°C for 0.5 h.[26] The mixture was then treated with cyclohexenone at −78°C for 1 h to give (*S*)-3-butylcyclohexanone in 89% yield and 35% ee (Table 1, entry 2).

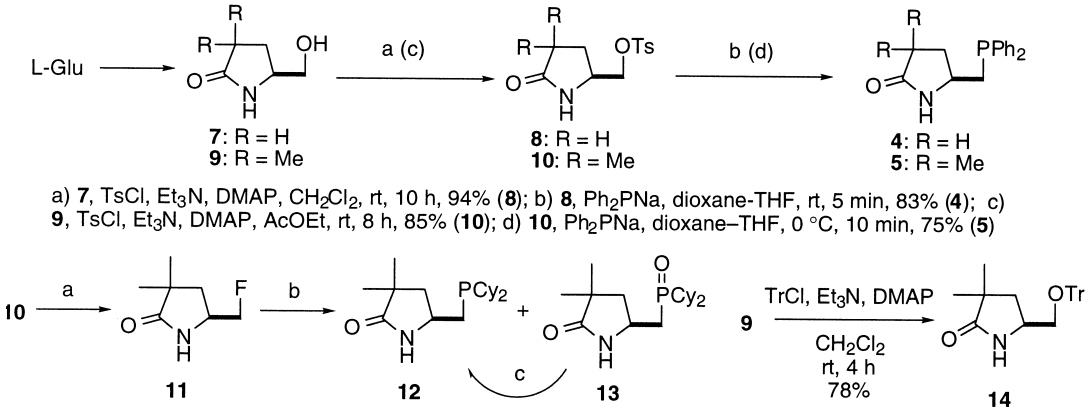
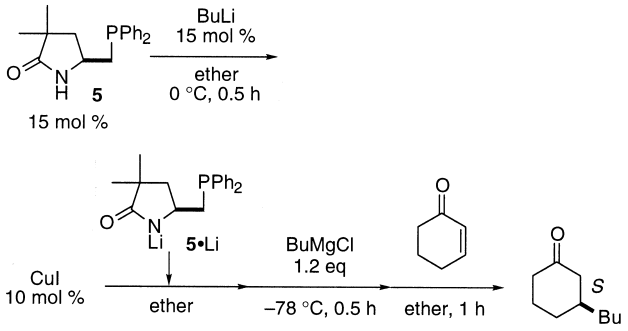


Figure 2. Synthesis of chiral phosphines, **4**, **5**, **12**, and reference lactam **14**.

Table 1. Effect of aging temperature and time on enantioselectivity



Aging conditions			Reaction results		
Entry	Temperature (°C)	Time (h)	Temperature (°C)	Yield (%)	ee (%)
1	−78	1	0	22	12
2	−78 to rt	1	−78	89	35
3	rt	1	−78	92	47
4	rt	0.3	0	20	31
5	rt	3	−78	96	19

Since the third procedure gave the best result, we optimized the reaction procedure. The aging conditions affected enantioselectivity (Table 1). Treatment of lithiated **5** with CuI at −78°C for 1 h resulted in quite poor reactivity, indicating that formation of cuprated lactam requires a temperature higher than −78°C (entry 1). Thus, treatment at room temperature for 1 h afforded the reagent of higher reactivity to give the product in 47% ee and 92% yield (entry 3). Longer aging time resulted in poorer enantioselectivity of 19% (entry 5).

The amount of catalysts, lithiated **5** and CuI, was able to be reduced to 7.5 and 5 mol% to afford the product in 44% ee and 90% yield (Table 2, entry 4). The best ratio of **5** to CuI is 1.5 as shown in Table 2.

The reaction is highly sensitive to other factors. For example, other solvents such as THF, toluene, hexane, methylene dichloride, and acetonitrile gave the product in marginal ees. Although copper bromide can be alternative to afford 23% ee, other copper salts such as copper chloride, cyanide, and triflate are not the choice to afford marginal selectivity.

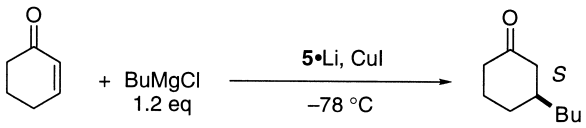
Since trityl-lactam **14** and phosphine oxide **13** gave the product in only 4 and 1% ee, the importance of phosphorus atom is apparent (Table 3, entry 4 and 5). Simple lactam-phosphine **4** gave the product in surprisingly poor 2% ee (entry 1), suggesting a directing effect of dimethyl substitution at the α-position of the carbonyl group of **5**. It was disappointing that dicyclohexylphosphine **12**, expected to coordinate more tightly to copper than the diphenylphosphine group of **5**, however, gave rise to a similar level of enantioselectivity (entry 3).

The reaction conditions above were applicable to the asymmetric conjugate addition reaction of butylmagnesium chloride with cycloalkenones to afford (*S*)-products in moderate enantioselectivity (Table 4).

Asymmetric Reaction of Diethylzinc

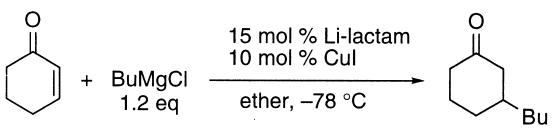
The catalytic activity of lactam-phosphine–copper complexes was examined using diethylzinc as an organometallic. A mixture of 10 mol% of **5** and 5 mol% of $Cu(OTf)_2$[27] in toluene was stirred at room temperature for

Table 2. Effect of amount of CuI and **5** on enantioselectivity



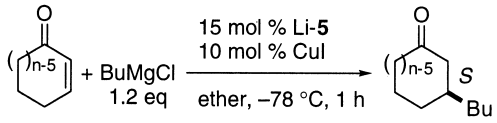
Entry	CuI (mol%)	**5** (mol%)	Time (h)	Yield (%)	ee (%)
1	10	10	1	95	38
2	10	15	1	92	47
3	10	30	2	40	8
4	5	7.5	1	90	44
5	20	30	1	96	42

Table 3. Asymmetric reaction using chiral lactam



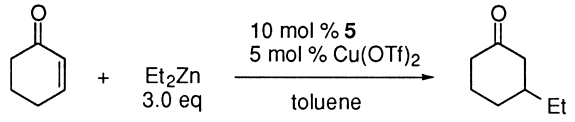
Entry	Lactam	Time (h)	Yield (%)	ee (%)	*R/S*
1	**4**	1	74	2	*R*
2	**5**	1	92	47	*S*
3	**12**	1	96	40	*S*
4	**13**	1	88	1	*R*
5	**14**	1.5	84	4	*R*

Table 4. Asymmetric reaction using **5**



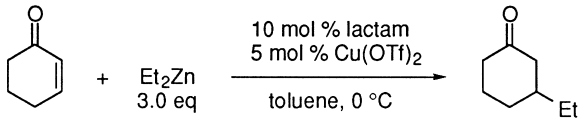
Entry	*n*	Yield (%)	ee (%)	*R/S*
1	5	75	23	*S*
2	6	92	47	*S*
3	7	47	18	*S*

Table 5. Temperature effect on enantioselectivity



Entry	Temperature (°C)	Time (min)	Yield (%)	ee (%)	*R/S*
1	20	15	83	19	*S*
2	0	20	84	35	*S*
3	−40	180	84	27	*S*
4	−78	3 d	80	7	*R*

Table 6. Asymmetric reaction using chiral lactam



Entry	Lactam	Time (min)	Yield (%)	ee (%)	*R/S*
1	**4**	30	82	19	*S*
2	**5**	20	84	35	*S*
3	**12**	10	93	31	*S*
4	**13**	420	73	9	*S*
5	**14**	180	76	6	*R*

1 h. Then, a solution of 3 equiv. of diethylzinc was added at 0°C and the mixture was stirred for 15 min at 0°C. To the mixture was added a solution of cyclohexenone in toluene and the whole was stirred for 20 min at 0°C. Usual workup and purification gave (*S*)-3-ethylcyclohexanone in 35% ee and 84% yield.[19] Toluene was the best solvent examined. Ether and THF gave marginal ees. Enantioselectivity was affected significantly by the reaction temperature as shown in Table 5. The antipode (*R*)-product was obtained at −78°C for 3 days (entry 4). At a temperature below −40°C, some reactive species giving poorer and reversed selectivity may be involved in the reaction.

The chiral lactam-phosphines exhibited a similar trend of enantioselectivity to that observed in the reaction of butylmagnesium chloride (Tables 3 and 6). The relatively higher 35 and 31% ees were obtained using **5** and **12** (Table 6, entry 2 and 3). The simple lactam-phosphine **4** gave 19% ee (entry 1). Enantiofacial differentiation using **5** and **12** is also the same as those of the reaction of butylmagnesium chloride.

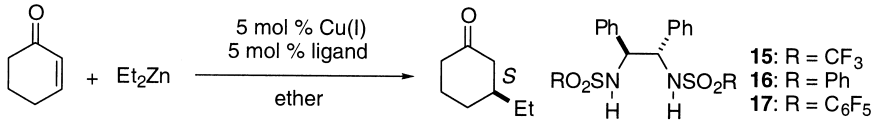
When the phosphine group is absent in the lactam ligand as shown by **13** and **14**, the reaction was slow, but gave the product in not marginal selectivity (Table 6, entry 4 and 5). This suggests the possibility of simple amides as a chiral catalyst. Then, the chiral bissulfonamides **15**–**17**[28] were examined for evaluation of their catalytic activity. The reactivity is apparently enhanced when the more acidic sulfonamide was used (Table 7, entry 1, 3, 5). The reagent prepared from trifluoromethanesulfonamide **15** was much more reactive than those derived from **17** and **16**. The electrophilic zinc in the Zn-amide derived from **15** should behave as a better Lewis acid to promote a faster reaction. On the other hand, higher enantioselectivity was obtained using phenylsulfonamide **16**.

The reactions of diethylzinc with cycloalkenones using **5** were examined (Table 8). Ethyl group was introduced to cyclopentenone and cycloheptenone in 24 and 32% ees, and in high yields. It was remarkable to find that the reaction with 4,4-dimethylcyclohex-2-enone gave the product in 64% ee and 94% yield after 4 h at 0°C (entry 4).

Conclusion

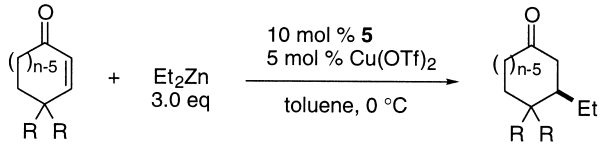
The conjugate addition reaction of butylmagnesium chloride and diethylzinc with cycloalkenone was catalyzed by a catalytic amount of copper(I) and chiral lactam-phosphine **5**. Covalent bond formation between lactam nitrogen and copper(I) and subsequent internal coordination by phosphorus group made a copper–ligand complex stable toward

Table 7. Asymmetric reaction using bissulfonamide



Entry	Cusalt	Et_2Zn/eq	Ligand	Temp (°C)	Time (h)	Yield (%)	ee (%)
1	CuCN	3.0	**15**	0	0.5	91	18
2	CuOTf	3.0	**15**	0	0.3	84	14
3	CuCN	3.0	**16**	rt	20	46	28
4	CuCN	5.0	**16**	rt	5	52	26
5	CuCN	3.0	**17**	0	4	76	18

Table 8. Asymmetric reaction with cycloalkenones using **5**



Entry	*n*	R	Time (min)	Yield (%)	ee (%)	*R/S*
1	5	H	20	70	24	*S*
2	6	H	20	84	35	*S*
3	7	H	30	80	32	*S*
4	6	Me	240	94	64	*R*

dissociation. Further studies aimed at sophisticated design of chiral copper species are in progress in our laboratories.

Experimental[29]

(+)-(*S*)-5-{[(4-Methylphenyl)sulfonyloxy]methyl}pyrrolidine-2-one (8). To a mixture of **7**[30] (5.0 g, 43.1 mmol) and TsCl (9.1 g, 47.4 mmol) in CH_2Cl_2 (90 mL) was added triethylamine (6.6 mL, 47.4 mmol) and DMAP (1.1 g, 8.62 mmol) under ice bath cooling and the whole was stirred for 10 h at room temperature. After addition of 20 mL of cold water, the mixture was extracted with AcOEt. The extract was washed with 10% HCl, sat. $NaHCO_3$, brine, and then dried over Na_2SO_4. Concentration and silica gel column chromatography (AcOEt) gave **8** as colorless plates of mp 125–126°C (AcOEt) and $[\alpha]_D^{25}=+20.4$ (*c* 1.05, $CHCl_3$). PMR δ: 1.78 (1H, m, CH_2), 2.30 (3H, m, CH_2, CH_2CO), 2.46 (3H, s, CH_3), 3.88 (1H, dd, *J*=7.4, 9.5 Hz, CH_2O), 3.92 (1H, m, CH), 4.05 (1H, dd, *J*=3.7, 9.5 Hz, CH_2O), 6.21 (1H, brs, NH), 7.37 (d, *J*=8.2 Hz, 2H, ArH), 7.79 (d, *J*=8.2 Hz, 2H, ArH). IR (nujol): 3200, 1680, 1160 cm^{-1}. MS *m/z*: 269 (M^+).

(+)-(*S*)-5-[(4-Diphenylphosphino)methyl]pyrrolidine-2-one (4). To a suspension of sodium (1.6 g, 69.9 mmol) in dioxane (30 mL) was added chlorodiphenylphosphine (3.0 mL, 16.7 mmol) at 0°C over 10 min. After being refluxed for 7 h, a solution of **8** (3.0 g, 11.1 mmol) in THF (20 mL) was added at 0°C. After being stirred for 5 min, the mixture was filtered through Celite to afford a red oil (4.1 g). Silica gel column chromatography (AcOEt) gave **4** (2.6 g, 83%) as colorless needles of mp 111–112°C (ether) and $[\alpha]_D^{25}=+27.2$ (*c* 1.27, $CHCl_3$). PMR δ: 1.87 (1H, m, CH_2), 2.28 (5H, m, CH_2P, CH_2O, one of CH_2), 3.67 (1H, m, CH), 6.07 (1H, brs, NH), 7.41 (10H, m, ArH). CMR δ: 29.0, 30.1, 36.5, 36.6, 52.1, 52.2, 128.6, 128.7, 129.1, 132.6, 132.7, 132.9, 137.3, 137.4, 177.5. IR (nujol): 3200, 1670 cm^{-1}. MS *m/z*: 283 (M^+). Anal. Calcd for $C_{17}H_{18}NOP$: C, 72.07; H, 6.40; N, 4.94. Found: C, 72.12; H, 6.35; N, 4.84.

(+)-(*S*)-3,3-Dimethyl-5-{[(4-methylphenyl)sulfonyloxy]methyl}pyrrolidin-2-one (10). To a mixture of **9**[15c] (13.0 g, 89 mmol) and TsCl (17.0 g, 89 mmol) in AcOEt (600 mL) was added triethylamine (12.0 mL, 89 mmol) and DMAP (11.0 g, 89 mmol) under ice bath cooling. The whole was stirred for 8 h at room temperature. After addition of cold water (100 mL), the mixture was extracted with AcOEt. The extract was washed with 10% HCl, sat. $NaHCO_3$, brine, and then dried over Na_2SO_4. Concentration and recrystallization gave **10** (22.4 g, 85%) as colorless plates (AcOEt) of mp 120–121°C and $[\alpha]_D^{25}=+17.8$ (*c* 1.35, $CHCl_3$). PMR δ: 1.15 (6H, s, CH_3), 1.55 (1H, dd, *J*=7.6, 12.5 Hz, CH_2), 2.53 (1H, dd, *J*=6.2, 12.5 Hz, CH_2), 2.46 (3H, s, $PhCH_3$), 3.86 (2H, m, CH, CH_2O), 4.09 (1H, m, CH_2O), 6.2 (1H, brs, NH), 7.37 (2H, d, *J*=8.1 Hz, ArH), 7.79 (2H, d, *J*=8.1 Hz, ArH). CMR δ: 21.6, 25.1, 25.2, 38.2, 39.8, 49.4, 72.5, 127.9, 130.0, 132.4, 145.3, 182.1. IR (nujol): 3200, 1650 cm^{-1}. MS *m/z*: 297 (M^+). Anal. Calcd for $C_{15}H_{21}NO_3$: C, 60.99; H, 7.17; N, 4.74. Found: C, 60.87; H, 7.24; N, 4.90.

(+)-(*S*)-5-[(Diphenylphosphino)methyl]-3,3-dimethylpyrrolidin-2-one (5). Small pieces of sodium (9.8 g, 424 mmol) were added to dioxane (200 mL) at 0°C over 0.5 h and then chlorodiphenylphosphine (18.0 mL, 101 mmol) was added to the mixture under ice bath cooling. After being refluxed for 7 h, a solution of **10** (20.0 g, 67.0 mmol) in THF (75 mL) was added at 0°C. After being stirred for 1 h, the mixture was filtered through Celite to afford a pale yellow oil (28 g). Silica gel column chromatography (PhH/AcOEt=2/1) gave **5** (15.6 g, 75%) as a white powder of mp 99–100°C (AcOEt) and $[\alpha]_D^{25}=+20.1$ (*c* 1.65, $CHCl_3$). PMR δ: 1.10 and 1.18 (each 3H, s, CH_3), 1.70 (1H, dd, *J*=8.2, 12.5 Hz, CH_2), 2.16 (1H, dd, *J*=6.6, 12.5 Hz, CH_2), 2.28 (2H, d, *J*=7.3 Hz, CH_2P), 3.63 (1H, m, CH), 5.90 (1H, brs, NH), 7.43 (10H, m, ArH). CMR δ: 24.6, 25.3, 36.6 (d, *J*=14.7 Hz), 40.6, 45.1 (d, *J*=8.5 Hz), 48.6 (d, *J*=17.1 Hz), 128.6, 128.7, 128.8, 129.1, 132.5, 132.6, 132.8, 132.9, 137.2, 137.4, 182.0. IR (nujol): 3200, 1670 cm^{-1}. MS *m/z*: 311 (M^+). Anal. Calcd for $C_{19}H_{22}NOP$: C, 73.29; H, 7.12; N, 4.50. Found: C, 72.96; H, 7.20; N, 4.41.

(+)-(*S*)-5-Fluoromethyl-3,3-dimethylpyrrolidin-2-one (11).[31] A mixture of **10** (1.06 g, 3.4 mmol) and KF (395 mg, 6.8 mmol) in diethylene glycol (10 mL) was stirred for 7 h at 150°C. After addition of water (10 mL), the mixture was extracted with AcOEt. The extract was washed with water and brine, and then dried over Na_2SO_4. Concentration and silica gel column chromatography (AcOEt) gave **11** (370 mg, 75%) as colorless needles (AcOEt) of mp 105–107°C and $[\alpha]_D^{25}=+27.2$ (*c* 1.27, $CHCl_3$). PMR δ: 1.20 (3H, s, CH_3), 1.21 (3H, s, CH_3), 1.62 (1H, dd, *J*=7.9, 12.8 Hz, CH_2), 2.04 (1H, dd, *J*=7.3, 12.8 Hz, CH_2), 3.91 (1H, dddd, *J*=3.4, 7.3, 7.3, 7.9 Hz, CH), 4,25 (1H, ddd, J_{HH}=7.3, 9.5 Hz, J_{HF}=48 Hz, CH_2F), 4.44 (1H, ddd, J_{HH}=3.4, 9.5 Hz, J_{HF}=48 Hz, CH_2F), 7.28 (1H, brs, NH). CMR δ: 25.25, 25.30, 37.1 (*J*=6 Hz), 39.9, 50.4 (*J*=20 Hz), 85.7 (*J*=172 Hz), 182.6. IR (nujol): 3200, 1660 cm^{-1}. MS *m/z*: 145 (M^+). Anal. Calcd for $C_7H_{12}NOF$: C, 57.91; H, 8.33; N, 9.65. Found: C, 57.85; H, 8.21; N, 9.82.

(+)-(*S*)-5-[(Dicyclohexylphosphino)methyl]-3,3-dimethylpyrrolidin-2-one (12) and oxide (13). To a solution of dicyclohexylphosphine (13.6 g, 68.8 mmol) in ether (100 mL) was added a hexane solution of BuLi (50 mL, 68.8 mmol) at room temperature and the mixture was stirred for 0.5 h at room temperature. After addition of a solution of **11** (5.0 g, 34.4 mmol) in dioxane (50 mL) under ice bath

cooling, the whole was stirred for 10 h at room temperature. Usual workup and purification by alumina column chromatography (AcOEt) gave **12** (445 mg, 4%) as a colorless oil and **13** (9.0 g, 77%) as a white solid.

12: $[\alpha]_D^{25}=+34.5$ (*c* 0.95, $CHCl_3$). PMR δ: 1.16 (3H, s, CH_3), 1.19 (3H, s, CH_3), 1.23–1.46 (12H, m, cyclohexyl-H), 1.59 (1H, dd, *J*=8.5, 12.5 Hz, CH_2), 1.69–1.97 (12H, m, cyclohexyl-H, P-CH and CH_2P), 2.21 (1H, dd, *J*=5.2, 12.5 Hz, CH_2), 3.51–3.66 (1H, m, CH), 7.04 (1H, s, NH). CMR δ: 24.0, 24.2, 24.6, 25.1, 25.2, 25.3, 25.50, 25.54, 25.2, 26.0, 26.2, 26.31, 26.33, 26.4, 26.5, 30.1 (d, *J*=12.0 Hz), 35.3, 36.5, 36.0, 36.3, 39.9, 45.0 (d, *J*=7 Hz), 47.1 (d, *J*=14.2 Hz), 180.9. IR (film): 3250, 1690 cm^{-1}. MS *m/z*: 323 (M^+). Anal. Calcd for $C_{19}H_{34}NOP$: C, 70.55; H, 10.6; N, 4.33. Found: C, 70.42; H, 9.80; N, 4.24.

13: $[\alpha]_D^{25}=+74.3$ (*c* 1.20, $CHCl_3$). PMR δ: 1.15 (3H, s, CH_3), 1.20 (3H, s, CH_3), 1.24–1.45 (12H, m, cyclohexyl-H), 1.59 (1H, dd, 1H, *J*=8.5, 12.5 Hz, CH_2), 1.69–1.97 (12H, m, cyclohexyl-H, P-CH and CH_2P), 2.21 (1H, dd, *J*=6,4, 12.5 Hz, CH_2), 3.93 (1H, m, CH), 6.79 (1H, s, NH). CMR δ: 24.5, 24.55, 24.59, 25.11, 25.13, 25.29, 25.50, 25.52, 25.8, 26.1, 26.2, 26.26, 26.3, 26.36, 26.40, 30.1 (d, *J*=58 Hz), 35.8, 36.3, 36.5, 37.0, 39.8, 45.7 (d, *J*=11 Hz), 47.1 (d, *J*=5.1 Hz), 181.2. IR (nujol): 3250, 1690, 1150 cm^{-1}. MS *m/z*: 339 (M^+). Anal. Calcd for $C_{19}H_{34}NO_2P$: C, 67.23; H, 10.10; N, 4.13. Found: C, 67.12; H, 10.33; N, 4.08.

Synthesis of 12 by reduction of 13. To a stirred suspension of **13** (4.0 g, 11.8 mmol) in CH_3CN (120 mL) was added triethylamine (8.2 mL, 59.0 mmol) at 0°C. After addition of trichlorosilane (8.8 mL, 64.9 mmol), the whole was refluxed for 16 h. After addition of degassed toluene (30 mL) and 30% NaOH (20 mL), the mixture was extracted with degassed toluene. The extract was washed with degassed water, degassed satd $NaHCO_3$ and degassed brine, and then dried over Na_2SO_4. Concentration and alumina column chromatography (hexane–ether=1:4) gave **12** (2.1 g, 52%).

(+)-(*S*)-3,3-Dimethyl-5-[(triphenylmethoxy)methyl]pyrrolidin-2-one (14). A mixture of **9** (1.3 g, 8.8 mmol), trityl chloride (3.43 g, 12.3 mmol), triethylamine (2.5 mL) and DMAP (215 mg, 1.76 mmol) in DMF (24 mL) was stirred for 4 h at room temperature. After addition of cold water (5 mL), the mixture was extracted with AcOEt. The extract was washed with 10% HCl, sat. $NaHCO_3$ and brine, and then dried over Na_2SO_4. Concentration and silica gel column chromatography (PhH–AcOEt=1:1) gave **14** (2.6 g, 78%) as a white solid. PMR δ: 1.11 and 1.17 (each 3H, s, CH_3), 1.44 (1H, dd, *J*=8.1, 12.3 Hz), 1.93 (1H, dd, *J*=7.0, 12.3 Hz), 2.87 (1H, t, *J*=9.0 Hz), 3.21 (1H, dd, *J*=3.4, 9.0 Hz), 3.81 (1H, dddd, *J*=3.4, 7.0, 8.1, 9.0 Hz), 5.83 (1H, brs), 7.20–7.50 (15H, m). IR (nujol): 3200, 1690 cm^{-1}. MS *m/z*: 385 (M^+).

General procedure for asymmetric conjugate addition of butylmagnesium chloride using 5 (Table 1, entry 3). To a solution of **5** (75 mg, 0.24 mmol, 15 mol%) in ether (3 mL) was added a hexane solution of BuLi (0.16 mL, 0.24 mmol, 15 mol%) at −78°C and the mixture was stirred for 0.5 h at 0°C. The above solution was added to a suspension of CuI (30 mg, 0.16 mmol, 10 mol%) in ether (10 mL) at room temperature. After being stirred for 1 h, BuMgCl (0.96 mL, 1.87 mmol, 1.2 equiv.) in ether was added at −78°C. After stirring for 30 min, a solution of cyclohex-2-enone (150 mg, 1.56 mmol) in ether (4 mL) was added dropwise over 15 min at −78°C and the whole was stirred for 1 h at the same temperature. Usual workup and purification by silica gel column chromatography (hexane–ether=9:1) gave (*S*)-3-butylcyclohexanone[32] (221 mg, 92 %) as a colorless oil of $[\alpha]_{405}^{25}=-38.4$ (*c* 1.05, $CHCl_3$) in 47% ee. The ee was determined to be 47% by CMR analysis of the corresponding diastereomeric ketals prepared with (*R,R*)-2,3-butanediol (*p*-TsOH in benzene at reflux, 95% yield).[33]

Asymmetric conjugate addition of diethylzinc to 4,4-dimethyl-2-cyclohexenone controlled by 5 (Table 8, entry 4). A mixture of **5** (37 mg, 0.12 mmol, 10 mol%) and $Cu(OTf)_2$ (22 mg, 0.06 mmol, 5 mol%) in toluene (9 mL) was stirred at room temperature for 1 h. Et_2Zn (3.6 mL, 3.63 mmol, 3.0 equiv.) in hexane was added at 0°C and the whole was stirred for 15 min at 0°C. To the mixture was added a solution of 4,4-dimethylcyclohex-2-enone (150 mg, 1.21 mmol) in toluene (2 mL) and the whole was stirred for 4 h at 0°C. Usual workup and purification by silica gel column chromatography (hexane–ether=4:1) gave the (*R*)-ethyl adduct[34] (175 mg, 94%) as a colorless oil of $[\alpha]_{405}^{25}=-13.7$ (*c* 1.20, $CHCl_3$) in 64% ee. PMR δ: 0.88 (3H, t, *J*=7.3 Hz), 0.99 (3H, s), 1.0 (1H, m), 1.03 (3H, s), 1.40 (1H, m), 1.53–1.75 (3H, m), 2.02 (1H, ddd, *J*=0.99, 12.1, 14.8 Hz), 2.22–2.49 (3H, m). CMR δ: 12.1, 19.4, 23.2, 28.6, 32.8, 38.2, 40.4, 42.2, 48.7, 212.2. IR (neat): 1710 cm^{-1}. MS *m/z*: 238 (M^+).

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