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TETRAHEDRON

An Asymmetric Conjugate Addition Reaction of Lithium Organocopper Reagent Controlled by A Chiral Amidophosphine

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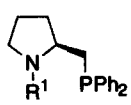
Abstract: Examination of the behaviors of the chiral amidophosphines **1-14** in the asymmetric conjugate addition reaction of lithium organocopper with chalcone and cycloalkenone revealed that the reaction efficiency is governed by many factors including copper salt, solvent, molecular ratio of copper and organolithium, and the structure of the substrate. The reaction with cycloalkenone gave the adduct in up to 94% ee under the stoichiometric conditions. © 1999 Elsevier Science Ltd. All rights reserved.

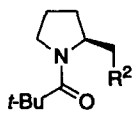
keywords: asymmetric reactions, copper and compounds, lithium and compounds

INTRODUCTION

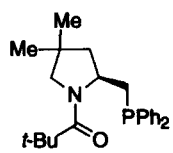
An enantioselective conjugate addition is a rapidly developing area in organocopper chemistry.[1] Chiral modification of heterocuprates has been the representative of these approaches wherein the chiral amides, alkoxides, and thiolates are employed as the chiral components of the cuprates.[2] Another interesting and recently growing approach is the use of a chiral external ligand as an asymmetric controller.[3] As part of our studies directed toward the asymmetric reactions employing the external chiral ligands,[4] we have been involved in the design and application of a new chiral ligand for organocuprates.[5] We describe herein in full detail that the conjugate addition of lithium cuprate to chalcone and cycloalkenone is highly controllable using the chiral bidentate amidophosphine ligands **1-14** designed on the basis of the concept of the metal differentiating coordination.[6]



R1
1: Me
2: *t*-BuCO
3: $(Me_2N)_2PO$
4: Me_2NCO
5: C_6F_5CO
6: C_6H_5CO
7: 1-NaphCO
8: CF_3CO
9: *p*-Ts



R2
10: SMe
11: SPh
12: NPh_2
13: OMe



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ASYMMETRIC CONJUGATE ADDITION TO ACYCLIC α,β-UNSATURATED KETONE

The asymmetric conjugate addition reaction of lithium organocuprate, generated from 3 equiv of organolithium and 1.5 equiv of copper iodide in ether, with α,β-unsaturated phenyl ketones was examined in the presence of 1.6 equiv of pivaloylamidophosphine **2**. Some of the results are summarized in Table 1. The absolute configuration and ee of the proucts were determined by the specific rotation.[7] The efficiency is

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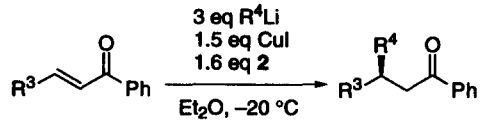
highly dependent on the β-substituent of the enone. The methyl substituent is not bulky enough and the selectivity was not high (Table 1, entry 1-3). The butyl and phenyl substituents are more bulky and the reactions with these enones gave the relatively high efficiency of 17-84% ee (entry 4-9). The enantioselectivity is also dependent on the organo-group of the cuprate. The methyl and vinyl groups were transferred in relatively high selectivity, but the selectivity by the phenyl group was not so high.

It is also important that the enantiofacial differentiation is dependent on the organo-group of the cuprate. Excepting the vinyl group, all of the methyl, butyl, and phenyl groups were introduced from the upper face of the enones as shown in the Table 1 (entry 1, 4, 6-8). Only the vinyl group was introduced from the bottom face of the enones (entry 5, 9, excepting entry 2).

Table 1. Reaction of lithium cuprate controlled by **2**[a]



entry	R^3	R^4	yield/%	ee/%	*R/S*
1	Me	Bu	95	16	*S*
2	Me	vinyl	46	7	*R*
3	Me	Ph	78	0	
4	Bu	Me	89	55	*R*
5	Bu	vinyl	35	50	*S*
6	Bu	Ph	93	17	*R*
7	Ph	Me	79	84	*S*
8	Ph	Bu	97	24	*S*
9	Ph	vinyl	67	73	*S*

[a] The absolute configuration and ee were determined by the specific rotation. See ref. 7.

THE SOLVENT DEPENDENT REVERSAL OF THE ENANTIOFACIAL DIFFERENTIATION

The effect of the solvent is also remarkable as shown in Table 2. We examined the ligands **1-14** in the reaction of lithium dimethyl- and dibutylcuprates with chalcone using ether, toluene, dimethyl sulfide (DMS), DME, and THF as the solvent. The enantioselectivities controlled by the ligands **1**, **9-13** were marginal, at most 5% ee in ether and THF. The reactions of dimethyl cuprate controlled by **2** gave the ees, 30-84%. The highest 90% ee was realized using the phosphine **14**[6] (entry 31). The highest ee 59% in the reaction of butylcuprate was observed using the pentaflurobenzoylamidophophine **5** (entry 21). However, the corresponding benzoylamide **6** was not effective.

It is surprising to find that the enantiofacial differentiation is critically governed by the solvent. The reactions of methylcuprate in ether, toluene, and DMS gave the (*S*)-product in 60-84% ee (entry 1-4), while those in THF and DME gave (*R*)-product in 50 and 30% ees (entry 5, 6). The affect of lithium bromide and HMPA is not significant (entry 2, 7).

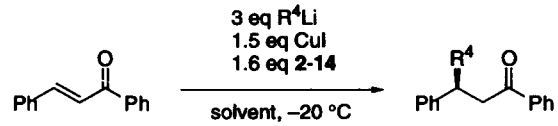
The reaction of dibutylcuprate-**2** is also governed by the solvent. Reversal of the enantiofacial differentiation was observed in ether and THF (entry 8-10).

The solvent dependent reversal of enantiofacial differentiation was the generally observed phenomena in the reactions controlled by other ligands as shown in Table 2. In the cases using the ligands **3**, **4** almost

complete reversals of the enantiofacial differentiation were observed by the reaction of methylcuprate (entry 11 vs 12, 15 vs 16). In the reaction of butylcuprate-3, although the ee was not so high, the reversal was also observed (entry 13 vs 14).

The origin of these solvent dependent reversals of the enanatiofacial differentiation is attributable to the structure variation of the cuprate coordinated by the bidentate amidophosphine in ether and THF. In ether, the amidophosphines act as the bidentate ligand to copper and lithium, while in THF the ligands act as the monodentate phosphine, due to the coordination of THF to lithium.[5a,b,8]

Table 2. Reaction of lithium organocuprate with chalcone controlled by **2-8**, and **14**[a]



entry	2-14	R^4	solvent	yield/%	ee/%	*R/S*	entry	2-14	R^4	solvent	yield/%	ee/%	*R/S*
1	2	Me	ether	79	84	*S*	17	4	Bu	ether	88	16	*S*
2	2	Me[b]	ether	89	60	*S*	18	4	Bu	THF	78	2	*R*
3	2	Me	toluene	87	78	*S*	19	5	Me	ether	72	40	*S*
4	2	Me	DMS	63	79	*S*	20	5	Me	THF	29	14	*R*
5	2	Me	THF	72	50	*R*	21	5	Bu	ether	87	59	*S*
6	2	Me	DME	34	30	*R*	22	5	Bu	THF	40	3	*S*
7	2	Me	ether-HMPA	3	78	*S*	23	6	Me	ether	84	54	*S*
8	2	Bu	ether	97	24	*S*	24	6	Me	THF	29	14	*R*
9	2	Bu	toluene	35	2	*S*	25	6	Bu	ether	92	2	*S*
10	2	Bu	THF	39	30	*R*	26	6	Bu	THF	71	0	
11	3	Me	ether	88	71	*S*	27	7	Me	ether	75	20	*S*
12	3	Me	THF	72	66	*R*	28	7	Me	THF	83	9	*S*
13	3	Bu	ether	88	19	*S*	29	8	Me	ether	89	37	*S*
14	3	Bu	THF	59	19	*R*	30	8	Me	THF	86	0	
15	4	Me	ether	88	67	*S*	31	14	Me	ether	99	90	*S*
16	4	Me	THF	70	68	*R*	32	14	Bu	ether	95	11	*S*

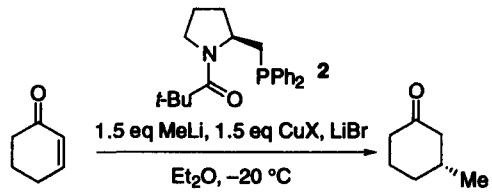
[a] The absolute configuration was determined by the specific rotation. See ref. 7. [b] Methyllithium-lithium bromide complex was used.

ASYMMETRIC CONJUGATE ADDITION REACTION WITH CYCLOHEXENONE

The reaction of organocopper-amidophosphine with cycloalkenone was found to be quite different from those with chalcone. The conditions used for the reaction of the cuprate with chalcone (Table 2, entry 1) was found not to be applicable to give 3-methylcyclohexanone in only 16% ee and 63% yield (Table 3, entry 1). Systematic examination of the reaction of methylcopper-lithium iodide, prepared from 1.5 equiv of

methyllithium and 1.5 equiv of copper iodide in ether, in the presence of 3 equiv of **2** was carried out. The reaction of methylcopper gave the better ee 26% (entry 2). The ee was determined by ^{13}C NMR analysis of the corresponding diastereomeric ketals prepared with (*R,R*)-2,3-butanediol.[9] The absolute configuration was determined to be *R* by the specific rotation.[10] Upon an addition of lithium bromide,[3c] the ee was improved to 55% (entry 3-6). The improvement of the ee was much more significant in the reaction of lithium methylcyanocuprate. Upon an addition of 12 equiv of lithium bromide, ee reached to 70% (entry 7, 10). The amount of the amidophosphine **2** is also critical to improve the selectivity to 80% ee (entry 8-12).

Table 3. Effects of copper source, LiBr, and **2** on the reaction of methylcopper with cyclohexenone



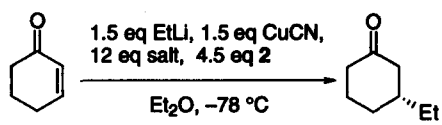
entry	CuX	2/eq	LiBr/eq	yield/%	ee/%	entry	CuX	2/eq	LiBr/eq	yield/%	ee/%
1 [a]	CuI	1.6	0	63	16	7	CuCN	3	0	47	4 [b]
2	CuI	3	0	44	26	8	CuCN	0.3	12	86	4
3	CuI	3	3	69	37	9	CuCN	1.5	12	99	24
4	CuI	3	6	83	47	10	CuCN	3	12	88	70
5	CuI	3	12	61	55	11	CuCN	4.5	12	99	76
6	CuI	3	24	26	52	12	CuCN	9	12	99	80

[a] A 3.0 eq of MeLi was used. The reaction temperature was –78 °C. [b] The absolute configuration was opposite.

The effect of lithium bromide was also confirmed in the reaction of lithium ethylcyanocuprate as summarized in Table 4. Contrary to the reaction of methylcyanocuprate, lithium ethylcyanocuprate reacted with cyclohexenone at the lower temperature of –78 °C. In the absence of lithium bromide, the reaction gave the product in 54% ee (entry 1). In the presence of 12 equiv of lithium bromide, the selectivity reached to 91% ee (entry 3). The addition of lithium chloride and iodide is not beneficial (entry 2, 4). The addition of lithium cyanide improves the selectivity, while the yield is moderate (entry 5).

The bromide ion is not the origin of the high selectivity, because an addition of ammonium bromide is not beneficial (entry 6).

Table 4. Effect of salt on the reaction



entry	salt	yield/%	ee/%
1	none	62	54
2	LiCl	77	41
3	LiBr	89	91
4	LiI	80	14
5	LiCN	38	86
6	Bu_4NBr	46	60

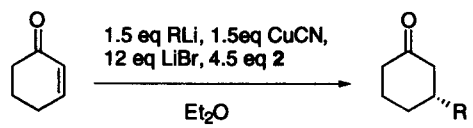
Although the optimum conditions for the high efficiency was established as above (Table 3, entry 11 and Table 4, entry 3), it was necessarily to improve the reaction efficiency of lithium methylcyanocuprate. The much more improvement was achieved through the addition of TMSCl-HMPA.

EFFECT OF TMSCL-HMPA

Since the reactivity activation of the cuprate by TMSCl is the established method,[11] effect of TMSCl on the reactivity was examined with lithium methyl- and other organocyanocuprates (Table 5). Upon an addition of 3 equiv of TMSCl, the reaction of methylcyanocuprate proceeded at the lower temperature of –78 °C to afford 3-methylcyclohexanone in 86% ee (entry 2). It is also important to add a mixture of TMSCl and cyclohexenone to the cuprate (entry 2 vs 3). The addition of TMSCl along with HMPA was more effective to afford the product in 92% ee (entry 4). The addition of HMPA alone was not effective (entry 6). Other TMS species were also not effective (entry 7-10).

However, this procedure is not applicable to the reaction of the more reactive cuprates, lithium ethyl-, butyl-, and phenylcyanocuprates (entry 11-16). In the absence of TMSCl-HMPA, the products, 3-ethyl-, 3-butyl-, and 3-phenylcyclohexanones were obtained in 91, 90, 73% ees, whereas in the presence of TMSCl-HMPA, these were obtained in 67, 77, and 29% ees.

Table 5. Effects of TMSCl and HMPA on the reaction of cyanocuprate[a]



entry	R	TMSCl/HMPA	temp/°C	yield/%	ee/%
1	Me	none	–20	99	76
2	Me	TMSCl	–78	99	86
3[b]	Me	TMSCl	–78	62	76
4	Me	TMSCl/HMPA	–78	66	92
5	Me	TMSCl/HMPA	–20	99	80
6	Me	HMPA	–20	99	74
7	Me	TMSBr/HMPA	–78	77	40
8	Me	TMSI/HMPA	–40	18	64
9	Me	TMSOTf/HMPA	–78	73	30
10	Me	TBDPSCl/HMPA	–20	27	71
11	Et	none	–78	89	91
12	Et	TMSCl/HMPA	–78	48	67
13	Bu	none	–78	97	90
14	Bu	TMSCl/HMPA	–78	96	77
15	Ph	none	–78	63	73
16	Ph	TMSCl/HMPA	–78	67	29

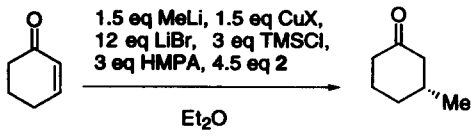
[a] TMSCl and HMPA were each 3 eq to cyclohexenone. A solution of TMSCl and cyclohexenone was added to the cuprate in ether. [b] Cyclohexeneone was added to the mixture of cuprate and TMSCl.

OPTIMIZATION OF THE REACTION CONDITIONS

The influence of copper salt is also remarkable as shown in Table 6. Copper thiocyanate and bromide

are not exceed copper cyanide (entry 1-3). Unfortunately, lithium dimethylcuprate is not the choice, giving 14% ee (entry 4). This poor selectivity by lithium dimethylcuprate clearly indicates that an extension to the catalytic reaction is not promising.[5,12]

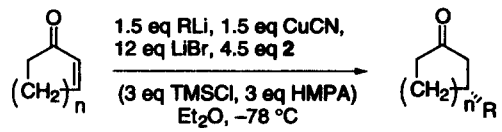
Table 6. Copper salt effect on methylcopper reaction



entry	CuX	temp/°C	yield/%	ee/%
1	CuCN	−78	66	92
2	CuSCN	−10	45	41
3	CuBr	−45	81	45
4	CuMe[a]	−78	81	14

[a] Generated from CuBr and methyllithium.

Table 7. Asymmetric reaction of cyanocuprate-2 with cycloalkenone[a]

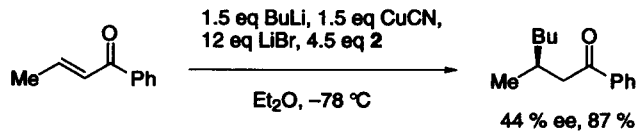


entry	n	R	yield/%	ee/%
1	1	Et	90	94
2	1	Bu	99	95
3[b]	2	Me	66	92
4	2	Et	89	91
5	2	Bu	97	90
6	2	vinyl	60	44
7	2	Ph	63	60
8[b]	3	Me	46	68
9[c]	3	Bu	92	74

[a] For the absolute configuration, see ref. 8. [b] TMSCl-HMPA was used. [c] The absolute configuration was not determined.

Under the optimized conditions, the asymmetric conjugate addition reactions of lithium organocyanocuprates with cycloalkenones gave the corresponding adducts in high ees and yields as shown in Table 7. The alkyl groups were introduced in higher selectivity than vinyl and phenyl groups.

The conditions were also applied to the acyclic enone above to give the higher selectivity 44% ee than 16% (Table 1, entry 1) as shown.



It is important to point out that the reaction of the cuprate generated from Grignard reagent, copper iodide, and **2** gave the adducts with the absolute configuration opposite to that obtained using lithium organocyanocuprate presented above.[5,12]

CONCLUSION

The fine tuning of the reaction conditions for the enantioselective conjugate addition reaction of organocopper to the acyclic- and cyclic enones was realized with respect to copper source, lithium salt, TMSCl, and solvent. As shown in Table 7, methyl, ethyl, butyl, vinyl, and phenyl groups were introduced into

cyclopentenone, cyclohexenone, and cycloheptenone to afford the corresponding 3-substituted cycloalkanones in 95-44% ee.

The present study revealed that the fine condition tuning is still essential in realizing high efficiency and much more efforts are needed to propose some useful guidances on the structure-enantioselectivity relationships for the development of the chiral ligand-mediated asymmetric reaction of organocopper species.

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EXPERIMENTAL

^{1}H- and ^{13}C-NMR were recorded in $CDCl_3$ unless otherwise noted. Chemical shift was presented in ppm downfield from tetramethylsilane. Data were reported as follows: integration, multiplicity, coupling constants (Hz), and assignments where relevant. Mass spectra were recorded under the electron impact (EI) conditions. Reactions were monitored by thin-layer chromatography. Melting points are uncorrected. The column chromatography was carried out using silica gel. The extract was washed with satd sodium bicarbonate, brine, and then dried over magnesium sulfate unless otherwise noted. THF, ether, DME, and toluene were distilled from sodium benzophenone ketyl. Ethyl-[13] and vinyllithium[14] were prepared according to the reported procedure. Titration of all the organometallic reagents was performed according to the reported method.[15] Copper iodide, bromide, chloride and thiocyanate were purified by the reported procedure.[16] Copper cyanide was dried in vauo at 50 °C over KOH and P_2O_5. Lithium cyanide was prepared by the reported procedure.[17] The phosphines **1-4** were prepared by the reported procedure.[6,12,18] All of the asymmetric reaction products are known compounds and showed identical spectra data.

General procedure for the asymmetric reaction with the acyclic enone. (*S*-(+)-3-phenylbutylophenone (Table 1, entry 7). An ether solution of methyllithium (low halide, 1.9 mmol, 1.3 mL) was added dropwise to a suspension of CuI (179 mg, 0.94 mmol) in ether (8 mL) at –20 °C. The solution was stirred for 25 min at –20 °C. A solution of **2** (351 mg, 0.99 mmol) in ether (3 mL) was added and the resulting suspension was stirred at –78 °C for 20 min. A solution of chalcone (130 mg, 0.63 mmol) in ether (5 mL) was added dropwise over 5 min at –20 °C and the red suspension was stirred for 1 h and quenched with satd NH_4Cl and 10% NH_3. After vigorous stirring for 0.5 h at rt, the mixture was extracted with ether. Concentration and chromatography (benzene/hexane, 4/1) gave the adduct (110 mg, 79%) as a colorless oil of $[\alpha]^{25}_D$ +12.6 (c 2.62, CCl_4). The ee was determined to be 84% by the HPLC analysis (Daicel ChiralPak AD, *i*-propanol/hexane 1/30, 0.5 mL/min, (*S*)-major 14 min, (*R*)-minor 17 min). Thebsolute configuration was determined to be *S* by the specific rotation.[7] ^{1}H NMR: 1.2 (d, *J*=6 Hz, 3H, CH_3), 3.0-3.5 (m, 3H), 7.0-7.8 (m, 10H). IR (CCl_4): 1690 cm^{-1}. MS *m/z*: 224 (M^+). The lligand **2** was recovered in 67%yield.

General procedure for the asymmetric reaction with the cycloalkenone. (*R*)-3-butylcyclohexanone (Table 7, entry 5). To a solution of copper cyanide (1.5 mmol) and lithium bromide (12 mmol) in ether (32 mL) was added butyllithium (1.5 mmol) in hexane at –78 °C, and the resulting pink solution was stirred for 20 min at the same temperature. A solution of **2** (4.6 mmol) in ether (16 mL) was added to the solution. The whole was stirred for 15 min at –78 °C. A solution of 2-cyclohexenone (n = 2, 1.0 mmol) in ether (4 mL) was

added and the whole was stirred for 0.5 h at −78 °C. Usual workup and chromatography (dichloromethane/hexane, 4:1) followed by distillation afforded (*R*)-3-butylcyclohexanone (n = 2, R = Bu) of $[\alpha]^{23}_D$ +7.21 °(c 1.04, toluene) in 97% yield.[10] The ee was determined to be 90% by ^{13}C NMR analysis of the corresponding diastereomeric ketals prepared with (*R,R*)-2,3-butanediol (*p*-TsOH in benzene at reflux, 98% yield). The ligand **2** was recovered in 93% yield.

(*S*)-(−)-*N*-Pentafluorobenzoyl-2-[(diphenylphosphino)methyl]pyrrolidine (5). Prepared from the corresponding amine and pentafluorobenzoyl chloride under the same conditions for **2**.[5,12] Purification by alumina chromatography (benzene/hexane, 4/1) gave **5** as powder of mp 84-85 °C (pentane) and $[\alpha]^{25}_D$ −93.3 (c 0.85, $CHCl_3$) in 86% yield. ^1H-NMR: 1.82-2.35 (m, 5H), 3.16-3.76 (m, 3H), 4.35 (m, 1H), 7.10-7.44 (m, 8H), 7.70 (m, 2H). ^{13}C-NMR: 156.6, 156.1, 128.4-145 (Ar), 56.8 (d, *J*=23 Hz, CHN), 56.3 (d, *J*=22 Hz, CHN), 47.9, 45.7, 34.8 (d, *J*=16 Hz, CH_2P), 32.2 (d, *J*=15 Hz, CH_2P), 30.8 (d, *J*=7 Hz), 24.0, 22.1 (Each carbon gave two signals due to the amide configurational isomer). IR (neat): 1650 cm^{-1}. MS *m/z*: 463 (M^+). Anal. Calcd for $C_{24}H_{19}NOF_5P$: C, 62.20; H, 4.10; N, 3.02. Found: C, 62.37; H, 4.09; N, 3.29.

(*S*)-(−)-*N*-1'-Naphthoyl-2-[(diphenylphosphino)methyl]pyrrolidine (6). Prepared by the same procedure for **5** as amorphous of mp 47-56 °C and $[\alpha]^{25}_D$ −133 (c 1.03, $CHCl_3$) in 32% yield. ^1H-NMR: 1.59-2.25 (m, 6H), 3.01-3.89 (m, 2H), 4.55 (m, 1H), 6.45, 6.87-7.48, 7.79 (m, 17H, ArH). ^{13}C-NMR: 169.0, 168.9, 123.7-139.2 (Ar), 56.8 (d, *J*=23 Hz, CHN), 55.4 (d, *J*=20 Hz, CHN), 48.8, 45.3, 33.8 (d, *J*=16 Hz), 32.8 (d, *J*=14 Hz, CH_2P), 30.9 (d, *J*=9 Hz, CH_2CH), 30.6 (d, *J*=10 Hz, CH_2CHN), 24.4, 22.1. (Each carbon gave two signals due to the amide configurational isomer). IR ($CHCl_3$): 1610 cm^{-1}. MS *m/z*: 423 (M^+). Anal. Calcd for $C_{28}H_{26}NOP$: C, 79.43; H, 6.15; N, 3.31. Found: C, 79.32; H, 6.26; N, 3.22.

(*S*)-(−)-*N*-Benzoyl-2-[(diphenylphosphino)methy]pyrrolidine (7). Prepared by the same procedure for **5** as powder of mp 92-92.5 °C (ether/hexane, 1:1) and $[\alpha]^{25}_D$ −115 (c 1.41, $CHCl_3$) in 95% yield. ^1H-NMR: 1.71-2.26 (m, 5H), 3.12 (ddd, *J*=4, 4, 14 Hz, 1H, CH_2P), 3.43 (m, 2H), 4.41 (m, 1H), 7.26-7.45 (m, 13H, ArH), 7.70 (m, 2H, ArH). ^{13}C-NMR: 169.9, 127.2-138.8 (Ar), 55.6 (d, *J*=20 Hz, CHN), 50.4, 32.9 (d, *J*=12 Hz, CH_2P), 31.4 (d, *J*=9 Hz, CH_2CHN), 25.4. IR (KBr): 1610 cm^{-1}. MS *m/z*: 373 (M^+). Anal. Calcd for $C_{24}H_{24}NOP$: C, 77.21; H, 6.43; N, 3.75. Found: C, 77.39; H, 6.53; N, 3.78.

(*S*)-(−)-*N*-Trifluoroacetyl-2-[(diphenylphosphino)methy]pyrrolidine (8). Prepared by the same procedure for **5** as colorless prisms of mp 72-74 °C and $[\alpha]^{25}_D$ −89.8 (c 1.24, $CHCl_3$) in 88% yield. ^1H-NMR: 1.95 (m, 5H), 2.92 (ddd, *J*=4, 4, 13 Hz, 1H, CH_2P), 3.53 (m, 2H), 4.14 (m, 1H), 7.3 (m, 10H, ArH). ^{13}C-NMR: 155.4 (q, *J*=36 Hz), 138.5 (d, *J*=11 Hz, *ipso*Ar), 136.4 (d, *J*=7 Hz, *ipso*Ar), 132.4-133.1 (Ar), 128.4-128.7 (Ar), 116.2 (q, *J*=288 Hz, CF_3), 57.6 (d, *J*=20 Hz, CHN), 46.8, 31.6 (d, *J*=15 Hz, CH_2P), 29.6 (d, *J*=9 Hz), 24.5. IR ($CHCl_3$): 1670 cm^{-1}. MS *m/z*: 365 (M^+). Anal. Calcd for $C_{19}H_{19}NOF_3P$: C, 62.47; H, 5.24; N, 3.83. Found: C, 62.43; H, 5.28; N, 4.04.

(*S*)-(−)-*N*-(4-Methylphenylsulfonyl)-2-[(diphenylphosphinyl)methy]pyrrolidine. Prepared by the same procedure for **5** after chromatography (AcOEt/hexane, 4/1) as white powder of mp 90-91 °C and $[\alpha]^{25}_D$ −207 (c 0.70, $CHCl_3$) in 78% yield. ^1H-NMR: 1.46 (m, 1H), 1.76 (m, 2H), 2.14 (m, 1H), 2.49 (ddd, *J*=12, 15, 15 Hz, 1H, CH_2P), 2.99 (m, 1H), 3.28 (ddd, *J*=2, 8, 15 Hz, 1H, CH_2P), 3.45 (m, 1H), 3.60 (m, 1H), 7.14 and 7.34 (d, *J*=8 Hz, each 2H, Ts), 7.45 (m, 3H), 7.61 (m, 3H), 7.76 (m, 2H), 7.97 (m, 2H). ^{13}C-NMR: 143.3, 127.3-134.3 (Ar), 55.3, 49.0, 36.4 (d, *J*=66 Hz, CH_2P), 32.1, 23.7, 21.2. IR ($CHCl_3$): 1475, 1160 cm^{-1}. MS

m/z: 438 (M^+-1). Anal. Calcd for $C_{24}H_{26}NO_3PS$: C, 65.60; H, 5.92; N, 3.19. Found: C, 65.48; H, 5.99; N, 3.41.

(*S*)-(–)-*N*-(4-Methylphenylsulfonyl)-2-[(diphenylphosphino)methy]pyrrolidine (9). A solution of the above oxide (1.4 mmol), trichlorosilane and triethylamine (2.1 mmol) in acetonitrile (5 mL) was stirred for 4 h at rt. Workup and recrystallization from ether-hexane (1:1) gave colorless prisms of mp 94-95 °C and $[\alpha]^{25}_D$ –290 (c 1.66, $CHCl_3$) in 51% yield. ^{1}H-NMR: 1.40-1.89 (m, 4H), 2.15 (ddd, *J*=5, 12, 14 Hz, 1H, CH_2P), 2.38 (s, 3H), 3.08 (m, 2H), 3.45 (m, 2H), 7.10-7.44 (m, 12H), 7.71 (m, 2H). ^{13}C-NMR: 143.1, 127.4-129.5 (Ar), 58.0 (d, *J*=21 Hz, CHN), 49.4, 36.1 (d, *J*=13 Hz, CH_2P), 31.8 (d, *J*=9 Hz), 24.1, 21.4. IR (KBr): 1340, 1150 cm^{-1}. Anal. Calcd for $C_{24}H_{26}NO_2PS$: C, 68.09; H, 6.15; N, 3.31. Found: C, 68.36; H, 6.19; N, 3.19.

(*S*)-(–)-*N*-(2',2'-Dimethylpropionyl)-2-pyrrolidinemethanol. A mixture of L-prolinol (99 mmol), pivaloyl chloride (99 mmol), and triethylamine (119 mmol) in dichloromethane (50 mL) was stirred for 10 min at 0 °C and quenched with satd sodium bicarbonate, and then extracted with dichloromethane. Concentration and recrystallization from hexane gave colorless prisms of mp 79.5-81 °C and $[\alpha]^{25}_D$ –70.9 (c 0.97, EtOH) in 82% yield. ^{1}H-NMR: 1.28 (s, 9H, *t*-Bu), 1.5-2.1 (m, 4H), 3.2-3.91 (m, 4H), 4.25 (m, 1H), 4.80 (brs, 1H, OH). ^{13}C-NMR: 179.2, 67.8, 62.4, 48.5, 39.1, 27.5, 27.3, 25.3. IR (neat) 3330, 1585 cm^{-1}. MS *m/z*: 185 (M^+). Anal. Calcd for $C_{10}H_{19}NO_2$: C, 64.83; H, 10.34; N, 7.56. Found: C, 65.04; H,10.21; N, 7.58.

(*S*)-(–)-*N*-(2',2'-Dimethylpropionyl)-2-[(methylthio)methyl]pyrrolidine (10). A mixture of the above alcohol (50 mmol), dimethyl disulfide (68 mmol) and tributylphosphine (68 mmol) in pyridine (70 mL) was stirred at rt for 2 d, and quenched with water, and then extracted with AcOEt. Concentration and chromatography (AcOEt/hexane, 1/9) gave **10** as a colorless oil of $[\alpha]^{25}_D$ –64.1 (c 1.36, EtOH) in 64% yield. ^{1}H-NMR: 1.24 (s, 9H, *t*-Bu), 1.87 (m, 4H), 2.16 (s, 3H), 2.41 (dd, 1H, *J*=9, 13 Hz), 2.90 (dd, *J*=3, 13 Hz, 1H), 3.63 (m, 2H), 4.30 (m, 1H). ^{13}C-NMR: 176.4, 58.4, 48.2, 39.1, 36.7, 27.9, 27.5, 24.9, 15.6. IR (neat): 1630 cm^{-1}. MS *m/z*: 215 (M^+). Anal. Calcd for $C_{11}H_{21}NOS$: C, 61.35; H, 9.83; N, 6.50. Found: C, 61.26; H, 9.65; N, 6.76.

(*S*)-(–)-*N*-(2',2'-Dimethylpropionyl)-2-[(phenylthio)methyl]pyrrolidine (11). A mixture of the above alcohol (7 mmol), diphenyl disulfide (10 mmol) and tributylphosphine (10 mmol) in pyridine (10 mL) was stirred at rt for 4 h. Workup and chromatography (AcOEt/hexane, 1/4) gave **11** as a colorless oil of $[\alpha]^{25}_D$ –9.37 (c 1.20, EtOH) in 99% yield. ^{1}H-NMR: 1.21 (s, 9H, *t*-Bu), 1.9 (m, 4H), 2.88 (dd, *J*=6, 9 Hz, 1H), 3.51 (dd, 1H, *J*=2, 9 Hz), 3.60 (m, 2H), 4.40 (m, 1H), 7.10-7.50 (m, 5H). ^{13}C-NMR: 176.7, 136.4, 128.8, 128.2, 125.4, 58.2, 48.5, 39.1, 35.2, 28.0, 27.5, 25.1. IR (neat): 1620 cm^{-1}. MS *m/z*: 277 (M^+). Anal. Calcd for $C_{16}H_{23}NOS$: C, 69.27; H, 8.36; N, 5.05. Found: C, 69.45; H, 8.07; N, 4.97.

(*S*)-(+)-*N*-*tert*-Butoxycarbonyl-2-[(*N',N'*-diphenylamino)methyl]pyrrolidine. A mixture of NaH (83 mmol) and diphenylamine (83 mmol) in THF (80 mL) was refluxed for 2.5 h. A solution of the corresponding tosylate in THF (15 mL) was added at rt and the whole was stirred for 2.5 h, and then satd. NH_4Cl was added and extracted with AcOEt. Concentration and chromatography (ether/hexane, 1/9) gave a pale yellow oil of $[\alpha]^{25}_D$ +3.46 (c 2.05, EtOH) in 78% yield. ^{1}H-NMR: 1.50 (s, 9H, *t*-Bu), 1.86 (m, 4H), 3.3-4.3 (m, 5H), 6.87-7.35 (m, 10H, ArH). ^{13}C-NMR: 154.5, 148.7, 129.2, 121.4, 120.8, 79.8, 55.6, 54.2, 46.6, 29.8, 28.7, 22.7. IR (neat): 1690 cm^{-1}. MS *m/z*: 352 (M^+). Anal. Calcd for $C_{22}H_{28}N_2O_2$: C, 74.97; H, 8.01; N, 7.95. Found: C, 75.18; H, 8.06; N, 7.71.

(*S*)-(–)-*N*-(2',2'-Dimethylpropionyl)-2-[(*N'N'*-diphenylamino)methyl]pyrrolidine (12). A solution of the above Boc derivative (1.1 mmol) and trifluoroacetic acid (21 mmol) in dichloromethane (5 mL) was stirred at rt for 26 h. The mixture was concentrated and the resulting black oil was dissolved in dichloromethane (1 mL) and triethylamine (11 mmol). Pivaloyl chloride (5.3 mmol) was added at 0 °C and the whole was stirred for 20 min. The reaction was quenched with satd sodium bicarbonate and thenextracted with AcOEt. Concentration and chromatography (AcOEt/hexane, 1/9) gave **12** as colorless needles of mp 78-79 °C (hexane) and $[\alpha]^{25}_{D}$ –41.0 (c 1.53, EtOH) in 73% yield. ^{1}H-NMR: 1.22 (s, 9H, *t*-Bu), 1.85 (m, 4H), 3.48 (dd, *J*=10, 15 Hz, 1H, CH_2NPh_2), 3.60 (m, 2H), 4.20 (dd, *J*=4, 15 Hz, 1H, CH_2NPh_2), 4.63 (m, 1H), 6.83-7.40 (m, 10H, ArH). ^{13}C-NMR: 176.9, 148.9, 129.2, 121.2, 57.9, 53.4, 48.0, 39.2, 27.7, 27.1, 25.1. IR (neat): 1620 cm^{-1}. MS *m/z*: 336 (M^+). Anal. Calcd for $C_{22}H_{28}N_2O$: C, 78.53; H, 8.39; N, 8.33. Found: C, 78.31; H, 8.58; N, 8.49.

(*S*)-(–)-*N*-(2',2'-Dimethylpropionyl)-2-(methoxymethyl)pyrrolidine (13). The above alcohol (16 mmol) in THF (20 mL) was added to a suspension of NaH (32 mmol) in THF (10 mL) at 0 °C. After 15 min, methyl iodide (81 mmol) was added and the mixture was stirred for 1 h, and quenched with satd NH_4Cl, and then extracted with AcOEt. Concentration and chromatography (AcOEt/hexane, 1/9) gave **13** as a pale yellow oil of $[\alpha]^{25}_{D}$ –85.3 (c 1.03, EtOH) in 94% yield. ^{1}H-NMR: 1.25 (s, 9H, *t*-Bu), 1.92 (m, 4H), 3.33 (s, 3H), 3.58 (m, 4H), 4.33 (m, 1H). ^{13}C-NMR: 176.2, 72.2, 58.6, 57.8, 47.9, 38.9, 27.4, 26.2, 24.8. IR (neat): 1620 cm^{-1}. MS *m/z*: 199 (M^+). HRMS. Calcd for $C_{11}H_{21}NO_2$ (M^+): 199.1573. Found: 199.1570.

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