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Peptidic Amidomonophosphane Ligand for Copper-Catalyzed Asymmetric Conjugate Addition of Diorganozincs to Cycloalkenones

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This paper is dedicated to Prof Masakatsu Shibasaki on the occasion of his 60th birthday.

Abstract: Peptidic modification of (*S*)-2-[(diphenylphosphino)methyl]pyrrolidine gave a dipeptide-connected amidomonophosphane ligand for the highly efficient, copper-catalyzed asymmetric conjugate addition reaction of organozinc reagents with cycloalkenones, giving 3-alkylated cycloalkanones in high enantioselectivity of up to 98% *ee*. A model that predicts the stereochemistry of the reaction is discussed.

Keywords: asymmetric catalysis; catalyst design; conjugate addition; copper; organozinc reagents

Introduction

The copper-catalyzed asymmetric conjugate addition reaction of organometallic reagents with activated olefins has been the subject of recent energetic research work.[1] Key to its successful accomplishment relies on the development of sophisticatedly designed chiral ligands for the metal catalysts.[2] For the most established copper-catalyzed asymmetric conjugate addition reaction of Grignard reagents with enones, a chiral amine[1a,b] was the first of the successful chiral sources of heterocuprates and was followed by the zinc complexes of chiral amino alcohols[3] and chiral thiols,[1g] and recently by a chiral selenide[4] and a chiral pyrazole derivative.[5] Other successful approaches for controlling high enantioselectivity rely on the coordination of a phosphorus atom with copper, and a chiral amidophosphane **1** proved to be a good ligand for the copper-catalyzed conjugate addition of Grignard reagents to enones,[6] which was followed by a chiral ferrocenyl-based monophosphane[7] as well as a bisphosphane.[8] Further brilliant successes have also been continuously reported by using dialkylzinc reagents as sources of alkyl nucleophiles, which are characterized by the use of a phosphorus-based ligand for copper.[9,10] Since the development of a phosphoroamidite by Alexakis' group,[11,12] binaphthol-based phosphorus ligands have been demonstrated to be really effective giving over 90% *ee* by the endeavors of the Feringa[13] and Zhang[14] groups. Highly efficient phosphane ligands were also developed by Imamoto[15] and Hoveyda.[16] These phosphorus ligands were shown to be applicable in the conjugate addition reaction of nitroalkenes[17–21] and α,β-unsaturated lactones.[22,23] Copper-catalyzed conjugate arylation,[24,25] vinylation[26] and kinetic resolution[27] have been the topics of the recent brilliant studies.[28]

It is natural for us to apply the amidophosphane **1** in the copper-catalyzed asymmetric conjugate addition of diorganozincs, because **1** was really effective in the conjugate alkylation of Grignard reagents[6] as well as the Rh(I)-catalyzed conjugate arylation of arylboronic acids.[29] Another reason is that we have a rich stock of amidophosphanes which were applied in the copper-catalyzed alkylation of diorganozinc reagents with imines[30] and the rhodium-catalyzed arylation of arylboronic acids with imines.[31] We have also turned our attention to the screening and new design of the amidophosphanes. We describe herein that dipeptidic amidophosphanes behave as a satisfactory ligand for copper to give the conjugate alkylation products with up to 98% *ee* (Figure 1 and Figure 2). A stereochemical model is also discussed.

Results and Discussion

Amino Acid-Connected Amidophosphane

The conjugate ethylation of cyclohexenone **2a** with diethylzinc was catalyzed by 6.5 mol% of pivaloyl-amidophosphane **1**[6,29] and 5 mol% of copper(II) triflate

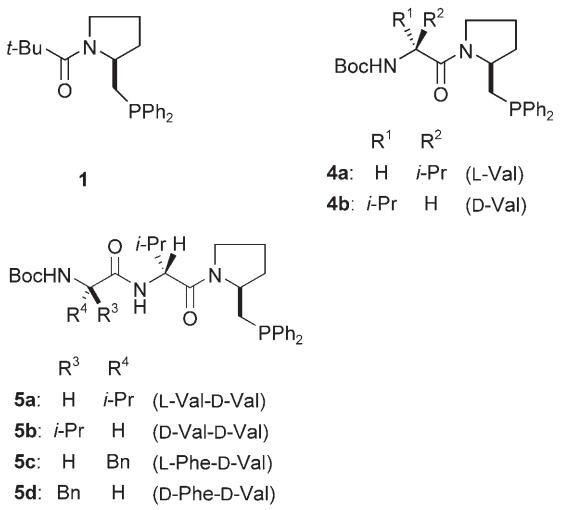


Figure 1. Peptidic amidomonophosphane ligands.

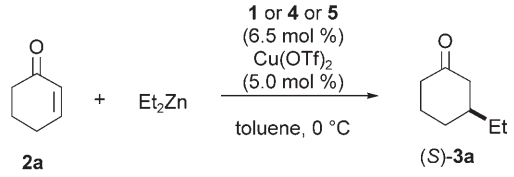


Figure 2. Copper-catalyzed conjugate ethylation.

in toluene at 0 °C for 1 h to afford (*S*)-3-ethylcyclohexanone **3a** with 13 % *ee* in 83 % yield (Table 1, entry 1). The enantioselectivity of **3a** was determined by a chiral stationary phase HPLC. *N*-Boc-L-valine connected amidophosphane **4a** was selected as a next ligand because **4a** was effective in the rhodium-catalyzed arylation of imines with arylboronic acids.[31,32] As has been expected the conjugate ethylation was catalyzed by **4a**-copper(II) triflate to give (*R*)-**3a** with moderate 56 % *ee* in 81 % yield (entry 2). It is interesting to know that L-Val-connected amidophosphane **4a** gave (*R*)-**3a**, while the parent pivaloyl amidophosphane **1** gave (*S*)-**3a** (entry 1). This suggests that the D-Val connected amidophosphane **4b** gives (*S*)-**3a** in better enantioselectivity.

In fact, the conjugate ethylation of cyclohexenone was conducted under the catalysis of the *N*-Boc-D-valine-connected amidophosphane **4b** and copper(II) triflate to give expectedly (*S*)-**3a** with higher 74 % *ee* in 84 % yield (entry 3). The dipeptide-connected amidophosphanes **5** are a logical extension from **4** to be surveyed for the better ligand.[33] The four Val-D-Val and Phe-D-Val connected ligands **5a–d** were examined (entries 4–7) and **5d** (D-Phe-D-Val) was found to be an extremely efficient ligand giving (*S*)-**3a** with 98 % *ee* in 87 % isolated yield (entry 7). It is also important to note that these dipeptidic amidophosphanes were recovered nearly quantitatively after the reaction and were reusable.

Other diorganozinc reagents including functionalized ones were applied in the asymmetric alkylation of cyclohexenone **2a** giving the corresponding substituted cyclohexanones **3** with 45–94 % *ee* (Table 2, entries 2–5). The catalytic conjugate ethylation of 4,4-dimethylcyclohexenone **2b**, cycloheptenone **2c** and cyclooctenone **2d** with **5d**-Cu(I) in toluene at 0 °C gave the corresponding products **3b, 3c**, and **3d** with 75 %, 86 %, and 61 % ees in good isolated yields (entries 6–8).

Plausible Stereochemical Pathway

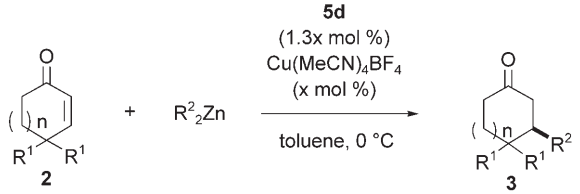
It is really interesting to note that a dipeptidic phosphane ligand **6** developed by Hoveyda[16] and **5d** have the same amino acid constituents, D-Phe and D-Val, albeit incorporated in the reverse amino acid sequence, as shown in Figure 3. The striking difference is the enantiofacial selection in that **6** gave (*R*)-**3a** and **5d** gave (*S*)-**3a**.[34] Another structural difference is the order of amino acid sequence; in **5d** the nitrogen of a chiral pyrrolidinylphosphane is acylated at the *C*-terminal of *N*-Boc-D-Phe-D-Val, while in **6** achiral diphenylphosphinobenzaldehyde is connected in the form of an imine at the *N*-terminal of D-Val-D-Phe amide.

The sense of enantiofacial selection by **5d**-Cu(I) is proposed by the model **7** illustrated in Scheme 1. The

Table 1. Copper-catalyzed asymmetric conjugate ethylation of cyclohexenone **2a**.

Entry	**1/4/5**	AA (**4**)	Time [h]	**3a**		
				Yield [%]	*ee* [%]	(*R*/*S*)
1	**1**	Piv	1	87	13	*S*
2	**4a**	L-Val	1	81	56	*R*
3	**4b**	D-Val	1	84	74	*S*
4	**5a**	L-Val-D-Val	1	92	21	*S*
5	**5b**	D-Val-D-Val	1	88	17	*S*
6	**5c**	L-Phe-D-Val	20	81	22	*S*
7	**5d**	D-Phe-D-Val	2	87	98	*S*

Table 2. *N*-Boc-D-Phe-D-Val-P (**5d**)-copper(MeCN)$_4$BF$_4$-catalyzed asymmetric conjugate alkylation of cycloalkenone **2** giving **3**.



Entry	**2**	R^1	n	R^2	x [mol %]	Time [h]	**3**	Yield [%]	*ee* [%]
1	**2a**	H	1	Et	5	2	**3a**	87	98
2	**2a**	H	1	Me	10	48	**3ab**	62	45
3	**2a**	H	1	*i*-Pr	2	5	**3ac**	97	94
4	**2a**	H	1	$(CH)_3Ph$	5	36	**3ad**	48	94
5	**2a**	H	1	$(CH)_5OAc$	5	17	**3af**	84	75
6	**2b**	Me	1	Et	5	41	**3b**	66	75
7	**2c**	H	2	Et	2	18	**3c**	78	86
8	**2d**	H	3	Et	5	36	**3d**	83	61

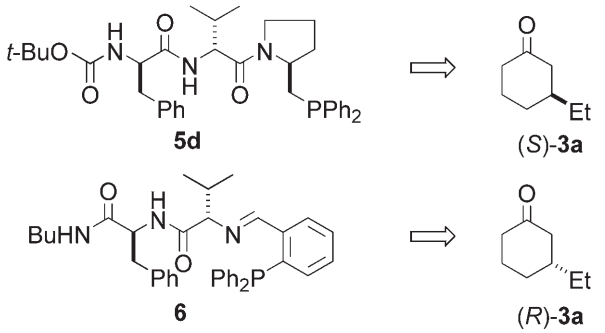
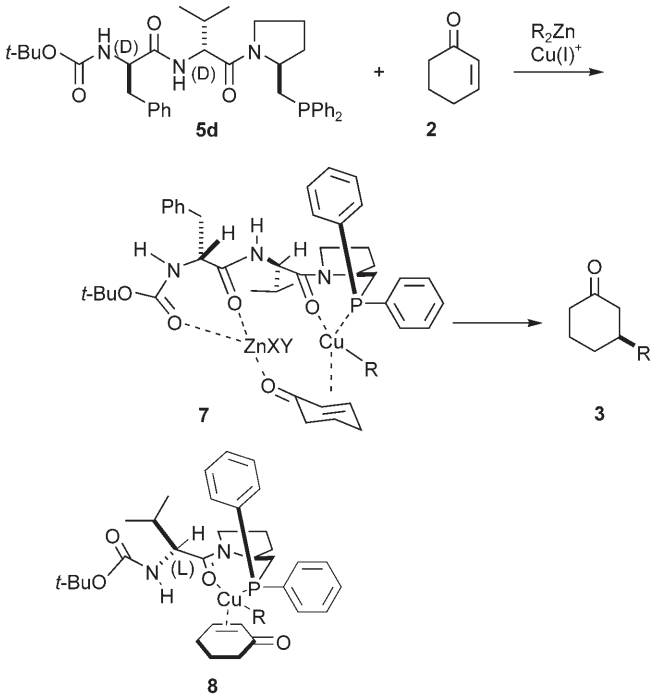


Figure 3. Dipeptidic phosphanes **5d** and **6**.



Scheme 1. Plausible stereochemical pathway.

phosphorus and carbonyl oxygen of the *C*-terminal amino acid form a 7-membered chelate with copper(I) as has been determined in a rhodium complex of **1**.[29b] Cyclohexenone **2a** coordinates with copper(I) by the C=C double bond from the face of the chelate opposite to an angular-like phenyl group on phosphorus. The small hydrogen of the C-terminal amino acid chiral center is on the plane of C–CO–N due to the allylic strain, and points toward pyrrolidine ring. Three carbonyl oxygens of Boc, the *N*-terminal amino acid, and cyclohexenone are coordinated by zinc(II). The alkyl group on Cu(I) is transferred on the *si*-face of cyclohexenone to give (*S*)-3-substituted cyclohexanone **3a** with the observed absolute configuration. When the *C*-terminal amino acid has the (L)-configuration as shown in Boc-L-Val **4a**, the steric bulk of the amino acid moiety would direct cyclohexenone to coordinate in the opposite way (**8**) giving (*R*)-**3a**.

Conclusions

In summary, we have disclosed a highly enantioselective catalytic conjugate addition reaction of cycloalkenones with dialkylzinc reagents. Key for these efficient enantioselective catalytic conjugate additions is a dipeptidic amidophosphane ligand for copper(I). Moreover, we propose a plausible working model to predict the observed sense of enantiofacial differentiation.

Experimental Section

General Remarks

Asymmetric reactions were carried out under argon. IR spectra were expressed in cm^{-1}. ^1H, ^{13}C and ^{31}P NMR spectra were taken in $CDCl_3$ at 500, 125 and 202 MHz, respectively. Chemical shift values are expressed in ppm relative to internal TMS or external 85% H_3PO_4 for ^{31}P. Abbreviations are as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad.

Preparation of Dialkylzinc[35]

In a Schlenk tube, hydroboration was performed by mixing alkene (10 mmol) and diethylborane, freshly prepared by mixing triethylborane (1.4 mL, 10 mmol) and borane-dimethyl sulfide complex (0.47 mL, 5 mmol) in a Schlenk tube at 0 °C for 5 min. After completion by stirring at room temperature, the solvent was carefully distilled off (0.5 mm Hg, 0 °C) for 0.5 h to afford a crude product, which was treated with a hexane solution of diethylzinc (2.0 mL, 20 mmol) at 0 °C. After 0.5 h, the excess diethylzinc and triethylborane were distilled off (0.8 mm Hg, 0 °C) for 3 h and the residue was diluted with toluene (10 mL) which was directly used in the asymmetric conjugate addition.

Syntheses of **4a** and **4b** were reported previously.[31]

(−)-*N*-Boc-L-Val-D-Val-2(*S*)-(diphenylphosphinomethyl)pyrrolidine (5a)

Under an argon atmosphere, to a solution of (*S*)-*N*-*tert*-butoxycarbonyl-2-[(diphenylphosphino)methyl]pyrrolidine (1.11 g, 3.0 mmol) in dioxane (4.4 mL) was added 5.4 N HCl-dioxane (11 mL, 60 mmol) at 0 °C over 5 min, and then the whole was stirred at room temperature for 1 h. The mixture was concentrated to give a yellow amorphous solid, to which in anhydrous DMF (30 mL) and CH_2Cl_2 (30 mL) were added *N*-Boc-L-Val-D-Val (3.03 mmol), HOOBt (523 mg, 3.21 mmol), EDC·HCl (691 mg, 3.6 mmol), and *N*-methylmorphorine (1.32 mL, 12.0 mmol) at −20 °C. After this temperature had been maintained for 30 min, the reaction mixture was stirred at 0 °C for 18 h and at room temperature for 1 h. AcOEt (100 mL), brine (20 mL), and 10% aqueous citric acid (20 mL) were added. The organic layer was washed with 10% aqueous citric acid (20 mL), saturated aqueous sodium bicarbonate (30 mL × 2), water (30 mL), and brine (30 mL), and then dried over Na_2SO_4. Concentration and silica gel column chromatography (hexane/ethyl acetate = 3/1) gave a pale yellow amorphous solid; yield: 1.41 g (92%); $[\alpha]_D^{25}$: −8.26 (*c* 1.09, benzene). ^1H NMR: δ = 0.85–1.15 (12H, m), 1.42 + 1.43 (total 9H, s), 1.89–2.16 (7H, m), 2.95 (1H, m), 3.50 (1H, m), 3.75 (1H, m), 4.10 (1H, m), 4.14 (1H, m), 4.50 (1H, m), 5.06 (1H, m), 6.55 (1H, d, *J* = 8.9 Hz), 7.23–7.64 (10H, m); ^{13}C NMR: δ = 17.9, 17.1, 17.7, 17.9, 19.1, 19.9, 20.8, 21.3, 23.5, 24.1, 28.0, 29.5 (d, *J* = 8.3 Hz), 30.3, 30.9, 31.3 (d, *J* = 14.3 Hz), 35.6 (d, *J* = 16.3 Hz), 45.2, 46.6, 55.5 (d, *J* = 21.6 Hz), 55.8, 59.4, 60.4, 79.3, 128.0, 128.1, 128.3, 128.4, 129.3, 129.4, 130.0 (d, *J* = 9.3 Hz), 131.0 (d, *J* = 10.3 Hz), 132.3 (d, *J* = 19.5 Hz), 132.6 (d, *J* = 19.5 Hz), 136.7 (d, *J* = 12.3 Hz), 138.8 (d, *J* = 12.3 Hz), 155.4, 169.4, 169.9, 170.2, 171.3; ^{31}P NMR: δ = −24.2 (1/13P, s), −24.3 (12/13P, s); IR (nujol): ν = 3350, 1720, 1630 cm^{-1}; EI-MS: *m/z* = 567 (M^+); anal. calcd. for $C_{32}H_{46}N_3O_4P$: C 67.70, H 8.17, N 7.40; found: C 67.48, H 8.02, N 7.45.

(−)-*N*-Boc-D-Val-D-Val-2(*S*)-(diphenylphosphinomethyl)pyrrolidine (5b)

Silica gel column chromatography (hexane/ethyl acetate = 3/1) gave a pale yellow amorphous solid; yield: 1.27 g (83%); $[\alpha]_D^{25}$: −96.7 (*c* 0.95, benzene). ^1H NMR: δ = 0.82–0.95 (11H, m), 1.01 + 1.03 (total 1H, d, *J* = 6.8 Hz), 1.40 (9H, s), 1.77–2.09 (7H, m), 2.96 (1H, m), 3.51 (1H, m), 3.77 (1H, m), 3.93 (1H, m), 4.17 (1H, m), 4.50 (1H, m), 4.99 (1H, m), 6.50 (1H, d, *J* = 8.6 Hz), 7.19–7.64 (10H, m); ^{13}C NMR: δ = 17.6, 17.8, 18.1, 19.2, 19.4, 21.7, 28.2, 29.5, 29.9, 30.2, 30.3, 30.7, 30.9 (d, *J* = 13 Hz), 31.4, 32.3 (d, *J* = 13.3 Hz), 45.3, 47.1, 55.3 (d, *J* = 19.6 Hz), 55.6 (d, *J* = 18.5 Hz), 79.7, 128.3, 128.4, 128.4, 128.5, 128.7, 131.2 (d, *J* = 12.3 Hz), 132.5 (d, *J* = 19.5 Hz), 132.9 (d, *J* = 19.5 Hz), 134.1, 134.2, 135.1 (d, *J* = 8.2 Hz), 136.7 (d, *J* = 12.3 Hz), 139.1 (d, *J* = 10.3 Hz), 155.6, 169.9, 170.2, 171.0, 171.6; ^{31}P NMR: δ = −24.2 (1/5P, s), −24.3 (4/5P, s); IR (nujol): ν = 3340, 1710, 1630 cm^{-1}; EI-MS: *m/z* = 567 (M^+); anal. calcd. for $C_{32}H_{46}N_3O_4P$: C 67.70, H 8.17, N 7.40; found: C 67.93, H 8.13, N, 7.20.

(−)-*N*-Boc-L-Phe-D-Val-2(*S*)-(diphenylphosphinomethyl)pyrrolidine (5c)

Silica gel column chromatography (hexane/ethyl acetate = 2/1) gave a pale yellow amorphous solid; yield: 1.39 g (84%); $[\alpha]_D^{25}$: −70.0 (*c* 1.08, benzene). ^1H NMR: δ = 0.55 + 0.71 + 0.76 + 0.80 + 0.85 + 0.91 (total 6H, d, *J* = 6.5 Hz), 1.39 + 1.42 (total 9H, s), 1.67–2.00 (6H, m), 2.98–3.11 (3H, m), 3.49 (1H, m), 3.66 (1H, m), 4.12 (1H, m), 4.33–4.47 (2H, m), 4.97 (1H, m), 6.60 (1H, d, *J* = 8.9 Hz), 7.14–7.76 (15H, m); ^{13}C NMR: d = 17.5, 17.7, 18.5, 19.1, 21.5, 23.5, 24.0, 27.9, 29.5 (d, *J* = 10.3 Hz), 29.9 (d, *J* = 8.3 Hz), 30.3 (d, *J* = 11.3 Hz), 31.2, 31.9 (d, *J* = 7.1 Hz), 32.0, 45.2, 46.6, 47.0, 55.0 (d, *J* = 18.5 Hz), 55.3 (d, *J* = 20.6 Hz), 55.7, 79.3, 126.3, 128.0, 128.1, 128.2, 128.3, 128.4, 128.5, 129.0, 129.2, 132.0, 132.2 (d, *J* = 18.5 Hz), 132.7 (d, *J* = 18.5 Hz), 134.0 (d, *J* = 20.5 Hz), 135.6 (d, *J* = 12.3 Hz), 136.5, 139.0 (d, *J* = 12.3 Hz), 154.9, 169.3, 169.3, 170.1, 170.9; ^{31}P NMR: δ = −24.0 (3/10P, s), −24.6 (7/10P, s); IR (nujol): ν = 3290, 1720, 1610 cm^{-1}; MS (FAB): *m/z* = 616 ($M + H^+$); HR-MS (FAB): *m/z* = 616.3320, calcd. for $C_{36}H_{46}N_3O_4P$ [$M + H^+$]: 616.3304.

(−)-*N*-Boc-D-Phe-D-Val-2(*S*)-(diphenylphosphinomethyl)pyrrolidine (5d)

Silica gel column chromatography (hexane/ethyl acetate = 2/1) gave a pale yellow amorphous solid; yield: 1.23 g (74%); $[\alpha]_D^{25}$: +2.15 (*c* 1.16, benzene). ^1H NMR: δ = 0.53 + 0.64 + 0.75 + 0.80 + 0.86 + 0.90 (total 6H, d, *J* = 6.8 Hz), 1.37 + 1.39 (total 9H, s), 1.71–2.11 (6H, m), 2.95–3.11 (3H, m), 3.47–3.64 (2H, m), 4.12 (1H, m), 4.15–4.49 (1H, m), 4.97 (1H, m), 6.59 (1H, d, *J* = 9.2 Hz), 7.03–7.67 (15H, m); ^{13}C NMR: 17.6, 17.8, 19.1, 19.2, 19.8, 23.4, 23.9, 27.9, 29.4 (d, *J* = 9.3 Hz), 30.8, 31.3 (d, *J* = 15.5 Hz), 37.7, 38.5, 55.3 (d, *J* = 21.5 Hz), 55.7, 79.3, 126.3, 127.9, 128.0, 128.1, 128.2, 128.2, 128.3, 128.4, 128.9, 132.2 (d, *J* = 19.5 Hz), 132.6 (d, *J* = 19.5 Hz), 136.3 (d, *J* = 10.3 Hz), 138.9 (d, *J* = 12.3 Hz), 154.9, 169.2, 169.7, 169.9, 170.9; ^{31}P NMR: −23.8 (12/13P, s), −24.2 (1/13P, s); IR (nujol): ν = 3300, 1720, 1610 cm^{-1}; MS (FAB):

m/z = 616 ($M+H^+$); HR-MS (FAB): *m/z* = 616.3294, calcd. for $C_{36}H_{46}N_3O_4P$ [$M+H^+$]: 616.3304.

Asymmetric Conjugate Ethylation of Cyclohexenone 2a with Diethylzinc by the Catalysis of 5d-Copper(I) giving (−)-(*S*)-3-Ethylcyclohexanone (3a; Table 1, entry 7)

A solution of **5d** (68.2 mg, 0.111 mmol) in 7.8 mL of toluene was added to a suspension of $Cu(MeCN)_4BF_4$ (26.7 mg, 0.085 mmol) in 24.5 mL of toluene. The resulting solution was stirred for 1 h at room temperature. A solution of cyclohexenone **2a** (1.7 mmol) in 22 mL of toluene was added at room temperature. After stirring at room temperature for 10 min, the mixture was cooled to 0 °C. A hexane solution of diethylzinc (3.4 mL, 3.4 mmol) was added at 0 °C and the whole was stirred at 0 °C for 2 h. The reaction was quenched with 10% HCl and stirred at room temperature for 0.5 h. The organic layer was separated and the water layer was extracted with diethyl ether. The combined organic layers were washed with saturated $NaHCO_3$ and brine, and then dried over Na_2SO_4. Concentration and silica gel column chromatography (hexane then hexane/diethyl ether = 20/1) gave (−)-(*S*)-3-ethylcyclohexanone **3a**[36] as a colorless oil; yield: 186 mg (87%); $[\alpha]_{365}^{22}$: −173.4 (*c* 0.68, $CHCl_3$). The *ee* was determined to be 98% by ^{13}C NMR of its diastereomeric aminal. ^1H NMR: δ = 0.95 (3H, t, *J* = 7.0 Hz), 1.3–2.5-(9H, m); IR (neat): ν = 1740 cm^{-1}; MS: *m/z* = 126 (M^+).

Determination of the *ee* of (−)-(*S*)-3a[6f-h]

A mixture of (−)-(*S*)-**3a** formed above (50 mg, 0.39 mmol), (−)-(*1S,2S*)-1,2-diphenylethane-1,2-diamine (100 mg, 0.47 mmol) and MS 4 Å (20 mg) in $CDCl_3$ (2 mL) was stirred at room temperature for 12 h. ^1H NMR: δ = 0.88 (3H, t, *J* = 7.2 Hz), 1.23–2.10(15H, m), 3.55 (1H, m), 2.98 (1H, m), 3.41 (1H, m), 3.82 (1H, m), 4.11 (1H, m), 5.15 (1H, m), 6.47 (1H, d, *J* = 7.6 Hz), 7.00–7.66 (15H, m); ^{13}C NMR: δ = 11.3, 20.0, 29.7, 31.6, 36.4 (major), 37.2 (minor), 39.7 (minor), 40.2 (major), 45.8 (major), 46.0 (minor). From these three sets of integration ratios (major/minor = 1/0.01, 1/0.01, 1/0.01), the *ee* was determined to be 98% *ee*.

(−)-*R*-3-Ethyl-4,4-dimethylcyclohexane-1-one (3b)

Silica gel column chromatography (hexane then hexane/diethyl ether = 20/1) gave (−)-(*R*)-**3b** as a colorless oil; yield: 173 mg (66%); $[\alpha]_D^{20}$: −17.2 (*c* 1.38, $CHCl_3$). The (*R*) absolute configuration and 75% *ee* were determined from the specific rotation.[6j] ^1H NMR: δ = 0.88 (3H, t, *J* = 7.3 Hz), 0.99 (3H, s), 1.03 (3H, s), 1.40 (1H, m), 1.54–1.75 (3H, m), 2.01 (1H, ddd, *J* = 0.99, 12.1, 14.8 Hz), 2.23–2.49 (3H, m); ^{13}C NMR: δ = 12.1, 19.4, 23.2, 28.6, 32.8, 38.2, 40.4, 42.3, 48.7, 212.2; IR (neat): ν = 1720 cm^{-1}; MS: *m/z* = 154 (M^+).

(−)-(*S*)-3-Ethylcycloheptan-1-one (3c)

Silica gel column chromatography (hexane then hexane/diethyl ether = 20/1) gave (−)-(*S*)-**3c** as a colorless oil; yield: 203 mg (85%); $[\alpha]_D^{20}$: −52.7 (*c* 1.09, $CHCl_3$). The *ee* was determined to be 86% from the specific rotation.[6i] ^1H NMR: δ = 0.88 (3H, t, *J* = 7.3 Hz), 0.99 (3H, s), 1.03 (3H, s), 1.40 (1H, m), 1.54–1.75 (3H, m), 2.01 (1H, ddd, *J* = 0.99 Hz, 12.1, 14.8 Hz), 2.23–2.49 (3H, m); ^{13}C NMR: δ = 12.1, 19.4, 23.2, 28.6, 32.8, 38.2, 40.4, 42.3, 48.7, 212.2; IR (neat): ν = 1720 cm^{-1}; EI-MS: *m/z* = 154 (M^+).

(+)-3-Cyclooctane-1-one (3d)[37]

Silica gel column chromatography (hexane then hexane/diethyl ether = 20/1) gave (+)-**3d** as a colorless oil; yield: 217 mg (83%); $[\alpha]_D^{25}$: +8.21 (*c* 1.23, $CHCl_3$). The *ee* was determined to be 61% by GC (γ-Dex 225, 30 m × 0.25 mm, 100 °C, major 28.0 min and minor 26.1 min). ^1H NMR: δ = 0.92 (3H, t, *J* = 7.3 Hz), 0.99 (3H, s), 1.14–1.96 (11H, m), 2.30–2.47 (4H, m); ^{13}C NMR: δ = 11.6, 23.7, 14.6, 27.7, 30.0, 33.0, 39.7, 42.9, 46.9, 217.2. IR (neat): ν = 1710 cm^{-1}; EI-MS: *m/z* = 149 (M^+).

(−)-(*S*)-3-Methylcyclohexane-1-one (3ab)

Silica gel column chromatography (hexane then hexane/diethyl ether = 20/1) gave (−)-(*S*)-**3ab** as a colorless oil; yield: 117 mg (62%); $[\alpha]_D^{25}$: −6.67 (*c* 1.14, $CHCl_3$). The *ee* was determined to be 45% from the specific rotation.[6h] ^1H NMR: δ = 0.88 (3H, t, *J* = 7.3 Hz), 1.01 (3H, d, *J* = 6.0 Hz), 1.34 (1H, m), 1.70 (1H, m), 1.82–2.08 (4H, m), 2.16–2.40 (3H, m); IR (neat): ν = 1720 cm^{-1}; MS: *m/z* = 112 (M^+).

(−)-3-Isopropylcyclohexan-1-one (3ac)

Silica gel column chromatography (hexane then hexane/diethyl ether = 20/1) gave (−)-**3ac** as a colorless oil; yield: 221 mg (97% yield); $[\alpha]_D^{20}$: −96.3 (*c* 1.36, $CHCl_3$). The *ee* was determined to be 94% *via* the diastereomeric ketal. ^1H NMR: δ = 0.91 (6H, t, *J* = 6.3 Hz), 1.22–2.43 (10H, m); IR (neat): ν = 2910, 1720 cm^{-1}; EI-MS: *m/z* = 140 (M^+).

Determination of the *ee* of (−)-3ac.[6h]

A mixture of (−)-**3ac** above (0.5 mmol), (*R,R*)-2,3-butanediol (0.71 mmol), MS 4 Å (40 mg), and *p*-toluenesulfonic acid monohydrate (10 mg) in benzene (15 mL) was refluxed for 12 h. After addition of 10% Na_2CO_3 (10 mL), the mixture was extracted with benzene (20 mL × 3). The organic layer was washed with brine and dried over Na_2SO_4. Concentration gave a colorless oil; yield: 89%. ^1H NMR: δ = 0.82 (6H, t, *J* = 6.3 Hz), 1.22–1.68 (16H, m), 3.60 (2H, m); IR (neat): ν = 2910, 1450 cm^{-1}; ^{13}C NMR: δ = 16.9, 17.0, 19.4, 19.6, 22.9, 23.0, 23.3, 28.1, 21.4, 36.1 (major), 37.1 (minor), 39.7 (major), 40.7 (minor), 40.9 (major), 41.5 (minor). 108.9. From these three sets of integration ratios, the *ee* was determined to be 94% *ee*.

(−)-(*S*)-3-(1-Phenylpropyl)cyclohexan-1-one (3ad)[13b]

Silica gel column chromatography (hexane then hexane/diethyl ether = 20/1) gave (−)-**3ad** as a colorless oil; yield: 176 mg (48%); $[\alpha]_D^{25}$: −7.04 (*c* 0.98, $CHCl_3$). The *ee* was determined to be 94% *via* the diastereomeric aminal. ^1H NMR: δ = 0.91 (6H, t, *J* = 6.3 Hz), 1.22–2.43 (10H, m); IR (neat): ν = 2910, 1720 cm^{-1}; EI-MS: *m/z* = 140 (M^+).

Determination of the *ee* of (−)-3ad by the Same Procedure as for 3a

IR (neat): $\nu = 2910$, 1450 cm^{-1}; ^{13}C NMR: $\delta = 11.3$, 23.1, 29.7, 31.7, 36.5 (minor), 37.3 (minor), 40.3, 45.8 (major), 46.0 (minor), 69.4, 70.1, 126.8, 127.0, 127.1, 127.3, 128.2, 128.3. From the two sets of integration ratio, the *ee* was determined to be 94% *ee*.

(−)-5-(3-Oxocyclohexyl)pentyl Acetate (3af)[38]

Silica gel column chromatography (hexane then hexane/diethyl ether = 20/1) gave (−)-**3af** as a colorless oil; yield: 323 mg (84%); $[\alpha]_D^{25}$: −7.04 (*c* 0.98, $CHCl_3$). The *ee* was determined to be 75% *via* the diastereomeric aminal. ^1H NMR: $\delta = 1.22$–1.54 (6H, m), 1.56–1.73 (2H, m), 1.75–1.87 (2H, m), 2.08 (3H, s), 2.14–2.30 (3H, m), 2.35–2.50 (2H, m), 4.11 (2H, t, $J = 6.7$ Hz); ^{13}C NMR: $\delta = 20.9$, 25.8, 27.4, 28.3, 29.6, 35.5, 37.1, 38.5, 45.2, 64.6, 171.2, 219.0; IR (neat): $\nu = 3560$, 1740 cm^{-1}; MS: $m/z = 213$ (M^+).

Determination of the *ee* of (−)-3af by the Same Procedure as for 3a

IR (neat): $\nu = 2910$, 1450 cm^{-1}; ^{13}C NMR: $\delta = 11.3$, 22.6 (minor), 22.9 (major), 28.2 (minor), 29.7 (major), 31.6, 37.3, 40.2, 11.3, 23.1, 29.7, 31.7, 36.5 (minor), 37.3 (minor), 40.3, 45.8, 69.3, 70.6, 126.8, 126.9, 127.2, 128.1. From the two sets of integration ratio, the *ee* was determined to be 75%.

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