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TETRAHEDRON

Catalytic Enantioselective Conjugate Addition of Grignard Reagents to Cyclic α,β-Unsaturated Carbonyl Compounds

Motomu Kanai,[a] Yuichi Nakagawa,[b] and Kiyoshi Tomioka*[b]

[a] Graduate School of Pharmaceutical Sciences, The University of Tokyo, Hongo, Bunkyo-ku, Tokyo 113-0033, Japan

[b] Graduate School of Pharmaceutical Sciences, Kyoto University, Yoshida, Sakyo-ku, Kyoto 606-8501, Japan

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Abstract: A catalytic asymmetric conjugate addition reaction of organocopper reagents, generated from copper salt, a chiral phosphine, and Grignard reagent, with cyclohexenone is highly dependent on the counter anion of copper species, solvents, Grignard reagents, and the structure of the chiral phosphine. The reaction using the combination of 8 mol% of copper iodide, 32 mol% of the amidophosphine **3**, and 1.2 equiv of organomagnesium chloride with cyclohexenone in ether at –78 °C gave the 3-substituted cyclohexanone in up to 92% ee and 90% yield.

keywords: asymmetric reactions, catalysis, Grignard reagents

INTRODUCTION

The conjugate addition reaction of an organocuprate with an enone has been a versatile carbon-carbon bond forming reaction. An approach toward the catalytic asymmetric reaction has been a challenging subject of the recent synthetic chemistry.[1,2] Since the epoch-making report by Lippard,[3] substantial progress has been achieved using a chirally modified heterocuprate, generated from the chiral copper amide, alkoxide, and thiolate.[4] Another attractive approach is the use of an external chiral coordinating ligand to copper.[5] In pioneering work by Kretchmer, (–)-sparteine was used as the chiral ligand to give, however, the adduct in quite low ee.[6] A chiral phosphine has been developed by Alexakis to achieve relatively high selectivity by the reaction of organolithium cuprate.[7,8] However, the successful catalytic reaction has not been reported until the recent reports that use a combination of copper triflate, a chiral phosphine, and dialkylzinc as an alkylating reagent.[9,10] Since the Grignard reagents are readily available from the corresponding organic halides, it is desirable to use Grignard reagents as the source of transferable alkyl group.[11] We describe herein that the catalytic asymmetric reaction of Grignard reagent with cycloalkenone is critically governed by some factors and proceeds in the presence of copper iodide and a chiral bidentate amidophosphine to achieve a high efficiency.[12]

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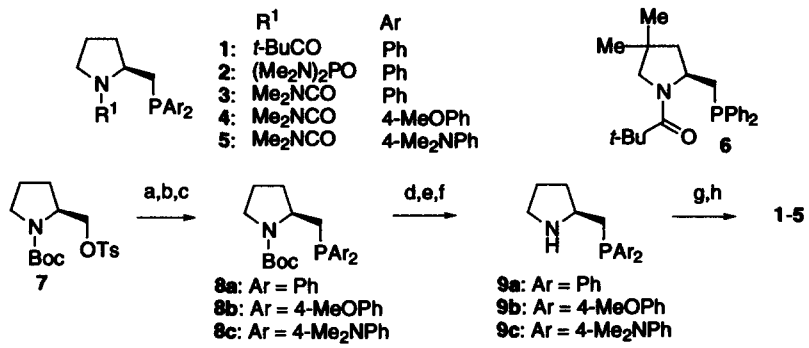
SYNTHESIS OF THE CHIRAL PHOSPHINES

The bidentate phosphines **1-3** have a diphenylphosphino group for the coordination to copper and a coordinating amide group to magnesium. The phosphines **4** and **5** have the electron releasing 4-methoxy- and 4-dimethylaminophenyl groups expecting more tight coordination to copper than the diphenylphosphino ligand. The phosphine **6** has the dimethyl groups on the pyrrolidine ring, expecting bulkiness.[13] These five chiral bidentate amidophosphines **1-5** were prepared from L-proline *via* **7**. The known tosylate **7** was converted to the phosphine **8** by the reaction with a metalated phosphine. Deprotection of **8** to the amine **9** and subsequent acylation gave the target phosphines **1-5**.

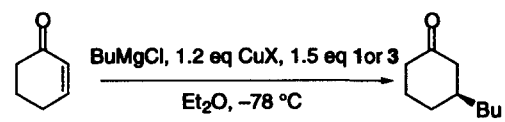


a) Ph_2PCl, Na, dioxane-THF, rt, 0.5 h, **8a** (77%). b) $(4\text{-MeOPh})_2PH$, KH, THF, **8b** (15%). c) $(4\text{-Me}_2NPh)_3P$, K, THF, **8c** (96%). d) TFA, CH_2Cl_2, rt, 4 h, **9a** (78%). e) HCl, dioxane, rt, **9b**. f) HCl, dioxane-EtOH, rt, **9c**. g) RCOCl, Et_3N, CH_2Cl_2, **1** (68%), **3** (95%), **4** (67%), **5** (90%). h) $(Me_2N)_2POCl$, NEt_3, CH_2Cl_2, **2** (79%).

FACTORS INFLUENCING THE ASYMMETRIC CONJUGATE ADDITION REACTION

The stoichiometric asymmetric reaction of butylmagnesium chloride with cyclohexenone in the presence of 1.2 equiv of copper salt and 1.5 equiv of the chiral phosphine was examined to optimize the reaction efficiency (Table 1). The dimethylaminocarbamoylphosphine **3** gave (*S*)-3-butylcyclohexanone **11d** in up to 98% ee higher than 89% ee obtained using the pivaloylamide **1** (entry 2, 5). The ee was determined by ^{13}C NMR analysis of the corresponding diastereomeric ketals of **11d** prepared with (*R*,*R*)-2,3-butanediol.[14] The absolute configuration was determined by the specific rotation.[15] Copper iodide and cyanide gave the higher ee than bromide (entry 3-5). Contrary to the asymmetric reaction of lithium organocuprate,[7,8c] an addition of lithium bromide is not beneficial (entry 8).

Table 1. Effect of copper salt and equiv of BuMgCl[a]



10 **11d**

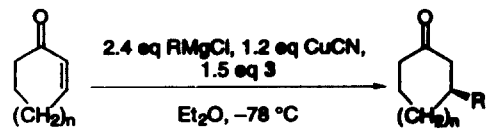
entry	CuX	BuMgCl/eq	1 or 3	yield/%	ee/%
1	CuI	2.4	1	91	86
2	CuCN	2.4	1	94	89
3	CuBr	2.4	3	80	76
4	CuI	2.4	3	99	90
5	CuCN	2.4	3	98	98
6	CuCN	1.2	3	49	15
7	CuCN	3.6	3	93	91
8[b]	CuCN	2.4	3	79	79

[a] The 1.2 equiv of CuX and 1.5 equiv of **1** or **3** were used. [b] The 10 equiv of LiBr was added.

The amount of Grignard reagent is critical. The 1.2 equiv of the reagent gave **11d** in only 15% ee and 49% yield (Table 1, entry 6). However, 2.4 and 3.6 equivs of butylmagnesium chloride gave **11d** in 98 and 91% ees (entry 4, 7). These results indicate that a reaction using a large excess of Grignard reagent to copper and the chiral phosphine, that is, a catalytic reaction may give the product in high ee.

Under the optimized conditions (Table 1, entry 5), the asymmetric reaction of Grignard reagents with cyclohexenone and cycloheptenone gave 3-substituted cycloalkanones **11** and **13** in good to high ees, excepting those of isopropyl and phenylmagnesium chlorides (Table 2). The sense of the asymmetric induction was same in the three products **11b,d,i** of which absolute configurations were determined. The organo group was introduced from the front face of **10**. The phosphine **3** was recovered in quantitative yield for reuse without any loss of optical purity.

Table 2. Asymmetric reaction mediated by **3**[a]



10: n = 1, **12**: n = 2 **11**: n = 1, **13**: n = 2

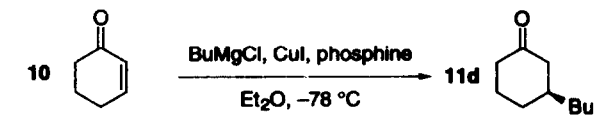
entry	n	R	product	yield/%	ee/%
1	1	Et	**11b**	63	75
2	1	Pr	**11c**	63	83
3	1	Bu	**11d**	98	98
4	1	Hex	**11e**	73	94
5	1	$PhCH_2$	**11f**	61	53
6	1	*i*-Pr	**11h**	40	15
7	1	Ph	**11i**	20	19
8	2	Bu	**13a**	61	82

[a] The absolute configuration was determined by the optical rotation.[15] The ratio of 1,4/1,2-addition was over 5.

A CATALYTIC ASYMMETRIC CONJUGATE ADDITION REACTION

A catalytic asymmetric reaction was examined using butylmagnesium chloride and copper iodide in the presence of the chiral phosphines **1-6** (Table 3). The ee and yield depend on the amount of copper and the chiral phosphine. The reaction of 1.2 equiv of butylmagnesium chloride catalyzed by 2 mol% of copper iodide and 3 mol% of **3** gave the product **11d** in 67% ee and 78% yield (entry 1). The ratio of 1,4- to 1,2-addition was 16. The enantiofacial selectivity was improved up to 90%, almost identical selectivity observed under the stoichiometric asymmetric reaction conditions (Table 1, entry 4), with the increased amount of 8 mol% of copper iodide and 32 mol% of **3** (entry 2-5). For the reaction employing the pivaloylamide **1**, a poorer selectivity of 80% was observed under the above conditions (entry 7). The

Table 3. Influence of the amount of CuI and phosphines **1-6**



entry	CuI mol%	phosphine	mol%	BuMgCl eq	yield %	ee %	1,4/1,2[a] %
1	2	**3**	3	1.2	78	67	16
2	2	**3**	10	1.2	69	74	9
3	8	**3**	10	1.2	89	67	65
4	8	**3**	20	1.2	83	80	12
5	8	**3**	32	1.2	92	90	32
6	8	**1**	10	1.2	85	70	31
7	8	**1**	32	1.2	87	80	18
8	10	**2**	30	1.5	54	25	5
9	8	**4**	10	1.2	47	81	2
10	8	**4**	32	1.2	5	70	0.1
11	2	**5**	3	1.2	70	75	5
12	8	**5**	10	1.2	74	80	8
13	8	**5**	32	1.2	18	87	1
14	8	**6**	32	1.2	82	92	18

[a] The ratio of 1,4- to 1,2-addition.

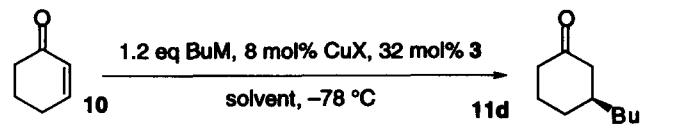
sterically tuned-up pivaloylamidophosphine **6** gave the highest ee of 92% and 82% yield (entry 14).

The HMPA-type amidophosphine **2** was not effective to give only 25% ee and 54% yield (entry 8). The 4-methoxy- and 4-dimethylaminophenylphosphines **4** and **5**, expecting stronger coordination of phosphorous to copper, gave **11d** in 81 and 80% ees in the presence of 8 mol% of copper iodide and 10 mol% of the phosphine, although the 1,4- to 1,2-selectivities were moderate (entry 9, 12). It is remarkable that 75% ee was observed by the reaction of 2 mol% of copper iodide and 3 mol% of **5** (entry 11). These results suggest that the strong coordination of the phosphine to copper is an important factor.[16] However, the Michael-type addition of the phosphine to the enone caused the decreased yield 18% upon an addition of 32 mol% of **5** (entry 13).

The procedure influenced the enantioselectivity. An addition of cyclohexenone to a mixture of copper iodide, **3**, and butylmagnesium chloride in ether gave the best 90% ee. Other procedures, an addition of butylmagnesium chloride to a mixture of copper iodide, **3**, and cyclohexenone, and simultaneous addition of butylmagnesium chloride and cyclohexenone to copper iodide and **3**, gave the lower ees, 64 and 85%, and lower yields, 43 and 57%. The ratio of 1,4- to 1,2-addition was also highly dependent on the procedure. Formation of an active species prior to the addition of cyclohexenone is important to achieve a high efficiency.

The influence of copper salt is quite remarkable (Table 4, entry 1-5). Contrary to the stoichiometric reaction in which copper cyanide is the choice of copper salt (Table 1, entry 5), the catalytic reaction using copper iodide gave the best efficiency in terms of ee, yield, and the ratio of 1,4- to 1,2-addition (entry 1). The halogen of Grignard reagent is also critical (entry 1, 6-9). Butylmagnesium chloride gave the best efficiency, also in terms of ee, yield, and the ratio of 1,4- to 1,2-addition. Other butylmagnesium species such as iodide and bromide gave the lower ees and yields. The influence of the halide may come from their coordinating potency to copper that should be competitive with the coordination of the phosphine to copper.[16,17] Consequently, it is reasonable to observe that dibutylmagnesium gave the best 94% ee, though the ratio of 1,4- to 1,2-addition is moderate (entry 7).

Table 4. Influence of copper salt, organomagnesium and solvent.



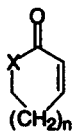
entry	CuX	solvent	BuM	yield/%	ee/%	1,4/1,2
1	CuI	ether	BuMgCl	92	90	32
2	CuI• SMe_2	ether	BuMgCl	73	76	64
3	CuCl	ether	BuMgCl	52	81	5
4	CuBr	ether	BuMgCl	56	77	3
5	CuCN	ether	BuMgCl	40	82	3
6	CuI	ether	$BuMgN(Pr\text{-}i)_2$	70	84	5
7	CuI	ether	Bu_2Mg	71	94	4
8	CuI	ether	BuMgI	27	46	2
9	CuI	ether	BuMgBr	10	68	1
10	CuI	DMS	BuMgCl	82	77	130
11	CuI	toluene	BuMgCl	90	73	11
12	CuI	$i\text{-}Pr_2O$	BuMgCl	29	18	1
13	CuI	THF	BuMgCl	55	0	11

Solvent effect is also remarkable (entry 1, 10-13). The relatively high ee and yield were obtained in ether, dimethylsulfide, and toluene, while the quite low ees 18 and 0% were observed in isopropyl ether and

THF.

Under the established conditions, 8 mol% of copper iodide and 32 mol% of **3** in ether at –78 °C, the catalytic asymmetric reaction of organomagnesium chloride with cycloalkenones **10, 12, 14** proceeded smoothly to afford the corresponding 3-substituted cycloalkanones **11, 13, 15** in up to 92% ee and good yields (Table 5). The reaction with α,β-unsaturated valerolactone **16** proceeded smoothly to give the corresponding adducts **17** in 76-91% ees (entry 13-14). The ee was determined by converting to the methyl esters **20** and **21** as shown in the experimental section. However, the reaction of methyl-, isopropyl-, benzyl-, phenyl- Grignard reagents failed to provide the high efficiency (entry 1, 6, 8, 9).

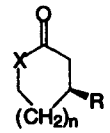
Table 5. Catalytic asymmetric addition of Grignard reagent.



10: n = 1, X = CH_2
12: n = 2, X = CH_2
14: n = 0, X = CH_2
16: n = 1, X = O

1.2 eq RMgCl, 8 mol% CuI, 32 mol% **3**

Et_2O, –78 °C



11: n = 1, X = CH_2
13: n = 2, X = CH_2
15: n = 0, X = CH_2
17: n = 1, X = O

entry	n	X	R	product	yield/%	ee/%	entry	n	X	R	product	yield/%	ee/%
1	1	CH_2	Me[a]	**11a**	23	5	9	1	CH_2	Ph[a]	**11i**	10	4
2	1	CH_2	Et	**11b**	83	73	10	0	CH_2	Bu	**15**	88	42
3	1	CH_2	Pr[b,c]	**11c**	77	72	11	2	CH_2	Bu[c]	**13a**	91	81
4	1	CH_2	Bu	**11d**	92	90	12	2	CH_2	$Ph(CH_2)_2$[c,e]	**13b**	70	83
5	1	CH_2	Hex[b,c]	**11e**	90	92	13	1	O	Pr[b]	**17a**	66	76
6	1	CH_2	$PhCH_2$[c]	**11f**	40	12	14	1	O	Bu[d]	**17b**	70	91
7	1	CH_2	$Ph(CH_2)_2$[e]	**11g**	74	87	15	1	O	Hex[b,c,d]	**17c**	70	90
8	1	CH_2	*i*-Pr[c]	**11h**	24	4							

[a] RMgBr was used. [b] CuI•SMe_2 was used instead of copper iodide. [c] The absolute configuration was not determined. [d] Ee was determined by ^1H NMR of the corresponding methyl esters **20** and **21** in the presence of Eu(hfc)$_3$. [e] Ee was determined by the chiral stationary phase HPLC.

CONCLUSION

The asymmetric conjugate addition reaction of Grignard reagent with α,β-unsaturated cyclic carbonyl compounds is governed by many factors, among which the halide of Grignard reagent, the counter anion of the copper salt, the amount and structure of the chiral phosphine, reaction procedure, and solvent are critical. The relatively high efficiency in terms of ee and yield has been achieved after optimization of these conditions. The chiral phosphine is recoverable in high yield for reuse without any loss of the optical purity.

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EXPERIMENTAL

General. Copper iodide, bromide, and chloride were purified by the reported procedure.[18] Copper cyanide was dried in vacuo at 50 °C. Reactions were monitored by thin-layer chromatography. The extract was washed with satd sodium bicarbonate (or 10% ammonium hydroxide), brine, and then dried over magnesium sulfate unless otherwise noted. The column chromatography was carried out using silica gel. Melting points and boiling points are uncorrected. ^{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: multiplicity, coupling constants, integration, and assignments where relevant. Mass spectra were recorded under electron impact (EI) conditions. Analytical HPLC was performed using Daicel Chiralcel AD.

(*S*)-(–)-*N*-*tert*-Butoxycarbonyl-2-[(diphenylphosphino)methyl]pyrrolidine (8a).[19] To a solution of chlorodiphenylphosphine (2.1 mmol) in dioxane (3 mL) was added sodium (8.9 mmol) and the whole was stirred under reflux for 6 h, and then diluted with THF (2 mL). A solution of **7** (1.5 mmol)[20] in THF (2 mL) was added. After stirring for 1 h at rt, the mixture was filtrated through celite pad and washed with benzene. Concentration and chromatography (ether/benzene, 1/19) afforded **8a** (77%) as a colorless oil of $[\alpha]^{20}_D$ –69.3 (c 1.09, $CHCl_3$). ^{1}H-NMR: 1.40 (s, 9H, *t*-Bu), 2.0 (m, 5H), 2.7 and 2.9 (m, each 1H, CH_2P), 3.4 (m, 2H), 3.9 (m, 1H), 7.4 (m, 10H). ^{13}C-NMR: 154.4, 139.1 (d), 137.9 (d), 133.0 (m, Ph), 128.5 (m, Ph), 79.5, 79.0, 55.6, 55.3, 46.8, 46.3, 34.1, 33.3, 31.5, 31.4, 28.8, 24.0, 23.2. IR (neat): 1690 cm^{-1}. MS *m/z*: 369 (M^+). Anal. Calcd for $C_{22}H_{28}NO_2P$: C, 71.54; H, 7.59; N, 3.79. Found: C, 71.47; H, 7.73; N, 3.77.

(*S*)-(–)-2-[(Diphenylphosphino)methyl]pyrrolidine (9a).[21] A solution of **8a** (28 mmol) in dichloromethane (60 mL) and trifluoroacetic acid (280 mmol) was stirred for 4 h at rt. The mixture was concentrated and dissolved in 6N HCl. After addition of sodium hydroxide, the mixture was extracted with dichloromethane. Concentration and distillation (150-160 °C/0.4 mmHg) gave **9a** (78%) as a colorless oil of $[\alpha]^{20}_D$ –29.4 (c 4.86, EtOH). ^{1}H-NMR: 1.40 (m, 1H), 1.63-2.00 (m, 3H), 2.22 (dd, *J*=8, 14 Hz, 1H, CH_2P), 2.33 (dd, *J*=7, 14 Hz, 1H, CH_2P), 2.80 (ddd, *J*=7, 8, 11 Hz, 1H), 3.01 (m, 2H), 7.35-7.45 (m, 10H). ^{13}C-NMR: 138.6 (d, *J*=16 Hz, ipsoAr), 132.7 (d, *J*=5 Hz), 132.4 (d, *J*=6 Hz), 128.2, 56.3 (d, *J*=15 Hz), 46.1, 35.6 (d, *J*=14 Hz), 32.4 (d, *J*=7 Hz), 25.0. IR (neat): 3300, 1430 cm^{-1}. MS *m/z*: 269 (M^+). Anal. (hygroscopic) Calcd for $C_{17}H_{20}NP \cdot 1/2H_2O$: C, 73.38; H, 7.55; N, 5.04. Found: C, 73.41; H, 7.29; N, 4.95. Hydrochloride: Colorless prisms of mp 124-125 °C and $[\alpha]^{25}_D$ –3.06 (c 0.62, EtOH). MS *m/z*: 269 (M^+-HCl). Anal. Calcd for $C_{17}H_{21}NPCl \cdot 1/7H_2O$: C, 66.21; H, 6.90; N, 4.54. Found: C, 66.22; H, 6.77; N, 4.42.

(*S*)-(–)-*N*-(2,2-Dimethylpropionyl)-2-[(diphenylphosphino)methyl]pyrrolidine (1). A solution of **9a** (7.4 mmol), pivaloyl chloride (11 mmol), and triethylamine (19 mmol) in dichloromethane (7 mL) was stirred for 0.5 h at 0 °C, and treated with satd sodium bicarbonate, and then extracted with dichloromethane. Concentration and recrystallization from ether (17 mL) gave **1** (68%) as colorless prisms of mp 97-97.5 °C and $[\alpha]^{25}_D$ –67.3 (c 1.45, $CHCl_3$). ^{1}H-NMR: 1.19 (s, 9H, *t*-Bu), 1.74-2.03 (m, 5H), 2.93 (brd, *J*=10 Hz, 1H, CH_2P), 3.52 and 3.71 (m, each 1H), 4.31 (m, 1H), 7.27-7.39 (m, 8H), 7.63 (m, 2H). ^{13}C-NMR: 176.3, 128.0-139.4 (Ph), 57.1 (d, *J*=18 Hz), 48.0, 39.1, 32.5 (d, *J*=13 Hz), 29.6 (d, *J*=11 Hz), 27.6, 25.5. IR (KBr): 1610 cm^{-1}. MS *m/z*: 353 (M^+). Anal. Calcd for $C_{22}H_{23}NOP$: C, 74.78; H, 7.93; N, 3.97. Found: C, 75.01; H, 8.02; N, 3.84.

(*S*)-(–)-*N,N,N',N'*-Tetramethyl-2-[(diphenylphosphino)methyl]pyrrolidinylphosphonic triamide (2). Prepared in 79% yield as colorless prisms of mp 54-57 °C and $[\alpha]^{25}_D$ –89.1 (c 1.16, $CHCl_3$). ^{1}H-NMR:

1.76-2.01 (m, 5H), 2.58 (d, *J*=9 Hz, 12H, CH_3), 2.80 (ddd, *J*=3, 5, 13 Hz, 1H, CH_2P), 3.15 (m, 2H), 3.71 (m, 1H), 7.27-7.44 (m, 8H), 7.55-7.61 (m, 2H). ^{13}C-NMR: 139.1, 137.7, 133.3-132.3, 128.5-128.2 (Ph), 56.4 (d, *J*=21 Hz), 46.4, 36.8, 35.7 (d, *J*=13 Hz, CH_2P), 31.9, 25.0. IR (KBr): 1480 cm^{-1}. MS *m/z* 403 (M^+). Anal. Calcd for $C_{21}H_{31}N_3OP_2$: C, 62.52; H, 7.75; N, 10.42. Found: C, 62.44; H, 7.56; N, 10.57

(*S*)-(+)-*N*-(*N'*,*N'*-Dimethylcarbamoyl)-2-[(diphenylphosphino)methy]pyrrolidine (3). Prepared in 95% yield as colorless prisms of mp 76-78 °C (ether-hexane) and $[\alpha]^{25}_D$ +28.2 (c 1.24, $CHCl_3$). ^{1}H-NMR: 1.64 (m, 1H), 1.80 (m, 2H), 2.16 (m, 1H), 2.25 (dd, *J*=9, 14 Hz, 1H, CH_2P), 2.63 (s, 6H, CH_3), 2.68 (m, 1H, CH_2P), 3.28 (m, 2H), 4.18 (m, 1H), 7.26-7.56 (m, 10H). ^{13}C-NMR: 163.1, 138.7 (d, *J*=56 Hz, ipsoPh), 132.3-132.8 (Ph), 128.0-128.3 (Ph), 56.3 (d, *J*=18 Hz, CHN), 50.8, 37.6, 33.6 (d, *J*=14 Hz, CH_2P), 32.0 (d, *J*=10 Hz), 25.5. IR ($CHCl_3$): 1610 cm^{-1}. MS *m/z* 340 (M^+). Anal. Calcd for $C_{20}H_{25}NOP$: C, 70.59; H, 7.35; N, 8.24. Found: C, 70.70; H, 7.49; N, 8.22.

Bis(4-methoxyphenyl)phosphine.[22] To a suspension of NaH (11 mmol) in ether (10 mL) was added diethyl phosphite (10 mmol) at 0 °C and stirred at rt for 0.5 h. 4-Methoxyphenylmagnesium bromide (21 mmol) in ether (18 mL) was added at 0 °C and the whole was stirred at rt for 0.5 h and then under reflux for 2 h, and then 10% HCl was added. The mixture was extracted with dichloromethane. Concentration and recrystallization from AcOEt gave bis(4-methoxyphenyl)phosphinous acid as colorless needles of mp 121-122 °C in 58% yield. ^{1}H-NMR: 3.84 (s, 6H, CH_3), 6.95 (dd, *J*=3, 8 Hz, 4H), 7.61 (dd, *J*=9, 13 Hz, 4H), 8.05 (d, *J*=447 Hz, PH). ^{13}C-NMR: 162.8, 132.5 (d, *J*=12 Hz), 122.9 (d, *J*=117 Hz), 114.3 (d, *J*=15 Hz), 55.3. IR (nujol): 1600 cm^{-1}. MS *m/z*: 262 (M^+), 246 (M^++1-CH_3), 231 (M^++1-$(CH_3)_2$).

To a solution of the above acid (3.9 mmol) in toluene (7 mL) was added trichlorosilane (15 mmol) and the whole was stirred at rt for 1 h and at 40 °C for 7 h. The mixture was diluted with benzene (30 mL) and poured onto 10% NaOH (30 mL), then filtrated through celite pad. The organic layer was concentrated, washed with brine, and then concentrated. ^{1}H-NMR analysis showed a 1:1 mixture of the starting phosphine oxide and the phosphine. This mixture was used in the next step without further purification.

(*S*)-(–)-*N*-*tert*-Butoxycarbonyl-2-[(bis(4-methoxyphenyl)phosphino)methyl]pyrrolidine (8b). A suspension of KH (5.5 mmol) and the above mixture (1.8 mmol) in THF (10 mL) was stirred at rt for 1 h. A solution of **7** (3.3 mmol) in THF (4 mL) was added at 0 °C and the whole was stirred for 0.5 h. After addition of satd NH_4Cl, the mixture was extracted with AcOEt. Concentration and chromatography gave **7** (42%) and **8b** (15%) as a colorless oil of $[\alpha]^{25}_D$ –51.2 (c 1.17, $CHCl_3$). ^{1}H-NMR: 1.42 (s, 9H, *t*-Bu), 1.93 (m, 5H), 2.64 (m, 1H), 3.33 (m, 2H), 3.78 (s, 6H, CH_3), 3.85 (m, 1H), 6.90 (dd, *J*=3, 8 Hz, 4H), 7.4 (m, 4H). ^{13}C-NMR: 160.2, 160.0, 154.2, 134.5 (d, *J*=10 Hz), 133.6 (d, *J*=9 Hz), 130.0 (d, *J*=11 Hz), 126.8 (d, *J*=11 Hz), 114.2 (d, *J*=8 Hz), 79.1, 55.3 (d, *J*=21 Hz, CHN), 55.1, 46.3, 34.1, 31.1 (d, *J*=9 Hz), 28.6, 23.4. IR (neat): 1675, 1590 cm^{-1}. MS *m/z*: 429 (M^+), 372 (M^+-*t*-Bu). Anal. Calcd for $C_{24}H_{32}NO_4P$: C, 67.12; H, 7.51; N, 3.26. Found: C, 67.17; H, 7.36; N, 3.22.

(*S*)-(+)-*N*-(*N'*,*N'*-Dimethylcarbamoyl)-2-[(bis(4-methoxyphenyl)phosphino)methyl]pyrrolidine (4). A mixture of **8b** (0.5 mmol) and hydrochloric acid (10 mmol) in dioxane (4 mL) was stirred at rt for 1.5 h. Concentration gave **9b** as a white amorphous, which was dissolved in dichloromethane (1 mL). Triethylamine (2.6 mmol) and dimethylcarbamoyl chloride (0.8 mmol) was added at 0 °C and the whole was stirred for 0.5 h. After addition of 10% sodium carbonate, the mixture was extracted with dichloromethane. Concentration and chromatography (AcOEt/hexane, 4/1) gave **4** (67%) as a colorless oil of $[\alpha]^{25}_D$ +27.1 (c 0.59, $CHCl_3$). ^{1}H-

NMR: 1.8-2.2 (m, 4H), 2.65 (m, 2H, CH_2P), 2.66 (s, 6H, CH_3), 3.25 (m, 2H), 3.73 (s, 6H, CH_3), 4.10 (m, 1H), 6.86 (dd, *J*=5, 8 Hz, 4H), 7.4 (m, 4H). ^{13}C-NMR: 163.0, 159.7, 159.7, 135.9 (d, *J*=21 Hz), 133.0 (d, *J*=20 Hz), 130.2 (d, *J*=10 Hz), 128.9 (d, *J*=10 Hz), 113.9 (d, *J*=7 Hz), 56.3 (d, *J*=17 Hz), 54.3, 54.8, 37.5, 34.1 (d, *J*=12 Hz, CH_2P), 31.9 (d, *J*=10 Hz), 25.5. IR (neat): 1630, 1580 cm^{-1}. MS *m/z*: 400 (M^+), 356 (M^+-Me_2N). Anal. Calcd for $C_{22}H_{29}N_2O_3P$: C, 65.99; H, 7.30; N, 7.00. Found: C, 65.82; H, 7.23; N, 6.93.

(*S*)-(–)-*N*-*tert*-Butoxycarbonyl-2-[(bis(4-*N*,*N*-dimethylaminophenyl)phosphino)methyl]pyrrolidine (8c).[23] To a suspension of tris(4-*N*,*N*-dimethylphenyl)phosphine[24] (21.5 mmol), prepared from 4-dimethylaminophenyllithium[25] and phosphorous trichloride, in THF (150 mL) was added potassium (50 mmol) and the resulting red suspension was stirred at rt for 18 h. A solution of **7** (7.2 mmol) in THF (20 mL) was added at 0 °C. The mixture was stirred for 0.5 h at 0 °C and quenched with EtOH. After addition of satd NH_4Cl, the mixture was extracted with AcOEt. Concentration and chromatography (AcOEt/benzene, 1/9) gave **8c** (96%) as a cloudy oil of $[\alpha]^{25}_D$ –61.3 (c 1.03, $CHCl_3$). ^{1}H-NMR: 1.45 (s, 9H, *t*-Bu), 1.87 (m, 5H), 2.7 (m, 1H), 2.94 (s, 12H, CH_3), 3.36 (m, 2H), 3.85 (m, 1H), 6.68 (brd, *J*=8 Hz, 4H), 7.33 (m, 4H). ^{13}C-NMR: 154.2, 150.6, 150.4, 133.8 (d, *J*=21 Hz), 133.5 (d, *J*=21 Hz), 124.6, 123.3, 112.2 (d, *J*=9 Hz), 79.0, 55.4 (d, *J*=21 Hz), 46.0, 40.2, 34.3, 33.3, 31.0, 28.6, 23.7, 23.0. (Some carbons were assigned to two signals because of amide configurational isomer.) IR (neat): 1680, 1590 cm^{-1}. MS *m/z*: 455 (M^+), 398 (M^+-*t*-Bu). HRMS Calcd for $C_{26}H_{38}N_3O_2P$ (M^+): 455.2704. Found: 455.2703.

(*S*)-(+)-*N*-(*N'*,*N'*-Dimethylcarbamoyl)-2-[(bis(4-*N*,*N*-dimethylaminophenyl)phosphino)-methyl]pyrrolidine (5). To a solution of **8c** (2.5 mmol) in ethanol (9 mL) was added 5.7N HCl in dioxane at 0 °C. The mixture was stirred for 3 h at rt. Concentration gave a white amorphous that was dissolved in a mixture of dichloromethane (4 mL) and triethylamine (12 mmol). *N*,*N*-Dimethylcarbamoyl chloride (7.4 mmol) was added at 0 °C. After 40 min, the mixture was concentrated and purified by chromatography (acetone/$CHCl_3$, 1/19) to give **5** (67%) as white powder of mp 98-99 °C (benzene/hexane, sealed) and $[\alpha]^{25}_D$ +29.2 (c 1.20, $CHCl_3$). ^{1}H-NMR: 1.6-2.2 (m, 4H), 2.6-3.0 (m, 2H, CH_2P), 2.97 (s, 6H, CH_3), 2.92 (s, 12H, CH_3), 3.25 (m, 2H), 4.12 (m, 1H), 6.69 and 7.35 (m, each 4H). ^{13}C-NMR: 163.1, 150.3, 133.7 (d, *J*=18 Hz), 133.4 (d, *J*=18 Hz), 125.1, 123.6, 112.2 (d, *J*=9 Hz), 112.5 (d, *J*=9 Hz), 56.5 (d, *J*=17 Hz), 50.4, 40.1, 40.1, 37.7, 34.3 (d, *J*=11 Hz), 31.9 (d, *J*=10 Hz), 25.5. IR (neat): 1630, 1590 cm^{-1}. HRMS Calcd for $C_{24}H_{35}N_4PO$ (M^+): 426.2552. Found: 426.2554.

Copper iodide–dimethyl sulfide complex.[26] CuI (0.11 mol) was packed in a column tube and washed successively by methanol (100 mL), ether (50 mL), and hexane (50 mL). Then CuI was dissolved in dimethyl sulfide (60 mL) and to this orange solution was added hexane (50 mL). The resulting colorless needles were filtrated, and washed successively by dimethyl sulfide/hexane (20 mL/30 mL, 10 mL/30 mL) and hexane (80 mL), and then dried to give the complex in 36% yield. dp 100-118 °C. Anal. Calcd for CuI•3/4SMe_2: C, 7.62; H, 1.91; S, 10.14. Found: C, 7.62, H, 1.84; S, 9.88.

General procedure for the asymmetric conjugate addition reaction under the stoichiometric conditions. (*S*)-(–)-3-butylcyclohexanone (11d) (Table 2, entry 3). To a mixture of CuCN (0.78 mmol) and **3** (0.98 mmol) in ether (15 mL) was added dropwise a solution of butylmagnesium chloride (1.6 mmol) in ether (1 mL) at –78 °C and the resulting white suspension was stirred for 20 min. A solution of cyclohexenone (0.65 mmol) in ether (4 mL) was added at –78 °C and the mixture was stirred for 35 min. Workup as usual and chromatography (ether/hexane, 1/2) gave **11d** as a colorless oil of $[\alpha]^{25}_{405}$ –81.1 (c 1.08,

$CHCl_3$)[15] in 98% yield. The ee was determined to be 98% by formation of the diastereomeric ketal (*vide infra*). The absolute configuration was determined to be *S* by the specific rotation. The phosphine **3** was recovered in 98% yield.

General procedure for the ketal formation. A mixture of **11d** (0.38 mmol), (*R,R*)-2,3-butanediol (0.71 mmol), and *p*-toluenesulfonic acid monohydrate (cat) in benzene (15 mL) was stirred under reflux with MS 4A trap for 4 h, and quenched with 10% sodium carbonate, and then extracted with benzene. Concentration gave the mixture of ketals of **11d** as a colorless oil in 90% yield. ^{13}C-NMR: 117.2, 78.2, 78.1, 44.9 ($CHCH_2$, major), 44.6 ($CHCH_2$, minor), 38.03, 37.97, 35.6, 30.5, 30.4, 22.8, 16.95, 16.9, 14.0. From the integration, ee was determined to be 98%.

(–)-3-Propylcyclohexanone (11c) (Table 2, entry 2). 83% ee and 63% yield. bp 200 °C/20 mmHg. $[\alpha]^{25}_{405}$ –74.3 (c 0.99, $CHCl_3$). ^{1}H-NMR: 0.90 (t, *J*=5 Hz, 3H), 1.2-2.4 (m, 13H). IR (neat): 1705 cm^{-1}.

The ketal of **11c**. ^{1}H-NMR: 0.88 (brt, *J*=6 Hz, 3H, CH_3), 1.15-1.7 (m, 19H), 3.26 (m, 2H, CHO). IR (neat): 2930, 2860 cm^{-1}. ^{13}C-NMR: 108.6, 78.0, 77.7, 43.9 ($CHCH_2$, major), 43.0 ($CHCH_2$, minor), 39.4, 37.2 ($OCCH_2$, minor), 36.1 ($OCCH_2$, major), 35.2 (CH_2, minor), 34.2 (CH_2, major), 31.8, 23.3 (CH_2, major), 23.0 (CH_2, minor), 19.8, 17.1, 17.0, 14.3.

(–)-3-Hexylcyclohexanone (11e) (Table 2, entry 4). 94% ee and 73% yield. bp 260 °C/20 mmHg. $[\alpha]^{25}_{405}$ –69.8 (c 1.08, $CHCl_3$). ^{1}H-NMR: 0.86 (brt, *J*=5 Hz, 3H, CH_3), 1.25-2.47 (m, 19H). IR (neat): 1710 cm^{-1}. MS *m/z*: 182 (M^+), 97 (M^+-Hex). ^{13}C-NMR: 212.0, 48.1, 41.4, 39.0, 36.5, 31.7, 31.2, 29.2, 26.5, 25.2, 22.5, 14.0.

The ketal of **11e**. ^{1}H-NMR: 0.87 (m, 3H, CH_3), 1.20-1.72 (m, 25H), 3.63 (m, 2H, CHO). IR (neat): 2930, 2850 cm^{-1}. ^{13}C-NMR: 108.6, 78.0, 77.7, 44.0 ($CHCH_2$, major), 43.0 ($CHCH_2$, minor), 37.1, 36.1 (CH_2, major), 35.5 (CH_2, minor), 35.0, 31.9, 31.8, 29.5, 26.7, 23.3 (CH_2, major), 23.0 (CH_2, minor), 19.8, 17.1, 16.9, 14.1.

(+)-3-Benzylcyclohexanone (11f) (Table 2, entry 6). 53% ee and 61% yield. $[\alpha]^{25}_{405}$ +64.1 (c 1.31, $CHCl_3$). ^{1}H-NMR: 1.28-2.47 (m, 9H), 2.63 (d, *J*=6 Hz, 2H), 7.09-7.38 (m, 5H). IR (neat): 1705 cm^{-1}. MS *m/z*: 188 (M^+). ^{13}C-NMR: 211.2, 139.3, 129.0, 128.3, 126.1, 47.7, 42.9, 41.3, 40.8, 30.9, 25.0.

The ketal of **11f**. ^{1}H-NMR: 0.9-1.75 (m, 15H), 2.45 (d, *J*=7 Hz, 2H), 3.49 (m, 2H), 7.2 (m, 5H). IR (neat): 2920 cm^{-1}. MS *m/z*: 260 (M^+), 169 (M^+-$PhCH_2$). ^{13}C-NMR: 140.5, 129.1, 128.0, 125.6, 108.3, 78.0, 77.6, 43.4, 42.7, 37.2 ($CHCH_2$, major), 36.7 ($CHCH_2$, minor), 37.0 (CH_2, major), 36.0 (CH_2, minor), 31.4, 23.0 (CH_2, minor), 22.6 (CH_2, major), 16.9.

(–)-3-Isopropylylcyclohexanone (11h) (Table 2, entry 6). 15% ee and 40% yield. $[\alpha]^{25}_{405}$ –38.6 (c 1.39, $CHCl_3$). ^{1}H-NMR: 0.91 (d, *J*=6 Hz, 6H), 1.22-2.43 (m, 10H). IR (neat): 1705 cm^{-1}. MS *m/z*: 140 (M^+).

The ketal of **11h**. ^{1}H-NMR: 0.82 (d, *J*=6 Hz, 6H, CH_3), 1.2-1.7 (m, 16H), 3.60 (m, 2H, CHO). IR (neat): 2950, 1450 cm^{-1}. ^{13}C-NMR: 108.9, 78.1, 78.0, 41.5 ($CHCH_2$, major), 40.9 ($CHCH_2$, minor), 40.7 ($CHCH_3$, major), 39.8 ($CHCH_3$, minor), 37.2 ($OCCH_2$, major), 36.1 ($OCCH_2$, minor), 32.44, 32.40, 28.1, 23.4, 23.0, 19.6, 19.4, 19.3, 17.1, 17.0, 16.9.

General procedure under the catalytic conditions. (11d) (Table 6, entry 4). A suspension of copper iodide (0.13 mmol) and **3** (0.42 mmol) in ether (13 mL) was stirred at rt for 20 min. A solution of butylmagnesium chloride (2.0 mmol) in ether (1.2 mL) was added at –78 °C. After stirring for 15 min, a

solution of cyclohexenone (1.7 mmol) in ether (5 mL) was added dropwise over 20 min and the whole was stirred for 20 min at –78 °C. Usual workup and chromatography (dichloromethane/hexane, 4/1) followed by short path distillation afforded **11d** as a colorless oil of $[\alpha]^{25}_{365}$ –146 (c 1.18, $CHCl_3$), $[\alpha]^{25}_{405}$ –74.2 (c 1.25, $CHCl_3$), $[\alpha]^{25}_{D}$ –7.38 (c 1.13, toluene)) in 90% ee and 92% yield. The ligand **3** was recovered in 90% yield.

(*R*)-(–)-3-(2-Phenylethyl)cyclohexanone (11g)[27] (Table 6, entry 7). 87% ee and 74% yield. $[\alpha]^{25}_{405}$ –68.7 (c 1.41, $CHCl_3$). ^{1}H-NMR: 1.4-2.73 (m, 13H), 7.20 (m, 5H). IR (neat): 1710 cm^{-1}. MS *m/z*: 202 (M^+). The ee was determined by the chiral stationary phase HPLC (Daicel Chiralcel AD, *i*-PrOH/hexane, 1/100). The absolute configuration was determined by converting to **18**.

(*R*)-(–)-Methyl 3-(3-oxocyclohexyl)propionate) (18).[15] A mixture of **11g** (1.0 mmol), ruthenium trichloride hydrate (0.02 mmol) and sodium metaperiodate (18 mmol) in a mixture of carbon tetrachloride (4 mL), acetonitrile (4 mL) and H_2O (8 mL) was stirred for 19 h at rt. Usual workup gave the corresponding carboxylic acid in 63% yield, which was methylated with diazomethane in ether at 0 °C. Chromatography (ether/hexane, 1/1) gave **18** in 75% yield as a colorless oil of $[\alpha]^{25}_{D}$ –9.28 (c 1.73, cyclohexane) (87% ee). ^{1}H-NMR: 3.69 (s, 3H), 1.4-2.52 (m, 13H). IR (neat): 1730, 1705 cm^{-1}. MS *m/z*: 184 (M^+). Ee was also determined by ^{13}C NMR analysis of the corresponding diastereomeric ketals of (*R*,*R*)-2,3-butanediol.

(–)-3-(2-Phenylethyl)cycloheptanone (13b) (Table 6, entry 7). 83% ee and 70% yield. $[\alpha]^{25}_{405}$ –105 (c 1.34, $CHCl_3$). The ee was determined by the chiral stationary phase HPLC (Daicel Chiralcel AD, *i*-PrOH/hexane, 1/20). ^{1}H-NMR: 1.4-1.98 (m, 9H), 2.4-2.73 (m, 6H), 7.20 (m, 5H). ^{13}C-NMR: 214.2, 142.0, 128.3, 125.7, 49.7, 43.8, 38.9, 36.6, 35.4, 33.2, 28.3, 24.3. IR (neat): 1695 cm^{-1}. MS *m/z*: 216 (M^+). HRMS Calcd for $C_{15}H_{20}O$ (M^+): 216.1515. Found: 216.1513.

(–)-Methyl 3-(3-oxocycloheptyl)propionate (19).[27] The same procedure for **18**. $[\alpha]^{25}_{D}$ –35.1 (c 0.88, $CHCl_3$) (83% ee). ^{1}H-NMR: 3.66 (s, 3H), 2.41 (m, 6H), 1.4-1.94 (m, 9H). ^{13}C-NMR: 213.8, 173.8, 51.6, 49.3, 43.8, 36.4, 35.4, 31.9, 31.5, 28.2, 24.2. IR (neat): 1735, 1695 cm^{-1}. MS *m/z*: 198 (M^+). HRMS Calcd for $C_{11}H_{18}O_3$(M^+): 198.1256. Found: 198.1252.

(*S*)-(–)-3-Propyloxan-2-one (17a)[15] (Table 6, entry 13). A CuI•SMe_2 complex was used. 76% ee and 66% yield. $[\alpha]^{25}_{D}$ –18.8 (c 6.05, $CHCl_3$). ^{1}H-NMR: 0.92 (m, 3H, CH_3), 1.35 (m, 4H), 1.54 (m, 1H), 1.98 (m, 2H), 2.14 (dd, *J*=10, 17 Hz, 1H), 2.69 (dd, *J*=6, 17 Hz, 1H), 4.26 (ddd, *J*=4, 11, 11 Hz, 1H), 4.41 (ddd, *J*=5, 5, 11 Hz, 1H). ^{13}C-NMR: 171.3, 68.3, 38.1, 36.3, 30.9, 28.6, 19.3, 13.7. IR (neat): 1730 cm^{-1}. MS *m/z*: 142 (M^+), 99 (M^+-Pr).

(*S*)-(–)-3-Butyloxan-2-one (17b)[15] (Table 6, entry 14). 90% ee and 70% yield. $[\alpha]^{25}_{D}$ –21.1 (c 4.53, $CHCl_3$). The ee was determined to be 90% by converting to **20** and ^{1}H-NMR analysis in the presence of the shift reagent (*vide infra*). ^{1}H-NMR: 0.90 (m, 3H), 1.3-2.17 (m, 11H), 2.7 (m, 1H), 4.35 (m, 2H, CH_2). IR (neat): 1730 cm^{-1}. MS *m/z*: 156 (M^+).

Methyl (*S*)-3-(methoxymethyl)nonanoate (20). The same procedure for **21** in 60%. The ee was determined be 91% by ^{1}H-NMR analysis in the presence of Eu(hfc)$_3$ (**20**/Eu(hfc)$_3$, 30 mg/20 mg, singlet signal of methyl ether appeared at 3.68 (major) and 3.65 ppm (minor), integration ratio 22/1). ^{1}H-NMR: 0.89 (m, 3H, CH_3), 1.2-2.0 (m, 11H), 2.25 (m, 2H, CH_2CO), 3.31 (s, 3H, CH_3), 3.40 (t, *J*=7 Hz, 2H, CH_2O), 3.66 (s, 3H, CH_3). IR (neat): 1730 cm^{-1}. MS *m/z*: 202 (M^+).

(–)-4-Hexyloxan-2-one (17c) (Table 6, entry 15). CuI•SMe_2 was used. 90% ee and 70% yield. $[\alpha]^{25}_{405}$ –47.1 (c 2.63, $CHCl_3$). The ee was determined by converting to **21** and ^{1}H-NMR analysis in the

presence of the shift reagent (*vide infra*). ^{1}H-NMR: 0.89 (m, 3H), 1.3-2.18 (m, 12H), 2.70 (m, 1H), 4.36 (m, 2H). ^{13}C-NMR: 171.3, 68.3, 36.4, 36.0, 31.5, 31.2, 29.0, 28.7, 26.2, 22.4, 13.9. IR (neat): 1730 cm^{-1}. MS *m/z*: 185 (M^++1). HRMS Calcd for $C_{11}H_{20}O_2$ (M^+): 184.1463. Found: 184.1470.

(+)-Methyl 3-(2-methoxyethyl)nonanoate (21). A mixture of **17c** (0.59 mmol) and sodium hydroxide (0.53 mmol) in ethanol (1 mL) and H_2O (1 mL) was stirred for 20 min at rt. Concentration gave sodium 3-(2-hydroxyethyl)nonanoate as white powder: ^{1}H-NMR (CD_3OD): 0.9 (m, 3H, CH_3), 1.33-2.11 (m, 15H), 3.61 (t, *J*=8 Hz, 2H). IR (neat): 1650, 1550 cm^{-1}. The suspension of the hydroxy acid and NaH (1.2 mmol) in THF (2 mL) was stirred at rt for 15 min, and then methyl iodide (5.92 mmol) was added. After methyl etherification was completed (checked by tlc), DMF (2 mL) was added and the whole was stirred for 35 min at rt. After an addition of satd NH_4Cl (20 mL), the mixture was extracted with AcOEt. Concentration and chromatography (AcOEt/hexane, 1/9) gave **21** (85%) as a colorless oil of $[\alpha]^{25}_{405}$ +0.33 (c 3.02, $CHCl_3$). The ee was determined be 90% by ^{1}H-NMR analysis in the presence of Eu(hfc)$_3$ (**21**/Eu(hfc)$_3$, 20 mg /20 mg, singlet signal of methyl ether appeared at 4.14 (major) and 4.09 ppm (minor), integration ratio 19/1). ^{1}H-NMR: 0.86 (t, *J*=7 Hz, 3H, CH_3), 1.25 (m, 10H), 1.55 (m, 2H), 1.95 (m, 1H), 2.27 (m, 2H), 3.29 (s, 3H, CH_3), 3.38 (t, *J*=8 Hz), 3.64 (s, 3H, CH_3). ^{13}C-NMR: 173.7, 70.7, 58.5, 51.3, 38.9, 34.1, 33.6, 32.4, 31.8, 29.4, 26.4, 22.6, 14.0. IR (neat): 1730 cm^{-1}. MS *m/z*: 215 (M^+-CH_3). Anal. Calcd for $C_{13}H_{26}O_3$: C, 67.79; H, 11.38. Found: C, 68.00; H, 11.16.

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