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Studies Aimed at Enhancement of Reactivity and Enantioselectivity of A Lithium Ester Enolate Using A Chiral Tridentate Lithium Amide

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Abstract: Tridentate chiral amines **7-13** mediated the asymmetric condensation reaction of lithium ester enolate **2** with benzaldehyde *p*-anisidine imine **3** giving the corresponding β-lactam **4** in up to 75% ee. It became apparent that coexistence of **2** and chiral lithium amides derived from **7-13** is an important factor for the enhancement of the reactivity and enantioselectivity of **2**.

Keywords: Asymmetric reactions, β-Lactam; Lithium enolates; Lithium amide

Introduction

Lithium ester enolate is among the established, powerful carbonucleophiles in the formation of carbon-carbon bonds.[2] The promising application of the reagent into asymmetric reactions relies on a chiral external ligand, which opens a catalytic methodology of an asymmetric reaction.[3,4] We have been involved in the stoichiometric and catalytic asymmetric reactions of lithium ester enolate **2** with benzaldehyde *p*-anisidine imine **3** based on a ternary complex reagent.[5] The reagent comprises three components; a chiral ether ligand **1**,[6] an achiral lithium amide such as LDA, and **2**, giving the corresponding β-lactams **4** in higher enantiomer excess (ee) than the corresponding binary complex comprised from **1** and **2** does.[7] Another remarkable feature of the ternary complex reagent is a reactivity enhancement of **2**. The reactivity of **2** increased in the order of **2** alone, **2** + LDA, **2** + **1**, and **2** + **1** + LDA. These reactivity differences indicate that coexistence of

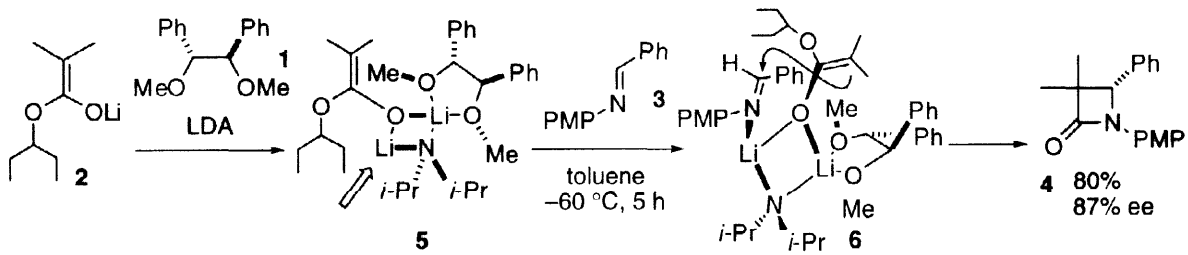

Fig. 1. Asymmetric condensation of **2** with **3** via ternary complex reagent **5**

the lithium amide and chiral ligand **1** is essential to increase the reactivity of the lithium ester enolate **2**.

Formation of the ternary complex reagent is attributable to a suitable spacial arrangement of the three components as shown in the assumed structure **5**. The lithium indicated by an arrow in **5** is available for the

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coordination of the imine **3**, providing the origin for the higher reactivity (Fig. 1). The β-lactam **4** is produced through **6**. The hypothesis above explains enhancement of the reactivity as well as the sense of enantiofacial selection. It is possible to expect that a chiral lithium amide bearing a coordinating moiety forms a binary complex with lithium ester enolate, which is endowed with an ability to enhance reactivity and enantioselectivity.[8] We describe herein our approach toward the enantioselective reaction of lithium ester enolate **2** employing a chiral lithium amide as a complexing agent.

Design of the binary complex of 2 and a lithium amide bearing a coordinating moiety

We assumed that three types of the binary complexes correspond to the ternary complex **5** as shown in Fig. 2. The first and second types of the complexes are characterized by the presence of the terminal Li-N bond, available from amines **7-9** and **10-12**, respectively. The amines **7-9** have the NH moiety on the carbon apart from the diphenylethane unit. The second type amines **10-12** have the NH on the diphenylethane unit. The third type complex has the internal Li-N bond, available from amine **13**.

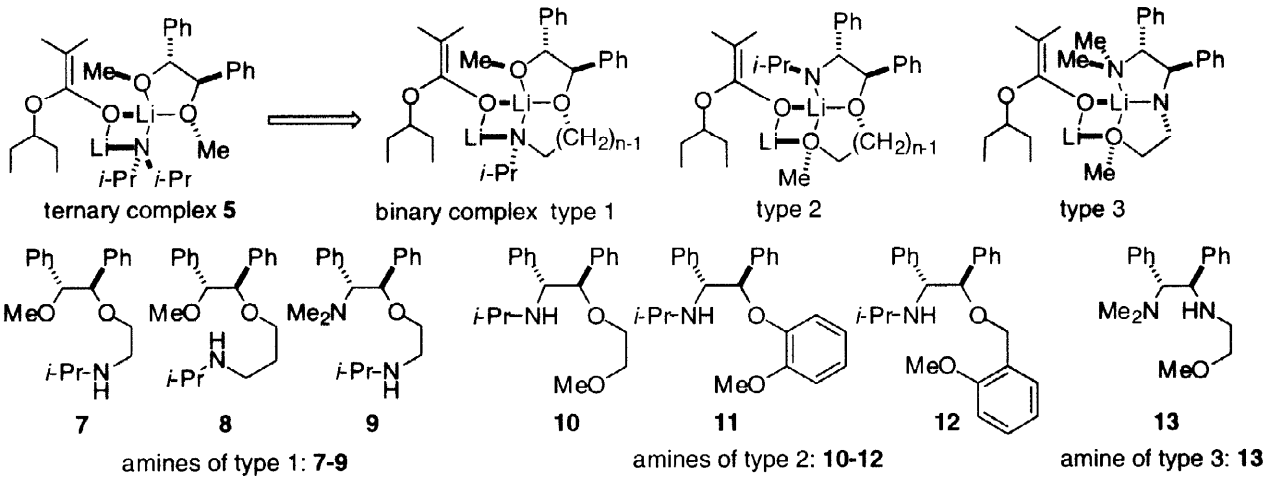

Fig. 2. Ternary and three types of binary complex and their amines **7-13**

Synthesis of the chiral amines 7-13

The chiral amines **7-13** were prepared starting from **14**,[9] **23**,[10] **26**, and **32**.[11] The chiral monoalcohol **14** was treated with a tosylate to give **15**, of which trityl group was removed to the alcohol **16**. Tosylation and amination followed by TFA treatment gave the amine **7**. Under the same scheme, **8** was prepared without any

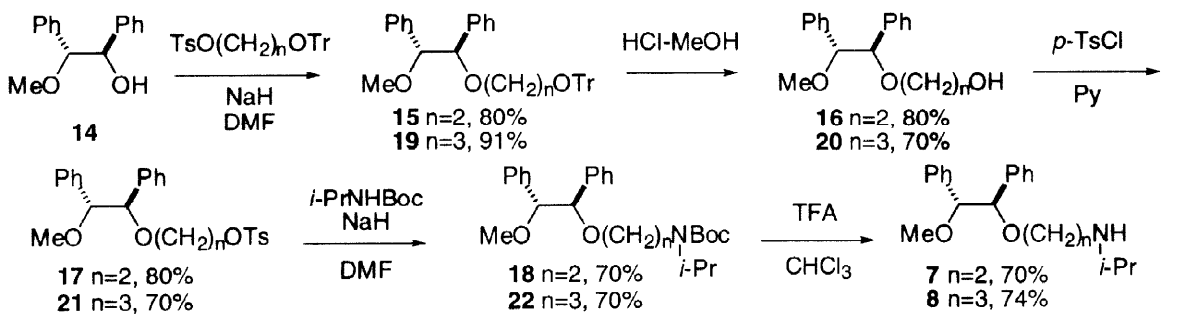

Fig. 3. Synthesis of type 1 amines **7** and **8**

event (Fig. 3). The dimethylamino analogue of **7**, **9** was prepared from **23** in three steps through ethoxycarbonylmethylation, amidation, and then reduction (Fig. 4). The amines of the type 2, **10-12** were prepared

starting from **26** *via* isopropylaminoalcohol **28**. Treatment of **28** with 1-methoxyethyl tosylate gave **10**. Likewise, **11** and **12** were prepared by the reaction with **29**,[12] and **31**,[13] respectively. The type 3 amine **13** was prepared through mono-acylation of **32**, dimethylation of amine, and then reduction.

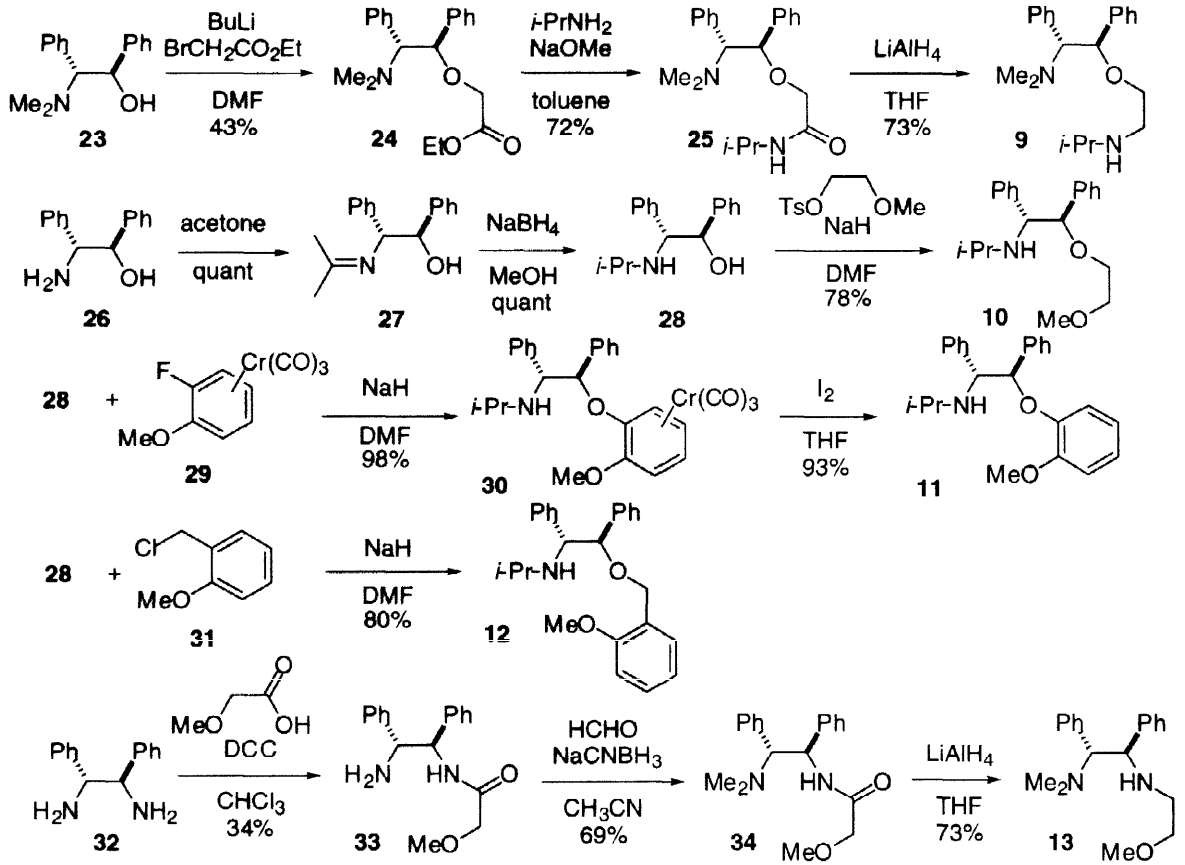

Fig. 4. Synthesis of type 1-3 amines **9-13**

Evaluation of the amines as the chiral ligand

The asymmetric reactions of the lithium ester enolate **2** with the imine **3** was examined in toluene under the three reaction conditions, **A-C**, as shown in Table 1. The conditions **A** and **B** are corresponding to the reactions using a binary complex. The conditions **C** correspond to the reaction of the ternary complex. Under the conditions **A**, amines **7-13** were lithiated with butyllithium at –78 °C for 0.5 h. The resulting lithium amides were used as a base for lithiation of 3-pentyl 2-methylpropanoate at –20 °C for 1 h to generate a complex of 2-chiral amine. The reaction with the imine **3** was conducted at –20 °C and monitored by tlc until the disappearance of **3** for the time indicated in the Table 1. This condensation step was same under the conditions **A-C**. Under the conditions **B**, LDA was used as a base to generate **2** (at –20 °C for 0.5 h). Then, amines **7-13** were added to a solution of **2**. The mixture was stirred at –20 °C for 1 h to generate a complex with **2**. Under the conditions **C**, **2** was generated with LDA, to which preformed lithium amides, generated from **7-13** by treatment with butyllithium at –78 °C for 1 h, were added. The resulting mixture was stirred at –20 °C for 1 h to form the complex. The ee of **4** was determined by chiral stationary phase HPLC (Daicel Chiralcel OD-H, *i*-PrOH/hexane = 1/10, 1 mL/min). The (*S*)-absolute configuration of **4** was determined by the specific rotation. The ligands **7-13** were recovered in 44-99% yield for reuse.

Under the conditions **A**, the yields of **4** were generally lower than those of the reactions conducted under

B and **C**. This indicates that a lithiating ability of the lithium amides derived from amines **7-13** is not high. Especially, the amine **13** is the poorest lithium amide for lithiation. The enantioselectivity was utmost 75% by the amine **9**.

Under the conditions **B**, a higher yield of 97-50% was obtained in every case than the reactions under the conditions **A**. It was remarkable that 73% ee and 92% yield were observed using the amine **13**. The amine **9** was also a good chiral ligand, giving 71% ee.

Under the conditions **C**, the great improvement in the yield was realized to afford **4** in 98-75% yield within a shorter reaction time than those conducted under conditions **A** and **B**. The selectivity was also improved in the reactions using amines **10**, **12**, and **13**. The amine **9** still gave a relatively high enantioselectivity. It is also interesting to note that the antipode of **4** was obtained when the amine **11** was used, albeit of the poor ee.

Table 1. Asymmetric reaction of ester enolate **2** with imine **3** mediated by amines **7-13** giving (*S*)-**4**.[a]

	Conditions **A**			Conditions **B**			Conditions **C**		
amine **7-13**	time/h	yield/%	ee/%	time/h	yield/%	ee/%	time/h	yield/%	ee/%
7	5	88	16	3	97	17	3	98	13
8	5	79	13	3	90	18	2	96	2
9	4	71	75	2	90	71	1	95	66
10	20	46	10	20	50	33	20	86	40
11	20	40	9	20	50	10	10	75	8[b]
12	20	80	17	20	82	15	4	96	48
13	20	14	30	3	92	73	2	96	74

a) The reaction was conducted using 2 equiv of 3-pentyl 2-methylpropanoate and 2.6 equiv of amines **7-13** at –20 °C in toluene under the conditions **A-C** described in the text. b) (*R*)-Enantiomer was obtained.

The results obtained using type 1 amines **7-9** indicate no significant differences in enhancement of reactivity and enantioselectivity under any conditions. Enhancement of the reactivity and enantioselectivity was observed when the chiral lithium amides derived from the type 2 amines **10** and **12** were used. Comparison of these amines with **11** bearing a phenolic etheral oxygen indicates that an aliphatic etheral oxygen is important in forming complex of **2** with a lithium amide ligand. Furthermore, since the amines **9** and **13** bearing a dimethylamino group gave the better selectivity and reactivity than other etheral ligands, the importance of the dimethylamino group is apparent for the formation of a tight complex.

Conclusion

It became apparent that coexistence of lithium ester enolate **2** and lithium amides derived from amines **7-13** is an important factor for higher yield and higher enantioselectivity. Amines of the type 1, **7** and **8**, are not the good chiral ligands. On the other hand, **9** bearing a dimethylamino group in place of the methoxy group at the terminal (**7** and **8**) is a promising prototype for the chiral ligand. The amines of type 2, **10-12**, are not promising. The amine of type 3, **13**, is promising to give **4** in the highest level of enantioselectivity, although the lithiating ability is marginal.

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Experimental[14]

(–)-(1*R*,2*R*)-2-Methoxy-1-(2-trityloxyethoxy)-1,2-diphenylethane (15). A solution of (+)-(1*R*,2*R*)-**14**[8] (4.56 g, 20 mmol) in 10 mL DMF at 0 °C was added to a suspension of NaH (60% oil dispersion, 576 mg, 24 mmol) in 5 mL of DMF. The mixture was stirred for 1 h at 80 °C. A solution of 2-trityloxyethyl tosylate[15] (11.0 g, 24 mmol) in 15 mL of DMF was added at 0 °C. After stirring for 20 h at 80 °C, the mixture was quenched with water and extracted with ether. The organic extracts were washed with brine and dried over Na_2SO_4. Concentration and chromatography (hexane/AcOEt = 10/1) gave **15** as a white solid (8.2 g, 80%) of mp 105-106 °C. $[\alpha]^{25}D$ –14.0 (*c* 1.05). PMR: 3.18-3.27 and 3.54-3.58 (each 2H, m, CH_2CH_2), 3.30 (3H, s, OMe), 4.36 and 4.56 (each 1H, d, *J* = 6.6, CH), 7.01-7.64 (25H, m, ArH). CMR: 57.4, 63.5, 68.7, 85.9, 86.4, 87.6, 126.8, 127.4, 127.5, 127.6, 127.7, 127.9, 127.97, 128.80, 138.5, 138.8, 144.2. IR (nujol): 1610, 1465 cm^{-1}. MS *m/z*: 514 (M^+). Anal. Calcd for $C_{36}H_{34}O_3$: C, 84.01; H, 6.66. Found: C, 83.52; H, 6.60.

(–)-(1*R*,2*R*)-2-Methoxy-1-(2-hydroxyethoxy)-1,2-diphenylethane (16). A suspension of **15** (7.0 g, 13.6 mmol) and conc. HCl (7 mL) in 135 mL of methanol was stirred for 2 h at rt. After concentration and dilution with ether, the mixture was washed successively with water, satd $NaHCO_3$, brine, and then dried over Na_2SO_4. Concentration and chromatography ($CHCl_3/CH_3OH$ = 9/1) gave **16** as a colorless oil (3.4 g, 91%) of bp 200 °C/1.0 mmHg. $[\alpha]^{25}D$ –17.5 (*c* 1.00). PMR: 2.94 (1H, brs, OH), 3.28 (3H, s, OMe), 3.40-3.48 (1H, m, CH_2), 3.62-3.74 (3H, m), 4.32 and 4.44 (each 1H, d, *J* = 7.3, CH), 7.02-7.26 (10H, m, ArH). CMR: 57.1, 61.6, 86.4, 87.9, 127.56, 127.7, 127.8, 128.0, 137.9, 138.4. IR (film): 3400, 1610 cm^{-1}. MS *m/z*: 273 (M^++1). Anal. Calcd for $C_{17}H_{20}O_3$: C, 74.97; H, 7.40. Found: C, 74.74; H, 7.40.

(–)-(1*R*,2*R*)-2-Methoxy-1-(2-tosyloxyethoxy)-1,2-diphenylethane (17). A solution of **16** (5.44 g, 20 mmol) and *p*-toluenesulfonyl chloride (4.56 g, 24 mmol) in 40 mL of pyridine was stirred for 20 h at 0 °C, and then diluted with AcOEt. The whole was successively washed with 0.2M aq $CuSO_4$, satd $NaHCO_3$, and brine, and then dried over Na_2SO_4. Concentration and chromatography (hexane/AcOEt = 10/1) gave **17** (6.8 g, 80%) as colorless oil of bp 200 °C/1.0 mmHg and $[\alpha]^{25}D$ –5.8 (*c* 0.835). PMR: 2.44 (3H, s, Me), 3.25 (3H, s, OMe), 3.54-3.58 and 4.1-4.19 (each 2H, m), 4.26 and 4.39 (each 1H, d, *J* = 6.6, CH), 6.91-7.33 (12H, m, ArH), 7.45-7.78 (2H, m, ArH). CMR: 21.6, 57.3, 66.7, 69.2, 86.3, 127.6, 127.69, 127.73, 127.75, 127.77, 127.79, 128.0, 128.7, 133.1, 137.8, 138.0, 144.6. IR (film): 3050, 1600, 1165 cm^{-1}. MS *m/z*: 427 (M^++1). Anal. Calcd for $C_{24}H_{26}O_5S$: C, 67.58; H, 6.14. Found: C, 67.54; H, 6.24.

(–)-(1*R*,2*R*)-1-[2-(*N*-Boc-*N*-isopropylamino)ethoxy]-2-methoxy-1,2-diphenylethane (18). To a suspension of NaH (60%, 640 mg, 16 mmol) in 15 mL of DMF at 0 °C was added dropwise a solution of *N*-Boc-isopropylamine (2.1g, 13.4 mmol) in 5 mL of DMF. After stirring for 45 min at rt, a solution of **17** (2.8 g, 6.6 mmol) in 10 mL of DMF was added. After stirring for 20 h at 75 °C, the mixture was quenched with water and extracted with ether. The extracts were washed with brine and dried over Na_2SO_4. Concentration and chromatography (hexane/acetone = 20/1) gave **18** (1.9 g, 70%) as a colorless oil of bp 210 °C/1.0 mmHg and $[\alpha]^{25}D$ –36.6 (*c* 0.65). PMR: 1.07 (6H, brd, *J* = 6.7, 2Me), 1.34 (9H, s, 3Me), 3.26-3.43 (4H, m), 3.30 (3H, s, OMe), 4.28-4.47 (3H, m, CH), 6.90-7.30 (10H, m, ArH). CMR: 20.5, 28.4, 41.6, 46.5, 57.3, 68.5, 79.1, 86.2, 87.5, 127.4, 127.60, 127.64, 127.7, 138.3, 138.7, 155.2. IR (film): 1690 cm^{-1}. MS *m/z*: 414 (M^++1). Anal. Calcd for $C_{25}H_{35}NO_4$: C, 72.61; H, 8.53; N, 3.39. Found: C,72.38; H, 8.59; N, 3.44.

(–)-(1*R*,2*R*)-1-[2-(*N*-Isopropylamino)ethoxy]-2-methoxy-1,2-diphenylethane (7). A solution of **18** (2.6 g, 6.4 mmol) and TFA (1 mL, 13 mmol) in 20 mL of $CHCl_3$ was stirred for 16 h at rt. The mixture was washed with 10% NaOH, brine, and dried over K_2CO_3. Concentration and chromatography ($CHCl_3$/MeOH = 10/1) gave **7** (1.4 g, 70%) as a colorless oil of bp 155 °C/1.5 mmHg and $[\alpha]^{25}D$ –39.1 (*c* 1.50). PMR: 0.99 and 1.02 (each 3H, d, *J* = 6.7, Me) 2.67-2.76 (3H, m), 3.25 (3H, s, OMe), 3.36-3.44 and 3.52-3.60 (each 1H, m), 4.31 and 4.41 (each 1H, d, *J* = 6.3, CH), 7.05-7.26 (10H, m, ArH). CMR: 22.7, 22.9, 46.8, 48.2, 57.4, 68.9, 85.9, 87.4, 127.47, 127.52, 127.6, 127.78, 127.81, 138.5, 138.8. IR (film): 3300 cm^{-1}. MS *m/z*: 314 (M^++1). Anal. Calcd for $C_{20}H_{27}NO_2$: C, 76.64; H, 8.68; N, 4.47. Found: C, 76.69; H, 8.59; N, 4.44. Treatment of the amine with HCl/ether gave the hydrochloride as colorless needles of mp 147-148 °C (AcOEt). Anal. Calcd for $C_{20}H_{27}NO_2$.HCl: C, 68.65; H, 8.07; N, 4.00. Found: C, 68.85; H, 8.10; N, 4.13.

(–)-(1*R*,2*R*)-2-Methoxy-1-(2-trityloxypropoxy)-1,2-diphenylethane (19). Prepared by the same procedure as for **15** from **14** (9.0 g, 43.5 mmol) and 3-trityloxypropyl tosylate[14] as a colorless gum in 91% yield of bp 250 °C/1.0 mmHg and $[\alpha]^{25}D$ –18.4 (*c* 0.95). PMR: 1.88-1.92 (2H, ddt, *J* = 6.6, 6.6, 6.6 CH_2), 3.08 and 3.12 (each 1H, dt, *J* = 6.6, 12, CH_2O), 3.23 (3H, s, OMe), 3.45 (2H, t, *J* = 6.6, CH_2O), 4.26 and 4.56 (each 1H, d, *J* = 6.6, CH), 6.93-7.43 (25H, m, ArH). CMR: 30.4, 57.4, 60.9, 66.6, 85.7, 86.3, 87.4, 126.8, 127.3, 127.4, 127.6, 127.7, 127.75, 127.81, 128.7, 138.4, 138.8, 144.4. IR (film): 1610, 1495 cm^{-1}. MS *m/z*: 529 (M^++1). Anal. Calcd for $C_{37}H_{36}O_3$: C, 84.06; H, 6.86. Found: C, 84.23; H, 6.91.

(–)-(1*R*,2*R*)-2-Methoxy-1-(2-hydroxypropoxy)-1,2-diphenylethane (20). Prepared by the same procedure for **16** from **19** (19.0 g, 36 mmol) as a colorless oil of bp 230 °C/1.0 mmHg and $[\alpha]^{25}D$ –23.2 (*c* 1.20) in 97% yield. PMR: 1.76-1.89 (2H, m), 3.26 (3H, s, OMe), 3.45-3.49 (2H, m), 3.65-3.69 (1H, brs, OH), 3.81-3.85 (2H, m), 4.27 and 4.41 (each 1H, d, *J* = 7.6, CH), 6.98-7.26 (10H, m, ArH). CMR: 31.5, 56.9, 62.7, 69.6, 86.3, 87.6, 127.68, 127.7, 127.8, 127.9, 137.7, 137.9. IR (film): 3400, 1495 cm^{-1}. MS *m/z*: 287 (M^++1). Anal. Calcd for $C_{18}H_{22}O_3$: C, 75.50; H, 7.74. Found: C, 75.28; H, 7.84.

(–)-(1*R*,2*R*)-2-Methoxy-1-(2-tosyloxypropoxy)-1,2-diphenylethane (21). Prepared by the same procedure for **17** from **20** (10 g, 35 mmol) in 70% yield as a colorless oil of $[\alpha]^{25}D$ –26.7 (*c* 0.99). PMR: 1.84-1.94 (2H, m), 2.45 (3H, s, Me), 3.23 (3H, s, OMe), 3.31-3.41 (2H, m), 4.08-4.15 (2H, m, CH_2OTs), 4.25 and 4.32 (each 1H, d, *J* = 6.7, CH), 6.95-6.99 (4H, m, ArH), 7.14-7.19 (6H, m, ArH), 7.32 and 7.75 (each 2H, d, *J* = 8.0, ArH). CMR: 21.6, 29.3, 57.4, 65.0, 68.0, 86.0, 87.4, 127.52, 127.55, 127.60, 127.68, 127.74, 127.8, 127.9, 129.8, 133.2, 138.2, 138.4, 144.6. IR (film): 1495, 1180, 1100 cm^{-1}. MS *m/z*: 441 (M^++1). Anal. Calcd for $C_{25}H_{28}O_5S$: C, 68.16; H, 6.41. Found: C, 67.86; H, 6.45.

(–)-(1*R*,2*R*)-1-[2-(*N*-Boc-*N*-isopropylamino)propoxy]-2-methoxy-1,2-diphenylethane (22) . Prepared as a colorless oil (4.1 g, 70%) of bp 230 °C/0.8 mmHg and $[\alpha]^{25}D$ –25.4 (*c* 0.65) by the same procedure for **18** from **21** (6.0 g, 13.6 mmol) and Boc-isopropylamine. PMR: 1.09 and 1.10 (each 3H, d, *J* = 6.7, Me), 1.41 (9H, s, 3Me), 1.76-1.84 (2H, m), 3.06 (2H, m, CH_2), 3.28 (3H, s, OMe), 3.3-3.4 (2H, m), 4.31 and 4.39 (each 1H, *J* = 6.6, CH), 6.9-7.05 (4H, m, ArH), 7.1-7.2 (6H, m, ArH). CMR: 20.7, 28.4, 31.0, 39.7, 46.5, 57.3, 67.5, 78.9, 85.8, 87.5, 127.4, 127.65, 127.68, 127.8, 138.4, 138.8, 155.3. IR (film): 1690, 1480 cm^{-1}. MS *m/z*: 428 (M^++1). Anal. Calcd for $C_{26}H_{37}NO_4$: C, 73.03; H, 8.72; N, 3.28. Found: C, 73.13; H, 9.01; N, 3.33.

(–)-(1*R*,2*R*)-1-[2-(*N*-Isopropylamino)propoxy]-2-methoxy-1,2-diphenylethane (8). Prepared by the same procedure for **7** from **22** (5 g, 12 mmol) as a colorless oil (2.8 g, 74%) of bp 210 °C/1 mmHg and $[\alpha]^{25}D$ –29.9 (*c* 0.70). PMR: 1.02 and 1.03 (each 3H, d, *J* = 6.4, Me), 1.65-1.79 (3H, m, NH, CH_2), 2.64 (2H, t, *J* = 6.7, NCH_2), 2.73-2.76 (1H, sep, *J* = 6.4, CH), 3.27 (3H, s, OMe), 3.37-3.44 (2H, m, CH_2), 4.31 and 4.31 (each 1H, d, *J* = 6.3, CH), 7.01-7.04 (4H, m, ArH), 7.16-7.18 (6H, m, ArH). CMR: 22.8, 30.0, 45.0, 48.7, 57.3,

68.2, 85.9, 87.6, 127.5, 127.5, 127.75, 127.78, 127.80, 138.4, 138.8. IR (film): 3400 cm^{-1}. MS *m/z*: 328 (M^++1). Anal. Calcd for $C_{21}H_{29}NO_2$: C, 77.02; H, 8.93; N, 4.28. Found: C, 76.78; H, 8.64; N, 4.28.

(–)-(1*R*,2*R*)-2-*N*,*N*-Dimethylamino-1-ethoxycarbonylmethoxy-1,2-diphenylethane (24). To a solution of **23** (5.3 g, 22 mmol) in 28 mL of DMF at –60 °C was added a hexane solution of BuLi (15.5 mL, 24 mmol). After stirring for 1 h at –60 °C, a solution of ethyl bromoacetate (7.35 g, 44 mmol) in 8 mL of DMF was added dropwise. The reaction mixture was stirred at –30 °C for 2 d, quenched with satd ammonium chloride, and then extracted with ether. The extract was washed with brine and dried over K_2CO_3. Concentration and chromatography ($CHCl_3$/MeOH = 10/1) gave **24** (3.0 g, 42%) as a colorless oil of bp 150 °C/1.0 mmHg and $[\alpha]^{25}D$ –37.6 (*c* 0.50). PMR: 1.26 (3H, t, *J* = 7.0, Me), 2.37 (6H, s, 2Me), 3.79 (1H, d, *J* = 6.8, CH_2), 3.89 (1H, d, *J* = 9.5, CH), 4.12 (1H, d, *J* = 6.8, CH_2), 4.17 (2H, q, *J* = 7.0, CH_2), 5.15 (1H, d, *J* = 9.5, CH), 6.97-7.36 (10H, m ArH). CMR: 14.2, 41.5, 60.6, 65.0, 74.6, 81.1, 127.0, 127.5, 127.8, 128.0, 128.5, 129.7, 134.7, 138.6, 170.9. IR (film): 3050, 1750 cm^{-1}. MS *m/z*: 328 (M^++1). Anal. Calcd for $C_{20}H_{25}NO_3$: C, 73.37; H, 7.70; N, 4.28 Found: C, 73.37; H, 7.96; N, 4.26.

(–)-(1*R*,2*R*)-2-*N*,*N*-Dimethylamino-1-isopropylaminocarboxymethoxy-1,2-diphenylethane (25). To a solution of **24** (2.0 g, 6.2 mmol) in 10 mL of toluene at 0 °C was added isopropylamine (1.1 g, 18 mmol) and sodium methoxide (34 mg, 0.6 mmol). The mixture was stirred at 55 °C for 1 d. Concentration and chromatography ($CHCl_3$/MeOH = 50/1) gave **25** (1.5 g, 72%) as white solid of mp 64 °C and $[\alpha]^{25}D$ –50.7 (*c* 0.89). PMR: 1.21 and 1.24 (each 3H, d, *J* = 6.7, Me), 2.29 (6H, s, 2Me), 3.79 and 3.93 (each 1H, d, *J* = 16, CH_2), 3.96 (1H, d, *J* = 9.8, CHN), 4.14 (1H, sep, *J* = 6.7, CH), 4.62 (1H, d, *J* = 9.8, CHO), 6.92-7.28 (10H, m, ArH), 8.20 (1H, brs, NH). CMR: 22.7, 22.9, 40.6, 42.1, 68.6, 74.3, 83.8, 127.3, 127.6, 128.0, 128.09, 128.13, 130.2, 133.0, 138.6, 170.0. IR (nujol): 1640 cm^{-1}. MS *m/z*: 341 (M^++1). Anal. Calcd for $C_{21}H_{28}N_2O_2$: C, 74.08; H, 8.29; N, 8.23. Found: C, 73.37; H, 8.12; N, 8.03.

(–)-(1*R*,2*R*)-2-*N*,*N*-Dimethylamino-1-[2-(isopropylamino)ethoxy]-1,2-diphenylethane (9). A suspension of $LiAlH_4$ (185 mg, 5 mmol) and **25** (1.7 g, 5 mmol) in 30 mL of THF was stirred under reflux for 4 h. After successive addition of 0.2 mL of water, 0.2 mL of 10% aq NaOH, and 0.6 mL of water, and filtration, concentration and chromatography ($CHCl_3$/MeOH = 5/1) gave a yellow oil (1.3 g). Distillation (160 °C/1.0 mmHg) gave **9** (1.14 g, 73%) as a colorless oil of $[\alpha]^{25}D$ –36.0 (*c* 1.00). PMR: 1.04 and 1.05 (each 3H, d, *J* = 6.1, Me), 2.32 (6H, s, 2Me), 2.74-2.78 (3H, m), 3.42-3.49 (m, 2H), 3.78 and 4.71 (each 1H, d, *J* = 9.2, CH), 6.97-7.15 (10H, m, ArH). CMR: 22.6, 23.0, 42,3, 47.0, 48.4, 68.5, 126.9, 127.3, 127.5, 127.8, 127.9, 129.5, 136.1, 140.0. IR (film): 3300 cm^{-1}. MS *m/z*: 327 (M^++1). Anal. Calcd for $C_{21}H_{30}N_2O$: C, 77.26; H, 9.26; N, 8.58. Found: C, 77.30; H, 9.50; N, 8.48.

(+)-(1*R*,2*R*)-2-Isopropylamino-1,2-diphenylethanol (28). A mixture of (–)-(1*R*,2*R*)-2-amino-1,2-diphenylethanol **26** (10.0 g, 47 mmol) and acetone (50 mL) was stirred under reflux for 1 d. Concentration gave **27** (11.9 g, quant) as pale yellow. PMR: 1.62 and 1.63 (each 3H, s, Me), 2.53 (1H, brs, OH), 4.22 and 4.78 (each 1H, d, *J* = 8.6, CH), 7.21-7.34 (10, m, ArH). CMR: 28.5, 70.1, 85.9, 95.3, 126.3, 127.2, 127.6, 127.9, 128.3, 128.7, 137.9, 139.8. IR (film): 1640 cm^{-1}. MS *m/z*: 254 (M^++1).

To a solution of **27** (11.0 g, 43.4 mmol) in 200 mL of methanol at 0 °C was added $NaBH_4$ (1.3 g, 34 mmol) portionwise. After stirring at rt for 3 h, an additional $NaBH_4$ (225 mg, 6 mmol) was added and stirring was continued for more 2 h. The mixture was quenched with water, concentrated and extracted with ether. The combined extracts were washed with brine and dried over Na_2SO_4. Concentration and chromatography ($CHCl_3$/MeOH = 10/1) afforded **28** (11.1 g, quant) as white solid of mp 65-66 °C and $[\alpha]^{25}D$ +43.0 (*c* 1.10). PMR: 1.01 and 1.06 (each 3H, d, *J* = 6.1, Me), 1.57 (2H, brs, NH, OH), 2.71 (1H, sep, *J* = 6.1, CH), 3.61 and 4.47 (each 1H, d, *J* = 9.0, CH), 6.97-7.34 (10H, m, ArH). CMR: 22.1, 24.4, 46.0, 67.3, 77.3, 126.9, 127.3,

127.5, 127.8, 128.3, 140.6, 141.2. IR (nujol): 3300, 1600 cm^{-1}. MS *m/z*: 256 (M^++1). Anal. Calcd for $C_{17}H_{21}NO$: C, 79.96; H, 8.29; N, 5.49. Found: C, 79.75; H, 8.18; N, 5.54.

(+)-(1*R*,2*R*)-2-Isopropylamino-2-(2-methoxyethoxy)-1,2-diphenylethane (10). A mixture of **28** (6.0 g, 23.5 mmol) and NaH (60%, 677 mg, 28 mmol) in DMF (30 mL) was stirred at rt for 0.5 h. A solution of 2-methoxyethyl-*p*-toluenesulfonate (46.5 g, 28 mmol) in DMF (8 mL) was added dropwise at 0 °C. After stirring at rt for 37 h, the mixture was diluted with ether, and washed with satd Na_2CO_3, brine, and then dried over K_2CO_3. Concentration and chromatography ($CHCl_3$/MeOH = 5/1) gave a yellow oil (6.7 g). Distillation (150 °C/1.0 mmHg) gave **10** (5.7 g, 78%) as a colorless oil of $[\alpha]^{25}D$ +23.7 (*c* 1.45). PMR: 0.95 and 1.02 (each 3H, d, *J* = 6.1, Me), 1.78 (1H, brs, NH), 2.63 (1H, sep, *J* = 6.1, CH), 3.63 (3H, s, OMe), 3.41-3.59 (4H, m), 3.92 and 4.24 (each 1H, d, *J* = 8.5, CH), 6.93-7.25 (10H, m, ArH). CMR: 21.7, 24.2, 46.1, 58.8, 67.1, 67.2, 68.3, 71.8, 87.2, 127.1, 127.5, 127.7, 127.8, 128.7, 139.0. IR (film): 3400 cm^{-1}. MS *m/z*: 314 (M^++1). Anal. Calcd for $C_{20}H_{27}NO_2$: C, 76.64; H, 8.68; N, 4.47. Found: C, 76.59; H, 8.73; N, 4.44.

(–)-(1*R*,2*R*)-2-Isopropylamino-1-[(2-methoxyphenyl)chromiumtricarbonyl)oxy]-1,2-diphenylethane (30). A mixture of (1*R*,2*R*)-**28** (740 mg, 2.9 mmol) and NaH (60%, 140 mg, 3.5 mmol) in DMF (6 mL) was stirred at rt for 0.5 h. A solution of 1-fluoro-2-methoxyphenylchromiumtricarbonyl complex **29** (760 mg, 3 mmol) in DMF (2 mL) was added at 0 °C. The mixture was stirred at rt for 0.5 h, then quenched with water and extracted with toluene. The organic extract was washed with water, brine and dried over K_2CO_3. Concentration and chromatography (hexane/acetone = 19/1) gave **30** in 98% yield as two diastereomers. Less polar diastereomer (678 mg, 48%) as a yellow gum of $[\alpha]^{25}D$ –115 (*c* 0.47). PMR: 0.98 and 1.06 (each 3H, d, *J* = 6.8, Me), 2.05 (1H, m), 2.65 (1H, brs, NH), 3.92 (3H, s, OMe), 4.15 and 4.82 (each 1H, d, *J* = 7.3, CHN), 4.73 (1H, brs, ArH-Cr), 5.03 (2H, s, ArH-Cr), 5.20 (1H, d, *J* = 6.1, ArH-Cr), 6.87-7.17 (10H, m, ArH). CMR: 22.1, 24.3, 46.0, 57.0, 66.6, 82.8, 85.7, 88.1, 89.0, 127.0, 127.3, 127.7, 128.2, 128.8, 131.4, 134.7, 137.6, 139.3, 233.5. IR (film): 3300 cm^{-1}. MS *m/z*: 361 (M^+-$Cr(CO)_3$). Anal. Calcd for $C_{27}H_{27}CrNO_5$: C, 65.18; H, 5.47; N, 2.82. Found: C, 65.29; H, 5.51; N, 2.53. More polar diastereomer (706 mg, 50%) as yellow needle-like crystals of mp 89 °C and $[\alpha]^{25}D$ –10.4 (*c* 0.50) after crystallization from a mixture of ether and pentane. PMR: 0.97 and 1.07 (each 3H, d, *J* = 6.4, Me), 2.23 (1H, brs, NH), 2.63 (1H, m, CH), 3.85 (3H, s, OMe), 4.14 (1H, d, *J* = 8.6, CHN), 4.76-4.79 (2H, m), 5.02 and 5.09 (each 1H, t, *J* = 6.1, ArH-Cr), 5.16 (1H, d, *J* = 6.4, ArH-Cr), 7.14-7.26 (10H, m, ArH). CMR: 22.1, 24.5, 45.9, 56.6, 67.0, 76.4, 85.3, 85.9, 88.6, 89.8, 127.4, 127.9, 128.1, 128.3, 128.7, 130.6, 133.7, 136.5, 233.2. IR (nujol): 3330 cm^{-1}. MS *m/z*: 361 (M^+-$Cr(CO)_3$). Anal. Calcd for $C_{27}H_{27}CrNO_5$: C, 65.18; H, 5.47; N, 2.82. Found: C, 65.26; H, 5.19; N, 2.78.

(–)-(1*R*,2*R*)-2-Isopropylamino-1-(2-methoxyphenoxy)-1,2-diphenylethane (11). A solution of iodine (2.85 g, 11 mmol) in THF (4 mL) was added dropwise at –78 °C to a solution of mixture of two diastereomers **30** (1.4 g, 2.8 mmol) in 4 mL of THF. The mixture was stirred at 0 °C for 0.5 h, then diluted with 40 mL of ether and washed with 10% sodium thiosulfate. The aqueous phase was treated with 30% potassium carbonate until alkaline and extracted with ether. The organic extract was washed with 30% potassium carbonate, brine and dried over K_2CO_3. Concentration and chromatography ($CHCl_3$/MeOH) followed by distillation (220 °C/0.8 mmHg) gave **11** (0.94 g, 93%) as a colorless solid of mp 67 °C and $[\alpha]^{25}D$ –3.1 (*c* 0.55). PMR: 0.97 and 1.11 (each 3H, d, *J* = 6.1, Me), 2.50 (1H, brs, NH), 2.65 (1H, sep, *J* = 6.1, CH), 3.92 (3H, s, OMe), 4.19 and 4.91 (each 1H, d, *J* = 8.6, CH), 6.59-6.67 and 6.84-6.88 (each 2H, m, ArH), and 7.00-7.14 (10H, m, ArH). CMR: 22.2, 24.6, 46.0, 55.9, 67.5, 88.0, 112.0, 117.0, 120.8, 121.8, 127.1, 127.2, 127.7, 127.8, 128.9, 139.2, 139.9, 148.3, 150.2. IR (nujol): 3300 cm^{-1}. MS *m/z*: 362 (M^++1). Anal. Calcd for $C_{24}H_{27}NO_2$: C, 79.74; H, 7.53; N, 3.87. Found: C, 79.70; H, 7.54; N, 3.92.

(–)-(1*R*,2*R*)-2-Isopropylamino-1-(2-methoxybenzyloxy)-1,2-Diphenylethane (12). A mixture of

(1*R*,2*R*)-**28** (2.55 g, 10 mmol) and NaH (60%, 0.48 g, 12 mmol) in DMF (10 mL) was stirred at rt for 0.5 h. A solution of 2-methoxybenzyl chloride (1.87 g, 12 mmol) in DMF (4 mL) was added dropwise at 0 °C. The mixture was stirred at rt for 2 h, and quenched with water and extracted with toluene. The extract was washed with brine and dried over K_2CO_3. Concentration and crystallization from hexane gave **12** (3.0 g, 80%) as a white solid of mp 67 °C and $[\alpha]^{25}D$ −1.9 (*c* 0.82). PMR: 0.94 and 1.03 (each 3H, d, *J* = 6.4, Me), 2.25 (1H, brs, NH), 2.59 (1H, sep, *J* = 6.4, CH), 3.79 (3H, s, OMe), 3.95 and 4.36 (each 1H, d, *J* = 8.6, CH), 4.40 and 4.42 (each 1H, d, *J* = 12, $PhCH_2$), 6.85-7.47 (14H, m, ArH). CMR: 22.1, 24.6, 46.0, 55.1, 66.3, 67.4, 86.7, 110.0, 120.3, 126.8, 127.4, 127.6, 127.8, 128.6, 128.7, 129.0, 139.3, 140.7, 157.2. IR (nujol): 3300 cm^{-1}. MS *m/z*: 376 (M^++1). Anal. Calcd for $C_{25}H_{29}NO_2$: C, 79.96; H, 7.78; N, 3.73. Found: C, 79.93; H, 7.82; N, 3.56.

(+)-(1*R*,2*R*)-1-Amino-2-methoxymethylenecarboxamido-1,2-diphenylethane (33). To a solution of (+)-(1*R*,2*R*)-**32** (5.0 g, 23.5 mmol) and 2-methoxyacetic acid (2.1 g, 23.5 mmol) in $CHCl_3$ (100 mL) at -5 °C, was added a solution of DCC (4.8 g, 24 mmol) in $CHCl_3$ (20 mL). After stirring at −5 °C for 0.5 h and at rt for 15 h, the precipitate was filtered off and the filtrate was washed with 1M $NaHCO_3$, brine, and dried over Na_2CO_3. Concentration and chromatography ($CHCl_3$/MeOH = 20/1) gave **33** (2.4 g, 36) as colorless powder of mp 82-83 °C and $[\alpha]^{25}D$ +29.1 (*c* 0.85). PMR: 1.36 (2H, brs, NH_2), 3.34 (3H, s, OMe), 3.76 and 3.89 (each 1H, d, *J* = 15, CH_2), 4.43 (1H, d, *J* = 3.4, CH), 5.16 (1H, dd, *J* = 3.4, 8.5, CHN), 7.10-7.38 (10H, m, ArH), 7.72 (1H, d, *J* = 8.5, NH). CMR: 58.0, 59.4, 59.7, 72.1, 126.5, 126.7, 127.4, 127.5, 128.3, 128.6, 140.1, 141.9, 169.3. IR (nujol): 1660 cm^{-1}. MS *m/z*: 285 (M^++1). Anal. Calcd for $C_{17}H_{20}N_2O_2$: C, 71.81; H, 7.09; N, 9.85. Found: C, 71.62; H, 7.17; N, 9.57.

(+)-(1*R*,2*R*)-1-*N*,*N*-Dimethlamino-2-methoxymethylenecarboxamido-1,2-diphenylthane (34). To a solution of **33** (3.6 g, 12.7 mmol) and formaldehyde (1.54 g, 38 mmol) in acetonitrile (12 mL) at 0 °C was added $NaCNBH_3$ (2.4 g, 38 mmol). After stirring at rt for 15 min, acetic acid was added. The solution was stirred for 2 h at rt. The mixture was concentrated and treated with 2N KOH (15 mL), and extracted with ether. The combined extract was washed with 0.5 N KOH and dried over K_2CO_3. Concentration and chromatography ($CHCl_3$/MeOH = 20/1) gave **34** (2.7 g, 69%) as colorless powder of mp 108 °C and $[\alpha]^{25}D$ +86.8 (*c* 0.85). PMR: 2.17 (6H, s, 2Me), 3.48 (3H, s, OMe), 3.73 (1H, d, *J* = 10, CHN), 3.95 (2H, s, CH_2), 5.23 (1H, dd, *J* = 5.2, 10, CHN), 7.04-7.25 (10H, m, ArH), 7.83 (1H, d, *J* = 5.2, NH). CMR: 40.9, 53.7, 59.3, 72.5, 73.5, 126.8, 127.4, 127.5, 127.7, 127.9, 129.7, 133.0, 140.8, 169.5. IR (nujol): 1670 cm^{-1}. MS *m/z*: 313 (M^++1). Anal. Calcd for $C_{19}H_{24}N_2O_2$: C, 73.05; H, 7.74; N, 8.97. Found: C, 73.06; H, 7.68; N, 8.85.

(+)-(1*R*,2*R*)-1-*N*,*N*-Dimethlamino-2-methoxyethylamino-1,2-diphenylethane (13). To a suspension of $LiAlH_4$ (356 mg, 9.6 mmol) in THF (35 mL) was added a solution of **34** (3.0 g, 9.6 mmol) in THF (15 mL) dropwise at 0 °C. The mixture was stirred under reflux for 4 h and then was added successively water (0.4 mL), 15% NaOH (0.4 mL) and water (1.2 mL) at 0 °C. Filtration, concentration, and chromatography ($CHCl_3$/MeOH = 20/1) followed by distillation (bp 165 °C/0.7 mmHg) gave **13** (2.1 g, 73%) as a colorless oil of $[\alpha]^{25}D$ +54.9 (*c* 0.84). PMR: 1.65 (1H, brs, NH), 2.18 (6H, s, 2Me), 2.58 (1H, ddd, *J* = 4, 5, 12, NCH_2), 2.72 (1H, ddd, *J* = 4, 4, 12, NCH_2), 3.36 (3H, s, OMe), 3.42 (1H, ddd, *J* = 4, 5, 10, OCH_2), 3.48 (1H, ddd, *J* = 2, 3, 10, OCH_2), 3.72 and 4.09 (each 1H, d, *J* = 10, CH), 6.99-7.25 (10H, m, ArH). CMR: 40.6, 46.9, 58.6, 62.8, 72.0, 74.1, 126.7, 126.9, 127.2, 127.7, 128.8, 130.0, 133.4, 141.5. IR (film): 3300 cm^{-1}. MS *m/z*: 299 (M^++1). Anal. Calcd for $C_{19}H_{26}N_2O$: C, 76.47; H, 8.78; N, 9.39. Found: C, 76.33; H, 8.57; N, 9.40.

General procedure for asymmetric condensation under the conditions C using 13. A solution of 3-pentyl 2-methylpropanoate (158 mg, 1 mmol) in toluene (2 mL) was added to a solution of LDA (1 mmol) in toluene (2 mL). After stirring for 1 h at −20 °C, a solution of lithiated **13** (1.3 mmol), generated from **13** and butyllithium in toluene (2 mL) for 1 h at −78 °C, was added at −78 °C. The mixture was stirred for 1 h at −20

°C. Then, a solution of **3** (0.5 mmol) in toluene (2.5 mL) was added at –78 °C. After stirring at –20 °C for 2 h, 10% HCl was added, and the mixture was extracted with ether. The organic layer was successively washed with water, satd sodium bicarbonate, brine, and then dried over sodium sulfate. Concentration followed by chromatography (ether/hexane = 1/3) gave (*S*)-**4a** as a colorless solid (135 mg, 96%) of $[\alpha]^{25}_{D}$ +95.9 (c 1.01). PMR: 0.84, 1.51 and 3.75 (each 3H, s, Me), 4.76 (1H, s, CH), 6.80 (2H, d, *J* = 8.9, ArH), 7.1-7.4 (7H, m, ArH). CMR: 17.9 (q), 22.8 (q), 55.2 (s), 55.4 (q), 66.5 (d), 114.2 (d), 118.4 (d), 126.6 (d), 128.6 (d), 127.9 (d), 131.4 (s), 135.6 (s), 155.8 (s), 170.8 (each s). IR (nujol): 1730 cm^{-1}. MS *m/z*: 281 (M^+). Anal. Calcd for $C_{18}H_{19}NO_2$: C, 76.84; H, 6.81; N, 4.98. Found: C, 77.04; H, 6.78; N, 4.96. HPLC (Daicel Chiralcel OD-H, hexane/*i*-PrOH = 100/1), 1.0 mL/min, 250 nm, 21 min (*R*), 25 min (*S*), 74% ee. The chiral ligand **13** was recovered quantitatively from aq. acidic solution.

References and Notes

(1) Visiting scientist from Faculty of Pharmacy, Assiut University, Egypt.

(2) (a) Caine, D. in *Carbon-Carbon Bond Formation* Augustine, R. L. Ed. Marcel Dekker, Inc. New York, 1979, p. 85. (b) Franklin, A. S.; Paterson, I. *Contemporary Organic Synthesis* **1994**, 317.

(3) (a) Tomioka, K. *Synthesis* **1990**, 541-549. (b) Noyori, R. *Asymmetric Catalysis in Organic Synthesis* John Wiley and Sons, Inc. New York, 1994. (c) Seyden-Penne, J. *Chiral Auxiliaries and Ligands in Asymmetric Synthesis* John Wiley and Sons, Inc., New York, 1995.

(4) (a) Tomioka, K.; Fujieda, H.; Hayashi, S.; Hussein, M. A.; Kambara, T.; Nomura, Y.; Kanai, M.; Koga, K. *Chem. Commun.* **1999**, 715-716. (b) Kambara, T.; Tomioka, K. *Chem. Pharm. Bull.* **1999**, *47*, 720-721.

(5) (a) Fujieda, H.; Kanai, M.; Kambara, T.; Iida, A.; Tomioka, K. *J. Am. Chem. Soc.* **1997**, *119*, 2060-2061. (b) Kambara, T.; Hussein, M. A.; Fujieda, H.; Iida, A.; Tomioka, K. *Tetrahedron Lett.* **1998**, *39*, 9055-9058.

(6) Shindo, M.; Koga, K.; Tomioka, K. *J. Org. Chem.* **1998**, *63*, 9351-9357.

(7) For the recently reported catalytic addition reaction of ester enolate equivalents with imines, see: (a) Ishitani, H.; Ueno, M.; Kobayashi, S. *J. Am. Chem. Soc.* **1997**, *119*, 7153-7154. (b) Hagiwara, E.; Fujii, A.; Sodeoka, M. *J. Am. Chem. Soc.* **1998**, *120*, 2474-2475. (c) Ferraris, D.; Young, B.; Dudding, T.; Lectka, T. *J. Am. Chem. Soc.* **1998**, *120*, 4548-4549.

(8) The similar reactivity enhancement phenomenon of butyllithium has been reported based on the NMR observation of heterodimeric complex. Arvidsson, P. I.; Davidsson, Ö.; Hilmersson, G. *Tetrahedron: Asymmetry* **1999**, *10*, 527-534, and references cited therein.

(9) Mizuno, M.; Kanai, M.; Iida, A.; Tomioka, K. *Tetrahedron* **1997**, *53*, 10699-10708.

(10) (a) Inoue, I.; Shindo, M.; Koga, K.; Kanai, M.; Tomioka, K. *Tetrahedron: Asymmetry* **1995**, *6*, 2527-2533. (b) Saigo, K.; Ogawa, S.; Kikuchi, S.; Kasahara, A.; Nohira, H. *Bull. Chem. Soc. Jpn* **1982**, *55*, 1568-1573.

(11) Pini, D.; Iuliano, A.; Rosini, C.; Salvadori, P. *Synthesis* **1990**, 1023-1024.

(12) Mahaffy, C. A. L. *J. Organometallic Chem.* **1984**, *262*, 33-37.

(13) Yates, P.; Macas, T. S. *Can. J. Chem.* **1987**, *66*, 1-10.

(14) Purification was carried out using silica gel column chromatography unless otherwise noted. Chemical shift was presented in ppm relative to internal TMS. Coupling constant (*J*) was presented in Hz. Specific rotation was measure in $CHCl_3$ unless otherwise noted.

(15) Schmidt, R. R.; Stump, C. M. *Tetrahedron* **1986**, *42*, 5941-5948.