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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. © 1999 Elsevier Science Ltd. All rights reserved.

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Introduction

Lithium ester enolate is among the established, powerful carbonucleophiles in the formation of carboncarbon 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

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 molety

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



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 for 0.5 h). Then, 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.

Conditions A Conditions **B** Conditions C amine 7-13 time/h yield/% ee/% time/h yield/% ee/% time/h yield/% ee/% 8 b

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

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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Experimental¹⁴

(-)-(1R,2R)-2-Methoxy-1-(2-trityloxyethoxy)-1,2-diphenylethane (15). A solution of (+)-(1R,2R)-14⁸ (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 tosylate¹⁵ (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 Na₂SO₄. Concentration and chromatography (hexane/AcOEt = 10/1) gave 15 as a white solid (8.2 g, 80%) of mp 105-106 °C. [α]²⁵D-14.0 (*c* 1.05). PMR: 3.18-3.27 and 3.54-3.58 (each 2H, m, CH₂CH₂), 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 C₃₆H₃₄O₃: C, 84.01; H, 6.66. Found: C, 83.52; H, 6.60.

(-)-(1R,2R)-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 NaHCO₃, brine, and then dried over Na₂SO₄. Concentration and chromatography (CHCl₃/CH₃OH = 9/1) gave 16 as a colorless oil (3.4 g, 91%) of bp 200 °C/1.0 mmHg. [α]²⁵D-17.5 (*c* 1.00). PMR: 2.94 (1H, brs, OH), 3.28 (3H, s, OMe), 3.40-3.48 (1H, m, CH₂), 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 C₁₇H₂₀O₃: C, 74.97; H, 7.40. Found: C, 74.74; H, 7.40.

(-)-(1R,2R)-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 CuSO₄, satd NaHCO₃, and brine, and then dried over Na₂SO₄. 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 C₂₄H₂₆O₅S: C, 67.58; H, 6.14. Found: C, 67.54; H, 6.24.

(-)-(1R,2R)-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 Na₂SO₄. 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 C₂₅H₃₅NO₄: 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 CHCl₃ was stirred for 16 h at rt. The mixture was washed with 10% NaOH, brine, and dried over K₂CO₃. Concentration and chromatography (CHCl₃/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 C₂₀H₂₇NO₂: 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 C₂₀H₂₇NO₂.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 tosylate¹⁴ 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, $J = 6.6, 6.6, 6.6 \text{ CH}_2$), 3.08 and 3.12 (each 1H, dt, $J = 6.6, 12, \text{CH}_2$ O), 3.23 (3H, s, OMe), 3.45 (2H, t, $J = 6.6, \text{CH}_2$ O), 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 C₃₇H₃₆O₃: 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 C₁₈H₂₂O₃: 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, CH₂OTs), 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 C₂₅H₂₈O₅S: 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, CH₂), 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 C₂₆H₃₇NO₄: 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 [α]²⁵D -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, CH₂), 2.64 (2H, t, J = 6.7, NCH₂), 2.73-2.76 (1H, sep, J = 6.4, CH), 3.27 (3H, s, OMe), 3.37-3.44 (2H, m, CH₂), 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 C₂₁H₂₉NO₂: C, 77.02; H, 8.93; N, 4.28. Found: C, 76.78; H, 8.64; N, 4.28.

(-)-(1R,2R)-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 K₂CO₃. Concentration and chromatography (CHCl₃/MeOH = 10/1) gave 24 (3.0 g, 42%) as a colorless oil of bp 150 °C/1.0 mmHg and [α]²⁵D -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, CH₂), 3.89 (1H, d, *J* = 9.5, CH), 4.12 (1H, d, *J* = 6.8, CH₂), 4.17 (2H, q, *J* = 7.0, CH₂), 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 C₂₀H₂₅NO₃: 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 (CHCl₃/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, CH₂), 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 C₂₁H₂₈N₂O₂: 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 LiAlH₄ (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 (CHCl₃/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 C₂₁H₃₀N₂O: 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 NaBH₄ (1.3 g, 34 mmol) portionwise. After stirring at rt for 3 h, an additional NaBH₄ (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 Na₂SO₄. Concentration and chromatography (CHCl₃/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 C₁₇H₂₁NO: C, 79.96; H, 8.29; N, 5.49. Found: C, 79.75; H, 8.18; N, 5.54.

(+)-(1R,2R)-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 Na₂CO₃, brine, and then dried over K₂CO₃. Concentration and chromatography (CHCl₃/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 C₂₀H₂₇NO₂: C, 76.64; H, 8.68; N, 4.47. Found: C, 76.59; H, 8.73; N, 4.44.

(-)-(1R,2R)-2-Isopropylamino-1-[(2-methoxyphenyl)chromiumtricarbonyl)oxy]-1,2-diphenylethane (30). A mixture of (1R,2R)-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 C₂₇H₂₇CrNO₅: 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 C₂₇H₂₇CrNO₅: C, 65.18; H, 5.47; N, 2.82. Found: C, 65.26; H, 5.19; N, 2.78.

(-)-(1R,2R)-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 K₂CO₃. Concentration and chromatography (CHCl₃/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 C₂₄H₂₇NO₂: C, 79.74; H, 7.53; N, 3.87. Found: C, 79.70; H, 7.54; N, 3.92.

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

(1R,2R)-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 K₂CO₃. Concentration and crystallization from hexane gave 12 (3.0 g, 80%) as a white solid of mp 67 °C and [α]²⁵D -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, PhCH₂), 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 C₂₅H₂₉NO₂: 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 CHCl₃ (100 mL) at -5 °C, was added a solution of DCC (4.8 g, 24 mmol) in CHCl₃ (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 NaHCO₃, brine, and dried over Na₂CO₃. Concentration and chromatography (CHCl₃/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, NH₂), 3.34 (3H, s, OMe), 3.76 and 3.89 (each 1H, d, *J* = 15, CH₂), 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 C₁₇H₂₀N₂O₂: C, 71.81; H, 7.09; N, 9.85. Found: C, 71.62; H, 7.17; N, 9.57.

(+)-(1R,2R)-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 NaCNBH₃ (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 K₂CO₃. Concentration and chromatography (CHCl₃/MeOH = 20/1) gave 34 (2.7 g, 69%) as colorless powder of mp 108 °C and [α]²⁵D +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, CH₂), 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 C₁₉H₂₄N₂O₂: C, 73.05; H, 7.74; N, 8.97. Found: C, 73.06; H, 7.68; N, 8.85.

(+)-(1R,2R)-1-N,N-Dimethlamino-2-methoxyethylamino-1,2-diphenylethane (13). To a suspension of LiAlH₄ (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 (CHCl₃/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 C₁₉H₂₆N₂O: 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 3pentyl 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 C₁₈H₁₉NO₂: 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.

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