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CATALYTIC ASYMMETRIC SYNTHESIS OF (*S*)-LAUDANOSINE BY HYDROAMINATION

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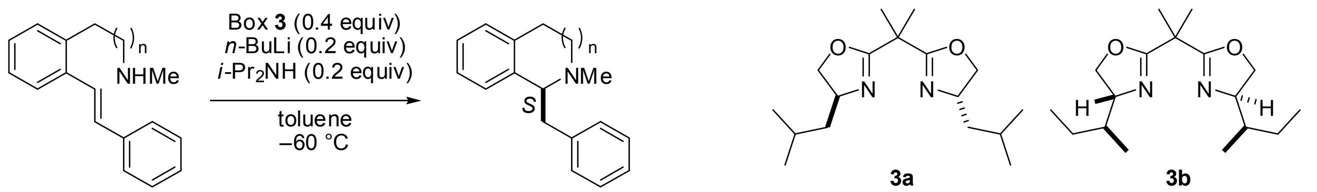
This paper is dedicated to Prof. Ei-ichi Negishi on the occasion of his 77th *kiju* birthday.

Abstract – Lithium amide–chiral bisoxazoline-catalyzed asymmetric intramolecular hydroamination was examined with respect to the structural variants of starting aminoalkenes. Substituents on the nitrogen and olefin of aminoalkenes were found to be important factors affecting reaction efficiency as well as enentioselectivity in the production of chiral tetrahydroisoquinolines and isoindolines. The catalytic asymmetric total synthesis of (*S*)-laudanosine highlights the utility of the asymmetric hydroamination.

INTRODUCTION

Asymmetric intramolecular hydroamination of aminoalkenes is a highly versatile C–N bond forming reaction useful for the synthesis of nitrogen-containing chiral heterocycles.[1] We have already reported the chiral bisoxazoline (box) **3a**–lithium diisopropylamide (LDA)-catalyzed asymmetric intramolecular hydroamination of aminoalkenes **1a** giving 1-benzyltetrahydroisoquinoline **2a** with 84% ee in 97% yield (Scheme 1).[2-4] 1-Benzylisoindoline **2b** with excellent 91% ee was also synthesized in 99% yield by the catalysis of chiral bisoxazoline **3b**–LDA. In this paper we describe the extension of this intramolecular hydroamination method to the cyclization of other type of aminoalkenes and further application to the asymmetric total synthesis of representative isoquinoline alkaloid (*S*)-laudanosine.



1a (n = 1)
1b (n = 0)

2a (n = 1): 97%, 84% ee (*S*)
2b (n = 0): 98%, 91% ee (*R*)

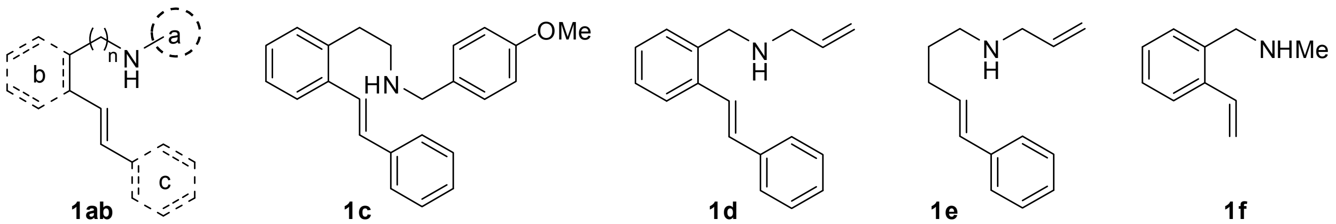
3a
(**1a** to **2a**)

3b
(**1b** to **2b**)

Scheme 1. Chiral box–LDA-catalyzed asymmetric intramolecular hydroamination of aminoalkenes **1**.

RESULTS AND DISCUSSION

The asymmetric intramolecular hydroamination of aminoalkenes **1a** and **1b** was effectively catalyzed by chiral box **3**–lithium amide catalyst.[2] The structural features of aminoalkenes **1a** and **1b** are (a) an *N*-methyl group, (b) an aromatic ring connecting an amino group and an olefin, and (c) phenyl group on a terminal carbon of olefin (Figure 1). To verify whether these features are essential for the reaction, other types of aminoalkenes **1c**–**f** were prepared and examined their possibilities in the intramolecular hydroamination.

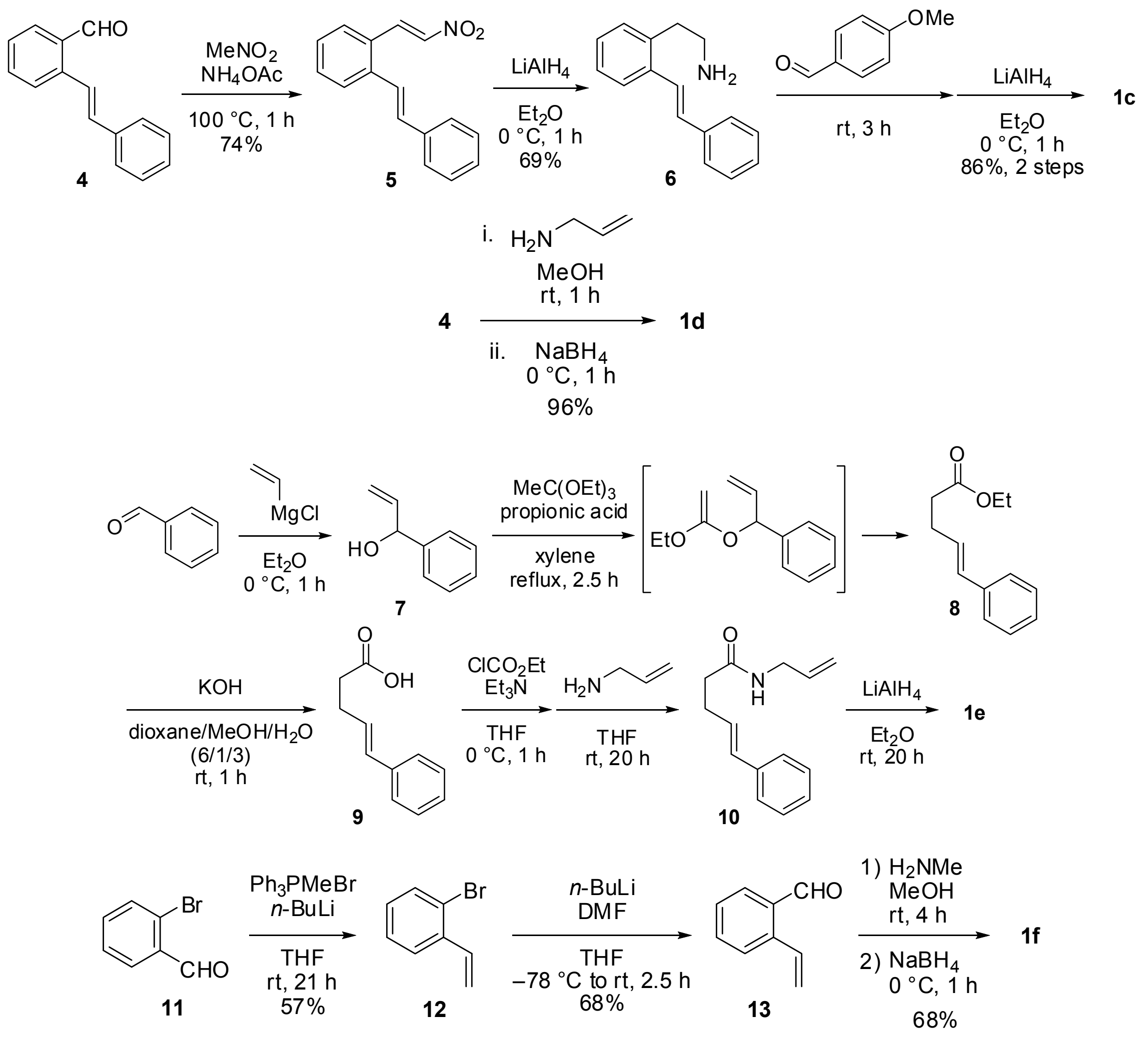


1ab **1c** **1d** **1e** **1f**

Figure 1. Aminoalkenes **1c**–**1f** for an asymmetric intramolecular hydroamination.

Synthesis of aminoalkenes 1c–1f

As shown in Scheme 2 *N*-PMB (4-methoxybenzyl) aminoalkene **1c** and *N*-allyl aminoalkene **1d** were prepared from the same aldehyde **4**, which was prepared by the Heck reaction of commercially available 2-bromobenzaldehyde and styrene.[5] The Henry reaction of **4** and following $LiAlH_4$ reduction of nitroalkene **5**[6] gave primary amine **6**.[7] Reductive 4-methoxybenzylation of **6** afforded *N*-PMB aminoalkene **1c**. Reductive amination of **4** with allylamine gave **1d**.[8] The sequential treatment of benzaldehyde with vinylmagnesium bromide,[9] Johnson–Claisen rearrangement,[10] hydrolysis of ethyl ester **8**, amidation of a carboxylic acid **9** with allylamine, and finally $LiAlH_4$ reduction of amide **10** gave **1e**. According to the reported procedure, **1f** was synthesized starting from 2-bromobenzaldehyde **11** by the Wittig olefination.[11] Halogen–lithium exchange of **12** and formylation with DMF gave **13**, and then reductive amination with methylamine gave **1f**.[11c,d]



Scheme 2. Synthesis of aminoalkenes **1c**–**1f**.

Asymmetric hydroamination of aminoalkenes 1c–f

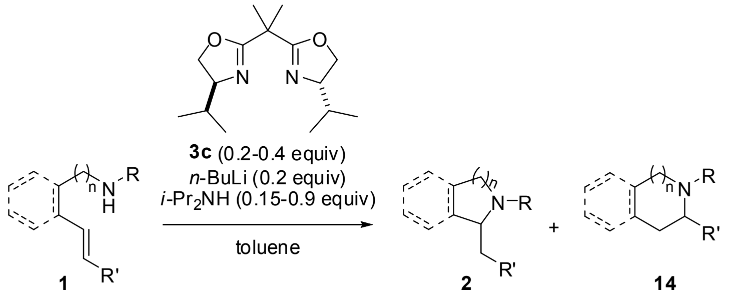
Substituents of amine were examined on the reaction efficiency and enantioselectivity (Figure 1, moiety (a) of **1ab**). From the synthetic viewpoint, easily removable PMB and allyl groups were selected as a candidate (Table 1, entries 3 and 4). *N*-PMB aminoalkene **1c** was treated with chiral box **3c** and LDA in toluene at 0 °C to give cyclized tetrahydroisoquinoline derivative **2c** in as high as 94% yield. However, enantioselectivity was only 11% ee (entry 3). Since the stereoselectivity of the corresponding *N*-methyl derivative **2a** is 71% ee by using the same box **3c** (entry 1),[2] *N*-PMB group was unfavorable for this asymmetric reaction. On the other hand, the reaction of *N*-allyl aminoalkene **1d**[12] gave isoindoline derivative **2d** with 83% ee in 98% yield (entry 4), which was almost same selectivity as that of *N*-methyl derivatives **2b**[2] (entries 2 and 4). These results indicated that methyl or allyl *N*-substituent led to the cyclization with better enantioselectivities.

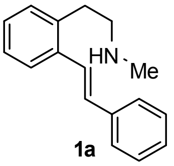
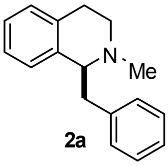
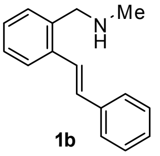
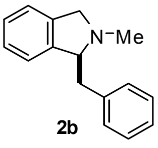
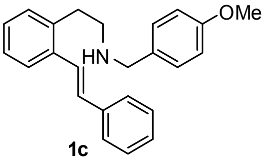
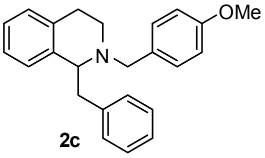
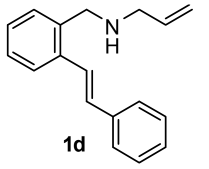
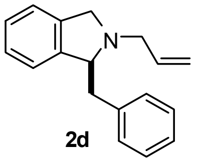
Aromatic ring connecting secondary amine and olefin moieties (Figure 1, (b) of **1ab**) was examined with respect to their effect on the reaction efficiency by the reaction of **1e** in which no aromatic ring exists.

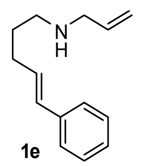
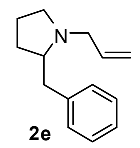
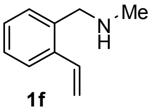
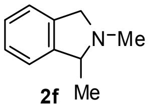
The hydroamination of **1e** gave **2e** in 90% yield; however, the enantioselectivity was only 18% ee (entry 5). This result indicated that the presence of aromatic ring was also important to achieve good enantioselectivity.

The terminal phenyl group of olefin, (c) moiety of **1ab** in Figure 1, affected regioselectivity as well as enantioselectivity. The reaction of **1f**, having no terminal phenyl group, afforded the expected 5-exo-cyclization product **2f** as the major one in 33% yield with 43% ee, 6-endo cyclization product **14f** in 7% yield, intermolecularly reacted dimer **15** in 28% yield, and recovered **1f** in 19% yield (entry 6). These results indicated that a terminal phenyl group directs originally favored 5-exo cyclization (entries 2, 4 and 5) by sterically blocking attack at the terminal olefin carbon.

Table 1. Chiral bisoxazoline **3c**–LDA-catalyzed asymmetric intramolecular hydroamination of aminoalkenes **1**.



Entry	**1**	**2**	temp (°C)	time (h)	**2** yield (%)	**2** ee (%)	**14** yield (%)
1[a]	 **1a**	 **2a**	–60	5	99	71	0
2[a]	 **1b**	 **2b**	–60	5	99	84	0
3	 **1c**	 **2c**	0	31	94	11[b]	0
4	 **1d**	 **2d**	–40	2	98	83[c]	0

5[d]	 **1e**	 **2e**	–40 to rt	21	90	18[b]	0
6[e]	 **1f**	 **2f**	–20	1	33	43[b]	7

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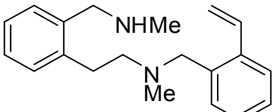
[a] ref 2.

[b] Absolute configuration was not determined.

[c] Absolute configuration was determined by the specific rotation after conversion of **2d** to **2b** by deallylation–methylation.

[d] The reaction was carried out at –40 °C for 3 h, at –20 °C for 3 h and then at room temperature for 15 h.

[e] Dimer **15** (28%) was also obtained, and **1f** (19%) was recovered.



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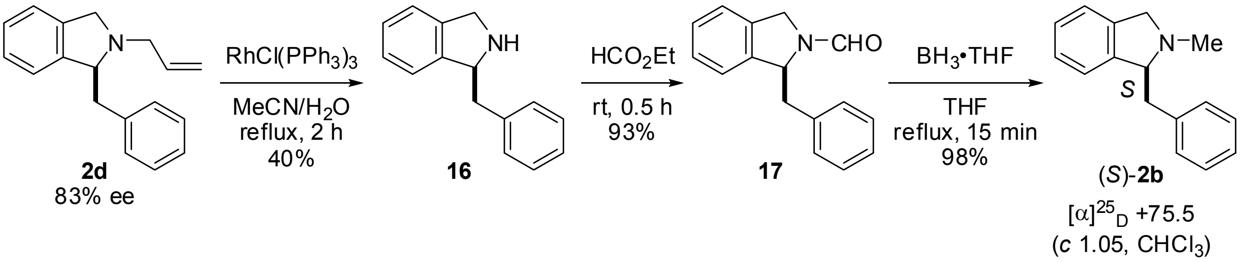
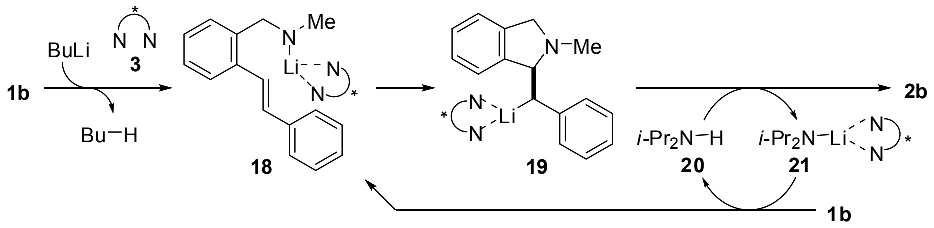
The absolute configuration of **2d** was unambiguously determined by correlating with (*S*)-**2b**[13] of the established configuration (Scheme 3). The sense of enantiofacial selectivity of *N*-allyl aminoalkene **1d** is identical with that of *N*-methyl aminoalkene **1b**.



Scheme 3. Correlation of **2d** with **2b**.

Reaction pathway of intramolecular hydroamination

The plausible reaction pathway was shown in Scheme 4. The aminoalkene **1b** was deprotonated by *n*-BuLi and/or LDA to give the corresponding lithium amide **18**, to which chiral bisoxazoline **3** coordinated. Aminolithiation of **18** gave cyclized product **19**, and subsequent protonation by *i*-Pr_2NH **20** and/or **1b** furnished hydroamination product **2b**, and *i*-Pr_2NLi **21** or **16**. In the case that **19** was protonated with *i*-Pr_2NH **20**, catalytic cycle was accomplished by the deprotonation of **1b** with LDA **21** to give **18** again. The possible stereoinduction step is kinetically controlled aminolithiation step, **18** to **19**, of which C–Li is immediately converted to C–H by protonation with **20** and/or **1b**.



Scheme 4. Reaction pathway of intramolecular hydroamination.

Stereoinduction of intramolecular hydroamination

The cyclization would proceed through transition state **A** not through **B** to avoid the steric repulsion between the bulky alkyl group of **3** (shown as R in **A**) and the aromatic ring of aminoalkene **1b** as shown in **B** to give (*S*)-product preferentially (Figure 2). The results of Table 1 supported this analysis; the aromatic rings of **1b** would contribute to the steric repulsion with the alkyl group of **3** in disfavored transition state **B**, and thus the absence of aromatic ring in **1e** reduces superiority of **A** over **B** to result in poorer enantioselectivities (Table 1, entries 5 and 6). Moreover, the bulky *N*-protecting group of **1c** caused another steric repulsion against the alkyl group of **3** as shown in **C**, which also resulted in poor enantioselectivity (Table 1, entry 3). A terminal phenyl group contributes to the selectivity of 5-exo/6-endo cyclization; in the reaction of **1f**, both 5-exo cyclization product **2f** (33%) and 6-endo cyclization product **14f** (7%) were obtained, whereas **1b**, **1d** and **1e** gave only 5-exo cyclization products. The absence of terminal phenyl group reduces the steric hindrance at the terminal of the olefin, and consequently 6-endo cyclization product **14f** and dimer **15** were produced. Apparently, this chiral bisoxazoline–lithium amide catalyst system is suitable for the asymmetric synthesis of 1-benzyltetrahydroisoquinolines and 1-benzylisoindolines.

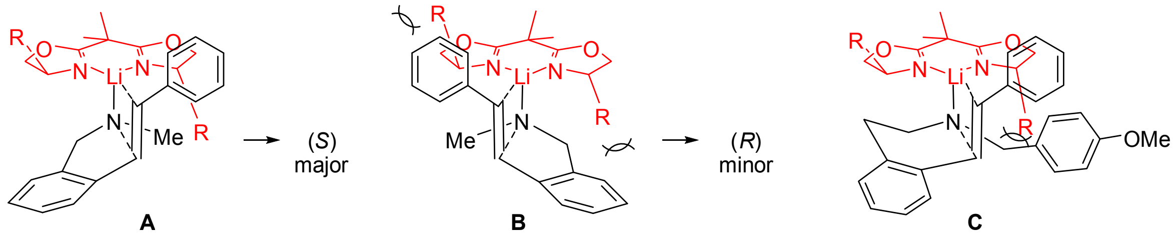
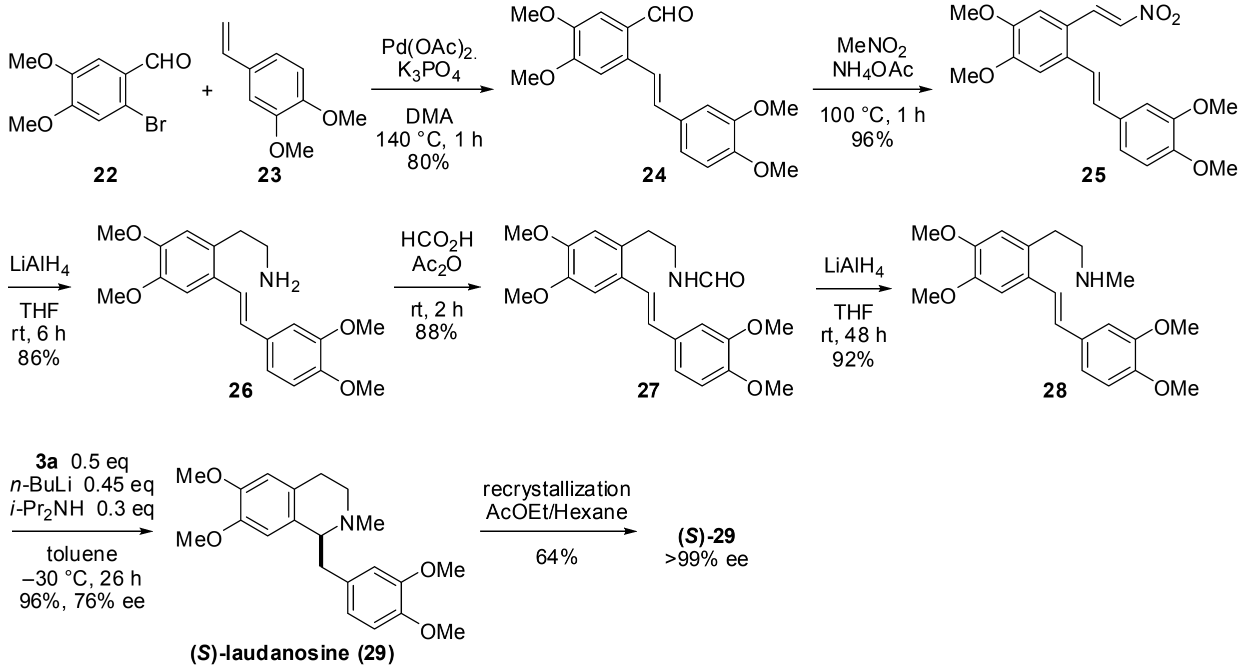


Figure 2. Plausible stereoinduction model for a chiral bisoxazoline–lithium amide-catalyzed asymmetric intramolecular hydroamination.

Asymmetric total synthesis of (*S*)-laudanosine

The asymmetric hydroamination was applicable for the total synthesis of opium alkaloid (*S*)-laudanosine (**29**).[14] Commercially available 6-bromoveratrylaldehyde **22** and 3,4-dimethoxystyrene **23** were coupled by the Heck reaction to give stilbene **24** in 80% yield (Scheme 5). Henry reaction gave nitroalkene **25**, whose $LiAlH_4$ reduction gave primary amine **26**. Formylation followed by $LiAlH_4$ reduction gave secondary *N*-methylamine **28**, a cyclization precursor of (*S*)-laudanosine **29**. The hydroamination reaction of **28** was carried out at –30 °C due to its low solubility at temperature lower than –30 °C to give desired (*S*)-laudanosine **29** in 96% yield with 76% ee. Optically pure (*S*)-**29** was obtained by recrystallization from hexane/ethyl acetate in 64% yield. Thus, catalytic asymmetric synthesis of optically pure (*S*)-laudanosine **29** was accomplished in 33% overall yield.



Scheme 5. Asymmetric total synthesis of (*S*)-laudanosine.

CONCLUSION

In conclusion, the substituents of aminoalkenes significantly affected the efficiency of the chiral bisoxazoline–lithium amide-catalyzed asymmetric hydroamination. This catalytic system was suitable for the preparation of chiral 1-benzyltetrahydroisoquinolines and 1-benzylisoindolines. Asymmetric total synthesis of (*S*)-laudanosine was achieved in 6 steps using catalytic asymmetric hydroamination as a key step.

EXPERIMENTAL

^1H NMR (500 MHz) and ^{13}C NMR (125 MHz) were measured in $CDCl_3$. Chemical shift values were expressed in ppm relative to an internal reference of tetramethylsilane (0 ppm) in ^1H NMR and $CDCl_3$ (77.0 ppm) in ^{13}C NMR. ^{13}C peak multiplicity assignments were made based on DEPT data. IR spectroscopy of oil and solid samples were measured as neat liquid films and KBr pellets, respectively. Coupling constants were shown in Herz. Abbreviations are as follows: s, singlet; d, doublet; t, triplet; m, multiplet; br, broad. The wave-numbers of maximum absorption peaks of IR spectroscopy were presented in cm^{-1}. Column chromatography was performed using silica gel as a stationary phase.

1-((*E*)-2-Nitrovinyl)-2-styrylbenzene (5)[7]: According to literature procedure,[6] a solution of **4**[5] (624 mg, 3 mmol) and NH_4OAc (231 mg, 3 mmol) in dry $MeNO_2$ (5.7 mL) was stirred at 100 °C for 1 h. After concentration, the residue was partitioned between AcOEt and water. The aqueous layer was extracted with AcOEt, and the combined organic extracts were washed with water and brine, dried over Na_2SO_4 and concentrated. Column chromatography (benzene/hexane 1/4-1/3) gave **5** (560 mg, 74%) as a bright red oil.

(*E*)-2-(2-Styrylphenyl)ethanamine (6)[7]: To a suspension of $LiAlH_4$ (7.75 g, 204 mmol) in dry Et_2O (100 mL) was added **5** (10.25 g, 40.8 mmol) in dry Et_2O (250 mL) at 0 °C and the mixture was stirred for 1 h. The reaction was quenched with water (7.8 mL), 10% NaOH (7.8 mL) and water (20 mL). After filtration, the filtrate was dried over K_2CO_3 and concentrated. Column chromatography (hexane/EtOAc 3/1, then EtOH) gave **6** (6.32 g, 69 %) as a pale yellow oil.

***N*-(4-Methoxybenzyl)-2-(styrylphenyl)ethanamine (1c)**: A suspension of **6** (1.41 g, 6.32 mmol) and *p*-anisaldehyde (856 mg, 6.32 mmol) in water (10 mL) was stirred vigorously at rt for 3 h. To the mixture was added $CHCl_3$ (20 mL) and it was stirred for 1 h at the same temperature. The mixture was extracted with $CHCl_3$, and the combined organic extracts were washed with brine and dried over K_2CO_3. Concentration gave 2.4 g of imine as a pale yellow oil. To a suspension of $LiAlH_4$ (932 mg, 25.3 mmol) in dry Et_2O (5 mL) was added imine (2.4 g) in dry Et_2O (4 mL) at 0 °C. The mixture was stirred for 1 h at 0 °C, and quenched with water (0.15 mL), 10% NaOH (0.15 mL) and water (0.45 mL) and then filtered through a Celite pad. The filtrate was dried over K_2CO_3 and concentrated. Column chromatography (AcOEt/hexane 1/5) gave **1c** (1.87 g, 86%) as a pale yellow oil. ^{1}H NMR: 1.50 (1H, br s), 2.89 (2H, t, J = 7.3), 2.99 (2H, t, J = 7.3), 3.75 (2H, s), 3.76 (3H, s), 6.80 (2H, d, J = 8.6), 6.99 (1H, d, J = 15.9), 7.18-7.40 (9H, m), 7.50 (2H, d, J = 8.6), 7.61 (1H, m). ^{13}C NMR: 34.0, 50.0, 53.2, 55.2, 113.8, 126.0, 126.2, 126.65, 126.74, 127.68, 127.72, 128.7, 129.2, 130.1, 130.5, 136.4, 137.7, 137.9. IR: 3024, 2932, 2831, 1612, 1512. EIMS *m/z*: 343 (M^+). Anal. Calcd for $C_{24}H_{25}NO$: C, 83.93; H, 7.34; N, 4.08. Found: C, 84.19; H, 7.46; N, 4.03.

(*E*)-*N*-(2-Styrylbenzyl)prop-2-en-1-amine (1d): To a solution of **4** (10.0 g, 48 mmol) in MeOH (100 mL) was added dropwise allylamine (5.4 mL, 72 mmol) at rt and the mixture was stirred for 1 h. Then the solution was cooled to 0 °C. To the solution was added portionwise $NaBH_4$ (1.83 g, 48 mmol) over 5 min. The mixture was stirred for 1 h and then concentrated. After addition of water (200 mL), the whole was extracted with ether (200+100+100 mL). The combined organic layers were washed with brine and dried over K_2CO_3. Concentration and column chromatography (hexane/EtOAc 5/1-1/2) gave **1d** (11.4 g, 95%) as a colorless oil. ^{1}H NMR: 1.34 (1H, br s), 3.33 (2H, d, *J* = 6.0), 3.91 (2H, s), 5.13 (1H, dd, *J* = 10.2, 1.5), 5.23 (1H, dd, *J* = 17.0, 1.5), 5.96 (1H, m), 7.04 (1H, d, *J* = 16.0), 7.20−7.40 (6H, m), 7.48 (1H, d, *J* = 16.0), 7.53 (2H, d, *J* = 7.7), 7.62-7.65 (1H, m). ^{13}C NMR: 50.9 (CH_2), 52.0 (CH_2), 116.2 (CH_2), 125.9 (CH), 126.0 (CH), 126.7 (CH), 127.5 (CH), 127.6 (CH), 127.7 (CH), 128.7 (CH), 129.5, (CH), 130.7 (CH), 136.6 (C), 136.9 (CH), 137.6 (C), 137.7 (C). IR: 3325, 3063, 3024, 2816, 1597, 1496, 1450. EIMS *m/z*: 249 (M^+). Anal. Calcd for $C_{18}H_{19}N$: C, 86.70; H, 7.68; N, 5.62. Found: C, 86.77; H, 7.69; N, 5.61.

(*E*)-*N*-Allyl-5-phenylpent-4-en-1-amine (1e)[9,10]: Under argon atmosphere, to a solution of benzaldehyde (5.1 mL, 50 mmol) in THF (72 mL) was added vinylmagnesium chloride (1.48 M, 41 mL, 60 mmol) at 0 °C. The solution was stirred for 1 h, diluted with Et_2O (100 mL), and then quenched with satd NH_4Cl (30 mL). The mixture was extracted with Et_2O (50 + 50 mL) and the combined organic extracts were concentrated to give **7** (7.83 g) as pale yellow oil. To a solution of **7** in xylene (125 mL) were added $HC(OEt)_3$ (34 mL, 250 mmol) and $EtCO_2H$ (0.5 g, 5 mmol) under argon atmosphere. The solution was heated at reflux for 2.5 h, and then diluted with AcOEt (400 mL). The whole was washed with satd $NaHCO_3$ (100 mL), water (100 mL) and brine (100 mL), and then dried over Na_2SO_4. Concentration gave **8** (13.0 g) as a pale yellow oil. To a solution of **8** in dioxane (95 mL), MeOH (16 mL) and water (50 mL) was added KOH (8.4 g, 150 mmol). The whole was stirred for 1 h at rt and then concentrated to remove MeOH. The residue was diluted with Et_2O (300 mL) and extracted with satd. aq. $NaHCO_3$ (300 + 100 + 100 mL). The combined aqueous layers were acidified with 10% HCl and extracted with Et_2O (500 + 200 + 100 mL). The combined organic extracts were concentrated to give **9** (5.9 g) as a white solid. To a solution of **9** in THF (125 mL) were added Et_3N (5.0 mL, 44 mmol), $ClCO_2Et$ (4.5 mL, 44 mmol) and allylamine (5 mL, 67 mmol) at 0 °C under argon atmosphere. The mixture was stirred for 10 min at 0 °C and for 20 h at rt, and then quenched with satd. aq. $NaHCO_3$ (50 mL). The whole was extracted with AcOEt (100 + 100 + 100 mL). The combined organic layers were washed with water (100 mL) and brine (100 mL), dried over Na_2SO_4, and concentrated to give **10** (7.9 g) as an orange oil. To a suspension of $LiAlH_4$ (6.4 g, 168 mmol) in Et_2O (100 mL) was added a solution of **10** in Et_2O (20 mL) and THF (130 mL) at 0 °C under argon atmosphere. The reaction was stirred for 20 h at rt, and was quenched with water (6.4 mL), 10% NaOH (6.4 mL) and water (19.2 mL). After filtration, the filtrate was dried over K_2CO_3 and concentrated. Column chromatography (acetone/hexane 1/1) gave **1e** (5.3 g, 5 steps 50%) as a pale yellow oil. ^{1}H NMR: 1.21 (1H, br s), 1.68 (2H, tt, *J* = 7.3, 7.3), 2.26 (2H, dt, *J* = 7.3, 7.3), 2.67 (2H, t, *J* = 7.3), 3.26 (2H, d, *J* = 5.8), 5.08 (1H, d, *J* = 10.4), 5.17 (1H, d, *J* = 17.1), 5.91 (1H, m), 6.22 (1H, dt, *J* = 15.9, 7.3), 6.40 (1H, d, *J* = 15.9), 7.19 (1H, m), 7.27–7.35 (4H, m). ^{13}C NMR: 29.7 (CH_2), 30.7 (CH_2), 48.9 (CH_2), 52.5 (CH_2), 115.7 (CH_2), 125.9 (CH), 126.9 (CH), 128.5 (CH), 130.1 (CH), 130.4 (CH), 137.0 (CH), 137.8 (C). IR: 3364, 2924, 1450. Anal. Calcd for $C_{14}H_{19}N$: C, 83.53; H, 9.51; N, 6.96. Found: C, 83.43; H, 9.81; N, 6.78.

1-Bromo-2-vinylbenzene (12)[11a]: Under argon atmosphere, to a suspension of $MePPh_3Br$ (134 g, 375 mmol) in dry THF (335 mL) was added *n*-BuLi (1.6 N in hexane, 234 mL, 375 mmol) at 0 °C. The mixture was stirred for 2 h. A solution of 2-bromobenzaldehyde **11** (62.0 g, 335 mmol) in dry THF (335 mL) was added at 0 °C. The whole was stirred for 19 h at rt and quenched with brine and extracted with benzene. The organic layers were washed with brine, dried over Na_2SO_4 and concentrated. Hexane (1.7 L) was added to the residue and the mixture was stirred for 1 h at 50 °C and filtered off $Ph_3P{=}O$. The filtrate was concentrated and then distilled (57 °C, 4 mmHg) to give **12** (35 g 57%) as a colorless oil. ^1H NMR: 5.35 (1H, d, $J = 11.0$), 5.69 (1H, d, $J = 17.4$), 7.05 (1H, dd, $J = 17.4, 11.0$), 7.09 (1H, t, $J = 7.7$), 7.25 (1H, t, $J = 7.7$), 7.54 (2H, d, $J = 7.7$). IR: 3063, 2361, 1836, 1628, 1589, 1466, 1412. EIMS *m/z*: 184 (M+2), 182 (M^+), 103 ($M^+ - Br$).

2-Vinylbenzaldehyde (13)[11a]: Under argon atmosphere, to a solution of **12** (20.0 g, 109 mmol) in dry THF (140 mL) was added *n*-BuLi (1.6 N in hexane, 69 mL, 110 mmol) at –78 °C. The mixture was stirred for 0.5 h at the same temperature, and then treated with Me_2NCHO (8.6 mL, 111 mmol) in dry THF (40 mL). The mixture was stirred for 1 h at –78 °C and for 1 h at rt, and then quenched with brine at 0 °C and extracted with $CHCl_3$. The organic layer was washed with brine, dried over Na_2SO_4 and concentrated. Distillation (58 °C, 0.3 mmHg) gave **13** (9.8 g, 68%) as a pale yellow oil. ^1H NMR: 5.51 (1H, d, $J = 11.0$), 5.70 (1H, d, $J = 17.4$), 7.40-7.47 (1H, m), 7.54 (1H, dd, $J = 11.0, 17.4$), 7.56-7.61 (2H, m), 7.83 (1H, d, $J = 7.4$), 10.29 (1H, s). ^{13}C NMR: 119.7, 127.7, 128.2, 131.5, 133.1, 133.6, 134.1, 140.8, 192.7. IR: 3062, 2846, 2738, 1697, 1596, 1566, 1481, 1411, 1296, 1203. EIMS *m/z*: 132 (M^+), 103 ($M^+ -$ CHO).

***N*-Methyl-1-(2-vinylphenyl)methanamine (1f)**[11c,d]: A 40% aqueous solution of $MeNH_2$ (20.8 mL, 240 mmol) was added to a solution of **13** (10.6 g, 80 mmol) in MeOH (180 mL). After stirring at rt for 4 h, $NaBH_4$ (3.04 g, 80 mmol) was added at 0 °C. The mixture was stirred for 1 h at rt and quenched with brine and concentrated. The resulting aqueous residue was extracted with $CHCl_3$. The organic layer was washed with brine, dried over K_2CO_3 and concentrated. Distillation (62 °C, 0.4 mmHg) gave **1f** (12.7 g, 68%) as a colorless oil. ^1H NMR: 1.42 (1H, br s), 2.47 (3H, s), 3.79 (2H, s), 5.33 (1H, dd, $J = 1.2, 11.0$), 5.69 (1H, dd, $J = 1.2, 17.4$), 7.06 (1H, dd, $J = 11.0, 17.4$), 7.15-7.35 (3H, m), 7.52 (1H, d, $J = 6.7$). ^{13}C NMR: 36.2 (CH_3), 53.7 (CH_2), 115.9 (CH_2), 125.8 (CH), 127.4 (CH), 127.7 (CH), 129.7 (CH), 134.2 (CH), 136.9 (C), 137.2 (C). IR: 3325, 3063, 3024, 2932, 2847, 2793, 1628, 1481, 1442. EIMS *m/z*: 147 (M^+), 132 ($M^+ - CH_3$).

General procedure of asymmetric hydroamination. 2-Allyl-1-benzylisoindoline (2d) (Table 1, entry 4): To a solution of **3c** (0.53 g, 2.0 mmol) and *i*-Pr_2NH (0.64 mL, 4.5 mmol) in toluene (40 mL) was added *n*-BuLi (1.57 M in hexane, 0.72 mL, 1 mmol) over 1 min at –78 °C under argon atmosphere. After stirring for 10 min, **1d** (1.24 g, 5.0 mmol) in toluene (10 mL) was added over 10 min. The brown solution was stirred for 2 h at –40 °C, and then quenched with satd NH_4Cl (10 mL) and 10% K_2CO_3 (10 mL). The separated aqueous layer was extracted with Et_2O (50 + 25 + 25 mL). The combined organic layers were washed with brine (30 mL), dried over K_2CO_3, and concentrated. Column chromatography (AcOEt/hexane 1/12) gave **2d**[8] (1.22 g, 98%) as a pale yellow oil of $[\alpha]^{25}_D$ + 44.4 (*c* 1.08, $CHCl_3$). Ee was determined by HPLC analysis to be 83% (Daicel Chiralpak AS-H×2, hexane/*i*-PrOH/Et_3N 200/1/0.1, 1 mL/min, 254 nm, major 8.4 min and minor 8.9 min).

2-(4-Methoxybenzyl)-1-benzyl-1,2,3,4-tetrahydroisoquinoline (2c): a colorless oil. $[\alpha]^{25}_D$ +0.48 (*c* 1.04, $CHCl_3$). 11% ee (HPLC, Daicel Chiralcel OJ-H, hexane/*i*-PrOH 100/1, 1.0 mL/min, 254 nm, minor 25.6 min and major 35.4 min). ^1H NMR: 2.52-2.56 (1H, m), 2.83-2.89 (2H, m), 2.94-3.00 (1H, m), 3.09-3.13 (1H, m), 3.30-3.36 (1H, m), 3.65 (1H, d, *J* = 13.2), 3.70 (1H, d, *J* = 13.2), 3.79 (3H, s), 3.87 (1H, m), 6.74 (2H, d, *J* = 8.6), 6.83-6.84 (1H, m), 7.00 (2H, d, *J* = 8.6), 7.06-7.15 (5H, m), 7.19-7.26 (3H, m). ^{13}C NMR: 24.4, 42.4, 42.8, 55.2, 57.2, 62.4, 113.5, 125.5, 125.8, 126.1, 127.9, 128.3, 129.0, 129.8, 131.5, 134.7, 138.2, 140.3, 158.5. IR: 3024, 2932, 2831, 1612, 1512. FABMS *m/z*: 344 ($M+H^+$). Anal. Calcd for $C_{24}H_{25}NO$: C, 83.93; H, 7.34; N, 4.08. Found: C, 84.15; H, 7.41; N, 3.98.

1-Allyl-2-benzylpyrrolidine (2e): a colorless oil. $[\alpha]^{25}_D$ −13.6 (*c* 1.15, $CHCl_3$). 18% ee (HPLC, Daicel Chiralcel OJ-H, hexane/*i*-PrOH 100/1, 0.5 mL/min, 254 nm, major 4.9 min and minor 4.4 min). ^1H NMR: 1.54 (1H, m), 1.64 (1H, m), 1.67-1.78 (2H, m), 2.21 (1H, m), 2.45 (1H, dd, *J* = 13.1, 9.5), 2.56 (1H, m), 2.89 (1H, dd, *J* = 13.2, 7.6), 3.05 (1H, dd, *J* = 13.1, 4.0), 3.12 (1H, m), 3.55 (1H, dd, *J* = 13.2, 5.5), 5.12 (1H, d, *J* = 10.1), 5.22 (1H, dd, *J* = 17.1, 1.2), 5.96 (1H, m), 7.15-7.20 (3H, m), 7.25-7.29 (2H, m). ^{13}C NMR: 21.5 (CH_2), 30.2 (CH_2), 40.6 (CH_2), 53.8 (CH_2), 57.1 (CH_2), 65.2 (CH), 116.6 (CH_2), 125.7 (CH), 128.0 (CH), 129.0 (CH), 135.9 (CH), 140.0 (C). IR: 2963, 2793, 1643, 1450, 1157, 1119, 995, 918, 748. EIMS: 201 (M^+). Anal. Calcd for $C_{14}H_{19}N$: C, 83.53; H, 9.51; N, 6.96. Found: C, 83.81; H, 9.63; N, 6.93.

1,2-Dimethylisoindoline (2f)[15] a colorless oil. $[\alpha]^{25}_D$ +19.0 (*c* 0.66, $CHCl_3$). 43% ee (HPLC, Daicel Chiralcel AD-H, hexane/*i*-PrOH 100/1, 0.5 mL/min, 254 nm, major 11.2 min and minor 12.6 min). ^1H NMR: 1.43 (3H, d, *J* = 6.1), 2.57 (3H, s), 3.64 (2H, m), 4.24 (1H, d, *J* = 11.6), 7.09-7.14 (1H, m), 7.17-7.25 (3H, m). ^{13}C NMR: 18.0 (CH_3), 39.8 (CH_3), 60.5 (CH_2), 65.3 (CH), 121.6 (CH), 122.0 (CH), 126.8 (CH x 2), 139.4 (C), 144.9 (C). IR: 3387, 3040, 2770, 1697, 1458. EIMS *m/z*: 147 (M^+), 132 ($M^+ - CH_3$).

2-Methyl-1,2,3,4-tetrahydroisoquinoline (14f)[16]: a colorless oil. ^1H NMR: 2.46 (3H, s), 2.68 (2H, t, *J* = 6.2), 2.93 (2H, t, *J* = 6.2), 3.58 (2H, s), 7.00-7.03 (1H, m), 7.09-7.16 (3H, m). ^{13}C NMR: 29.1 (CH_2), 46.1 (CH_3), 52.8 (CH_2), 57.9 (CH_2), 125.6 (CH), 126.0 (CH), 126.4 (CH), 128.6 (CH), 133.8 (C), 134.7 (C).

IR: 3364, 3024, 2924, 2777, 1705, 1589, 1458. EIMS *m/z*: 147 (M^+).

***N*-Methyl-2-(2-((methylamino)methyl)phenyl)-*N*-(2-vinylbenzyl)ethanamine (15):** a colorless oil. ^{1}H NMR: 1.58 (1H, br s), 2.30 (3H, s), 2.44 (3H, s), 2.60-2.64 (2H, m), 2.86-2.90 (2H, m), 3.57 (2H, s), 3.69 (2H, s), 5.25 (1H, m), 5.64 (1H, m), 7.09-7.53 (9H, m). ^{13}C NMR: 30.2 (CH_2), 36.2 (CH_3), 42.0 (CH_3), 53.2 (CH_2), 58.9 (CH_2), 60.0 (CH_2), 115.1 (CH_2), 125.6 (CH), 126.1 (CH), 127.1 (CH), 127.3 (CH), 128.3 (CH), 129.0 (CH), 129.8 (CH), 130.3 (CH), 134.7 (CH), 136.0 (C), 137.6 (C), 137.9 (C), 138.8 (C). IR: 3325, 3063, 3017, 2939, 2839, 2785, 1628, 1450. HRMS-FAB *m/z*: $[M+H]^+$ calcd for $C_{20}H_{27}N_2$, 295.2169; found, 295.2177.

Determination of the absolute configuration of 2d.

(*S*)-1-Benzylisoindoline (16): Under argon atmosphere, to a solution of **2d** (500 mg, 2.0 mmol, 83% ee) in MeCN/water (4/1, 25 mL) was added $RhCl(PPh_3)_3$ (32 mg, 0.1 mmol). The mixture was heated at reflux for 2 h and diluted with AcOEt. To the mixture was added water (20 mL), and the whole was extracted with AcOEt (30+20+10 mL). The combined organic layers were washed with brine and dried over K_2CO_3. Concentration and column chromatography (hexane/AcOEt/Et_3N 10/2/1) gave 168 mg (40% yield) of 1-benzylisoindoline **16** as a pale yellow oil. $[\alpha]^{25}_{D}$ −22.7 (*c* 1.00, $CHCl_3$). ^{1}H NMR: 1.94 (1H, br s), 2.87 (1H, dd, *J* = 13.6, 8.4), 3.13 (1H, dd, *J* = 13.6, 5.2), 4.15 (1H, d, *J* = 13.7), 4.20 (1H, d, *J* = 13.7), 4.65 (1H, dd, *J* = 8.4, 5.2), 7.09 (1H, d, *J* = 6.7), 7.17-7.24 (6H, m), 7.28-7.31 (2H, m). ^{13}C NMR: 42.7 (CH_2), 51.3 (CH_2), 64.6 (CH), 122.4 (CH), 122.5 (CH), 126.3 (CH), 126.5 (CH), 127.0 (CH), 128.4 (CH), 129.3 (CH), 139.0 (C), 141.6 (C), 144.0 (C). IR: 3063, 3024, 2916, 2839, 1597, 1458. EIMS *m/z*: 209 (M^+). Anal. Calcd for $C_{15}H_{15}N$: C, 86.08; H, 7.22; N, 6.69. Found: C, 85.88; H, 7.46; N, 6.71.

(*S*)-1-Benzylisoindoline-2-carbaldehyde (17): A solution of **16** (100 mg, 0.48 mmol) in ethylformate (7.7 mL, 48 mmol) was heated at reflux for 0.5 h. Concentration and column chromatography (hexane/AcOEt 1/1) gave 105 mg (93% yield) of **17** as a red oil. $[\alpha]^{25}_{D}$ +6.53 (*c* 1.00, $CHCl_3$). The rotamers with 70:30 ratio were observed in ^{1}H NMR. ^{1}H NMR: Major Rotamer: 3.01 (1H, dd, *J* = 13.8, 6.7), 3.16 (1H, dd, *J* = 13.8, 5.2), 4.32 (1H, d, *J* = 15.6), 4.84 (1H, d, *J* = 15.6), 5.31 (1H, dd, *J* = 6.7, 5.2), 6.90 (1H, m), 7.04-7.32 (8H, m), 8.02 (1H, s); Minor Rotamer: 3.24 (1H, dd, *J* = 13.2, 2.8), 3.32 (1H, dd, *J* = 13.2, 7.0), 4.13 (1H, d, *J* = 13.4), 4.64 (1H, d, *J* = 13.4), 5.58 (1H, m), 7.04-7.32 (9H, m), 8.41 (1H, s). ^{13}C NMR: 39.3 (CH_2), 44.5 (CH_2), 49.2 (CH_2), 51.4 (CH_2), 62.3 (CH), 64.3 (CH), 122.5 (CH), 123.0 (CH), 123.1 (CH), 123.5 (CH), 126.4 (CH), 127.0 (CH), 127.5 (CH), 127.7 (CH), 127.8 (CH), 127.9 (CH), 128.2 (CH), 128.6 (CH), 129.8 (CH), 130.0 (CH), 135.8 (C), 136.1 (C), 136.5 (C), 139.3 (C), 139.6 (C), 161.5 (CH), 161.7 (CH). IR: 1651. FABMS *m/z*: 238 $[M+H]^+$. Anal. Calcd for $C_{16}H_{15}NO$: C, 80.98; H, 6.37; N, 5.90. Found: C, 80.90; H, 6.34; N, 5.95.

(*S*)-1-Benzyl-2-methylisoindoline (2b): Under argon atmosphere, to a solution of **17** (100 mg, 0.42 mmol) in THF (4.7 mL) was added BH_3–THF solution (0.9 N in THF, 2.3 mL, 2.1 mmol) at room temperature over 2 min. The mixture was heated at reflux for 15 min and added water (4.7 mL), and then heated at reflux for 2.5 h. The whole was extracted with AcOEt (10 + 5+ 5 mL). The combined organic layers were washed with brine and dried over K_2CO_3. Concentration and column chromatography (hexane/AcOEt 1/1) gave 92 mg (98% yield) of (*S*)-**2b**[13] as a colorless oil. $[\alpha]^{25}_{D}$ +75.5 (*c* 1.05, $CHCl_3$). ^{1}H NMR: 2.47 (3H, s), 3.04 (1H, dd, *J* = 14.1, 7.1), 3.12 (1H, dd, *J* = 14.1, 5.8), 3.67 (1H, d, *J* = 13.1), 4.01 (1H, dd, *J* = 7.1, 5.8), 4.28 (1H, d, *J* = 13.1), 6.88 (1H, d, *J* = 7.7), 7.09-7.33 (8H, m). ^{13}C NMR: 41.2, 41.3, 60.9, 71.4, 122.1, 122.6, 126.2, 126.6, 126.9, 128.4, 129.6, 139.4, 139.7, 143.7. IR: 3026, 2925, 2771, 1601, 1454, 1354, 1151. FABMS *m/z*: 224 $[M+H]^+$.

Asymmetric total synthesis of (*S*)-laudanosine.

(*E*)-2-(3,4-Dimethoxystyryl)-4,5-dimethoxybenzaldehyde (24): Under argon atmosphere, to a suspension of K_3PO_4 (50 g, 236 mmol), **22** (41.3 g, 169 mmol) and **23** (111 g, 674 mmol) in *N*,*N*-dimethylacetamide (339 mL) was added $Pd(OAc)_2$ (3.79 g, 16.9 mmol). The mixture was heated at 140 °C for 0.5 h. Additional $Pd(OAc)_2$ (1.26 g, 5.63 mmol) was added and the mixture was stirred for 0.5 h at the same temperature. The mixture was poured onto ice water, filtered through a Celite pad and extracted with $CHCl_3$. The organic extracts were washed with water and brine, and dried over Na_2SO_4. Concentration and column chromatography (AcOEt/hexane 10/1, then AcOEt) followed by recrystallization from AcOEt/hexane gave **24** (49 g, 89%) as yellow needles of mp 158–159 °C. ^{1}H NMR: 3.92, 3.96, 3.97, and 4.03 (each 3H, s), 6.89 (1H, d, *J* = 8.3), 6.91 (1H, d, *J* = 15.9), 7.09-7.11 (3H, m), 7.38 (1H, s), 7.75 (1H, d, *J* = 15.9), 10.33 (1H, s). ^{13}C NMR: 55.86, 55.91, 56.0, and 56.1 (CH_3 x 4), 108.7 (CH), 109.0 (CH), 111.1 (CH), 111.3 (CH), 119.2 (C), 120.3 (CH), 121.6 (CH), 126.4 (C), 130.0 (C), 133.2 (CH), 136.0 (C), 149.3 (C), 149.5 (C), 153.8 (C), 190.2 (CH). IR (nujor): 1663, 1597, 1512. EIMS *m/z*: 328 (M^+). Anal. Calcd for $C_{19}H_{20}O_5$: C, 69.50; H, 6.14. Found: C, 69.69; H, 6.08.

4-(4,5-Dimethoxy-2-((*E*)-2-nitrovinyl)styryl)-1,2-dimethoxybenzene (25)[17]: A solution of **24** (656 mg, 2 mmol) and NH_4OAc (154 mg, 2 mmol) in dry nitromethane (3.8 mL) was stirred at 100 °C for 2 h and then concentrated. The residue was partitioned between AcOEt and water. The aqueous layer was extracted with AcOEt, and the combined organic extracts were washed with water and brine, and dried over Na_2SO_4. Concentration and column chromatography (AcOEt/hexane 2/1) followed by recrystallization from AcOEt/hexane gave **25** (712 mg, 96%) as red needles of mp 180–181 °C. ^{1}H NMR: 3.93, 3.95, 3.97, and 4.00 (each 3H, s), 6.86 (1H, d, *J* = 15.9), 6.90 (1H, d, *J* = 8.3), 6.96 (1H, s), 7.07 (1H, d, *J* = 2.2), 7.08 (1H, s), 7.11 (1H, dd, *J* = 2.2, 8.3), 7.24 (1H, d, *J* = 15.9), 7.51 (1H, d, *J* = 13.2), 8.45 (1H, d, *J* = 13.2). ^{13}C NMR: 55.90 (CH_3), 55.91 (CH_3), 56.0 (CH_3 x 2), 109.1 (CH), 109.2 (CH), 109.4 (CH), 111.3 (CH), 120.2 (CH), 120.3 (C), 122.3 (CH), 129.8 (C), 133.1 (CH), 134.5 (C), 136.0 (CH), 136.7 (CH), 148.9 (C), 149.3 (C), 149.6 (C), 152.7 (C). IR: 3109, 1620, 1597, 1516. EIMS *m/z*: 371 (M^+). Anal. Calcd for $C_{20}H_{21}NO_6$: C, 64.68; H, 5.70; N, 3.77. Found: C, 64.47; H, 5.78; N, 3.60.

(*E*)-2-(2-(3,4-Dimethoxystyryl)-4,5-dimethoxyphenyl)ethanamine (26): To a suspension of $LiAlH_4$ (5.28 g, 139 mmol) in dry THF (150 mL) was added a solution of **25** (12.9 g, 34.8 mmol) in dry Et_2O (550 mL) under ice-water bath. After stirring at rt for 6 h, the excess of $LiAlH_4$ was successively quenched with water (5.3 mL), 10% NaOH (5.3 mL) and water (15.9 mL). After filtration, the filtrate was dried over K_2CO_3. Concentration and column chromatography (AcOEt, then $CHCl_3$/EtOH/25% aq. NH_3 160/9/1) gave **26** (4.11 g, 86%) as a right brown oil. ^{1}H NMR: 1.25 (2H, br s), 2.88 (2H, t, *J* = 6.7), 2.95 (2H, t, *J* = 6.7), 3.89, 3.90, 3.938, and 3.943 (each 3H, s), 6.70 (1H, s), 6.85 (1H, d, *J* = 15.9), 6.87 (1H, d, *J* = 8.3), 7.03-7.09 (2H, m), 7.11 (1H, s), 7.17 (1H, d, *J* = 15.9). ^{13}C NMR: 37.0 (CH_2), 43.4 (CH_2), 55.84 (CH_3), 55.87 (CH_3), 55.88 (CH_3), 55.92 (CH_3), 108.6 (CH), 109.3 (CH), 111.3 (CH), 113.1 (CH), 119.2 (CH), 124.2 (CH), 128.3 (CH), 128.8 (C), 130.2 (C), 130.9 (C), 147.7 (C), 148.5 (C), 148.8 (C), 149.1 (C). IR: 3368, 3306, 1605, 1516. EIMS *m/z*: 343 (M^+). Anal. Calcd for $C_{20}H_{25}NO_4$: C, 69.95; H, 7.34; N, 4.08. Found: C, 69.80; H, 7.44; N, 4.02.

(*E*)-*N*-(2-(3,4-Dimethoxystyryl)-4,5-dimethoxyphenyl)formamide (27): A mixture of **26** (31 g, 90 mmol), HCO_2H (100 mL, 2.7 mol) and Ac_2O (86 mL, 0.9 mol) was stirred at rt for 2 h. The mixture was diluted with water, basified with 10% NaOH and extracted with $CHCl_3$. The organic extracts were washed with brine and dried over Na_2SO_4. Concentration and column chromatography (AcOEt/$CHCl_3$ 1/1, then $CHCl_3$/EtOH/25% aq. NH_3 80/9/1) followed by recrystallization from AcOEt/hexane gave **27** (29.4 g, 88%) as colorless needles of mp 131.5–132.5 °C. ^{1}H NMR: 2.98 and 3.52 (each 2H, t, *J* = 7.1), 3.90, 3.91, 3.95, and 3.99 (each 3H, s), 5.64 (1H, br s), 6.68 (1H, s), 6.87 (1H, d, *J* = 15.9), 6.88 (1H, d, *J* = 8.3), 7.09 (1H, dd, *J* = 1.6, 8.3), 7.14 (1H, s), 7.16 (1H, d, *J* = 1.6), 7.27 (1H, d, *J* = 15.9), 8.16 (1H, s). ^{13}C NMR: 32.7 (CH_2), 39.6 (CH_2), 55.93 (CH_3), 55.97 (CH_3), 55.99 (CH_3), 56.00 (CH_3), 108.5 (CH), 109.0 (CH), 111.3 (CH), 113.0 (CH), 119.8 (CH), 123.6 (CH), 128.8 (CH), 128.9 (C), 129.2 (C), 130.7 (C), 148.1 (C), 148.7 (C), 149.0 (C), 149.3 (C), 161.3 (CH). IR: 3364, 1674, 1605, 1516. EIMS *m/z*: 371 (M^+). Anal. Calcd for $C_{21}H_{25}NO_5$: C, 67.91; H, 6.78; N, 3.77. Found: C, 67.69; H, 6.81; N, 3.73

(*E*)-2-(2-(3,4-Dimethoxystyryl)-4,5-dimethoxyphenyl)-*N*-methylethanamine (28)[18]: To a 1.0 M THF solution of $LiAlH_4$ (17.8 mL, 17.8 mmol) was added **27** (1.65 g, 4.46 mmol) in dry THF (80 mL) under ice-water bath. The mixture was stirred for 48 h at rt and then quenched with water (0.7 mL), 10% NaOH (0.7 mL) and water (2.1 mL) at 0 °C. After filtration, the filtrate was dried over K_2CO_3 and concentrated. Column chromatography (AcOEt/$CHCl_3$ 1/1, then $CHCl_3$/ethanol/25% aq. NH_3 80/9/1) followed by recrystallization from AcOEt/hexane gave **28** (1.47 g, 92%) as colorless needles of mp 108–109 °C. ^{1}H NMR: 1.51 (1H, br s), 2.46 (3H, s), 2.82 (2H, t, *J* = 7.1), 2.93 (2H, t, *J* = 7.1), 3.90, 3.91, 3.94, and 3.95 (each 3H, s), 6.72 (1H, s), 6.86 (1H, d, *J* = 15.9), 6.87 (1H, d, *J* = 8.2), 7.05 (1H, d, *J* = 1.8), 7.08 (1H, dd, *J* = 1.8, 8.2), 7.11 (1H, s), 7.20 (1H, d, *J* = 15.9). ^{13}C NMR: 33.3, 36.3, 53.0, 55.80, 55.82, 55.85, 108.5, 109.1, 111.3, 113.0, 119.3, 124.0, 128.2, 128.6, 130.3, 130.9, 147.6, 148.5, 148.7, 149.1. IR: 3317, 1605,

1516. EIMS *m/z*: 357 (M^+).

(*S*)-(+)-Laudanosine (29)[19]: Under argon atmosphere, to a solution of **3a** (147 mg, 0.5 mmol) and *i*-Pr_2NH (0.04 mL) in toluene (5 mL) was added *n*-BuLi (1.6 N in hexane, 0.09 mL, 0.15 mmol) at –78 °C, and the solution was stirred for 10 min. A solution of **28** (179 mg, 0.5 mmol) in toluene (10 mL) was added over 2.5 h by a syringe pump at –30 °C. After addition of *n*-BuLi (1.6 N in hexane, 0.09 mL, 0.15 mmol), another solution of **28** (179 mg, 0.5 mmol) in toluene (10 mL) was added over 2.5 h. Additional *n*-BuLi (1.6 N in hexane, 0.09 mL, 0.15 mmol) was added and then the solution was stirred for 21 h at the same temperature.[20] The reaction mixture was quenched with satd. aq. NH_4Cl (5 mL) and basified with 10% aqueous K_2CO_3. The whole was extracted with AcOEt. The organic extracts were washed with brine and dried over K_2CO_3. Concentration and column chromatography (AcOEt/hexane 1/1, then AcOEt) gave **29** (344 mg, 96%) as a pale yellow solid of mp 88–90 °C and $[\alpha]^{25}_D$ +35.9 (*c* 1.05, $CHCl_3$) and **3a** (146 mg) quantitatively. 76% ee (HPLC, Daicel Chiralcel OD-H, hexane/*i*-PrOH 7/3, 1.0 mL/min, 254 nm, major 7.2 min and minor 17.9 min). Recrystallization of **29** (76% ee) from AcOEt/hexane afforded **29** (220 mg, 64%) of 99% ee as a white solid of mp 85–86 °C and $[\alpha]^{25}_D$ +57.3 (*c* 0.98, $CHCl_3$).[19] (Lit.[19b]: mp 87–88 °C and $[\alpha]^{29}_D$ +54.4 (*c* 0.20, $CHCl_3$). ^{1}H NMR: 2.54 (3H, s), 2.58 (1H, m), 2.73-2.86 (3H, m), 3.12-3.20 (2H, m), 3.57 (3H, s), 3.69 (1H, m), 3.79 (3H, s), 3.84 (3H, s), 3.85 (3H, s), 6.07 (1H, s), 6.56 (1H, s), 6.60 (1H, d, *J* = 1.8), 6.64 (1H, dd, *J* = 1.8, 8.0), 6.77 (1H, d, *J* = 8.0). ^{13}C NMR: 25.5 (CH_2), 40.8 (CH_2), 42.6 (CH_3), 46.9 (CH_2), 55.5 (CH_3), 55.68 (CH_3), 55.73 (CH_3), 55.8 (CH_3), 64.8 (CH), 111.0 (CH), 111.1 (CH), 111.2 (CH), 113.0 (CH), 121.8 (CH), 126.1 (C), 129.3 (C), 132.5 (C), 146.3 (C), 147.26 (C), 147.31 (C), 148.6 (C). IR: 2932, 2839, 2793, 1605, 1512. EIMS *m/z*: 357 (M^+).

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