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A new non-natural chiral auxiliary: design, synthesis, and resolution of 1-mesitylethylamine and its application in the asymmetric aza-Diels–Alder reaction

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Abstract

1-Mesitylethylamine was designed as a new non-natural chiral auxiliary. Racemic 1-mesitylethylamine could be synthesized in two steps from mesityl cyanide and could be resolved via separation of diastereomeric carbamates derived from (−)-menthyl chloroformate, followed by reduction with DIBAL and acidic hydrolysis. Imines, prepared from enantiopure 1-mesitylethylamine and aromatic aldehydes, reacted with Danishefsky's diene in the presence of a Lewis acid to give cycloaddition products, 4-pyridone derivatives, with high diastereoselectivity.

1. Introduction

Chiral auxiliaries have been used in the synthesis of many kinds of optically active compounds for two decades. Most of these chiral auxiliaries are natural compounds or their derivatives.[1,2] However, they have some limitations: (i) Both enantiomers are not always obtainable; the auxiliaries do not necessarily give a product with the desired configuration. (ii) It is necessary to modify their skeleton according to a target asymmetric reaction. In contrast, non-natural chiral auxiliaries are expected to be more valuable in that both enantiomers can be available and appropriately used in a target asymmetric reaction to obtain a product with desired configuration if a method for the resolution of the corresponding racemate is developed.

Optically active 1-phenylethylamine (Fig. 1a) is one of the most common non-natural chiral auxiliaries, and is used in various asymmetric reactions.[3] However, high diastereoselectivity is not always realized,

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depending on the asymmetric reaction. In order to improve the asymmetric induction ability, we have tried to simply modify the benzene ring of 1-phenylethylamine and applied it to various asymmetric reactions. For example, we have reported the highly diastereoselective Staudinger reaction of ketene derivatives with imines prepared from 1-(2,6-dichlorophenyl)ethylamine[4] (Fig. 1b) and the highly diastereoselective alkylation of imines derived from 1-(2,5-dimethoxyphenyl)ethylamine (Fig. 1c) with alkylmetals.[5] These reactions proceeded with higher stereoselectivity than those of 1-phenylethylamine-derived imines due to an electrostatic attractive interaction[4] or a chelate effect.[5] In contrast, there was no attempt to introduce such a substituent as this could effect a sterically repulsive interaction to the phenyl group of 1-phenylethylamine. This circumstance prompted us to develop a new non-natural chiral auxiliary having sterically demanding substituent(s). Finally, as such a derivative, we designed 1-mesitylethylamine **1**,[6,7] which has two methyl sustituents at the *ortho* positions on the benzene ring of 1-phenylethylamine.

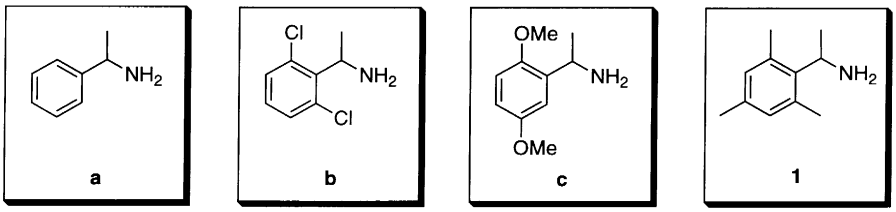
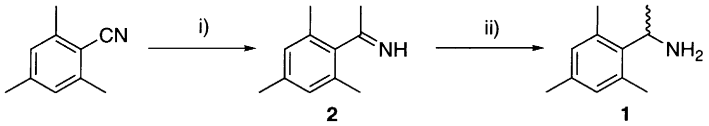


Fig. 1. 1-Phenylethylamine and its derivatives

We would like to report the synthesis and resolution of 1-mesitylethylamine, and its application to an asymmetric reaction.

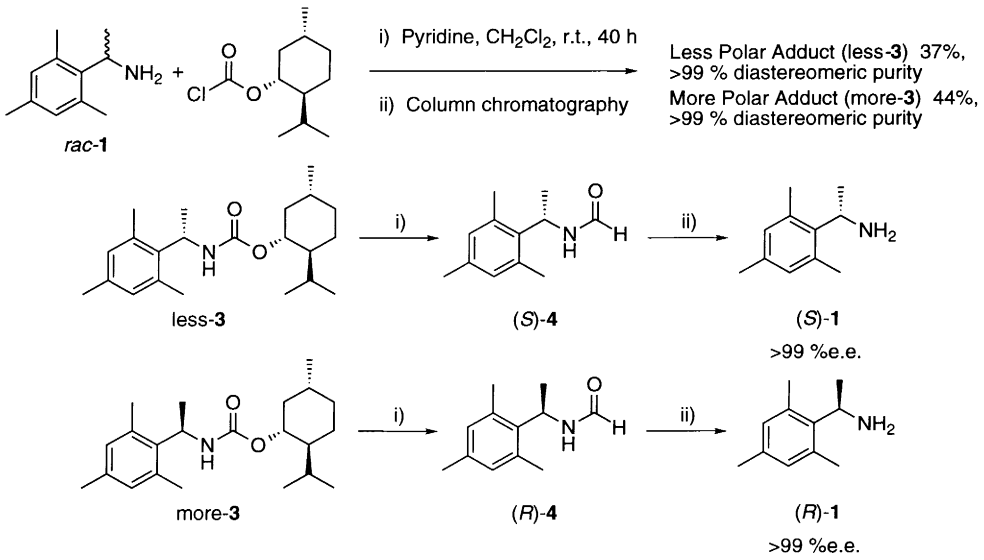
2. Results and discussion

We first tried the synthesis and resolution of 1-mesitylethylamine. Racemic 1-mesitylethylamine *rac*-**1** could be synthesized in two steps from mesityl cyanide (Scheme 1). In the next stage, we tried to resolve *rac*-**1** by using various enantiopure acids, such as mandelic acid, tartaric acid and their derivatives, amino acids, and so on by the diastereomeric salt method. However, all trials were unsuccessful. Next, we tried to resolve a pair of σ-bonded diastereomers. As a result, a mixture of diastereomeric carbamates,[8,9] derived from (−)-menthyl chloroformate, could be separated into diastereomerically pure isomers of **3** by column chromatography on a preparative scale. The reduction of each of the diastereomers of **3** with diisobutylaluminium hydride (DIBAL) gave the corresponding formamide derivative **4**, which was converted into **1** upon acidic hydrolysis (Scheme 2). Each enantiomer of **1** thus obtained was confirmed to have more than 99% e.e. on the basis of HPLC analyses.



Scheme 1. Synthesis of racemic 1-mesitylethylamine. *Reagents and conditions:* (i) MeMgI, $CeCl_3$, THF, reflux, 16 h, 47%; (ii) liq. NH_3, Na, EtOH, THF, reflux, 1 h, 88%

The absolute configuration of enantiopure **1** was determined by an X-ray crystallographic analysis. Fig. 2 shows the crystal structure of the salt consisting of enantiopure **1**, derived from the more polar diastereomer, and (−)-dibenzoyl-L-tartaric acid. As can be seen from Fig. 2, the absolute configuration of enantiopure $(-)_D$-**1**, derived from the more polar carbamate, is *R*.



Scheme 2. Resolution of racemic 1-mesitylethylamine. *Reagents and conditions:* (i) DIBAL, THF, rt, 40 h (less-**3**) 72%, (more-**3**) 79%; (ii) concd HCl, MeOH, reflux, 6 h (less-**3**) 90%, (more-**3**) quant.

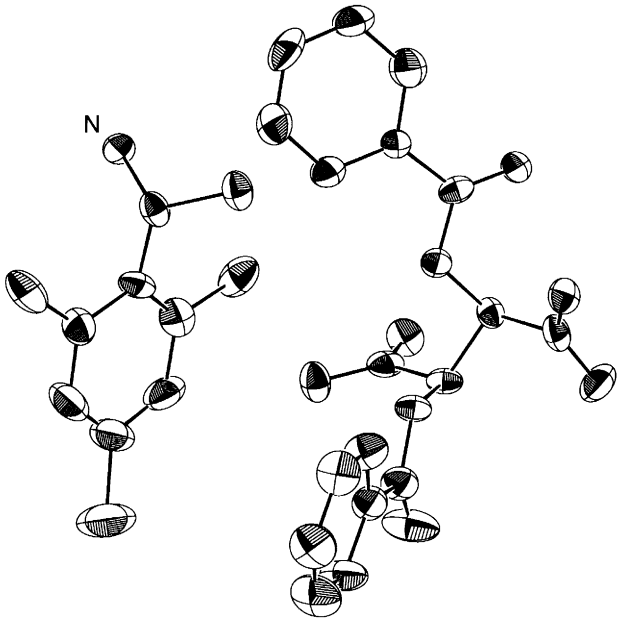
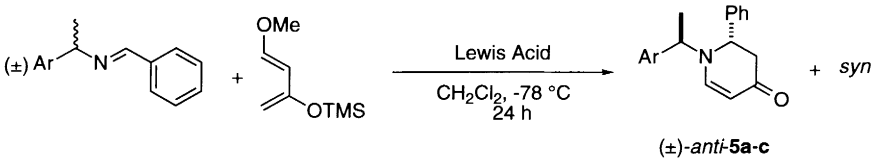


Fig. 2. ORTEP drawing of (*R*)-1-mesitylethylamine·(−)-dibenzoyl-L-tartaric acid

We then tried to apply the non-natural chiral auxiliary **1** to an asymmetric reaction; the asymmetric aza-Diels–Alder reaction of an imine with Danishefsky's diene was selected.[10–24] In order to examine the effect of the substituents on the benzene ring, racemic imines prepared from 1-phenylethylamine derivatives and benzaldehyde were allowed to reacted with Danishefsky's diene in the presence of zinc chloride in dichloromethane. The results are shown in Table 1. When 1-(2,5-dimethoxyphenyl)ethylamine was used as the imine component, the *anti*-/*syn*-selectivity was diminished (entry 1) in comparison with the result of the 1-phenylethylamine-based imine (entry 6) reported by Yamamoto et al.,[10,11] although the adduct was obtained in moderate yield. This result indicates that the methoxy group at the *ortho*

position on the benzene ring, which would contribute to the chelation with zinc chloride, is not favorable for the formation of the *anti*-adduct. In contrast, when 1-mesitylethylamine was used as the imine component, high *anti*-selectivity was achieved (entry 2), which was better than that of the reaction of the 1-phenylethylamine-derived imine.[10,11]

Table 1
Effect of the substituent(s) of 1-arylethylamine derivatives in the aza-Diels–Alder reaction



(±)-*anti*-**5a-c**

Entry	Ar	Product	Lewis acid	Yield/%	*Anti* : *Syn* [1)]
1	2,5-$(MeO)_2C_6H_3$	**5a**	$ZnCl_2$	63	79:21
2	Mesityl	**5b**	$ZnCl_2$	52	99:1
3			$ZnBr_2$	49	95:5
4			$Zn(OTf)_2$	25	>99:1
5[2)]			$BF_3{\cdot}OEt_2$	60	99:1
6[3)]	Ph	**5c**	$BF_3{\cdot}OEt_2$	41	94:6

1) Diastereomeric ratio was determined by ^{1}H-NMR.
2) –78 °C- 0 °C, 24 h.
3) ref. 10,11.

On the basis of these results, we next sought a Lewis acid of choice among $ZnBr_2$, $Zn(OTf)_2$ and $BF_3{\cdot}OEt_2$ for the reaction of the imine, derived from 1-mesitylethylamine and benzaldehyde, with Danishefsky's diene (entries 3–5). It was found that $BF_3{\cdot}OEt_2$ was the most effective Lewis acid from the standpoint of both yield and selectivity.

The relative configuration of the main product **5b** was determined by an X-ray crystallographic analysis of its racemic crystal as shown in Fig. 3.

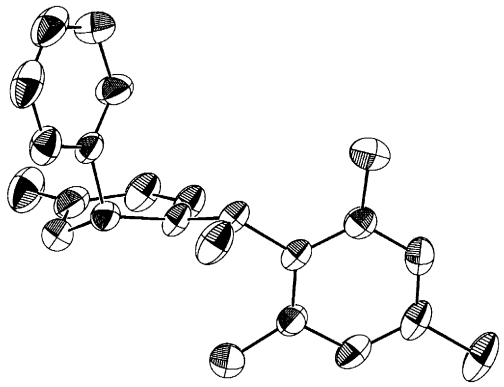
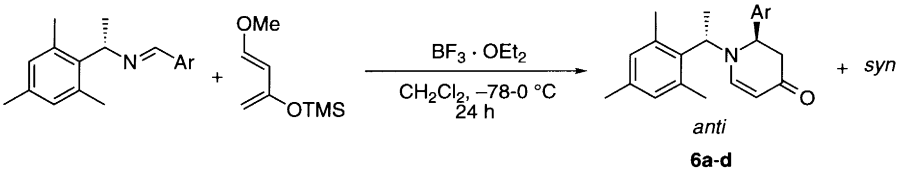


Fig. 3. Relative configuration of the cycloaddition product **5b**

Finally, we carried out the asymmetric aza-Diels–Alder reaction of enantiopure imines, prepared from enantiopure 1-mesitylethylamine and aromatic aldehydes, with Danishefsky's diene (Table 2). As can be seen from Table 2, the reaction proceeded smoothly to give the corresponding cycloaddition products[25] with high *anti*-selectivity.

Table 2
Asymmetric aza-Diels–Alder reaction of aldimines with Danishefsky's diene



Entry	Ar	Product	Yield/%	*Anti*:*Syn* [1)]
1[2)]	Ph	**6a**	59 (53)	99:1 (99:1)
2	4-MeOC$_6$H$_4$	**6b**	40	98:2
3	3-Pyridyl	**6c**	25	>99:1
4	1-Naphthyl	**6d**	38	99:1

1) Diastereomeric ratio was determined by ^{1}H-NMR.
2) The values in parentheses are those when (*R*)-amine was used.

3. Conclusion

A method has been developed for the synthesis of racemic 1-mesitylethylamine from mesityl cyanide in two steps. A diastereomeric mixture of carbamates, derived from racemic 1-mesitylethylamine and menthyl chloroformate, could be easily separated by column chromatography to give both diastereomers, which were converted into enantiopure 1-mesitylethylamine upon reduction with DIBAL, followed by acidic hydrolysis. As an application of enantiopure 1-mesitylethylamine, it was used as a chiral auxiliary in the asymmetric aza-Diels–Alder reaction; the reaction of 1-mesitylethylamine-derived imines with Danishefsky's diene proceeded smoothly to give the cycloaddition products with high *anti*-selectivity, which was superior to that of the reaction of 1-phenylethylamine-derived imines. The high *anti*-selectivity was considered to arise from the steric effect of methyl substituents at the *ortho* positions of the benzene ring.

4. Experimental

4.1. General

All starting materials were obtained from commercial suppliers and used without purification. Dichloromethane was distilled over calcium hydride and preserved on molecular sieves (MS) 4 A. Tetrahydrofuran was distilled over sodium benzophenone ketyl before use. Column chromatography was carried out by using Merck silica gel 60. Preparative thin layer chromatography was performed on a glass plate using Wako gel W-B5F. ^{1}H NMR spectra were recorded on a Varian Mercury 300 at 300

MHz using tetramethylsilane (TMS) as an internal standard. Chemical shifts are reported as ppm in a δ scale downfield from TMS. ^{13}C NMR spectra were recorded at 75.3 MHz upon referring residual $CHCl_3$ (δ 77.00 ppm) in $CDCl_3$. Infrared spectra were recorded on a JASCO IR 810 for neat films on a NaCl plate or tablets of KBr. Melting points were determined on a Laboratory Devices MEL-TEMP apparatus. Optical rotations were recorded on a JASCO DIP-360 instrument. Analytical HPLC were performed using a Cica-Merck superspher® (Si 60, 4 μm, 25 cm) column with a detector wavelength of 254 nm. High resolution mass spectra were carried out by a JOEL JMS-AX 505H spectrometer. X-Ray crystallographic analyses were performed on a Mac Science MXC18 four-cycle diffractometer, and the structures were solved and refined by applying CRYSTAN-GM package.[26]

1-(2,5-Dimethoxyphenyl)ethylamine was synthesized by the method previously reported.[5] 1-Methoxy-3-trimethylsiloxy-1,3-butadiene (Danishefsky's diene) was synthesized according to the method reported in the literature.[27]

4.2. *Synthesis of racemic 1-mesitylethylamine* rac-***1***

To a solution of dried cerium chloride (13.7 g, 55.6 mmol) in tetrahydrofuran (25 ml) were successively added dropwise a solution of methylmagnesium iodide in tetrahydrofuran (0.87 M, 63.5 ml, 55.2 mmol), and a solution of mesityl cyanide[28] (8.07 g, 55.6 mmol) in tetrahydrofuran (100 ml) at 0°C under argon. The solution was refluxed for 16 h and then carefully quenched with water (60 ml) at 0°C. The organic layer was separated, and the water layer was extracted with AcOEt (4×100 ml). The combined organic layer and extracts were dried over $MgSO_4$. After filtering $MgSO_4$ off, the filtrate was concentrated under reduced pressure. The residue thus obtained was purified by silica gel column chromatography to give 1-mesitylethylideneamine **2** (4.22 g, 26.2 mmol, 47%), which was used in the following reaction without further purification. ^{1}H NMR ($CDCl_3$): 2.21 (s, 6H), 2.27 (s, 3H), 2.28 (s, 3H) 6.85 (s, 2H). ^{13}C NMR ($CDCl_3$) 19.15, 20.92, 128.26, 132.44, 137.28. IR (NaCl) 3400, 1645, 1635, 1615, 1430, 1380 cm^{-1}.

To liquid ammonia (200 ml) was added dropwise a solution of **2** (6.93 g, 43.0 mmol) in tetrahydrofuran (20 ml) at −78°C under argon, and the solution was stirred for 30 min at this temperature. Dry ethanol (20 ml) was added to the solution at −78°C, and the mixture was stirred for 15 min. Finally, to the solution was added sodium (2.84 g, 123.5 mmol), and the reaction mixture was refluxed for 1 h, quenched carefully with water (60 ml), and left for 12 h at room temperature to remove ammonia. The resultant solution was extracted with Et_2O (3×100 ml), and the combined extracts were dried over $MgSO_4$. After filtering $MgSO_4$ off, the filtrate was concentrated under reduced pressure. The oily residue was purified by bulb-to-bulb distillation to give racemic 1-mesitylethylamine *rac*-**1** (6.20 g, 38.0 mmol, 88%); 85°C/0.7 mmHg; which was used for the resolution without further purification. ^{1}H NMR ($CDCl_3$) 1.44 (d, *J*=6.87 Hz, 3H), 2.24 (s, 3H), 2.43 (s, 6H), 4.59 (q, *J*=6.87 Hz, 1H), 6.81 (s, 2H). ^{13}C NMR ($CDCl_3$) 20.57, 20.96, 22.14, 47.25, 130.25, 135.50, 135.61, 139.48. IR (NaCl) 3350, 1610, 1450, 850 cm^{-1}.

4.3. *Resolution of racemic 1-mesitylethylamine*

To a solution of *rac*-**1** (4.18 g, 25.6 mmol) and pyridine (2.3 ml) in dichloromethane (50 ml) was added dropwise a solution of (−)-menthyl chloroformate (7.31 g, 33.4 mmol) in dichloromethane (15 ml) at 0°C, and the solution was stirred for 40 h at room temperature. Then, the solution was successively washed with 1 M HCl aq. (3×30 ml), 1 M NaOH aq. (3×30 ml), water (3×30 ml), and brine (3×30 ml), and was dried over $MgSO_4$. After filtering $MgSO_4$ off, the filtrate was concentrated under reduced pressure. The oily residue was purified by silica gel column chromatography (AcOEt:hexane, 1:100) to give the pair of the diastereomers. The crude less-polar fraction was purified by bulb-to-bulb distillation to give the less-polar carbamate (less-**3**) (3.30 g, 9.6 mmol, 37%); 170°C/0.7 mmHg; $[\alpha]_D^{20}$ −55.1 (c

1.04, $CHCl_3$). ^1H NMR ($CDCl_3$) 0.70–1.07 (m, 11H), 1.22–1.28 (m, 1H), 1.47 (d, *J*=7.14 Hz, 3H), 1.55–1.70 (m, 3H), 1.87 (m, 1H), 2.11 (m, 1H), 2.17 (s, 1H), 2.23 (s, 3H), 2.40 (s, 6H), 4.44 (dt, *J*=4.40, 6.40 Hz, 1H), 5.00 (m, 1H), 5.24 (br, 1H), 6.81 (s, 2H). ^{13}C NMR ($CDCl_3$) 16.42, 20.00, 20.62, 20.70, 20.75, 21.95, 23.51, 26.18, 31.26, 34.26, 41.41, 47.06, 47.25, 74.60, 130.13, 135.09, 136.04, 136.44, 155.53. IR (NaCl) 3280, 1700, 1450, 1050 cm^{-1}. Anal. calcd for $C_{22}H_{35}NO_2$: C, 76.48; H, 10.21; N, 4.05. Found: C, 76.32; H, 10.28; N, 4.04. HPLC 4.05 min (FR 1.0 ml/min, 2-PrOH:hexane, 1:50).

The crude more-polar fraction was recrystallized from MeOH:H_2O (20 ml:3 ml) to give more-polar carbamate (more-**3**) (3.90 g, 11.3 mmol, 44%); mp 116–118°C; $[\alpha]_D^{20}$ −55.2 (c 1.02, $CHCl_3$). ^1H NMR ($CDCl_3$) 0.40–1.30 (m, 12H), 1.46 (d, *J*=6.04 Hz, 3H), 1.50–1.70 (m, 3H), 1.80–2.15 (m, 3H), 2.23 (s, 3H), 2.40 (s, 6H), 4.40–4.60 (m, 1H), 4.94–5.18 (m, 1H), 5.20–5.34 (br, 1H), 6.80 (s, 2H); ^{13}C NMR ($CDCl_3$) 15.29, 16.46, 19.49, 20.14, 20.63, 20.74, 20.83, 21.95, 22.62, 23.50, 24.66, 26.20, 31.30, 34.25, 41.49, 46.88, 47.37, 74.34, 130.15, 135.06, 136.02, 136.51, 155.51. IR (KBr) 3270, 1705, 1395, 1320, 1070, 1055 cm^{-1}. Anal. calcd for $C_{22}H_{35}NO_2$: C, 76.48; H, 10.21; N, 4.05. Found: C, 76.64; H, 10.11; N, 4.19. HPLC 4.96 min (FR 1.0 ml/min, 2-PrOH:hexane, 1:50).

To a solution of more-**3** (3.00 g, 8.68 mmol) in tetrahydrofuran (100 ml) was added dropwise DIBAL in tetrahydrofuran (1.0 M, 26.0 ml) at 0°C under argon, and the solution was stirred at room temperature for 40 h. The reaction mixture was quenched with the saturated Rochelle salt (50 ml). The organic layer was separated, and the water layer was extracted with AcOEt (2×100 ml). The combined organic layer and extracts were dried over $MgSO_4$. After filtering $MgSO_4$ off, the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (AcOEt:hexane, 1:9) to give (−)-menthol (1.14 g, 7.31 mmol, 85%) and (*R*)-*N*-formyl-1-mesitylethylamine ((*R*)-**4**) (1.30 g, 6.80 mmol, 79%); mp 113–115°C; $[\alpha]_D^{20}$ +108.2 (c 1.02, $CHCl_3$). ^1H NMR ($CDCl_3$) 1.49 (d, *J*=7.14 Hz, 3H), 2.23 (s, 3H), 2.40 (s, 6H), 5.54 (dq, *J*=7.14, 7.41 Hz), 6.32 (br, 1H), 6.81 (s, 2H), 8.09 (s, 1H). ^{13}C NMR ($CDCl_3$) 19.72, 20.60, 20.76, 44.26, 130.18, 135.21, 135.45, 136.43, 160.24. IR (KBr) 3250, 1670, 1650, 1540, 1375 cm^{-1}. Anal. calcd for $C_{12}H_{17}NO$: C, 75.35; H, 8.96; N, 7.32. Found: C, 75.05; H, 8.78; N, 7.43.

From less-**3** (*S*)-*N*-formyl-1-mesitylethylamine ((*S*)-**4**) was similarily obtained; 72%; mp 114–116°C; $[\alpha]_D^{20}$ −109.8 (c 1.03 $CHCl_3$). The spectral data were the same as those of (*R*)-*N*-formyl-1-mesitylethylamine. Anal. calcd for $C_{12}H_{17}NO$: C, 75.35; H, 8.96; N, 7.32. Found: C, 75.28; H, 8.80; N, 7.18.

To a solution of (*R*)-**4** (0.75 g, 3.92 mmol) in MeOH (10 ml) was added dropwise concentrated HCl (3 ml) and the solution was refluxed for 6 h. After being cooled, the solution was concentrated under reduced pressure. To the resultant residue was added water (20 ml), and the solution was washed with Et_2O (3×10 ml). The water layer was basified with solid NaOH (pH=12) at 0°C and extracted with Et_2O (3×10 ml). The combined extracts were dried over $MgSO_4$. After filtering $MgSO_4$ off, the solution was concentrated under reduced pressure, and the residue was purified by bulb-to-bulb distillation to give (*R*)-1-mesitylethylamine ((*R*)-**1**) (0.64 g, 3.92 mmol, 100%); 85°C/0.7 mmHg; $[\alpha]_D^{18}$ −45.6 (c 0.98, $CHCl_3$). The ^1H and ^{13}C NMR data were the same as those of *rac*-**1**. IR (NaCl) 3380, 1615, 1440 cm^{-1}. Elemental analysis was performed for the salt with cinnamic acid. Anal. calcd for $C_{20}H_{25}NO_2$ ((*R*)-**1**·(*E*)-cinnamic acid): C, 77.14; H, 8.09; N, 4.50. Found: C, 77.02; H, 7.92; N, 4.49. The e.e. of the optically active amine was determined by HPLC after derivatizing it into the carbamate with (−)-menthyl chloroformate.

(*S*)-1-Mesitylethylamine (*S*)-**1** was similarly obtained from (*S*)-**4**; 90°C/0.85 mmHg, 90%; $[\alpha]_D^{18}$ +45.2 (c 1.01, $CHCl_3$). The spectral data were the same as those of (*R*)-**1**. Anal. calcd for $C_{20}H_{25}NO_2$ ((*S*)-**1**·(*E*)-cinnamic acid): C, 77.14; H, 8.09; N, 4.50. Found: C, 77.01; H, 8.04; N, 4.57.

4.4. General procedure for the preparation of imines

To a solution of an aldehyde (1 mmol) in CH_2Cl_2 (3 ml) were added an equimolar amount of 1-mesitylethylamine and a large excess of MS 4 A at room temperature. After 12 h, the mixture was filtered through a Celite pad, and the filtrate was concentrated in vacuo. The crude imine was used for the next reaction without further purification.

4.5. General procedure for the aza-Diels–Alder reaction

To a solution of $BF_3 \cdot Et_2O$ (0.5 M CH_2Cl_2 solution, 1.25 ml, 0.63 mmol) in CH_2Cl_2 (1 ml) was added dropwise a solution of an imine (0.5 mmol) in CH_2Cl_2 (3 ml) at 0°C, and then the mixture was stirred for 10 min at this temperature. The mixture was then cooled to −78°C, and to the mixture was added dropwise a solution of Danishefsky's diene (1.5 mmol) in CH_2Cl_2 (2 ml). The reaction mixture was allowed to be warmed up gradually to 0°C over a period of 12 h. After being stirred for 12 h at this temperature, the reaction mixture was quenched with aqueous saturated $NaHCO_3$ (5 ml). The organic layer was separated, successively washed with 1 M NaOH (3×5 ml), saturated $NaHCO_3$ (3×5 ml), water (3×5 ml) and brine (3×5 ml), and dried over $MgSO_4$. After filtering $MgSO_4$ off, the solution was concentrated under reduced pressure. The residue was separated by preparative thin layer chromatography to give the cycloaddition product.

4.5.1. *2,3-Dihydro*-N-*(1-(2,5-dimethoxyphenyl)ethyl)-2-phenyl-4-pyridone* ***5a***

Oil; ^{1}H NMR ($CDCl_3$) 1.39 (d, *J*=6.93 Hz, 3H), 2.57 (dd, *J*=6.93, 16.2 Hz, 1H), 2.73 (dd, *J*=6.77, 16.3 Hz, 1H), 3.70 (s, 3H), 3.79 (s, 3H), 4.67 (dd, *J*=6.76, 6.93 Hz, 1H), 4.81 (q, *J*=6.93 Hz, 1H), 4.97 (d, *J*=7.59, 1H), 6.77–6.85 (m, 3H), 7.19–7.37 (m, 6H). ^{13}C NMR ($CDCl_3$) 17.76, 43.74, 55.16, 55.67, 59.48, 98.07, 112.67, 114.81, 127.06, 128.47, 128.72, 139.37, 149.83, 151.30, 152.32, 153.29, 190.15. IR (NaCl) 1650, 1590, 1510, 1230 cm^{-1}. HRMS calcd for ($C_{21}H_{23}NO_3$): 337.1678. Found: 337.1669. The diastereomeric ratio was determined by ^{1}H NMR [1.39 ppm (79%), 1.51 ppm (21%)].

4.5.2. *(2*R*)-2,3-Dihydro*-N-*((*S*)-1-mesitylethyl)-2-phenyl-4-pyridone* ***6a***

Mp 140–143°C. $[\alpha]_D^{19}$ −253.0 (c 0.89, $CHCl_3$). ^{1}H NMR ($CDCl_3$) 1.51 (d, *J*=7.02 Hz, 3H), 2.25 (s, 3H), 2.34 (s, 6H), 2.63 (dd, *J*=2.59, 16.5 Hz, 1H), 3.22 (dd, *J*=8.05, 16.7 Hz, 1H), 4.92 (q, *J*=7.02, 1H), 4.92 (d, *J*=6.88 Hz, 1H), 5.04 (d, *J*=8.05 Hz, 1H), 6.88 (s, 2H), 7.04 (d, *J*=6.88 Hz, 1H), 7.25–7.33 (m, 5H). ^{13}C NMR ($CDCl_3$) 17.86, 20.73, 20.92, 43.28, 55.63, 58.68, 98.56, 126.41, 127.96, 128.94, 130.72, 133.78, 136.49, 137.51, 138.43, 151.86, 189.33. IR (KBr) 1655, 1600, 1355 cm^{-1}. HRMS calcd for ($C_{22}H_{25}NO$): 319.1936. Found: 319.1954. The diastereomeric ratio was determined by ^{1}H NMR [2.98 ppm (1%), 3.22 ppm (99%)]. The relative configuration of the cycloaddition product was determined using **5b**.

4.5.3. *(2*S*)-2,3-Dihydro*-N-*((*R*)-1-mesitylethyl)-2-phenyl-4-pyridone (the antipode of* ***6a****)*

$[\alpha]_D^{20}$ +252.8 (c 0.89, $CHCl_3$). HRMS calcd for ($C_{22}H_{25}NO$): 319.1936. Found: 319.1917. The spectral data were the same as those of **6a**.

4.5.4. *(2*R*)-2,3-Dihydro*-N-*((*S*)-1-mesitylethyl)-2-(4-methoxyphenyl)-4-pyridone* ***6b***

Oil; $[\alpha]_D^{20}$ −318.7 (c 2.62, $CHCl_3$). ^{1}H NMR ($CDCl_3$) 1.52 (d, *J*=6.87 Hz, 3H), 2.26 (s, 3H), 2.27 (s, 6H), 2.59 (ddd, *J*=1.09, 1.37, 16.5 Hz, 1H), 3.18 (dd, *J*=7.97, 16.5 Hz, 1H), 3.79 (s, 3H), 4.89 (q, *J*=7.14, 1H), 4.91 (d, *J*=16.7 Hz, 1H), 4.97 (dd, *J*=7.97 Hz, 1H), 6.84 (d, *J*=9.05 Hz, 2H), 6.85 (s, 2H), 7.00 (dd, *J*=1.10, 7.96 Hz, 1H), 7.22 (d, *J*=8.51 Hz, 2H). ^{13}C NMR ($CDCl_3$) 17.87, 20.66, 20.89, 43.40, 55.24,

55.51, 58.25, 98.20, 114.22, 127.64, 130.45, 130.64, 133.68, 136.47, 137.42, 151.81, 159.20, 189.59. IR (NaCl) 1650, 1590, 1520, 1260 cm^{-1}. HRMS calcd for ($C_{23}H_{27}NO_2$): 349.2042. Found: 349.2039. The diastereomeric ratio was determined by ^1H NMR [2.96 ppm (2%), 3.18 ppm (98%)].

*4.5.5. (2*R*)-2,3-Dihydro-*N*-((*S*)-1-mesitylethyl)-2-(1-naphthyl)-4-pyridone* ***6c***

Oil; $[\alpha]_D^{20}$ +79.5 (c 1.89, $CHCl_3$). ^1H NMR ($CDCl_3$) 1.41 (d, *J*=7.14 Hz, 3H), 2.28 (s, 3H), 2.37 (s, 6H), 2.81 (dd, *J*=1.37, 16.2 Hz, 1H), 3.36 (dd, *J*=8.65, 16.4 Hz, 1H), 4.96 (d, *J*=17.3 Hz, 1H), 5.01 (q, *J*=7.14 Hz, 1H), 5.96 (d, *J*=8.24 Hz, 1H), 6.89 (s, 2H), 7.16 (d, *J*=7.69 Hz, 1H), 7.39–7.61 (m, 4H), 7.80–7.95 (s, 3H). ^{13}C NMR ($CDCl_3$) 17.65, 20.73, 20.92, 41.66, 54.10, 55.61, 97.89, 121.75, 123.53, 124.99, 125.73, 126.68, 128.65, 129.53, 129.62, 130.75, 131.35, 134.02, 134.68, 136.40, 137.51, 152.75, 189.26. IR (NaCl) 1640, 1590 cm^{-1}. HRMS calcd for ($C_{26}H_{27}NO$): 369.2092. Found: 369.2079. The diastereomeric ratio was determined by ^1H NMR [3.07 ppm (1%), 3.36 ppm (99%)].

*4.5.6. (2*R*)-2,3-Dihydro-*N*-((*S*)-1-mesitylethyl)-2-(3-pyridyl)-4-pyridone* ***6d***

Oil; $[\alpha]_D^{20}$ +251.2 (c 1.12, $CHCl_3$). ^1H NMR ($CDCl_3$) 1.55 (d, *J*=7.14 Hz, 3H), 2.26 (s, 3H), 2.27 (s, 6H), 2.59 (dd, *J*=1.37, 16.5 Hz, 1H), 3.25 (dd, *J*=7.97, 16.5 Hz, 1H), 4.90 (q, *J*=7.14 Hz, 1H), 4.96–5.06 (m, 2H), 6.84 (s, 2H), 7.08 (d, *J*=7.97, 1H), 7.20–7.30 (m, 1H), 7.67 (d, *J*=7.97 Hz, 1H), 8.53 (m, 2H). ^{13}C NMR ($CDCl_3$) 17.90, 20.70, 20.87, 42.84, 55.97, 56.81, 99.03, 123.6, 130.8, 133.3, 134.1, 136.3, 137.7, 148.1, 149.5, 151.6, 188.7. IR (NaCl) 1640, 1590 cm^{-1}. HRMS calcd for ($C_{21}H_{24}N_2O$): 320.1888. Found: 320.1901.

4.6. X-Ray crystallographic analysis

X-Ray crystal data for **5b**: Monoclinic; $P2_1/a$; colorless crystal; *a*=19.241(2), *b*=12.158(2), *c*=7.759(1) Å; β=94.42(1)°; *Z*=4; *R*=0.060; *GOF*=0.915.

X-Ray crystal data for ((*R*)-**1**·(−)-dibenzoyl-L-tartaric acid): Orthorhombic; $P2_12_12_1$; colorless crystal; *a*=7.8680(8), *b*=24.639(4), *c*=28.223(4) Å; *Z*=8; *R*=0.049; *GOF*=1.783.

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