HETEROCYCLES, Vol. 90, No. 2, 2015, pp. 950 - 966. © 2015 The Japan Institute of Heterocyclic Chemistry
Received, 30th June, 2014, Accepted, 29th July, 2014, Published online, 7th August, 2014
DOI: 10.3987/COM-14-S(K)63

ENANTIODIVERGENT SYNTHESIS OF WIELAND-MIESCHER KETONE ANALOG MEDIATED BY A CHIRAL PYRIDINYLMETHYLAMINE DERIVATIVE

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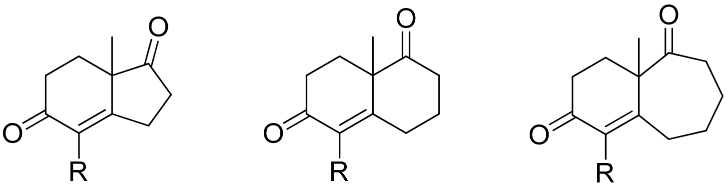
This paper is dedicated to Prof. Dr. Isao Kuwajima on the occasion of his 77th birthday.

Abstract – A new enantiodivergent route to provide the Wieland-Miescher ketone analog (**3b**) bearing a 7-membered ring *via* the intramolecular aldol reaction of the trione (**5**) mediated by a single chiral pyridinylmethylamine derivative (**13e**) was established. Although the enantioselectivities of **3b** were moderate, the complete inversion of the enantioselectivities was observed based on the amount of additional trifluoroacetic acid (TFA). The basicity of the nitrogen atom on the pyridine ring was very important for this enantiodivergent behavior.

INTRODUCTION

Hajos-Parrish (**1a**), Wieland-Miescher (**2a**) ketones and their analogs (**1b**, **2b**), which include carbobicyclic enediones, have been highly useful synthons for the total synthesis of a variety of natural products and pharmaceutically important compounds (Figure 1).[1-7] These useful enediones have been easily prepared by amino acid-mediated asymmetric intramolecular aldol reactions.[8] This asymmetric aldol reaction was first reported by Hajos *et al.* and has been widely recognized to involve an enamine-based mechanism.[2,3] However, there have been few reports on how to prepare **3** bearing a 7-membered ring, in spite of their interesting reaction profiles.[1,9] For example, the inversion of enantioselectivities in the asymmetric aldol reactions of the triones **4** and **5**, mediated by (*S*)-phenylalanine [(*S*)-Phe, **6**] in the presence of a Brønsted acid, has been observed to give (*S*)-**2b** and (*R*)-**3b**, respectively. Equally, different chemoselectivities have also been observed upon the treatment of **2b** and **3b** with sodium borohydride in EtOH.[1a,10] Whereas a hydride stereoselectively attacked at the cyclohexanone carbonyl in **2b** from the α-face to afford **7**, **3b** kinetically and stereoselectively reacted at the conjugated carbonyl to give **8** (Scheme 1). Since many pharmaceutically important natural products containing a 7-membered carbocycle have been isolated,[11] the enedione (**3**) has been significant as a potential chiral synthon to achieve the total synthesis of these products.

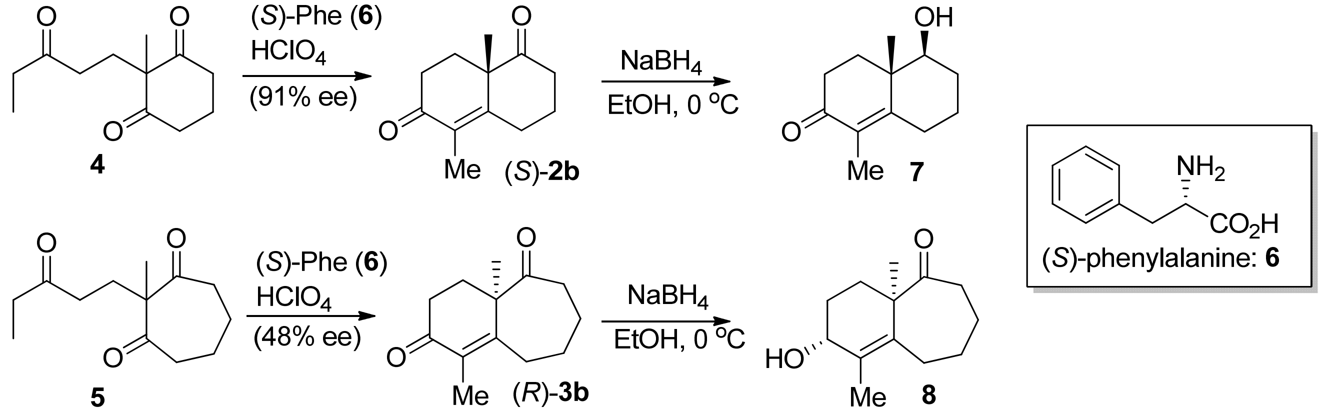


1a: R = H
1b: R = Me

2a: R = H
2b: R = Me

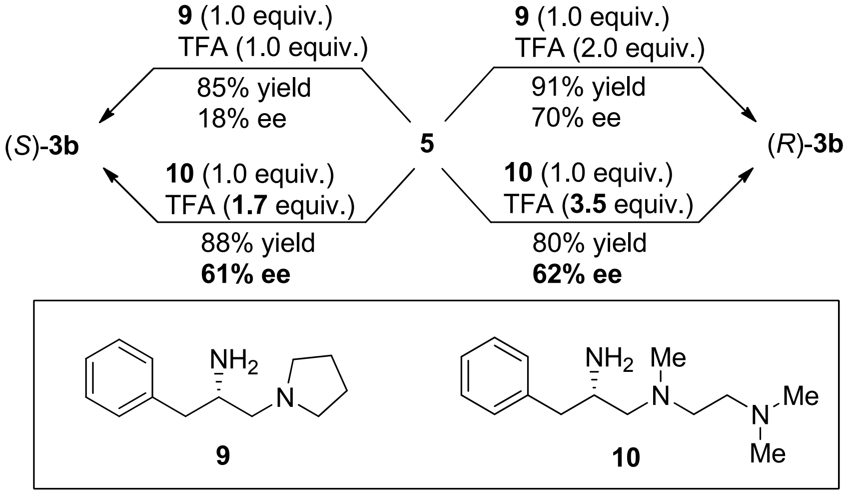
3a: R = H
3b: R = Me

Figure 1

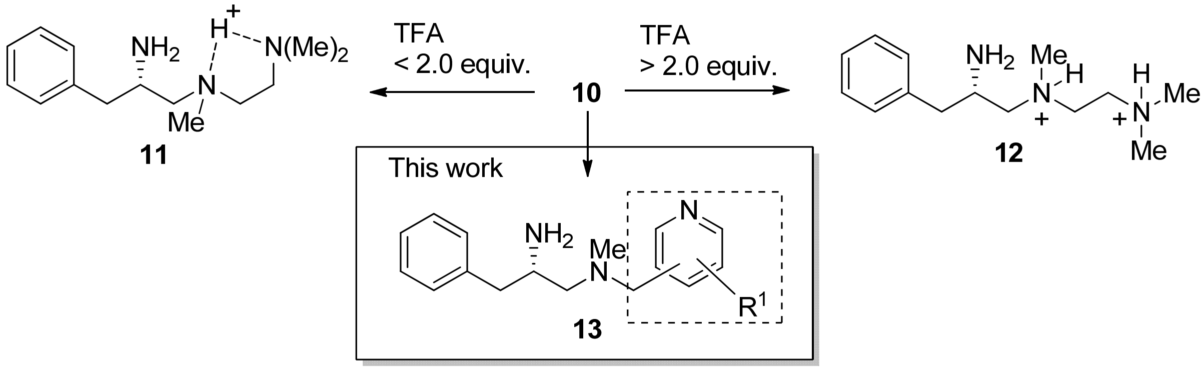


Scheme 1

We previously reported the preparation of (*R*)- and (*S*)-**3b** *via* the asymmetric intramolecular aldol reaction of the trione (**5**), which was easily prepared from 2-methylcycloheptane-1,3-dione,[12] mediated by the chiral diamine (**9**).[1c] The aldol reaction using a stoichiometric amount of **9** in the presence of 2.0 equivalents of TFA afforded (*R*)-**3b** accompanied with 70% ee. However, the inversion of enantioselectivity was observed under the condition of 1.0 equivalent of TFA with a lower ee value. Recently, we established the enantiodivergent preparation of **3b**[13] using a known chiral triamine (**10**) which was easily prepared from (*S*)-Phe (**6**).[14] The enantioselectivities of **3b** depended on the amount of additional TFA. The reaction mediated by a stoichiometric amount of **10** in the presence of 1.7 equivalents and 3.5 equivalents of TFA independently afforded (*S*)- and (*R*)-**3b** respectively (Scheme 2). Although the ee values were moderate, we have enantiodivergently achieved the preparation of both enantiomers of **3b** using a single chiral mediator (**10**). Also, we have found that the inversion point of the enantioselectivity existed at around 2.0 equivalents of TFA. We have speculated that this enantiodivergent behavior of **10** was due to a dynamic conformational change in the ethylene diamine moiety. Under less than 2.0 equivalents of TFA, the ethylene diamine moiety coordinated to a proton in a bidentate fashion to form a folding conformation (**11**). On the other hand, an extended conformation (**12**) might be preferred under more than 2.0 equivalents of (or an excess amount of) TFA, because of the electrostatic repulsion due to formation of the diammonium structure. Since we are strongly interested in this unique phenomenon concerning **10**, we now report the preparation of new chiral mediators (**13**) installing a pyridine moiety as a basic functionality and their reactivity for the asymmetric aldol reaction of **5** (Scheme 3).



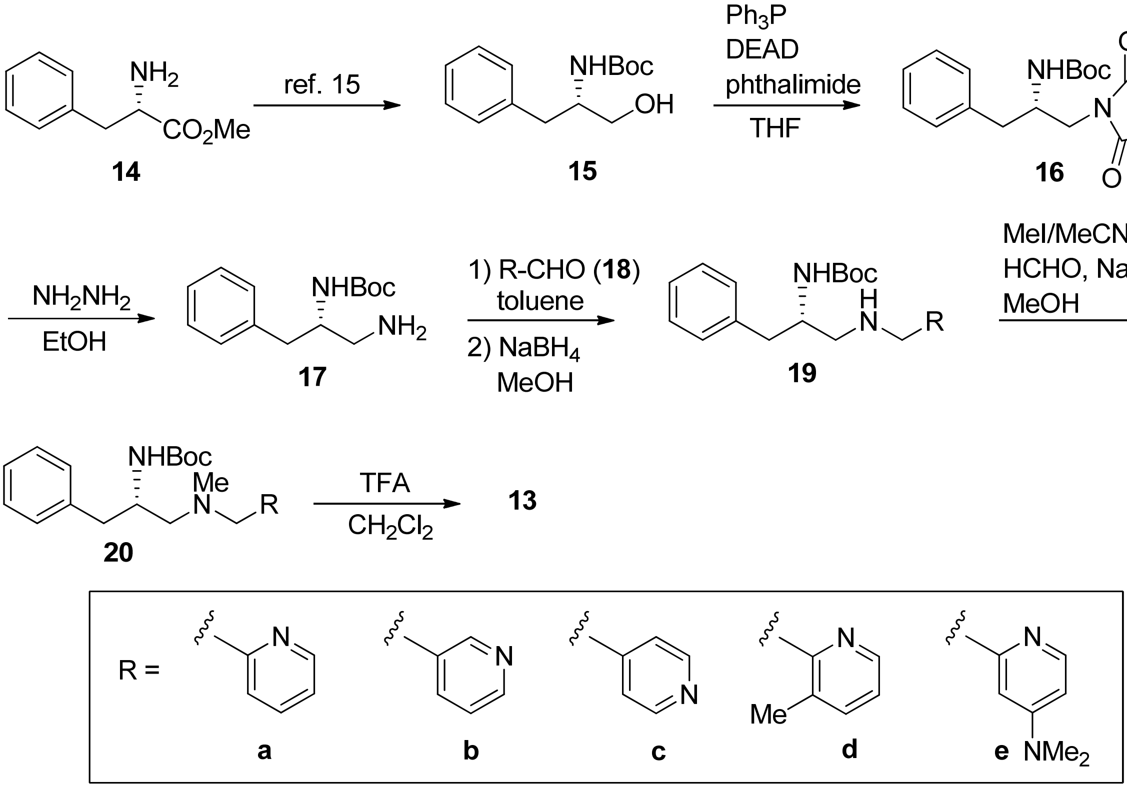
Scheme 2



Scheme 3

RESULTS AND DISCUSSION

We initially studied the preparation of new chiral amine mediators (**13**). According to the known procedure,[15] the alcohol (**15**) was obtained from the commercially available (*S*)-phenylalanine methyl ester (**14**). The Mitsunobu reaction[16] using phthalimide and following deprotection in the presence of hydrazine hydrate afforded the known amine intermediate (**17**).[17] Next, we introduced a variety of pyridinylmethyl groups by the reductive alkylation of **17**. Thus, the azeotropic reaction of **17** in the presence of the corresponding commercially available or known aldehyde (**18**)[18,19] to form imines and the following sodium borohydride reduction in MeOH smoothly proceeded to yield **19**. Although the direct methylation of **19a** using methyl iodide in MeCN afforded **20a** in moderate yield, trace amounts of **20b** and **20c** were obtained under the same reaction conditions. The Eschweiler-Clarke reaction[20] succeeded in producing the corresponding methylation products (**20b**-**20e**). Finally, the Boc group was removed in the presence of TFA to yield the desired **13** (Scheme 4).



Scheme 4

Next, we examined the asymmetric aldol reaction of **5** mediated by **13** in the presence of different amounts of TFA. According to the reaction conditions using **10**,[13] a stoichiometric amount of **13** was used for the reaction in the presence of 1.7 or 3.5 equivalents of TFA in DMSO at 90 °C. The results are compiled in Table 1. All of the amines (**13**) mediated the reaction to afford **3b** with a moderate enantioselectivity. However, among the tested amines, **13a**-**13d** gave (*R*)-**3b** using both amounts of TFA and no enantiodivergent behaviors were observed. In the case of using **13e**, (*S*)- and (*R*)-**3b** were obtained using different amounts of TFA. The ee values in each case were almost inverted (Table1, entries 9 and 10).

We next determined the effects of the quantities of TFA on the yield and ee of the aldol reaction of **5** mediated by **13e**. All reactions were carried out with 1.0 equivalent of **13e** in DMSO at 90 °C in the presence of TFA over the range of 1.0 to 3.5 equivalents (see Table 2 and Figure 2). All of the yields under the tested reaction conditions almost averaged around 80%. However, the absolute configuration of **3b** changed from *S* to *R* at the point between 1.7 and 2.0 equivalents of TFA. The ee values reached a plateau in the range of 2.5 to 3.5 equivalents of TFA. Based on these results, the inversion point of the enantioselectivity existed at around 1.8 equivalents of TFA.

Table 1. The aldol reaction of **5** mediated by **13**

$$\mathbf{5}\ \xrightarrow[\text{DMSO, 90 }^{\circ}\text{C}]{\substack{\mathbf{13}\text{ (1.0 equiv.)} \\ \text{TFA (}n\text{ equiv.)}}}\ \mathbf{3b}$$

Entry	Amine (**13**)	TFA (equiv.)	Time (h)	Yield[a] (**3b**, %)	Ee[b] (**3b**, %)	Absolute configuration of **3b**
1	**13a**	1.7	60	59	72	*R*
2	**13a**	3.5	131	59	67	*R*
3	**13b**	1.7	86	56	74	*R*
4	**13b**	3.5	113	72	75	*R*
5	**13c**	1.7	54	60	69	*R*
6	**13c**	3.5	144	61	66	*R*
7	**13d**	1.7	48	75	74	*R*
8	**13d**	3.5	120	80	69	*R*
9	**13e**	1.7	47	82	47	*S*
10	**13e**	3.5	252	74	54	*R*

[a] Isolated yield.

[b] Determined by HPLC equipped with a chiral stationary phase column.

In the cases of using **13b** and **13c**, the pyridine unit hardly coordinated to an ammonium proton, like **11**, due to a structural restriction (Scheme 5). In spite of their protonation modes (**21a ~ d, 22a ~ d**), both conformations (**21** and **22**) seemed to be almost the same at the point of steric hindrance around an ammonium proton which plays a key role in the transition state of the aldol reaction of **5** (*vide infra*). From this reason, the pyridinylmethyl counterpart in **13b** and **13c** hardly affected the C-C bond formation process during the aldol reaction to afford (*R*)-**3b** using both amounts of TFA.

In the cases of **13a**, **13d** and **13e** bearing a common pyridin-2-yl-methyl substituent tolerating the bidentate coordination to the ammonium proton, a dynamic equilibrium between the coordinated (**23**) and dissociated (**24**) conformation might exist in the presence of less than 1.8 equivalents of TFA (Scheme 6). Comparing **23a** and **24a** (R^1 = R^2 = H), there were no or only slight steric differences around the ammonium proton. Although the big difference in the steric hindrance due to the direction of the methyl substituent (R^1) between **23d** and **24d** (R^1 = Me, R^2 = H) existed in the case of **13d**, the aldol reaction mediated by **13d** afforded (*R*)-**3b** accompanied by almost the same ee for both amounts of TFA. This result suggested that the reaction with less than 1.8 equivalents of TFA proceeded through **24** being similar to the diammonium conformer (**25**) in the presence of an excess amount of TFA.

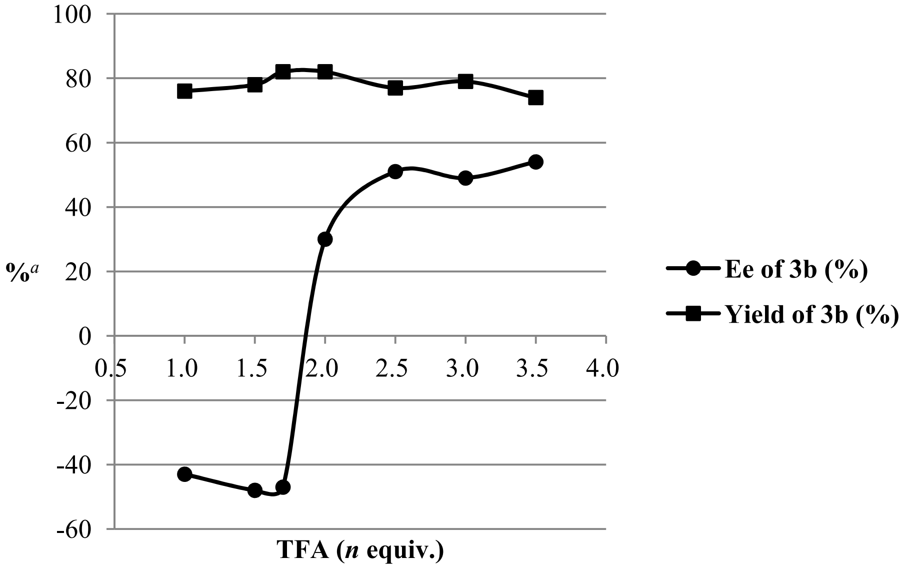
Table 2. Effects of the amount of TFA for the aldol reaction of **5** mediated by **13e**

$$\mathbf{5} \xrightarrow[\text{DMSO, 90 }^{\circ}\text{C}]{\mathbf{13e}\text{ (1.0 equiv.)} \\ \text{TFA (}n\text{ equiv.)}} \mathbf{3b}$$

Entry	TFA (equiv.)	Time (h)	Yield[a] (**3b**, %)	Ee[b] (**3b**, %)	Absolute configuration of **3b**
1	1.0	20	76	43	*S*
2	1.5	42	76	48	*S*
3	1.7	60	82	47	*S*
4	2.0	120	82	30	*R*
5	2.5	148	77	51	*R*
6	3.0	156	79	49	*R*
7	3.5	252	74	54	*R*

[a] Isolated yield.

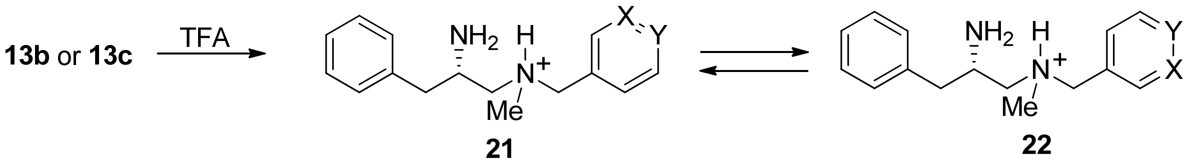
[b] Determined by HPLC equipped with a chiral stationary phase column.



[a] Ee values of (*S*)-**3b** are listed with a minus.

Figure 2. Effects of the level of TFA on the aldol reaction of **5** mediated by **13e**

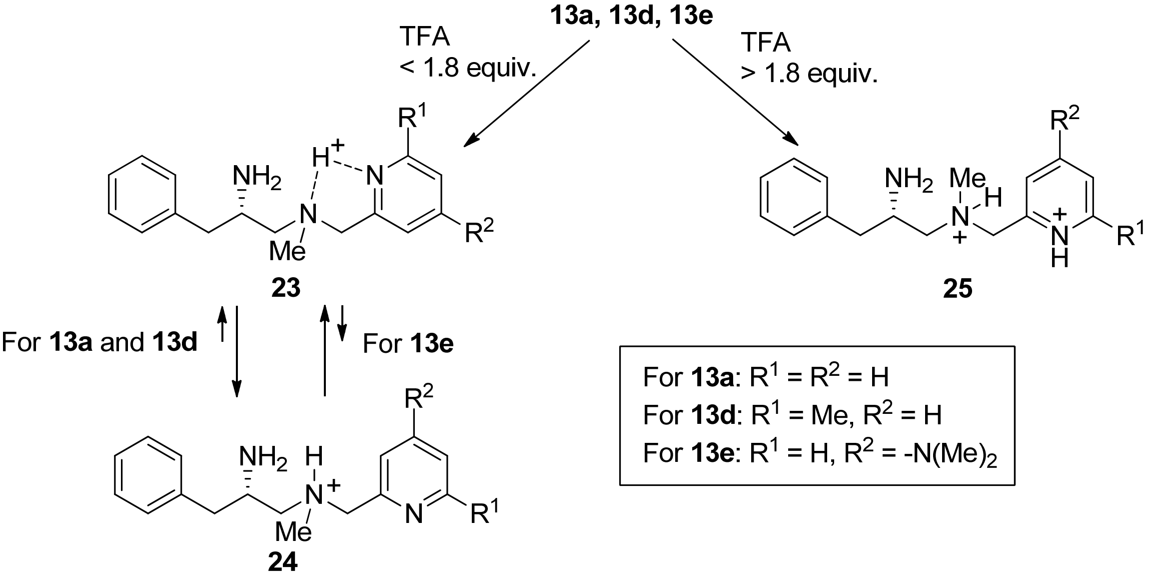
The increasing basicity of the pyridine nitrogen by installing a 4-dimethylamino substituent [R^2 = -$N(Me)_2$] in **13e**, **23** was the favored conformer in the equilibrium to invert the enantioselectivity to give (*S*)-**3b**. Comparing the well-known p*K*a values of the conjugated acids of trialkylamine (**26**), pyridine (**27**) and 4-dimethylaminopyridine (DMAP, **28**), whereas the basicity of the trialkylamine and DMAP are almost the same, pyridine is a much weaker base (Figure 3).[21] Since only **13e** having DMAP appeared to undergo the same phenomenon as **10**, the basicity of the pyridine nitrogen must be a very important factor to exhibit the enatiodivergent fashion in the aldol reaction of **5**.



For **13b**:
a: X = N, Y = CH
b: X = NH^+, Y = CH

For **13c**:
c: X = CH, Y = N
d: X = CH, Y = NH^+

Scheme 5



For **13a**: $R^1 = R^2 = H$
For **13d**: R^1 = Me, R^2 = H
For **13e**: R^1 = H, R^2 = -$N(Me)_2$

Scheme 6

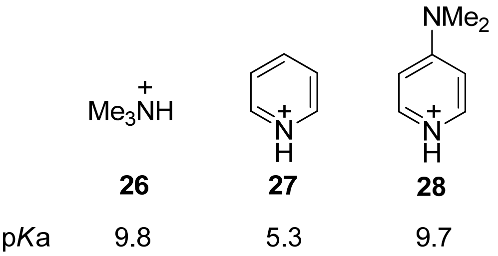


Figure 3. p*K*a Values of the conjugated acid of a trialkylamine and pyridines

In the aldol reaction of **5**, we could not observe the initially formed β-hydroxy ketones under the reaction conditions using **13**. Dehydration of the β-hydroxy ketones to afford the corresponding conjugated enone rapidly occured. We previously proposed the possible transition states (TSs) of the aldol reaction of **5** mediated by the diamine (**9**) *via* the enamine mechanism.[1c] According to our proposed model, four TSs concerning the *cis*/*trans* and *syn*/*anti* (*cis*, *trans*: *cis*- or *trans*-fused carbocycles, *syn*, *anti*: conformation between olefinic and hydrogen bonding sites) were considered (Figure 4). Among the TSs, the *trans*-*anti* and *cis*-*anti* forming a chair conformation of the 6-membered ring including the hydrogen bonding nitrogen and oxygen atoms are relatively more stable than the *trans*-*syn* and *cis*-*syn* forming a boat conformation. As already mentioned, under more than 1.8 equivalents of TFA, the hydrogen bond in **23** dissociated and the diammonium ion (**25**) was formed. This result means that the DMAP moiety in **13e** would be oriented away from the C-C bond forming site. In comparison with the two *anti*-TSs (**29** and **31**), **31** appears to be not favored due to steric repulsion between the methyl enamine and a 7-membered carbocycle. Consequently, the *trans*-*anti*-TS (**29**) to afford (*R*)-**3b** after the dehydration should be relatively more favored than **31** and the other *syn*-TSs (**30** and **32**). This behavior was almost the same as the previously reported reaction using **9**.[1c] Since **13a**-**13d** hardly coordinated to form in the bidentate fashion like **23** (*vide supra*), these mediators afforded (*R*)-**3b** *via* a similar TS like **29** in spite of the different amount of TFA.

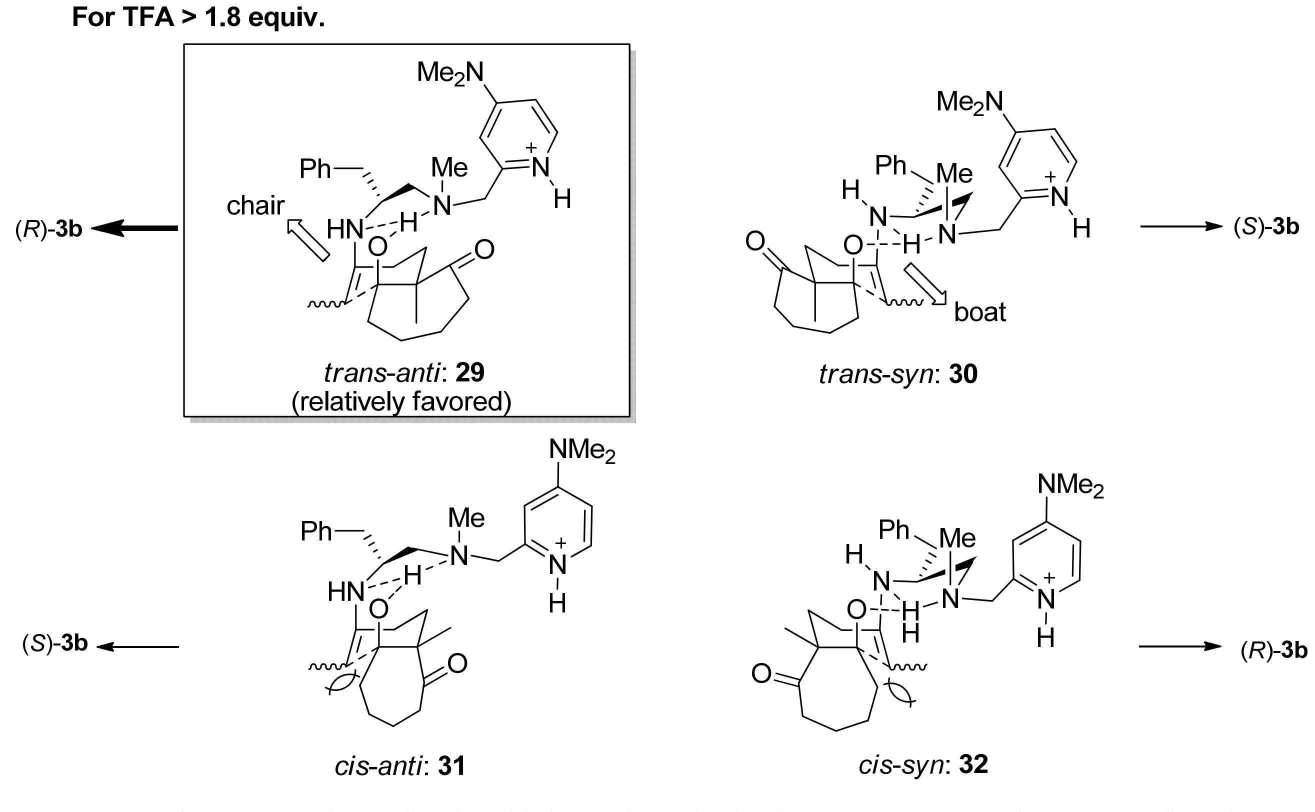


Figure 4. The proposed TSs for the aldol reaction of **5** in the presence more than 1.8 equiv. of TFA

For less than 1.8 equivalents of TFA, the pyridine nitrogen atom of the DMAP moiety in **13e** coordinated to the ammonium hydrogen which resulted in a change in the energies of the four TSs described above. For the *trans-anti*-TS (**33**), this coordination fixed the pyridine ring upon the cycloheptanone to generate a severe steric repulsion between the carbocycle and the pyridine. Also, for the *cis-anti* TS (**35**), a similar repulsion between the angular methyl substituent and the coordinated pyridine, accompanied the same repulsion as in TS (**31**). These facts relatively make the energies of the *anti*-TSs (**33** and **35**) higher than those of the *syn*-TSs (**34** and **36**). Comparing the two *syn*-TSs, a steric repulsion between the carbocycle and methyl enamine moiety existed in **36**. Based on these reasons, **34** is the relatively favored TS among the four proposed TSs to afford (*S*)-**3b** *via* the rapid dehydration of the corresponding β-hydroxy ketone (Figure 5).

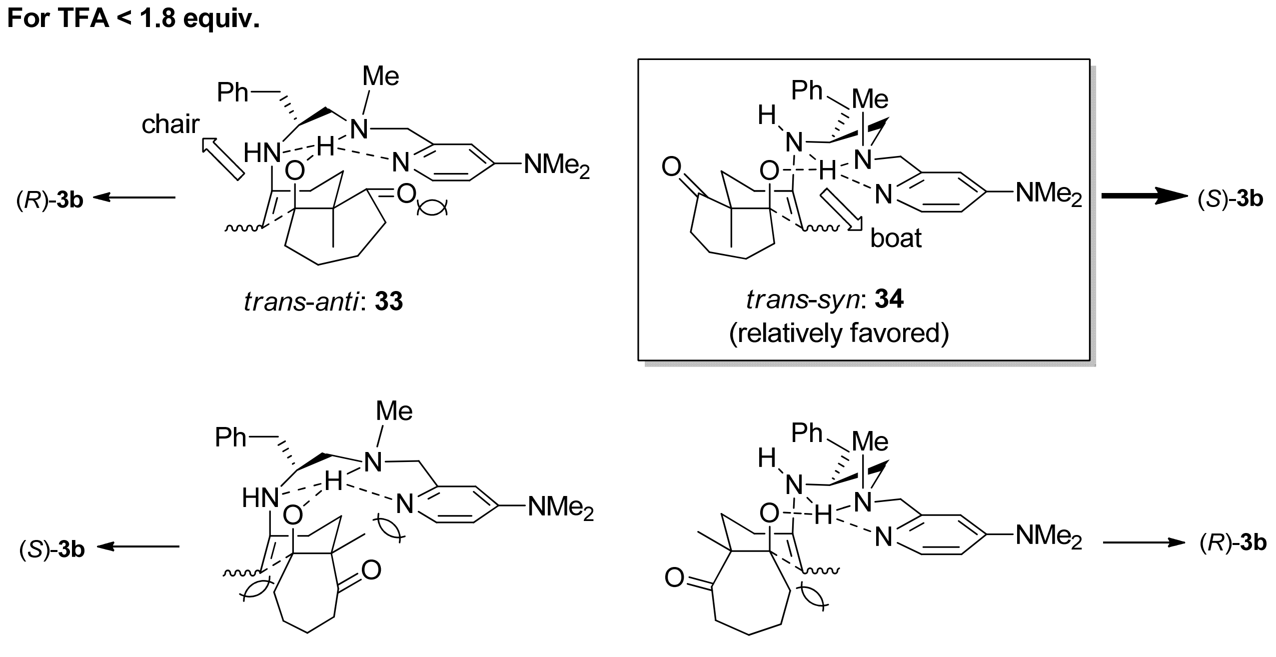


Figure 5. The proposed TSs for the aldol reaction of **5** mediated by **13e** in the presence of less than 1.8 equiv. of TFA

In conclusion, we have established a new enantiodivergent route to provide the Wieland-Miescher ketone analog (**3b**) bearing a 7-membered ring *via* the intramolecular aldol reaction of the trione (**5**) mediated by a single chiral pyridinylmethylamine (**13e**) in the presence of TFA. Although the enantioselectivities of **3b** were moderate, the complete inversion of ee was observed due to the amount of additional TFA. This unique phenomenon was due to the dynamic conformational change of **13e** depending on the amount of TFA. The basicity of the nitrogen atom on the pyridine ring was very important for this enantiodivergent behavior. Further work on the details of the reaction mechanism and the developments of a more efficient mediator for the reactions are currently in progress.

EXPERIMENTAL

The ^{1}H NMR spectra and ^{13}C NMR spectra were recorded using a JEOL-AX-400 (^{1}H 400 MHz, ^{13}C 100 MHz) spectrometer and calibrated using tetramethylsilane or $CDCl_3$ as the internal standard. The mass spectra were recorded by a JEOL-DX-303 or JEOL JMS-MS700 spectrometer. The enantiomeric excesses were determined by a HITACHI HPLC LaChrom instrument equipped with a chiral stationary phase column. Optical rotations were measured using a JASCO DIP 370 digital polarimeter.

Typical procedure for reductive pyridinylmethylation of 17.[22]

A mixture of **17** (2.00 g, 7.99 mmol) and 2-pyridinecarboxaldehyde (**18a**) (910 mg, 9.59 mmol) in toluene (20 mL) was heated to reflux under azeotropic reaction conditions using a Dean-Stark apparatus for 2 h. After cooling, the toluene was removed under reduced pressure. The residue was dissolved in MeOH (20 mL), then sodium borohydride (360 mg, 9.59 mmol) was added in small portions over 10 min in the ice bath. After removing an ice bath, the mixture was stirred at rt for 4 h. Acetone (10 mL) was then added to the mixture to quench the reaction and the solvent was removed under reduced pressure. The residue was dissolved in AcOEt and washed with saturated aqueous $NaHCO_3$ and brine. After drying the mixture (Na_2SO_4), the solvent was removed under reduced pressure and the residue was chromatographed (AcOEt/hexane/NH_4OH = 20/1/0.2, v/v) to afford **19a** 2.53 g (93%) as a pale yellow oil.

(*S*)-*tert*-Butyl {1-phenyl-3-[(pyridin-2-ylmethyl)amino]propan-2-yl}carbamate (19a)

$[\alpha]_D^{22}$ +8.4 (*c* 1.00, $CHCl_3$); ^{1}H-NMR ($CDCl_3$) δ 1.41 (s, 9H), 1.98 (brs, 1H), 2.62 (dd, *J* = 6.3 Hz, 12.1 Hz, 1H), 2.67 (dd, *J* = 4.8 Hz, 12.1 Hz, 1H), 2.77 (dd, *J* = 7.7 Hz, 13.5 Hz, 1H), 2.86-3.00 (brm, 1H), 3.82-3.90 (brm, 1H), 3.84 (d, *J* = 14.0 Hz, 1H), 3.91 (d, *J* = 14.0 Hz, 1H), 4.97 (brs, 1H), 7.13-7.30 (m, 7H), 7.62 (dt, *J* = 1.9 Hz, 7.7 Hz, 1H), 8.55 (d, *J* = 4.8 Hz, 1H); ^{13}C-NMR ($CDCl_3$) δ 28.2, 38.8, 51.2, 54.9, 78.8, 121.8, 122.1, 126.1, 128.2, 129.2, 136.2, 138.0, 149.1, 155.5, 159.5; EIMS (*m*/*z*) 341 (M^+), 284, 121 (100%), 92, 57; HRMS calcd for $C_{20}H_{27}N_3O_2$ 341.2103. Found 341.2098.

(*S*)-*tert*-Butyl {1-phenyl-3-[(pyridin-3-ylmethyl)amino]propan-2-yl}carbamate (19b)

Yield: 62% (as a yellow oil); $[\alpha]_D^{22}$ +8.8 (*c* 1.00, $CHCl_3$); ^{1}H-NMR ($CDCl_3$) δ 1.41 (s, 9H), 1.72 (brs, 1H, 2.59 (dd, *J* = 6.8 Hz, 12.1 Hz, 1H), 2.67 (dd, *J* = 4.8 Hz, 12.1 Hz, 1H), 2.76 (dd, *J* = 7.2 Hz, 12.6 Hz, 1H), 2.80-2.91 (brm, 1H), 3.72 (d, *J* = 13.5 Hz, 1H), 3.80 (d, *J* = 13.5 Hz, 1H) 3.96 (brs, 1H), 4.68 (brs, 1H), 7.16-7.24 (m, 6H), 7.63 (d, *J* = 7.7 Hz, 1H), 8.49 (*d*, *J* = 4.8 Hz, 1H), 8.52 (s, 1H); ^{13}C-NMR ($CDCl_3$) δ 28.2, 38.9, 50.7, 51.0, 51.4, 79.0, 123.1, 126.1, 128.2, 128.4, 129.1, 135.6, 137.8, 148.2, 149.4, 155.5; EIMS (*m*/*z*) 341 (M^+), 284, 121 (100%), 92, 57; HRMS calcd for $C_{20}H_{27}N_3O_2$ 341.2103. Found 341.2110.

(*S*)-*tert*-Butyl {1-phenyl-3-[(pyridin-4-ylmethyl)amino]propan-2-yl}carbamate (19c)

Yield: 63% (as a yellow oil); $[\alpha]_D^{23}$ +3.1 (*c* 1.00, $CHCl_3$); ^{1}H-NMR ($CDCl_3$) δ 1.41 (s, 9H), 1.60-1.80 (brm, 1H), 2.59 (dd, *J* = 6.8 Hz, 12.1 Hz, 1H), 2.66 (dd, *J* = 4.8 Hz, 12.1 Hz, 1H), 2.77 (dd, *J* = 6.8 Hz, 13.0 Hz, 1H), 2.82-2.93 (brm, 1H), 3.74 (d, *J* = 14.5 Hz, 1H), 3.80 (d, *J* = 14.5 Hz, 1H), 3.97 (brs, 1H), 4.67 (brs, 1H), 7.10-7.40 (m, 7H), 8.52 (d, *J* = 6.3 Hz, 2H); ^{13}C-NMR ($CDCl_3$) δ 28.2, 28.3, 39.2, 51.7, 52.4, 79.4, 121.5, 122.9, 126.5, 128.5, 128.6, 129.3, 137.8, 138.0, 149.8, 149.9, 155.7; EIMS (*m*/*z*) 341 (M^+), 284, 121 (100%), 92, 57; HRMS calcd for $C_{20}H_{27}N_3O_2$ 341.2103. Found 341.2106.

(*S*)- *tert*-Butyl {1-({[6-methylpyridin-2-yl)methyl]amino}-3-phenylpropan-2-yl}carbamate (19d)

Yield: 52% (as a yellow oil); $[\alpha]_D^{22}$ +2.7 (*c* 1.00, $CHCl_3$); ^{1}H-NMR ($CDCl_3$) δ 1.42 (s, 9H), 1.95 (brs, 1H), 2.55 (s, 3H), 2.60 (dd, *J* = 6.3 Hz, 12.6 Hz, 1H), 2.66 (dd, *J* = 4.8 Hz, 12.0 Hz, 1H), 2.75 (dd, *J* = 8.2 Hz, 14.0 Hz, 1H), 2.83-3.00 (brm, 1H), 3.79 (d, *J* = 14.0 Hz, 1H), 3.87 (d, *J* = 14.0 Hz, 1H), 3.76-3.98 (brm, 1H), 5.03 (s, 1H), 7.02 (t, *J* = 8.7 Hz, 2H), 7.12-7.32 (m, 5H), 7.51 (t, *J* = 7.7 Hz, 1H); ^{13}C-NMR ($CDCl_3$) δ 24.5, 28.4, 39.0, 51.2, 51.7, 55.0, 79.1, 119.2, 121.5, 126.3, 128.3, 129.4, 136.7, 138.2, 155.7, 158.0, 158.9; EIMS (*m*/*z*) 355 (M^+), 135 (100%), 106, 57; HRMS calcd for $C_{21}H_{28}N_3O_2$ 355.2260. Found 355.2263.

(*S*)-*tert*-Butyl {1-{{[4-(dimethylamino)pyridin-2-yl]methyl}amino}-3-phenylpropan-2-yl}carbamate (19e)

Yield: 68% (as an orange colored oil); $[\alpha]_D^{21}$ +1.7 (*c* 1.00, $CHCl_3$); ^{1}H-NMR ($CDCl_3$) δ 1.41 (s, 9H), 2.05 (brs, 1H), 2.61 (dd, *J* = 6.3 Hz, 12.5 Hz, 1H), 2.65 (dd, *J* = 4.8 Hz, 12.5 Hz, 1H), 2.76 (dd, *J* = 7.7 Hz, 13.0 Hz, 1H), 2.83-3.04 (brm, 1H), 2.99 (s, 6H), 3.72 (d, *J* = 14.0 Hz, 1H), 3.79 (d, *J* = 14.0 Hz, 1H), 3.89 (brs, 1H), 5.10 (brs, 1H), 6.38 (dd, *J* = 2.4 Hz, 5.9 Hz, 1H), 6.46 (d, *J* = 2.4 Hz, 1H), 7.12-7.31 (m, 5H), 8.17 (d, *J* = 5.9 Hz, 1H); ^{13}C-NMR ($CDCl_3$) δ 28.3, 28.4, 39.1, 51.1, 51.7, 55.5, 78.9, 104.7, 104.8, 105.11, 105.13, 126.2, 128.3, 129.4, 138.3, 149.3, 154.8, 155.6, 159.4; EIMS (*m*/*z*) 384 (M^+), 311, 164 (100%), 135, 91, 57; HRMS calcd for $C_{22}H_{32}N_4O_2$ 384.2525. Found 384.2513.

Direct methylation of 19a using MeI.[22]

To a stirred solution of **19a** (2.50 g, 7.33 mmol) in MeCN (27 mL) was added MeI (1.36 mL, 22.0 mmol) at rt. After stirring at the same temperature for 12 h, the solvent was removed under reduced pressure. The residue was dissolved in AcOEt and the mixture was washed with saturated aqueous $NaHCO_3$ and brine. After drying the mixture (Na_2SO_4), the solvent was removed under reduced pressure and the residue was chromatographed (AcOEt/hexane/NH_4OH = 10/10/0.03, v/v) to afford **20a** 1.00 g (39%) as a pale yellow oil.

(*S*)-*tert*-Butyl {1-[methyl(pyridin-2-ylmethyl)amino]-3-phenylpropan-2-yl}carbamate (20a)

$[\alpha]_D^{21}$ +1.7 (*c* 1.00, $CHCl_3$); ^{1}H-NMR ($CDCl_3$) δ 1.43 (s, 9H), 2.27 (s, 3H), 2.40 (d, *J* = 7.2 Hz, 2H), 2.79 (dd, *J* = 6.3 Hz, 13.5 Hz, 1H), 2.84-3.00 (m, 1H), 3.62 (d, *J* = 14.5 Hz, 1H), 3.72 (d, *J* = 14.5 Hz, 1H), 3.94 (brs, 1H), 4.97 (brs, 1H), 7.14-7.28 (m, 6H), 7.38 (d, *J* = 7.7 Hz, 1H), 7.64 (dt, *J* = 1.9 Hz, 7.7 Hz, 1H), 8.54 (d, *J* = 4.8 Hz, 1H); ^{13}C-NMR ($CDCl_3$) δ 28.3, 38.9, 42.7, 49.6, 59.9, 63.7, 78.9, 121.9, 122.9, 126.1, 128.1, 129.4, 136.3, 138.0, 148.9, 155.7, 159.1; EIMS (*m*/*z*) 355 (M^+), 135 (100%), 92, 57; HRMS calcd for $C_{21}H_{29}N_3O_2$ 355.2260. Found 355.2211.

Typical procedure for Eschweiler-Clarke reaction of 19.[22]

To a stirred solution of **19b** (3.51 g, 10.3 mmol) and formalin (37 w/v %, 3.10 mL, 30.8 mmol) in MeOH (25 ml) was added $NaBH_4$ (776 mg, 20.5 mmol) in an ice bath. After stirring at the same temperature for 30 min, the same amounts of formalin and $NaBH_4$ were added every 30 min for three times. The mixture was stirred at rt for 12 h after the final addition and the solvent was removed under reduced pressure. The residue was dissolved in AcOEt and the mixture was washed with saturated aqueous $NaHCO_3$ and brine, and then dried (Na_2SO_4). The solvent was removed under reduced pressure and the residue was chromatographed (AcOEt/hexane/NH_4OH = 50/50/0.4, v/v) to afford **20b** 3.08 g (85%) as a pale yellow oil.

(*S*)-*tert*-Butyl {1-[methyl(pyridin-3-ylmethyl)amino]-3-phenylpropan-2-yl}carbamate (20b)

$[\alpha]_D^{24}$ +12.1 (*c* 1.00, $CHCl_3$); ^{1}H-NMR ($CDCl_3$) δ 1.43 (s, 9H), 2.18 (s, 3H), 2.34 (dd, *J* = 7.2 Hz, 12.6 Hz, 1H), 2.38 (dd, *J* = 7.7 Hz, 12.6 Hz, 1H), 2.80-2.92 (m, 2H), 3.44 (d, *J* = 13.5 Hz, 1H), 3.54 (d, *J* = 13.5 Hz, 1H), 3.99 (brs, 1H), 4.59 (brs, 1H), 7.15-7.30 (m, 6H), 7.63 (d, *J* = 7.7 Hz, 1H), 8.48-8.54 (m, 2H); ^{13}C-NMR ($CDCl_3$) δ 28.4, 28.5, 39.0, 42.2, 55.0, 59.3, 79.2, 78.0, 123.3, 126.3, 128.3, 129.5, 134.3, 136.1, 136.5, 137.8, 138.4, 148.6, 150.3, 155.6; EIMS (*m*/*z*) 355 (M^+), 135 (100%), 92, 57; HRMS calcd for $C_{21}H_{29}N_3O_2$ 355.2260. Found 355.2263.

(*S*)-*tert*-Butyl {1-[methyl(pyridin-4-ylmethyl)amino]-3-phenylpropan-2-yl}carbamate (20c)

Yield: 61% (as a pale yellow oil); $[\alpha]_D^{25}$ +32.0 (*c* 1.01, $CHCl_3$); ^{1}H-NMR ($CDCl_3$) δ 1.42 (s, 9H), 2.19 (s, 3H), 2.32-2.42 (m, 2H), 2.82-2.92 (brm, 2H), 3.44 (d, *J* = 14.0 Hz, 1H), 3.54 (d, *J* = 14.0 Hz, 1H), 3.40-4.05 (brm, 1H), 4.69 (brs, 1H), 7.16-7.30 (m, 7H), 8.52 (dd, *J* = 1.4 Hz, 4.3 Hz, 2H); ^{13}C-NMR ($CDCl_3$) δ 28.3, 28.4, 39.0, 42.5, 49.3, 56.4, 60.8, 79.1, 121.4, 123.6, 126.3, 128.2, 129.2, 129.4, 137.8, 148.2, 149.6, 155.6; EIMS (*m*/*z*) 355 (M^+), 135 (100%), 92, 57; HRMS calcd for $C_{21}H_{29}N_3O_2$ 355.2260. Found 355.2258.

(*S*)-*tert*-Butyl {1-{methyl[(6-methylpyridin-2-yl)methyl]amino}-3-phenylpropan-2-yl}carbamate (20d)

Yield: 82% (as a pale yellow oil); $[\alpha]_D^{25}$ +11.8 (*c* 1.00, $CHCl_3$); ^{1}H-NMR ($CDCl_3$) δ 1.44 (s, 9H), 2.28 (s, 3H), 2.29-2.43 (m, 2H), 2.55 (s, 3H), 2.76 (dd, *J* = 6.8 Hz, 13.7 Hz, 1H), 2.88-3.02 (brm, 1H), 3.57 (d, *J* = 14.1 Hz, 1H), 3.72 (d, *J* = 14.1 Hz, 1H), 3.40-4.00 (brm, 0.5H), 5.29 (brs, 0.5H), 7.00 (d, *J* = 7.8 Hz, 1H), 7.12-7.28 (m, 6H), 7.52 (t, *J* = 7.8 Hz, 1H); ^{13}C-NMR ($CDCl_3$) δ 24.4, 28.4, 39.1, 42.9, 50.0, 59.6, 63.7, 79.0, 119.9, 121.5, 126.1, 128.2, 129.6, 136.6, 138.2, 155.9, 157.9, 158.5; EIMS (*m*/*z*) 369 (M^+), 149 (100%), 106, 57; HRMS calcd for $C_{21}H_{30}N_3O_2$ 369.2416. Found 369.2429.

(*S*)-*tert*-Butyl{1-{{[4-(dimethylamino)pyridin-2-yl]methyl}(methyl)amino}-3-phenylpropan-2-yl}-carbamate (20e)

Yield: 79% (as a pale yellow oil); $[\alpha]_D^{21}$ +10.6 (*c* 1.00, $CHCl_3$); ^{1}H-NMR ($CDCl_3$) δ 1.42 (s, 9H), 2.28 (s, 3H), 2.33 (dd, *J* = 6.3 Hz, 13.0 Hz, 1H), 2.39 (dd, *J* = 8.2 Hz, 13.0 Hz, 1H), 2.75 (dd, *J* = 7.2 Hz, 13.5 Hz, 1H), 2.90-3.10 (m, 1H), 3.00 (s, 6H), 3.48 (d, *J* = 14.0 Hz, 1H), 3.62 (d, *J* = 14.0 Hz, 1H), 3.89 (brs, 1H), 5.25 (brs, 1H), 6.40 (dd, *J* = 2.9 Hz, 6.3 Hz, 1H), 6.62 (brs, 1H), 7.15-7.27 (m, 5H), 8.16 (d, *J* = 6.3 Hz, 1H); ^{13}C-NMR ($CDCl_3$) δ 28.3, 39.0, 42.8, 49.8, 59.4, 64.1, 78.7, 105.1, 105.2, 126.0, 128.0, 129.4, 138.1, 148.9, 154.8, 155.7, 158.9; EIMS (*m*/*z*) 398 (M^+), 325, 178 (100%), 135, 91, 57; HRMS calcd for $C_{23}H_{34}N_4O_2$ 398.2682. Found 398.2698.

Typical procedure for deprotection of Boc group in 20.

To a stirred solution of **20b** (3.00 g, 8.40 mmol) in CH_2Cl_2 (25 mL) was added TFA (8.70 mL, 113 mmol) in an ice bath. After removing the ice bath, the mixture was stirred at rt for 34 h, then extracted with H_2O. The combined aqueous layer was basified by granular NaOH and extracted with CH_2Cl_2. The combined organic layer was washed with saturated aqueous $NaHCO_3$ and brine, then dried (Na_2SO_4). The solvent was removed under reduced pressure and the residue was chromatographed ($MeOH/CHCl_3/NH_4OH$ = 10/20/0.1, v/v) to afford **13b** 1.60 g (74%) as a pale yellow oil.

(*S*)-*N*^{1}-Methyl-3-phenyl-*N*^{1}-(pyridin-3-ylmethyl)propane-1,2-diamine (13b)

$[\alpha]_D^{25}$ +21.6 (*c* 1.01, $CHCl_3$); ^{1}H-NMR ($CDCl_3$) δ 1.65 (brs, 2H), 2.18 (s, 3H), 2.32-2.44 (m, 2H), 2.47 (dd, *J* = 8.7 Hz, 13.5 Hz, 1H), 2.75 (dd, *J* = 4.8 Hz, 13.5 Hz, 1H), 3.18-3.25 (m, 1H), 3.48 (d, *J* = 13.0 Hz, 1H), 3.57 (d, *J* = 13.5 Hz, 1H), 7.19-7.32 (m, 6H), 7.64 (d, *J* = 7.7 Hz, 1H), 8.50 (dd, *J* = 1.4 Hz, 4.3 Hz, 1H), 8.54 (d, *J* = 1.5Hz, 1H); ^{13}C-NMR ($CDCl_3$) δ 42.20, 42.23, 50.1, 60.1, 64.3, 123.3, 126.2, 128.4, 129.2, 134.5, 136.5, 139.2, 148.5, 150.3; EIMS (*m*/*z*) 255 (M^+), 164, 135, 120, 93 (100%), 92; HRMS calcd for $C_{16}H_{21}N_3$ 255.1735. Found 255.1730.

(*S*)- *N*^{1}-Methyl-3-phenyl-*N*^{1}-(pyridin-2-ylmethyl)propane-1,2-diamine (13a)

Yield: 71% (as pale yellow oil); $[\alpha]_D^{25}$ +28.7 (*c* 1.00, $CHCl_3$); ^{1}H-NMR ($CDCl_3$) δ 1.61 (brs, 2H), 2.28 (s, 3H), 2.40-2.50 (m, 3H), 2.76 (dd, *J* = 4.3 Hz, 13.5 Hz, 1H), 3.18-3.26 (m, 1H), 3.63 (d, *J* = 14.0 Hz, 1H), 3.76 (d, *J* = 15.0 Hz, 1H), 7.13-7.33 (m, 4H), 7.27-7.32 (m, 2H), 7.44 (d, *J* = 8.2 Hz, 1H), 7.65 (dt, *J* = 1.4 Hz, 7.2 Hz, 1H), 8.53 (d, *J* = 4.8 Hz, 1H); ^{13}C-NMR ($CDCl_3$) δ 42.1, 42.9, 50.1, 64.37, 64.40, 121.9, 122.9, 126.1, 128.4, 129.2, 136.4, 139.2, 149.0, 159.4; EIMS (*m*/*z*) 255 (M^+), 164, 135 (100%), 120, 92; HRMS calcd for $C_{16}H_{21}N_3$ 255.1735. Found 255.1745.

(*S*)-*N*^{1}-Methyl-3-phenyl-*N*^{1}-(pyridin-4-ylmethyl)propane-1,2-diamine (13c)

Yield: 73% (as pale yellow oil); $[\alpha]_D^{25}$ +24.0 (*c* 1.01, $CHCl_3$); ^{1}H-NMR ($CDCl_3$) δ 1.62 (brs, 2H), 2.20 (s, 3H), 2.37 (d, *J* = 6.3 Hz, 2H), 2.48 (dd, *J* = 8.8 Hz, 13.7 Hz, 1H), 2.76 (dd, *J* = 4.9 Hz, 13.7 Hz, 1H), 3.16-3.26 (m, 1H), 3.47 (d, *J* = 14.1 Hz, 1H), 3.58 (d, *J* = 14.1 Hz, 1H), 7.19-7.33 (m, 7H), 8.53 (dd, *J* = 1.5 Hz, 4.4 Hz, 2H); ^{13}C-NMR ($CDCl_3$) δ 42.2, 42.5, 50.1, 61.7, 64.5, 123.7, 126.3, 128.4, 129.2, 139.1, 148.4, 149.8; EIMS (*m*/*z*) 255 (M^+), 164, 135, 120, 93 (100%), 92; HRMS calcd for $C_{16}H_{21}N_3$ 255.1735. Found 255.1722.

(*S*)-*N*^{1}-Methyl-*N*^{1}-[(6-methylpyridin-2-yl)methyl]-3-phenylpropane-1,2-diamine (13d)

Yield: 77% (as a pale yellow oil); $[\alpha]_D^{25}$ +35.3 (*c* 1.00, $CHCl_3$); ^{1}H-NMR ($CDCl_3$) δ 1.70 (brs, 2H), 2.28 (s, 3H), 2.40 (d, *J* = 6.0 Hz, 2H), 2.46 (dd, *J* = 8.8 Hz, 13.2 Hz, 1H), 2.53 (s, 3H), 2.76 (dd, *J* = 4.5 Hz, 13.2 Hz, 1H), 3.17-3.25 (m, 1H), 3.59 (d, *J* = 14.1 Hz, 1H), 3.72 (d, *J* = 14.1 Hz, 1H), 7.01 (d, *J* = 7.3 Hz, 1H), 7.19-7.29 (m, 6H), 7.54 (t, *J* = 7.4 Hz, 1H); ^{13}C-NMR ($CDCl_3$) δ 24.2, 42.1, 42.8, 50.0, 64.26, 64.31, 119.5, 121.2, 125.9, 128.2, 129.0, 136.4, 139.2, 157.3, 158.7; EIMS (*m*/*z*) 269 (M^+), 149 (100%), 106; HRMS calcd for $C_{17}H_{23}N_3$ 269.1892. Found 269.1900.

(*S*)-*N*^{1}-{[4-(Dimethylamino)pyridin-2-yl]methyl}-*N*^{1}-methyl-3-phenylpropane-1,2-diamine (13e)

Yield: 51% (as a pale yellow oil); $[\alpha]_D^{25}$ +17.7 (*c* 1.00, $CHCl_3$); ^{1}H-NMR ($CDCl_3$) δ 1.60 (brs, 2H), 2.30 (s, 3H), 2.40 (d, *J* = 6.8 Hz, 2H), 2.46 (dd, *J* = 8.7 Hz, 13.5 Hz, 1H), 2.77 (dd, *J* = 4.8 Hz, 13.5 Hz, 1H), 2.99 (s, 6H), 3.16-3.25 (m, 1H), 3.51 (d, *J* = 14.0 Hz, 1H), 3.64 (d, *J* = 14.0 Hz, 1H), 6.39 (dd, *J* = 2.4 Hz, 5.8 Hz, 1H), 6.70 (d, *J* = 2.4 Hz, 1H), 7.19-7.22 (m, 3H), 7.26-7.31 (m, 2H), 8.15 (d, *J* = 5.8 Hz, 1H); ^{13}C-NMR ($CDCl_3$) δ 39.0, 42.2, 43.1, 50.1, 64.5, 64.7, 105.20, 105.22, 126.0, 128.3, 129.2, 139.4, 149.0, 154.8, 159.3; EIMS (*m*/*z*) 298 (M^+), 254, 178, 136 (100%), 120, 91, 44; HRMS calcd for $C_{18}H_{26}N_4$ 298.2157. Found 298.2158.

Typical procedure for the aldol reaction of 5.

A stirred mixture of **5** (100 mg, 0.476 mmol), **13a** (121 mg, 0.476 mmol) and TFA (92 mg, 0.809 mmol) in DMSO (1 mL) was heated at 90 °C for 60 h. After cooling, saturated aqueous $NaHCO_3$ was added to the mixture, then extracted with AcOEt. The combined organic layer was washed with brine and dried (Na_2SO_4). The solvent was removed under reduced pressure and the residue was chromatographed (AcOEt/hexane = 1/3, v/v) to afford (*R*)-**3b** 58 mg (59%) as pale yellow crystals. All of the spectroscopic data were identical to those of (*R*)-**3b** previously reported.[1a] According to the known method,[1a] the optical purity of the obtained (*R*)-**3b** was determined to be 72% ee by HPLC equipped with a chiral stationary phase column. HPLC conditions; column: Chiralpak AS-H, mobile phase: EtOH/hexane = 10/90 (v/v), detection: UV 254 nm, flow rate: 1.0 mL/min, *R*t = 9.09 min for (*R*)-**3b** and 10.1 min for (*S*)-**3b**.

ACKNOWLEDGEMENTS

This work was supported by a Grant-in-Aid for Scientific Research from the Ministry of Education, Culture, Sports, Science and Technology of the Japanese Government.

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22. Some peaks of the new compounds (**19**-**20**) in ^{1}H-NMR spectra were observed as the very broad signals. Also, there were some slightly different signals due to the isomers in ^{13}C-NMR spectra. Since no other signals due to the isomers in **13** were observed after the deprotection of Boc group, these results suggested that we detected the corresponding rotamers based on the Boc group in **19**-**20**.