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A NEW CHIRAL SYNTHESIS OF A BICYCLIC ENEDIONE CONTAINING A SEVEN-MEMBERED RING MEDIATED BY A COMBINATION OF CHIRAL AMINE AND BRØNSTED ACID

Takashi Nagamine, Kohei Inomata,* and Yasuyuki Endo*

Tohoku Pharmaceutical University, 4-4-1 Komatsushima, Aoba-ku, Sendai 981-8558, Japan, E-mail: inomata@tohoku-pharm.ac.jp

This paper is dedicated to Professor Ryoji Noyori on the occasion of his 70th birthday.

Abstract – Several chiral amines bearing a heterocyclic moiety such as pyrrolidine, piperazine or tetrazole were prepared from L-phenylalanine. The enantioselectivity of the intramolecular asymmetric aldol reaction mediated by a combination of the synthetic chiral amine and a Brønsted acid to construct an enedione containing a seven-membered ring was examined in detail. A remarkable increase of enantioselectivity depending on the amount of Brønsted acid was observed.

Wieland-Miescher ketone (**1a**) and its homologues (**1b**) and (**2**), which include carbobicyclic enediones, have been highly useful synthons in the total synthesis of a variety of natural products (Figure 1).[1-4] These useful enediones have been easily prepared from corresponding triones (**4**) by amino acid-mediated asymmetric intramolecular aldol reactions.[5-7] This asymmetric aldol reaction was first reported by Hajos et al and has been widely recognized to involve an enamine-based mechanism.[8, 9] In a variety of amino acids, the aldol reaction of **4a** and **4c** was mediated by L-proline (L-Pro, **5**) to afford **1a** and **2a** in high yield and high ee, respectively.[5] The reaction of **4a** and **4c** mediated by L-phenylalanine (L-Phe, **6**) has also been reported and shown to be accompanied by a lower ee.[5c] Uda and Hagiwara successfully extended the reaction of **4d** using L-Phe (**6**) in the presence of a Brønsted acid such as camphorsulfonic acid (CSA) to construct a Wieland-Miescher ketone homologue (**1b**) bearing a methyl substituent at C-1.[7e] Although the reactions of **4b** and **4d** to prepare enediones (**1b**, **2b**) have been successfully mediated by a variety of primary amino acids such as L-Phe, L-valine and L-alanine,[5c,7d] the attempt using L-Pro containing a secondary amine moiety has hardly been successful. Those reactions of trione **4** mediated by L-amino acid afforded the products **1** or **2** whose absolute configurations at the quaternary carbon were

invariably *S* (Scheme 1).[5, 10] However, there has been little development of this reaction for the purpose of constructing new ring systems such as enedione (**3**) encompassing a 7-membered carbocycle.[11-14] Since many pharmaceutically important natural products containing a 7-membered carbocycle have been isolated,[15] enedione (**3**) has been attractive as a potential chiral synthon to achieve total synthesis of these products.

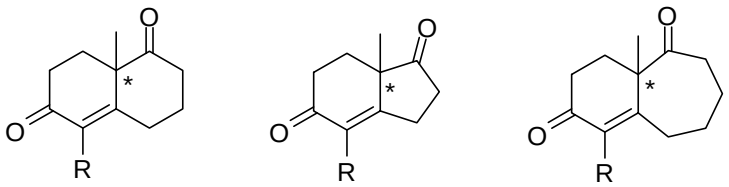
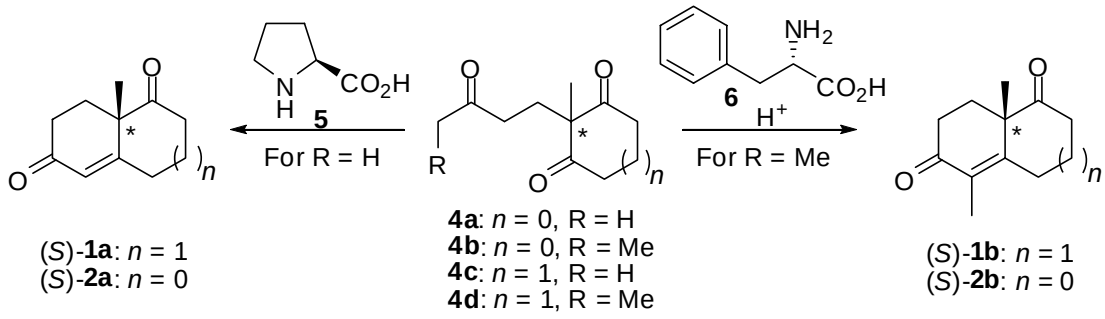


Figure 1

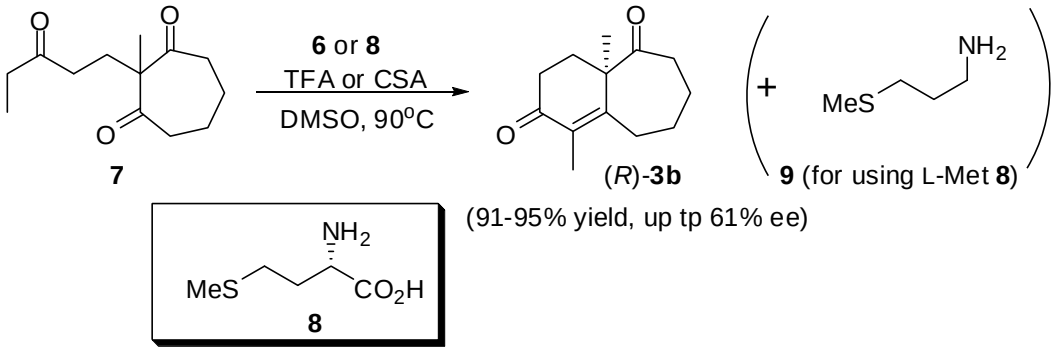


Scheme 1

Recently, we reported the L-Methionine (L-Met, **8**)- or L-Phe-mediated asymmetric intramolecular aldol reaction of trione (**7**) in the presence of CSA or trifluoroacetic acid (TFA) as a Brønsted acid to prepare a new bicyclic enedione [(*R*)-**3b**] containing a 7-membered ring.[14] Strikingly, the process was characterized by an inversion of enantioselectivity when compared with the similar reaction using the trione (**4d**). However, the ee value of the reaction to afford (*R*)-**3b** was only moderate (Scheme 2). In addition to the moderate ee value, a catalytic process of the reaction was not successful due to the easy decarboxylation of L-Met during the reaction to afford an achiral primary amine (**9**).[16] This result means that an amino acid is not always a suitable mediator for this type of reaction. In connection with an ongoing synthetic project, we need to improve this method.

On the other hand, in the area of organocatalysis,[17] chiral amines, especially based on an L-Pro structure, have been employed as new catalysts to achieve highly efficient asymmetric reactions, including intra- and intermolecular aldol reactions.[18, 19] Amine-Brønsted acid catalysis has also been utilized in asymmetric cycloaddition[20] and 1,4-addition reactions[21, 22] to construct new chiral centers. In those studies, the authors reported that an ammonium moiety produced from amine and Brønsted acid plays a key role in stabilizing the transition state as a result of hydrogen bonding between the catalyst and the

substrate. This means that an ammonium counterpart in the chiral amine catalysts becomes a powerful hydrogen bonding donor working like a carboxylic acid in an amino acid catalyst to stabilize a transition state in important asymmetric reactions. However, to our knowledge, there have been few attempts to use amine catalysts in the intramolecular aldol reaction to construct Wieland-Miescher ketone and its homologues,[23] so our goal was to use some known or new chiral amines (**10**) based on a structure of L-Phe to synthesize **3b** more efficiently. Specifically, we attempted to use chiral amines such as **11**[20a, 24] and **12**,[25] which were easily prepared from L-Phe, containing pyrrolidine, piperazine and tetrazole heterocycles for the aldol reaction of **7** in the presence of a Brønsted acid (Figure 2). We report here the new reaction conditions mediated by a combination of Brønsted acid and several amines **11** and **12** to afford (*R*)-**3b** with higher ee than those reported previously.



Scheme 2

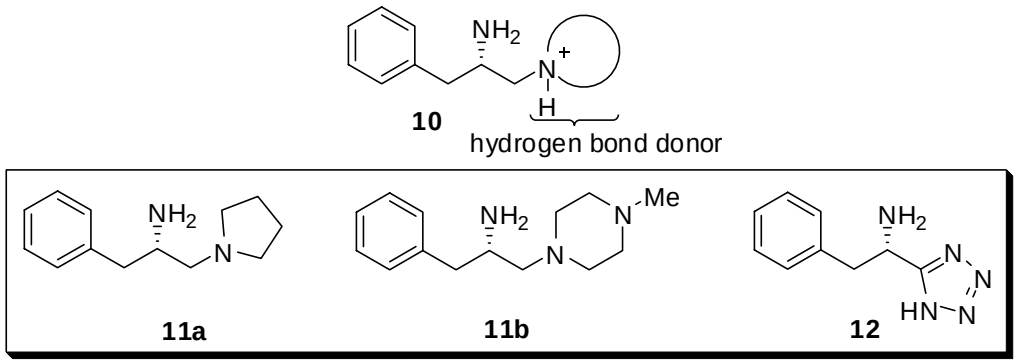
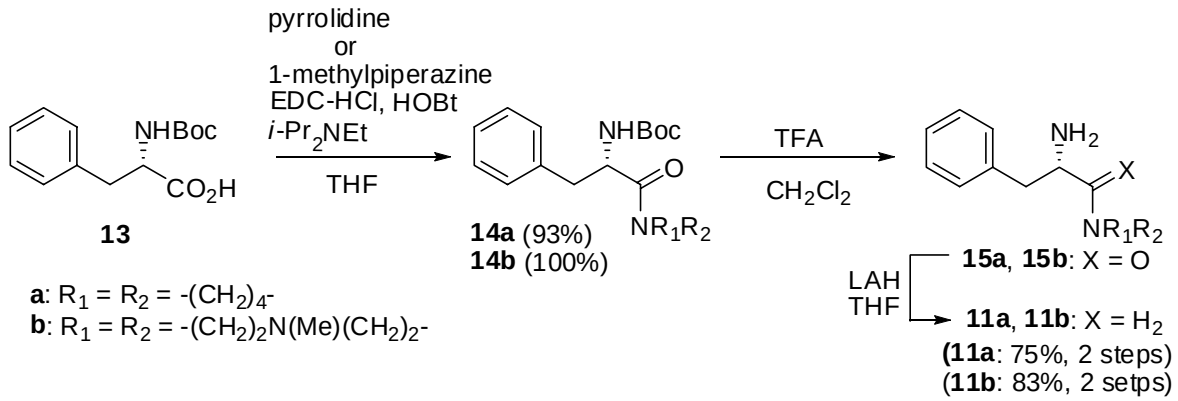


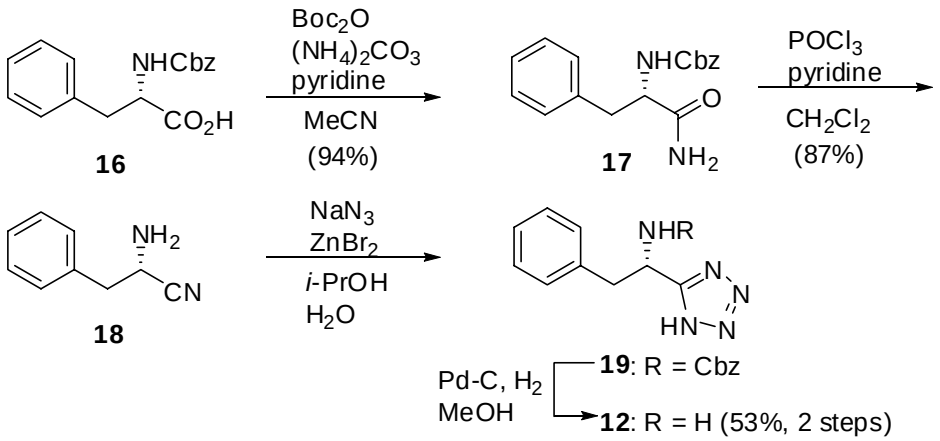
Figure 2

In a similar synthesis reported by Seto,[26b] chiral amines (**11**) were prepared from *N*-*tert*-butyloxy-L-Phe (*N*-Boc-L-Phe, **13**). Thus, **13** was converted to corresponding amide (**14**)[26] by the use of a standard coupling reaction with pyrrolidine or 1-methylpiperazine in the presence of 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDC) in high yield, respectively. After deprotection of the Boc-moiety in an acidic condition, the resulting amide (**15**) was reduced by lithium aluminium hydride (LAH) to afford a known diamine (**11a**) and a new one (**11b**), respectively (Scheme 3).

Preparation of **12** bearing tetrazole was achieved in a similar way with the synthesis of (*S*)-5-pyrrolidine-2-yl-1*H*-tetrazole.[27] *N*-Cbz-L-Phe (**16**) was first converted to amide (**17**)[28] by the coupling reaction in the presence of di-*tert*-butyldicarbonate (Boc_2O) in 94% yield.[28b] The dehydration of an amide using phosphorus (V) oxychloride in the presence of pyridine afforded nitrile (**18**) in 87% yield.[29] According to Sharpless's method,[30b] 1,3-dipolar cycloaddition of sodium azide to construct a tetrazole unit was easily achieved to afford known **19**,[30] which was next deprotected by a hydrogenolysis condition using a palladium carbon catalyst, to afford the desired **12** at 53% yield in 2 steps (Scheme 4).



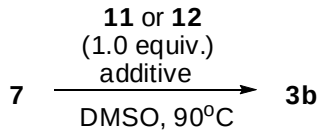
Scheme 3



Scheme 4

We examined the effects of prepared chiral amines (**11**) and (**12**) on the aldol reaction of the trione (**7**). All of the reactions were carried out under the same conditions in the presence of a stoichiometric amount of amine with or without TFA in DMSO at 90°C. The results are compiled in Table 1. First of all, the aldol reaction mediated by an amine **11** or **12** without Brønsted acid afforded **3b** at a moderate or slightly high yield accompanied with quite low ee (entries 1, 6, and 10). The reaction using **11a** in the presence of 1.0 equivalent of TFA as a Brønsted acid showed a slightly improved yield and better enantioselectivity for (*S*)-**3b** (entry 2).[31] We next examined the amount effects of TFA on the reaction using **11a**. The

reactions of **11a** in the presence of 1.5 equiv. or 2.0 equiv. of TFA, respectively, inverted the enantioselectivity of the resulting **3b** and increased the ee value, depending on the amount of TFA. The use of (+)-camphorsulfonic acid (CSA) as an additive was not successful, because a slower reaction and lower ee than entry 4 were observed (entry 5). The absolute configuration of the product (**3b**) in entry 4 was assigned as *R* by comparison with the optical rotation of (*R*)-**3b** reported previously.[14] Specifically, the optical rotation of product (*R*)-**3b** in entry 4 was $[\alpha]_D$ –59.8 ($CHCl_3$, 70% ee), lit.[14a] $[\alpha]_D$ –83.4 ($CHCl_3$, >99% ee). In the case of **11b**, the addition of 2.0 equiv. of TFA greatly improved both the yield and ee of **3b** compared to entry 6, but a prolonged reaction time was observed (entry 8). Since **11b** had a triamine structure, we also examined the condition in the presence of 3.0 equiv. of TFA. However, the reaction proceeded very slowly and a remarkable improvement of the enantioselectivity was not observed (entry 9). In the case of using **12**, the reaction proceeded very smoothly to afford (*R*)-**3b** at high yield accompanied with moderate ee (entries 11-13).



Entry	Amine	Additive (equiv.)	Time (h)	Yield[a, b] (%)	Ee[c] (%)	Config.[d]
1	**11a**	none	32	65	1.5	*S*
2	**11a**	TFA (1.0)	17	85	18	*S*
3	**11a**	TFA (1.5)	10	95	34	*R*
4	**11a**	TFA (2.0)	10	91	70	*R*
5	**11a**	(+)-CSA (2.0)	72	71 (82)	45	*R*
6	**11b**	none	39	67	3	*R*
7	**11b**	TFA (1.0)	24	85	7	*S*
8	**11b**	TFA (2.0)	123	88	69	*R*
9	**11b**	TFA (3.0)	96	71 (78)	67	*R*
10	**12**	none	6	86	18	*S*
11	**12**	TFA (0.5)	8	91	38	*R*
12	**12**	TFA (1.0)	9	95	57	*R*
13	**12**	TFA (1.5)	24	89	56	*R*
14[e]	**11a**	TFA (0.6)[f]	21	90	56	*R*
15[g]	**11a**	TFA (2.0)	138	93	84	*R*

[a] Isolated yield.

[b] Yields in parentheses were based on the recovery of starting **7**.

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

[d] Absolute configuration of a major enantiomer of **3b**.

[e] Catalytic amount of **11a** (0.3 equiv.) was used as a mediator.

[f] 2.0 equiv. of TFA to amine (**11a**) was used.

[g] Reaction was carried out at 50°C.

Table 1

Next, we tried to extend this process to a catalytic version. The reaction using 0.3 equiv of **11a** in the presence of 0.6 equiv of TFA in DMSO at 90 ^{o}C afforded (*R*)-**3b** in high yield but accompanied by lower ee than that of entry 4 (entry 14). This result means that the catalytic reaction using **11a** was not very effective. Finally, we examined the reaction temperature. Although the reaction using **11a** at 50^{o}C prolonged the reaction time, using this temperature we succeeded in improving the enantioselectivity greatly, accompanied by a high yield (entry 15). The 84% ee observed in entry 15 was the highest enantioselectivity to afford **3b** in our present and previous experiments. A reaction temperature less than 50^{o}C was not practical because the reaction hardly proceeded. Since we previously reported that we could obtain optically pure material of **3b** by fractional recrystallization from (*R*)-**3b** over 68% ee, the achieved 84% ee of **3b** was enough optical purity to provide an enantiopure material as a chiral synthon. Based on these results, we considered our chiral synthesis of (*R*)-**3b** to be better than the methods reported previously by us.[14]

In the aldol reaction of **7**, there exists the possibility of producing eight stereoisomers as a result of three newly generated stereogenic centers. Since we could not isolate the initially formed β-hydroxy ketones under the conditions using a chiral amine **11** or **12**, dehydration to afford **3b** must occur rapidly. The transition states predicted for the stereoisomers are shown in Figure 3. In the presence of enough Brønsted acid such as a condition using 2.0 equiv. of TFA, the amino moiety in **11** would be protonated to generate a corresponding ammonium salt. We think that this hydrogen in the ammonium salt could form a hydrogen bond to the β-oxygen atom originating from ketone functionality and a nitrogen atom in the enamine moiety to stabilize the transition state. Among these hydrogen-bonding models, two of the *syn* (*syn*, *anti*: conformation between olefinic and ammonium moieties) transition states (**25**) and (**27**), which will afford aldol products (**21**) and (**23**), respectively, are considered to be slightly higher in energy because of relatively unstable chair-boat conformations in the 6,6-fused-bicycle, resembling bicyclo[3.3.1]nonane, while the *anti* transition states (**24**) and (**26**), which will afford **20** and **22**, respectively, have chair-chair conformations. Kwon *et al*. reported that a chair-chair conformation in bicyclo[3.3.1]nonane is more stable than a chair-boat conformation.[32,33] They also showed that the free energy difference between those two conformers in bicyclo[3.3.1]nonane is 2.3-2.5 kcal/mol by means of *ab* initio and density functional theory (DFT) calculations. Thus, the aldol reaction should proceed through *anti* transition states, (**24**) and/or (**26**). In comparison with the *trans*-*anti* (*cis*, *trans*: *cis*- or *trans*-fused carbocycles) transition state (**24**) and the *cis*-*anti* one (**26**), **26** appears to be disfavored because of steric repulsion between the methyl enamine and a 7-membered carbocycle in **26**. Consequently, the *trans*-*anti* transition state (**24**) should be most favored, affording the aldol product (**20**), which would give rise to (*R*)-**3b** after dehydration (Figure 3).

When no or poor Brønsted acid was used, lower ee of the resulting **3b** was noted (Table 1). This result indicates that the reaction with a poor acid could not generate hydrogen bonds and the amino moiety in a

side chain would be oriented away from the C-C bond forming site. Since the three favorable transition states (**28**), (**29**), and (**31**), which would afford **20**, **21**, and **23**, respectively, might have very similar potential energy, no or lower enantioselectivity was observed (Figure 4). Among the proposed transition states, the *cis-anti* one (**30**) is considered to be slightly higher energy due to the same steric repulsion described above. To date, we have no evidence to suggest which transition state is more stable. Further investigations into the effects of Brønsted acids, and calculations of the energy differences of our proposed transition states are currently under way.

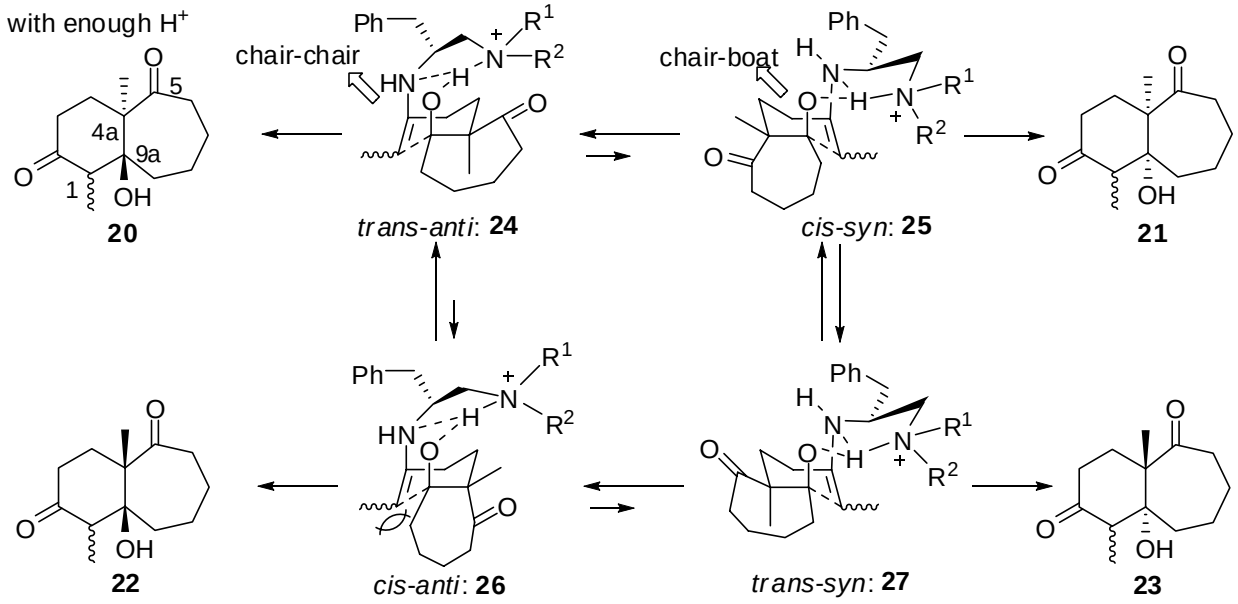


Figure 3

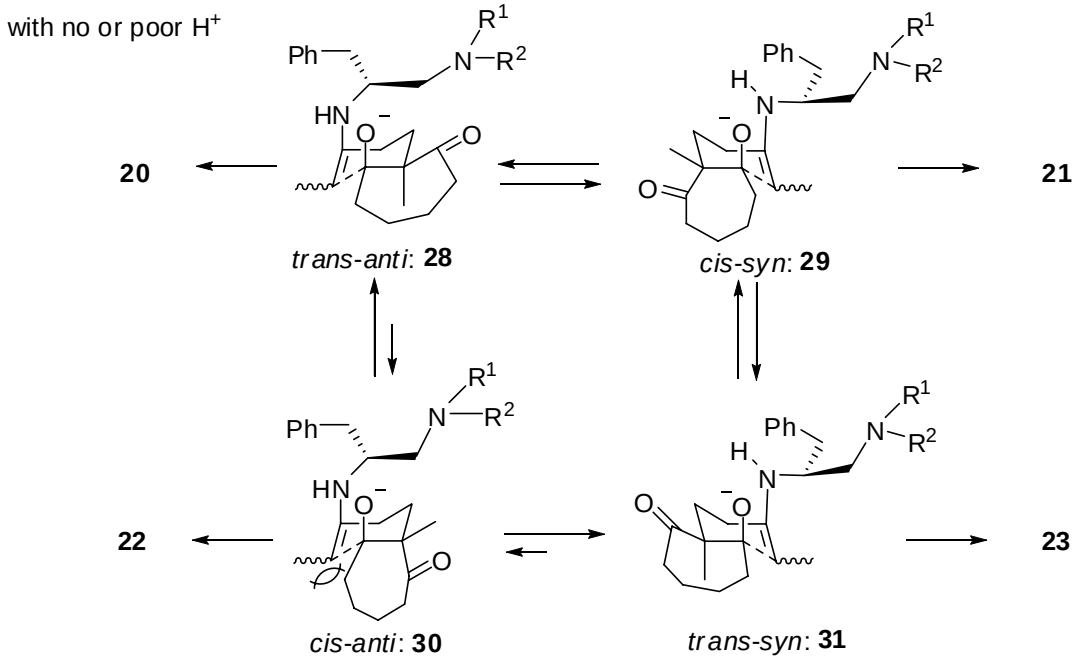


Figure 4

In conclusion, we have established a procedure to prepare new and known chiral amines based on a structure of L-Phe. We also have established an alternative chiral route to provide (*R*)-**3b** by using the combination of synthetic chiral amine and Brønsted acid. In the reaction, an interesting inversion of enantioselectivity depending on the amount of a Brønsted acid was observed. Furthermore, under optimized conditions, we have achieved the synthesis of (*R*)-**3b** with over 80% ee for the first time. These results may enable the creation of efficient organocatalysts for a wide variety of asymmetric reactions. Further work on a detail of the reaction mechanism and the development of a more efficient mediator for the reactions is currently in progress.

EXPERIMENTAL

Melting points are uncorrected. IR spectra were recorded on a JASCO FT–IR 5000 spectrometer. ^{1}H NMR spectra and ^{13}C NMR spectra were recorded on a JEOL AX–400 (^{1}H 400 MHz, ^{13}C 100 MHz) spectrometer and calibrated using trimethysilane as the internal standard. Mass spectra were recorded on a JEOL DX–303 or a JEOL JMS-MS700 spectrometer. Elemental analysis was done with a Perkin Elmer CHN-2400 II. Enantiomeric excesses were determined with a Waters HPLC 600 instrument equipped with a chiral stationary phase column. Optical rotations were measured with a JASCO DIP–370 digital polarimeter.

Typical procedure of coupling reaction

To a stirred solution of the *N*-Boc-L-Phe (**13**) (3 g, 11.3 mmol), 1-hydroxybenzotriazole (HOBt) (1.83 g, 13.5 mmol), EDC hydrochloride (2.60 g, 13.6 mmol) and diisopropylethylamine (*i*-Pr_2NEt) (2.36 mL, 13.6 mmol) in THF (30 mL) was added pyrrolidine (0.67 mL, 13.6 mmol) at 0^{o}C and the mixture was stirred at rt for 24h. H_2O (10 mL) was added to the mixture to quench the reaction. The mixture was extracted with ethyl acetate (AcOEt), was washed with brine, and was dried (Na_2SO_4). The solvent was removed under reduced pressure. The residue was chromatographed on silica gel (AcOEt/hexane = 1/2) to afford **14a** 3.3 g (93%) as colorless oil.

tert-Butyl (*S*)-1-oxo-3-phenyl-1-(pyrrolidin-1-yl)propan-2-carbamate (14a)

$[\alpha]_D^{20}$ +37.5 (*c* 1.0, $CHCl_3$), lit.,[26a] $[\alpha]_D^{25}$ +39.3 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28-7.20 (m, 5 H), 5.42 (d, *J* = 8.8 Hz, 1 H), 4.59 (q, *J* = 8.5 Hz, 1 H), 3.46-3.26 (m, 3 H), 3.00 (dd, *J* = 6.0, 12.8 Hz, 1 H), 2.94 (dd, *J* = 9.4, 12.6 Hz, 1 H), 2.59-2.52 (m, 1 H), 1.77-1.47 (m, 4 H), 1.42 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.9, 155.0, 136.6, 129.4, 128.3, 126.8, 79.5, 53.6, 46.2, 45.6, 40.2, 28.3, 25.7, 23.9; EI MS: *m/z* 318 (M^+), 120 (100%); HRMS calcd for $C_{18}H_{26}N_3O_3$: 318.1943, found: 318.1947.

tert-Butyl (*S*)-1-oxo-3-phenyl-1-(4-methylpiperazin-1-yl)propan-2-carbamate (14b)

Yield 100% (colorless oil); $[\alpha]_D^{21}$ +4.7 (*c* 1.1, MeOH); IR (film) ν cm^{-1} 3432, 3296, 3062, 3029, 2977, 2938, 2798, 1708, 1643, 1523, 1496, 1455, 1392, 1367, 1293, 1250, 1171, 1051, 1024, 1003, 867, 753, 701; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30-7.17 (m, 5 H), 5.43 (d, *J* = 8.8 Hz, 1 H), 4.82 (q, *J* = 7.9 Hz, 1

H), 3.62-3.46 (m, 2 H), 3.33-3.27 (m, 1 H), 3.02-2.09 (m, 3 H), 2.34-2.12 (m, 3 H) 2.22 (s, 3 H), 1.77-1.73 (m, 1 H), 1.42 (s, 9 H); ^{13}C NMR (100MHz, $CDCl_3$) δ 169.8, 154.9, 136.4, 129.5, 128.4, 126.8, 79.5, 54.3, 54.2, 50.8, 45.7, 45.2, 41.7, 40.3, 28.2, EI MS: *m/z* 347 (M^+, 100%); HRMS calcd for $C_{19}H_{29}N_3O_3$: 347.2209, found: 347.2200.

Typical procedure of deprotection of 14 and reduction of amide (15)

To a stirred solution of **14a** (3.33 g, 10.4 mmol) in CH_2Cl_2 (20 mL) was added TFA (10 mL, 57.1 mmol) at 0^{o}C. After stirring the mixture for 1h, the solvent was removed under reduced pressure. The residue was dissolved to CH_2Cl_2, and then the mixture was washed with brine and was dried (Na_2SO_4). The solvent was removed under reduced pressure to afford crude **15a**, which was used in the next reaction without further purification. To a stirred suspension of LAH (0.7 g, 18.5 mmol) in THF (10 mL) was added a solution of the crude **15a** in THF (20 mL) over 10 min at 0^{o}C. The mixture was heated to reflux for 13h and then quenched with H_2O at 0^{o}C. After stirring the mixture at rt for 2h, it was filtered through a Celite pad and the filtrate was evaporated under reduced pressure. The residue was chromatographed ($CHCl_3$/MeOH/NH_4OH = 200/10/1 to 100/10/1) to afford **11a** 1.6 g (75%) as pale yellow oil.

(*S*)-1-Phenyl-3-(pyrroidin-1-yl)propyl-2-amine (11a)

$[\alpha]_D^{21}$ +15.4 (*c* 1.0, $CHCl_3$), lit.,[20a] $[\alpha]_D^{27}$ +16.2 (*c* 1.1, $CHCl_3$); IR (film) ν cm^{-1} 3370, 3305, 2963, 2927, 2875, 2785, 1602, 1584, 1495, 1454, 746, 701; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32-7.28 (m, 2 H), 7.23-7.19 (m, 3 H), 3.15 (m, 1 H), 2.78 (dd, *J* = 4.6, 13.4 Hz, 1 H), 2.62-2.39 (m, 6 H), 2.31 (dd, *J* = 4.2, 11.8 Hz, 1 H), 1.81-1.70 (m, 4 H) 1.43 (br s, 2 H, D_2O exchangeable); ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.5, 129.3, 128.4, 126.1, 63.2, 54.4, 51.3, 42.6, 23.5; EI MS: *m/z* 204 (M^+), 84 (100%); HRMS calcd for $C_{13}H_{20}N_2$: 204.1626, found: 204.1624.

(*S*)-1-(4-Methylpiperazin-1-yl)-3-phenylpropyl-2-amine (11b)

Yield 83% (pale yellow oil); $[\alpha]_D^{21}$ +16.1 (*c* 1.0, $CHCl_3$); IR (film) ν cm^{-1} 3366, 3084, 3061, 3026, 2937, 2795, 1602, 1495, 1457 1283, 1166, 1014, 747, 701; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32-7.28 (m, 2 H), 7.23-7.20 (m, 3 H), 3.19 (m, 1 H), 2.74 (dd, *J* = 4.4, 13.2 Hz, 1 H), 2.68-2.21 (br m, 8 H), 2.47 (dd, *J* = 8.8, 13.2 Hz, 1 H), 2.34-2.21 (m, 2 H), 2.28 (s, 3 H), 1.53 (br s, 2 H, D_2O exchangeable); ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.1, 129.1, 128.2, 126.0, 64.6, 55.1, 53.3, 49.0, 45.9, 42.0; EI MS: *m/z* 233 (M^+), 133 (100%); HRMS calcd for $C_{14}H_{23}N_3$: 233.1892, found: 233.1888.

(*S*)-*N*-Benzyloxycarbonylphenylalanine amide (17)

To a stirred solution of *N*-Cbz-L-Phe (5 g, 16.7 mmol) and pyridine (0.85 mL, 10.5 mmol) in MeCN (50 ml) was added Boc_2O (5 ml, 21.7 mmol) and anmmonium carbonate 1.66 g (21.1 mmol) at 0^{o}C. After stirring the mixture at rt for 22h, H_2O was added to it at 0^{o}C. The mixture was extracted with Et_2O, was washed with brine and was dried (Na_2SO_4). The solvent was removed under reduced pressure. The residue was chromatographed (hexane/AcOEt = 1/1 to 1/3) to afford **17** 4.67 g (94%) as a colorless solid.

Mp 162-163°C (colorless needles from AcOEt); $[\alpha]_D^{22}$ -6.5 (*c* 1.0, MeOH), lit.,[28a] $[\alpha]_D^{25}$ -6.8 (*c* 1.0, MeOH); IR (KBr), ν, cm^{-1} 3419, 3319, 3201, 1692, 1659, 1610, 1535, 748, 699; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38-7.20 (m, 10 H), 5.64 (br s, 1 H), 5.33 (br s, 2 H), 5.09 (s, 2 H), 4.50-4.35 (m, 1 H), 3.14 (dd, *J* = 6.2, 13.4, 1 H), 3.05 (dd, *J* = 7.3, 13.4, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.1, 156.0, 136.3, 136.0, 129.3, 128.8, 128.6, 128.3, 128.0, 127.2, 67.1, 55.8, 38.4; EI MS: *m/z* 298 (M^+), 91 (100 %); HRMS calcd for $C_{17}H_{18}N_2O_3$: 298.1317, found: 298.1315; Anal. Calcd for $C_{17}H_{18}N_2O_3$: C, 68.44; H, 6.08; N, 9.39. Found: C, 68.45; H, 6.03; N, 9.42.

(*S*)-1-Benzyloxycarbonylamino-2-phenylpropionitrile (18)

To a stirred solution of **17** (1 g, 3.36 mmol) in pyridine (4.2 mL) and CH_2Cl_2 (0.8 mL) was added phosphorus (V) oxychloride (0.42 mL, 4.47 mmol) at -10°C. After stirring the mixture for 1h at the same temperature, it was poured into H_2O and was extracted with AcOEt. The combined organic layer was washed with brine and was dried (Na_2SO_4). The solvent was removed under reduced pressure. The residue was chromatographed (hexane/AcOEt = 5/1) to afford **18** 820 mg (87%).

Mp 132-133 °C (Colorless needles from hexane/CH_2Cl_2); $[\alpha]_D^{25}$ -66.4 (*c* 0.75, DMF), lit.,[30a] $[\alpha]_D^{27}$ -66 (*c* 0.95, DMF); IR (KBr), ν, cm^{-1} 3326, 1697, 1535, 743, 695; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40-7.30 (m, 8 H), 7.27-7.25 (m, 2 H), 5.13 (s, 2 H), 5.06 (br s, 1 H), 4.95-4.83 (m, 1 H), 3.13 (dd, *J* = 5.8, 13.8, 1 H), 3.06 (dd, *J* = 7.0, 13.8, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.9, 135.5, 133.6, 129.4, 128.9, 128.6, 128.4, 128.2, 127.9, 118.0, 67.6, 43.7, 38.9; EI MS: *m/z* 280 (M^+), 91 (100 %); HRMS calcd for $C_{17}H_{16}N_2O_2$: 280.1212, found: 280.1216; Anal. Calcd for $C_{17}H_{16}N_2O_2$: C, 72.84; H, 5.75; N, 9.99. Found: C, 72.81; H, 5.72; N, 10.09.

(*S*)-1-Amino-2-phenylethyl-1-2*H*-tetrazole (12)

To a stirred solution of **18** (2 g, 7.14 mmol) in 2-propanol (15 mL) and H_2O (30 mL) were added sodium azide (930 mg, 14.3 mmol) and zinc bromide (804 mg, 3.57 mmol) at rt. The mixture was heated to reflux for 18h. After cooling, 10% HCl was added to the mixture at 0°C, and the mixture was extracted with AcOEt. The combined organic layer was washed with brine and was dried (Na_2SO_4). The solvent was removed under reduced pressure to afford crude **19**, which was used in the next reaction without further purification. A suspension of crude **19** and 10% Pd-C (470 mg) in MeOH (40 mL) was stirred vigorously under hydrogen gas at rt for 20h. The mixture was filtered through a Celite pad and the filtrate was evaporated under reduced pressure. The residue was recrystalized from MeOH to afford **12** 713 mg (53%, 2 steps) as colorless cubes.

Mp 271°C (decomposition); $[\alpha]_D^{23}$ +47.4 (*c* 0.75, DMSO), lit.,[25] $[\alpha]_D^{27}$ +46.4 (*c* 0.74, DMSO); IR (KBr), ν, cm^{-1} 2823, 2634, 2173, 1633, 1536, 752, 699; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.30 (br s, 2 H), 7.23-7.10 (m, 5 H), 4.66 (t, *J* = 7.2 Hz, 1 H), 3.40 (br s, 1 H), 3.33 (dd, *J* = 8.4, 13.6 Hz, 1 H), 3.17 (dd, *J* = 5.6, 13.6 Hz, 1 H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 158.5, 136.4, 129.4, 128.2, 126.6, 48.7; EI MS:

m/z 189 (M^+), 98 (100 %); HRMS calcd for $C_9H_{11}N_5$: 189.1014, found: 189.1011.

Typical procedure of aldol reaction of 7

To a stirred solution of TFA (104 mg, 1.78 mmol) in DMSO (0.5 mL) were added **11a** (182 mg, 0.89 mmol) in DMSO (1.0 mL) and **7** (200 mg, 0.89 mmol) in DMSO (0.5 mL) at rt. The mixture was heated at 90^{o}C for 10h. After cooling, the mixture was dissolved to AcOEt, was washed with saturated aqueous $NaHCO_3$ and brine, and was dried ($MgSO_4$). The solvent was removed under reduced pressure. The residue was chromatographed (hexane/AcOEt = 7/1) to afford **3b** 167 mg (91%) as pale yellow crystals. The optical purity was determined to be 70% ee by HPLC with a chiral stationary phase column. HPLC conditions: Chiralpak AS-H (Daicel Chemical Industries, LTD), ethanol/hexane = 10/90 (v/v), flow rate 1.0 mL/min. detected at 254 nM, t_R = 9.9 min for (*R*)-**3b**, 11.1 min for (*S*)-**3b**.

$[\alpha]_D^{23}$ -59.8 (*c* 1.0, $CHCl_3$, 70% ee), lit.,[14a] $[\alpha]_D^{27}$ -83.4 (*c* 1.0, $CHCl_3$, >99% ee). All of the spectroscopic data were identical to those reported by us previously.[14]

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