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AN ALTERNATIVE CHIRAL SYNTHESIS OF WIELAND-MIESCHER KETONE MEDIATED BY (*S*)-2-(PYRROLIDINYLMETHYL)PYRROLIDINE: REMARKABLE EFFECTS OF BRØNSTED ACID

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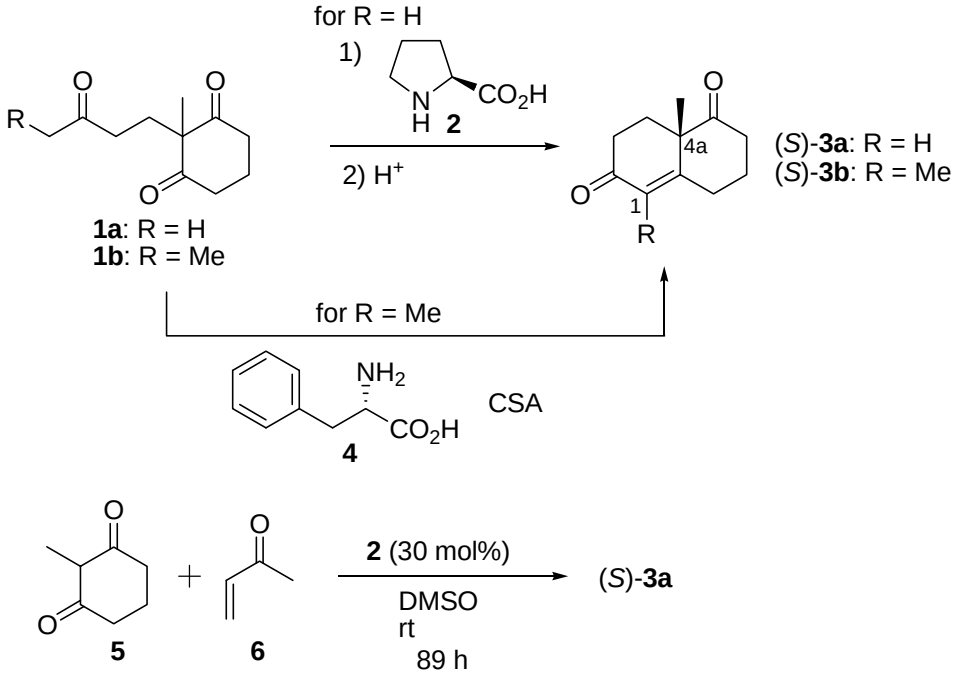
This paper is dedicated to Professor Ekkehard Winterfeldt on the occasion of his 75th birthday.

Abstract – The enantioselectivity of the intramolecular asymmetric aldol reaction mediated by (*S*)-2-(pyrrolidinylmethyl)pyrrolidine to prepare Wieland-Miescher ketone was examined in detail. A remarkable inversion of enantioselectivity was observed when a Brønsted acid was used as a co-catalyst. Development of the reaction to Robinson annulation was successfully achieved by the use of (*S*)-2-(pyrrolidinylmethyl)pyrrolidine as a Brønsted base, followed by trifluoroacetic acid as a Brønsted acid.

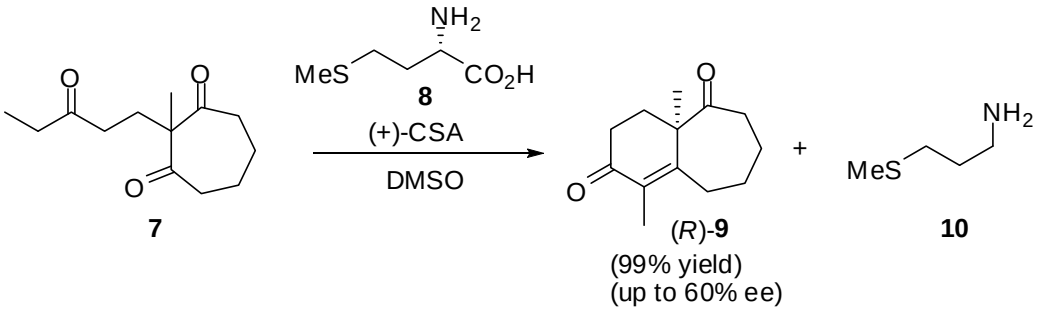
Wieland-Miescher ketone (**3a**), which was prepared by L-proline (L-Pro)-mediated asymmetric intramolecular aldol reaction of the trione (**1a**), has been a very useful synthon in total syntheses of a variety of natural products.[1,2] This asymmetric aldol reaction has become known as the Hajos-Parrish-Eder-Sauer-Wiechert (HPESW) reaction,[3,4] and has been widely recognized to involve an enamine-based mechanism.[5,6] In the optimized procedure, HPESW reaction of **1a** mediated by L-Pro afforded (*S*)-**3a** in the order of 70% ee.[3g] Fractional crystallization was required to obtain the optically pure material. Uda and Hagiwara successfully extended the reaction of **1b** by using L-phenylalanine (L-Phe, **4**) as a mediator in the presence of camphorsulfonic acid (CSA) to construct a Wieland-Miescher ketone analog [(*S*)-**3b**] bearing a methyl substituent at C-1 in 83% yield with 80% ee (Scheme 1).[7] Recently, Barbas reported L-Pro-mediated asymmetric Robinson annulation between 2-methylcyclohexane-1,3-dione (**5**) and methyl vinyl ketone (MVK, **6**) to afford (*S*)-**3a** in 47% yield accompanied with 76% ee (Scheme 1).[8] It has been shown that this synthesis, comprising three reactions (Michael addition, aldol reaction and dehydration) can be performed as a one-pot synthesis.

Notwithstanding the variety of substituents, those reactions mediated by L-amino acids afforded products **3** whose absolute configuration at C-4a was invariably *S*.[9] The results suggested us that the use of unnatural D-amino acid as a reaction mediator would be required, when the preparation of an antipode (*R*)-**3** would be needed. Therefore, developments of new and alternative routes to provide **3** have been still required.[4]



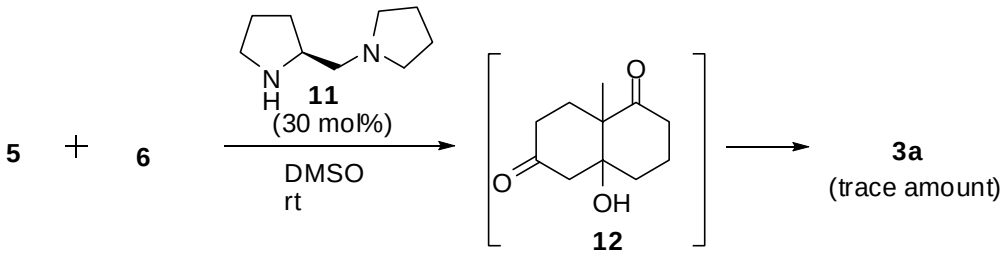
Scheme 1

Recently, we have reported the L-methionine (**8**, L-Met)- or L-Phe-mediated asymmetric intramolecular aldol reaction of the trione (**7**) to prepare a new bicyclic enedione [(*R*)-**9**] containing a 7-membered ring.[10] During this research, we found that L-Met decomposed to generate a corresponding achiral amine (**10**) by through decarboxylation reaction.[11] This result means that an amino acid is not always a suitable mediator for the HPESW reaction (Scheme 2).



Scheme 2

On the other hand, in the area of organocatalysis,[12] (*S*)-2-(pyrrolidinylmethyl)pyrrolidine (**11**) has been employed as a new catalyst to achieve highly efficient asymmetric reactions, including intra- and intermolecular aldol reaction.[13] Amine-Brønsted acid catalysis has also been utilized in asymmetric Diels-Alder reaction and 1,4-addition reaction to construct new chiral centers.[14,15] In those reports, 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 catalyst and substrate. However, to our knowledge, there have been few attempts to use amine catalysts in the HPESW reaction.[4f-k] Barbas *et al* reported that Robinson annulation of **5** and **6** in the presence of a catalytic amount of **11** afforded a trace amount of **3a**.[8] They noted that the diamine (**11**) mediated both the Michael addition step of **5** to afford **1a** and the aldol process of **1a** to afford β-hydroxyketone (**12**), but the final dehydration step to afford **3a** hardly proceeded (Scheme 3). However, they did not give details of the absolute configuration or yield of the aldol products (**12**) and (**3a**). Hayashi and co-workers have reported asymmetric intramolecular aldol reactions mediated by **11** to construct new 6-6 fused bicycles.[16] Inspired by that work, we considered that a diamine catalyst such as **11** would require a hydrogen bonding site to fix the transition state of the aldol reaction and that the addition of a Brønsted acid would promote both the aldol and the dehydration step. We wish to report here an alternative chiral synthesis of Wieland-Miescher ketone (**3a**) using a combination of (*S*)-2-(pyrrolidinylmethyl)pyrrolidine (**11**) and Brønsted acid, and also to report a remarkable inversion of enantioselectivity due to addition of Brønsted acid.[17]

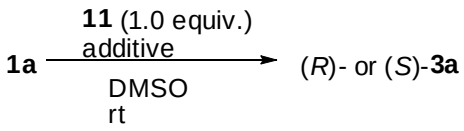


Scheme 3

We first examined the effects of Brønsted acid on the aldol reaction of the trione (**1a**) mediated by diamine (**11**). All of the reactions were carried out under the same conditions in the presence of a stoichiometric amount of **11** with 1.0 or 1.5 equiv. of Brønsted acid in DMSO at rt. The results are compiled in Table 1. First of all, the aldol reaction mediated by **11** without Brønsted acid afforded (*S*)-**3a** in 55% yield with 19% ee (entry 1). The reaction in the presence of acetic acid (AcOH) as a Brønsted acid showed a shorter reaction time, with a slightly improved yield and better enantioselectivity for (*S*)-**3a** (entry 2). As indicated in Table 1, since the p*K*a value of AcOH in DMSO is higher than that in H_2O, the expected protonation on the diamine (**11**) to produce a corresponding ammonium salt might not occur under the reaction conditions employed.[18,19] Interestingly, the aldol reaction using PPTS, which has a

lower p*K*a value in DMSO than that of AcOH, afforded (*R*)-**3a** in 64% yield with 70% ee. The same tendency was observed with other organic acids, such as dichloroacetic acid (DCA), (−)-CSA and *p*-toluenesulfonic acid (*p*-TsOH), having lower p*K*a values in H_2O than that of AcOH (entries 4-8). The reactions shown in entries 4-8 afforded (*R*)-**3a** in 64-81% yield with 54-70% ee. The aldol reactions in the presence of sulfonic acids made the reaction time shorter than in the case of using AcOH. With a stronger acid than *p*-TsOH, such as TFA or trifluormethanesulfonic acid (TfOH), the reactions required longer times to reach completion and afforded (*R*)-**3a** in moderate yield with higher ee than that obtained with sulfonic acids (entries 9-12). These results suggested to us that 1) the combination of diamine (**11**) and a stronger Brønsted acid than AcOH inverted the enantioselectivity compared with the reaction using **11** only or the combination of **11** and AcOH, 2) protonation on the diamine (**11**) to produce the corresponding ammonium salt was very important for achieving higher ee. Optically pure material of (*R*)-**3a** could be obtained after recrystallization of the product in entry 10. Since the highest ee value was observed in entry 10, 1.5 equiv. of TFA was selected as an additive for further optimization.

Table 1



Entry	Additive (equiv.)	p*K*a[a,b]	Time (h)	Yield[c] (%)	Ee[d] (%)	Absolute Configuration
1	-	-	27	55	19	*S*
2	AcOH (1.5)	4.76 (12.3)	9	68	25	*S*
3	PPTS (1.5)	5.21 (3.4)	4	64	70	*R*
4	DCA[e] (1.5)	1.29	12	81	70	*R*
5	(-)-CSA (1.0)	−2.6[f] (1.6)[f]	4	68	72	*R*
6	(-)-CSA (1.5)		4	74	54	*R*
7	*p*-TsOH (1.0)	−1.34	8	70	70	*R*
8	*p*-TsOH (1.5)		4	75	65	*R*
9	TFA (1.0)	−0.25	16	60	77	*R*
10	TFA (1.5)		48	53	81	*R*
11	TfOH (1.0)	−14 (0.3)	8	58	75	*R*
12	TfOH (1.5)		20	65	80	*R*

[a] p*K*a values of additives measured in H_2O.[18]

[b] p*K*a values measured in DMSO are shown in parentheses.[19]

[c] Isolated yield.

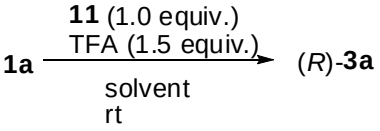
[d] Determined by HPLC equipped with a chiral stationary phase column.

[e] Dichloroacetic acid.

[f] p*K*a values of methanesulfonic acid instead of CSA.

We next examined the solvent effects in the aldol reaction of **1a**. Thus, all of the reactions were carried out with a stoichiometric amount of diamine (**11**) in the presence of 1.5 equiv. of TFA in several solvents. The results are compiled in Table 2. Non-protic polar solvents such as DMF and acetonitrile exhibited the same tendency as the reaction in DMSO, and afforded (*R*)-**3a** in moderate yield with 73-77% ee (entries 2 and 3). Although benzene, a non-polar solvent, also afforded (*R*)-**3a** in relatively higher yield than other solvents, the ee value was only 35% ee.

Table 2



Entry	Solvent	Time (h)	Yield[a] (%)	Ee[b] (%)
1	DMSO	48	53	81
2	DMF	43	56	73
3	MeCN	43	54	77
4	benzene	47	75	35

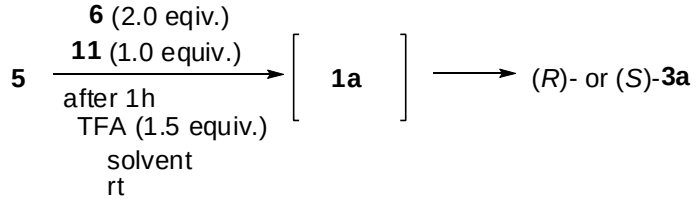
[a] Isolated yield.

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

Finally, we tried to extend the reaction to Robinson annulation. All of the reactions were carried out under same conditions utilizing a stoichiometric amount of **11** with or without TFA in several solvents at rt. The results are summarized in Table 3. The reaction without TFA proceeded to afford (*S*)-**3a** in 26% yield with 20% ee (entry 1). This result means that the diamine (**11**) mediated Robinson annulation to afford the antipode of **3a**, and that we needed to avoid the competing reactions to obtain (*R*)- or (*S*)-**3a** with and without Brønsted acid, respectively. However, in preliminary experiments, Robinson annulation did not proceed when TFA was added at the beginning of the reaction, because the addition of TFA suppressed the first Michael addition of **5** to MVK (**6**) in Robinson annulation. Monitoring the reaction in entry 1 by the use of TLC indicated that a lot of Michael adduct (**1a**) and only a trace amount of (*S*)-**3a** were observed after 1 h. This result means that **11** acts as a Brønsted base for the first Michael addition step. Based on this result, we decided to add TFA at 1 h after addition of diamine **11**. Although Robinson annulation of **5** in DMSO required a longer reaction time than the aldol reaction of **1a** (entry 9 in Table 1), (*R*)-**3a** was obtained in 47% yield with 75% ee (entry 2 in Table 3). The absolute configuration of the product (**3a**) in entry 2 was assigned as *R* by comparison with the optical rotation of (*R*)-**3a** reported previously.[4f] Specifically, the optical rotation of product (*R*)-**3a** in entry 2 was $[\alpha]_D$ –72.2 (benzene, 75% ee), lit.,[4f] $[\alpha]_D$ -100 (benzene, 100% ee). Almost the same results, except for reaction time, were obtained

in DMF and CH_3CN (entries 3 and 4 in Table 3) when compared with the results in Table 2 (entries 2 and 3 in Table 2). Other non-protic polar solvents such as THF, dioxane and CH_2Cl_2 were not suitable solvents for the Robinson annulation, because lower ee of (*R*)-**3a** was observed (entries 5-7). The reactions both in a non-polar solvent (benzene or toluene) and in a protic polar solvent (MeOH) failed to achieve high ee of (*R*)-**3a** (entries 8-10). As in Barbas's report, the Robinson annulation of **5** mediated by L-Pro afforded (*S*)-**3a** in 49% yield with 76% ee (entry 11).[8] Therefore, we could achieve to develop an alternative route to provide the antipode (*R*)-**3a** without using unnatural D-Pro (entry 1).

Table 3



Entry	Solvent	Time (h)	Yield[a] (%)	Ee[b] (%)	Absolute Configuration
1[c]	DMSO	144	26	20	*S*
2	DMSO	80	47	75	*R*
3	DMF	90	50	67	*R*
4	MeCN	80	56	66	*R*
5	THF	120	62	28	*R*
6	dioxane	120	60	43	*R*
7	CH_2Cl_2	130	69	5	*R*
8	benzene	105	72	34	*R*
9	toluene	105	70	33	*R*
10	MeOH	72	40	40	*R*
11[d, e]	DMSO	89	49	76	*S*

[a] Isolated yield.

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

[c] TFA was not added.

[d] L-Pro was used instead of **11** and TFA was not added.

[e] The result was previously reported in ref. 8.

In the aldol reaction of **1a** to afford a 6-6 fused bicycle, there exists the possibility of producing four stereoisomers as a result of two newly generated stereogenic centers. Since we could not isolate the initially formed β-hydroxy ketones under the conditions using **11** and TFA, dehydration to afford **3a** must occur rapidly. The transition states predicted for all of the stereoisomers are shown in Figure 1. In the presence of Brønsted acid, the pyrroridinylmethyl moiety in **11** would be protonated to generate a corresponding ammonium salt. We think that this hydrogen in the ammonium salt could hydrogen-bond

to the β-oxygen atom originated 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 pyrroridinylmethyl moieties) transition states (**16**) and (**20**) 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 (**13**) and (**17**) 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.[20,21] 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, (**13**) and/or (**17**). In comparison with the *trans-anti* (*cis*, *trans*: *cis*- or *trans*-fused carbocycles) transition state (**13**) and the *cis-anti* one (**17**), **17** appears to be disfavored because of steric repulsion between a methyl substituent and a pyrrolidine ring. Consequently, the *trans-anti* transition state (**13**) should be most favored, affording the 4a*R*, 8a*S* aldol product (**14**), which would give rise to (*R*)-**3a** after dehydration (Figure 1).

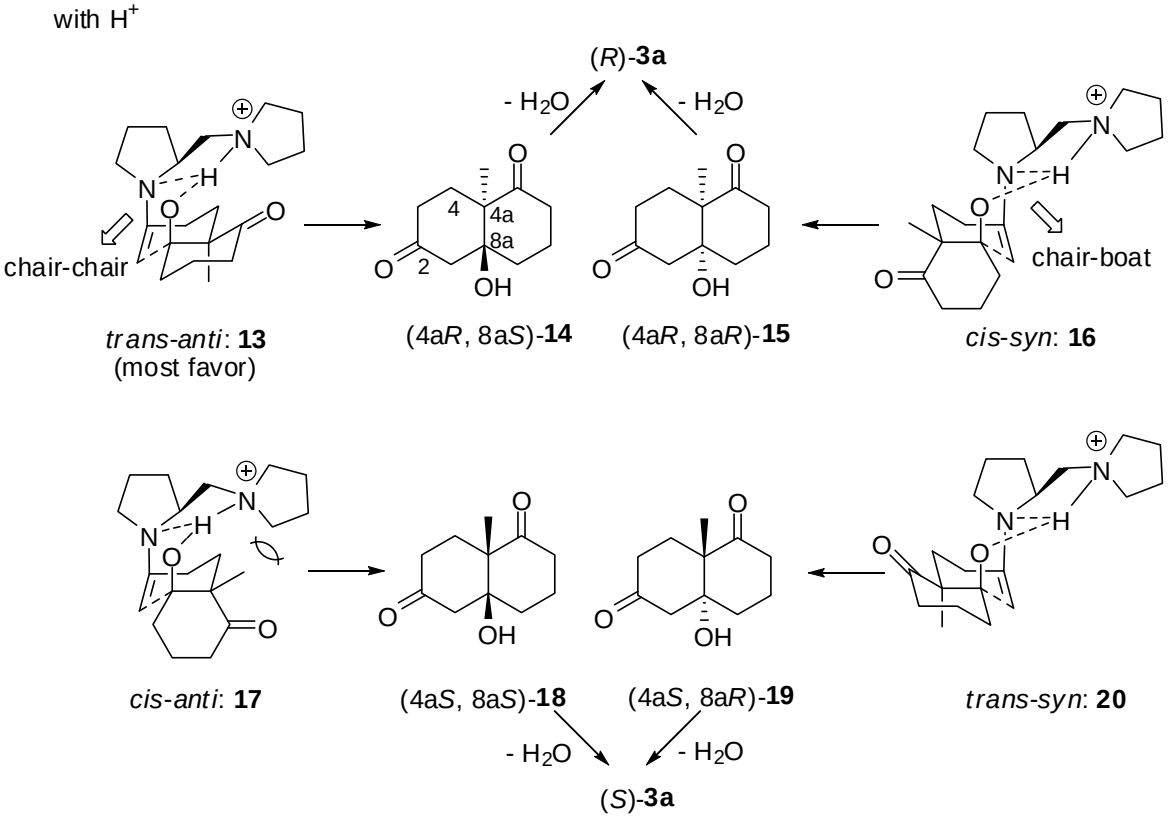


Figure 1

When no Brønsted acid was used, inversion of enantioselectivity was noted with lower ee (Table 1, entry 1). This result indicates that the reaction without an acid could not generate hydrogen bonds and the

pyrrolidinylmethyl moiety would be oriented away from the C-C bond forming site. The two favorable *anti*-transition states (**21**) and (**22**) might have very similar potential energy (Figure 2). In the non-hydrogen bonding model, there is also the possibility that the aldol reaction proceeds through *syn*-type transition states (**23**) and (**24**). To date, we have no evidence to suggest which transition state is more stable, *syn* or *anti*. However, the transition states (**22**) and/or (**24**) which lead to (*S*)-**3a** might be slightly more favored than the other two, (**21**) and (**23**) which lead to (*R*)-**3a**. Further investigations into the effects of Brønsted acid, and calculations of the energy differences of our proposed transition states are under way.

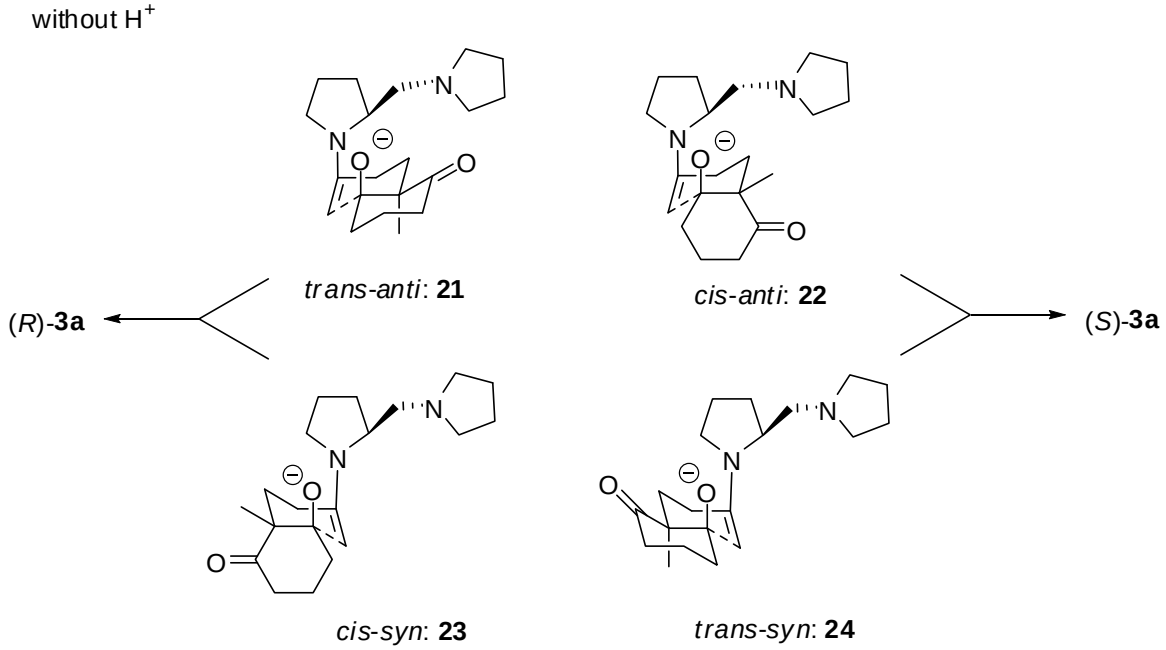


Figure 2

In conclusion, we have established an alternative chiral route to provide (*R*)-**3a** by using the combination of (*S*)-2-(pyrrolidinylmethyl)pyrrolidine and TFA. In the reaction, a remarkable inversion of enantioselectivity with or without a Brønsted acid was observed. Furthermore, development of the reaction to Robinson annulation has been succeeded. Under the optimized condition, (*R*)-**3a** was obtained almost same result, except for the enantioselectivity, as the reaction mediated by L-Pro.[8] These results may enable the creation of diverse and efficient organocatalysts for a wide variety of reactions. Further work on a detail of the reaction mechanism and a development of 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 intramolecular aldol reaction of 1a

To a stirred solution of the trione (**1a**) (147 mg, 0.75 mmol) in DMSO (1.5 mL) was added the amine (**11**) (121 μL, 0.75 mmol) and (TFA 86 μL, 1.1 mmol) at rt. The reaction mixture was stirred at rt for 48 h, then diluted with ethyl acetate (AcOEt), washed with saturated aqueous $NaHCO_3$ and brine, and dried ($MgSO_4$). The solvent was removed under reduced pressure. The crude product was chromatographed on silica gel (AcOEt/CH_2Cl_2/hexane = 1/1/4) to afford (*R*)-**3a** 70 mg (53%) as a pale yellow oil. The optical purity was determined to be 75% ee by HPLC with a chiral stationary phase. HPLC conditions: Chiralcel OD, 2-propanol/hexane = 1/10 (v/v), flow rate 1.0 mL/min, detected at 254 nm, t_R = 14.6 min for (*S*)-**3a**, 15.7 min for (*R*)-**3a**. Optically pure material was obtained by recrystallization as follows: compound (*R*)-**3a** (200 mg, 82% ee) was recrystallized from Et_2O/hexane to afford (*R*)-**3a** (55 mg, >99% ee) as colorless needless. For optically pure (*R*)-**3a**: mp 49.5-50 °C, lit.,[4b] 48.5-49 °C. $[\alpha]_D^{25}$ -100 (*c* 1.00, benzene), lit.,[4f] $[\alpha]_D^{25}$ -100 (*c* 1.40, benzene). IR (film) ν_{max} 1714, 1668. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.46 (s, 3H), 1.67-1.78 (m, 1H), 2.10-2.19 (m, 3H), 2.44-2.53 (m, 4H), 2.68-2.77 (m, 2H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ 22.8, 23.2, 29.6, 31.7, 33.5, 37.6, 50.5, 125.8, 165.8, 198.2, 211.0. EIMS (m/z) 178 (M^+, 100%). HRMS calcd for $C_{11}H_{14}O_2$ 178.0994, found 178.0988. Anal. Calcd for $C_{11}H_{14}O_2$ C, 74.13; H, 7.92. Found C, 74.03; H, 8.16.

Typical procedure of Robinson annulation of 5

To a stirred solution of 2-methylcyclohexane-1,3-dione (**5**) (96 mg, 0.75 mmol) and the amine (**11**) (121 μL, 0.75 mmol) in DMSO 1.5 mL was added MVK (**6**) (122 μL, 1.5 mmol) at rt with stirring. After 1 h, TFA (86 μL, 1.1 mmol) was added to the mixture, and stirring was continued at rt for 80 h. The mixture was diluted with AcOEt, washed with saturated aqueous $NaHCO_3$ and brine, and dried ($MgSO_4$). The solvent was removed under reduced pressure. The crude product was chromatographed on silica gel (AcOEt/CH_2Cl_2/hexane = 1/1/4) to afford (*R*)-**3a** (63 mg, 47%) as a pale yellow oil. The optical purity was determined to be 75% ee by HPLC as described above.

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