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anti-Selective direct asymmetric Mannich reactions catalyzed by chiral pyrrolidine-based amino sulfonamides

Taichi Kano, Yoshio Hato, Akihiro Yamamoto, Keiji Maruoka*

Department of Chemistry, Graduate School of Science, Kyoto University, Sakyo, Kyoto 606-8502, Japan

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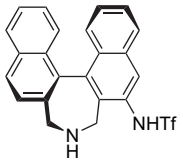
Abstract

The novel pyrrolidine-based amino sulfonamides (*R*,*R*)-**2**, (*S*)-**3**, and (*S*)-**4** were designed and synthesized as organocatalysts and successfully applied for the *anti*-selective direct asymmetric Mannich reaction.

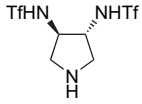
Keywords: Mannich reaction; Organocatalyst; Asymmetric synthesis; Enamine catalysis

1. Introduction

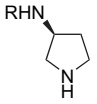
Development of highly stereoselective asymmetric reactions using organocatalysts has become a research area of great importance, and a number of new organocatalysts have been devised for this purpose.[1] Accordingly, we already designed several binaphthyl-based secondary amine catalysts for aldol and other reactions involving enamine intermediates in their transition state.[2] Among them, chiral binaphthyl-based amino sulfonamide (*S*)-**1** showed excellent reactivity, diastereo- and enantioselectivities in the *anti*-selective direct asymmetric Mannich reaction between aldehydes and α-imino esters.[2b,3,4] However, sterically hindered aldehydes gave the corresponding Mannich products in only moderate yields, probably due to the low nucleophilicity of (*S*)-**1**.[2b] In this context, we have designed and synthesized a new chiral amino sulfonamide catalyst possessing a highly nucleophilic pyrrolidine core and two acidic triflamide groups from L-tartaric acid as an inexpensive chiral starting material.[3f] We are also interested in the design of chiral pyrrolidine-type catalysts possessing a triflamide or a more acidic nonafluorobutylsulfonamido (nonaflamide, Nf–NH–) group. We here report the synthesis of new pyrrolidine-based amino sulfonamides (*R*,*R*)-**2**, (*S*)-**3**, and (*S*)-**4**, and their application to the *anti*-selective direct asymmetric Mannich reaction.



(*S*)-**1**



(*R*,*R*)-**2**



(*S*)-**3** (R = Tf)
(*S*)-**4** (R = Nf)

2. Results and discussion

Our catalyst design is based on the proposal of transition-state structures in the direct asymmetric Mannich reaction as shown in Scheme 1. When L-proline is used as a catalyst, the α-carboxyl group of L-proline controls the orientation of the enamine moiety by the steric repulsion and the coordination pattern of the α-imino ester **5** by the acid–base interaction, respectively. Consequently, the *Si*-face of the α-imino ester approaches the *Re*-face of the enamine to furnish the *syn*-product *syn*-**6** (Scheme 1).[5] On the other hand, the reaction using (*R*,*R*)-**2**, (*S*)-**3** or (*S*)-**4** would be expected to give the *anti*-product *anti*-**6** as a result of the opposite facial orientation of the α-imino ester **5**.[3c,3e] In addition, the sterically less

* Corresponding author. Tel./fax: +81 75 753 4041.
E-mail address: maruoka@kuchem.kyoto-u.ac.jp (K. Maruoka).

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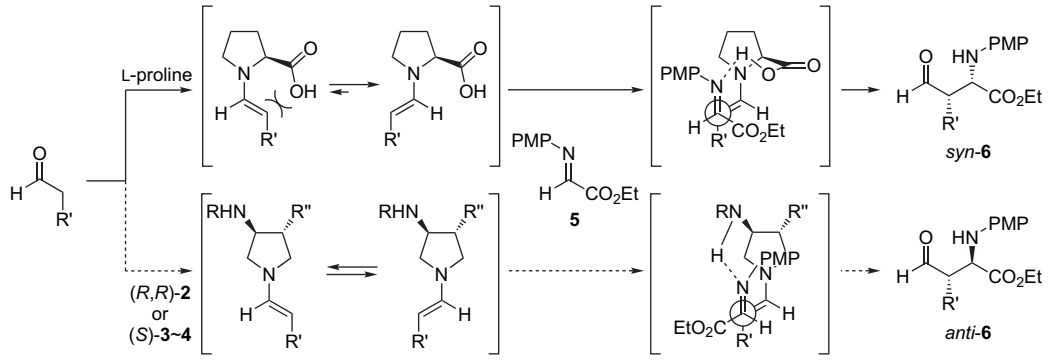
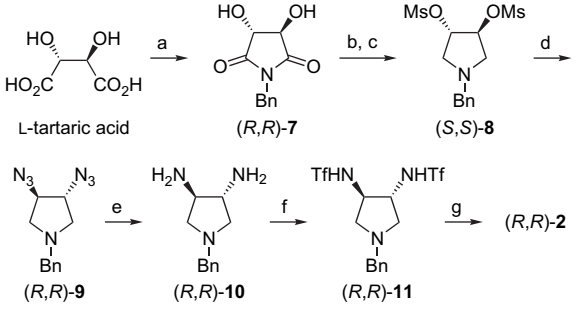


Scheme 1.

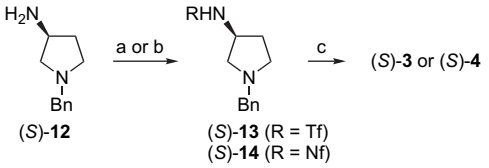
hindered (*R*,*R*)-**2**, and far less hindered (*S*)-**3** and (*S*)-**4** would be capable of reacting with even bulky aldehydes and ketones, which were found to be unsuitable substrates for the less nucleophilic (*S*)-**1**.

The synthesis of the requisite chiral pyrrolidine (*R*,*R*)-**2** began with the conversion of L-tartaric acid to the corresponding imide (*R*,*R*)-**7** by the direct condensation with benzylamine (Scheme 2). Reduction of (*R*,*R*)-**7** with $LiAlH_4$ and subsequent mesylation of both hydroxyl groups afforded amino dimesylate (*S*,*S*)-**8** (95% yield in two steps), which was then converted with NaN_3 into diazide (*R*,*R*)-**9** in 56% yield. The resulting azide groups were reduced in the presence of Pd/C under H_2 atmosphere to give triamine (*R*,*R*)-**10** in 99% yield. Treatment of (*R*,*R*)-**10** with Tf_2O and *i*-Pr_2NEt gave bis(triflamide) (*R*,*R*)-**11** in 76% yield. Finally, reductive cleavage of the benzyl group provided the pyrrolidine-based amino sulfonamide (*R*,*R*)-**2** in 93% yield, which was purified by an ion exchange resin.



Scheme 2. Reagents and conditions: (a) benzylamine, *o*-xylene, reflux, 99%; (b) $LiAlH_4$, THF, reflux; (c) MsCl, Et_3N, CH_2Cl_2, rt, 95% in two steps; (d) NaN_3, DMF, 100 °C, 56%; (e) H_2, Pd/C, EtOH, rt, 99%; (f) Tf_2O, *i*-Pr_2NEt, CH_2Cl_2, −78 °C, 76%; (g) H_2, Pd/C, AcOH, rt, 93%.

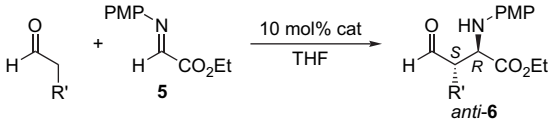
The chiral pyrrolidines (*S*)-**3** and (*S*)-**4** were prepared in a two-step sequence from commercially available (*S*)-1-benzyl-3-aminopyrrolidine ((*S*)-**12**) as shown in Scheme 3. Treatment of (*S*)-**12** with the corresponding sulfonic anhydride gave triflamide (*S*)-**13** and nonaflamide (*S*)-**14** in moderate yields, respectively. Hydrogenative debenzylation of (*S*)-**13** and (*S*)-**14** proceeded smoothly in ethanol to provide the pyrrolidine-based amino sulfonamide (*S*)-**3** and (*S*)-**4**, respectively, which could be used as catalyst in the direct asymmetric Mannich reaction without treatment with an ion exchange resin.



Scheme 3. Reagents and conditions: (a) Tf_2O, *i*-Pr_2NEt, CH_2Cl_2, 0 °C, 59%; (b) Nf_2O, *i*-Pr_2NEt, CH_2Cl_2, −78 °C to rt 89%; (c) H_2, Pd/C, EtOH, rt, 99% for (*S*)-**3**, 60% for (*S*)-**4**.

The new catalysts (*R*,*R*)-**2**, (*S*)-**3**, and (*S*)-**4** thus obtained, were utilized in the direct asymmetric Mannich reaction of

Table 1
anti-Selective Mannich reactions of aldehydes[a]



Entry	R′	Catalyst	Conditions (°C, h)	% Yield[b] (*anti*/*syn*)[c]	% ee[d]
1	Me	(*R*,*R*)-**2**	−20, 9	64 (14:1)	98[e]
2	Me	(*S*)-**3**	−20, 9	50 (14:1)	99[e]
3	Me	(*S*)-**4**	−20, 9	65 (14:1)	99[e]
4	Et	(*R*,*R*)-**2**	−20, 2	82 (16:1)	94
5	Et	(*S*)-**3**	−20, 3	75 (12:1)	98
6	Et	(*S*)-**4**	−20, 3	76 (14:1)	98
7	*i*-Pr	(*R*,*R*)-**2**	−20, 1	93 (11:1)	95
8	*i*-Pr	(*S*)-**3**	−20, 4	88 (10:1)	98
9	*i*-Pr	(*S*)-**4**	−20, 4	88 (8:1)	98
10	*t*-Bu	(*R*,*R*)-**2**	−20, 24	88 (18:1)	90
11	*t*-Bu	(*S*)-**3**	−20, 46	92 (20:1)	99
12	*t*-Bu	(*S*)-**4**	−20, 30	99 (>20:1)	98

[a] The reaction of an aldehyde (3 equiv) and α-imino ester **5** was carried out in THF in the presence of a catalyst (10 mol %) at −20 °C.

[b] Isolated yield.

[c] Determined by ^1H NMR.

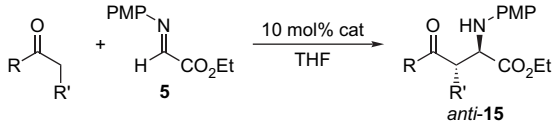
[d] The enantiomeric excess of the *anti*-isomer *anti*-**6** was determined by HPLC analysis using chiral column (Chiralpak AS-H). The absolute configuration was determined by comparison of the HPLC retention times of **6** with the reported data.[2b,3a]

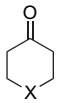
[e] The enantiomeric excess and the absolute configuration of the *anti*-isomer *anti*-**6** were determined by HPLC analysis using chiral column (Chiralpak AD-H) after reduction.[2b]

aldehydes and results are summarized in Table 1. In each case, the Mannich reaction between an aldehyde and α-imino ester **5** with 10 mol % of a catalyst proceeded in THF at −20 °C to give the corresponding *anti*-product *anti*-**6** predominantly with excellent enantioselectivity. The reaction of less hindered propanal gave moderate yields of *anti*-**6** (R′=Me) due to the competing self-aldol reaction (entries 1–3), while the use of a sterically congested 3,3-dimethylbutanal resulted in the retardation of the reaction rate, the corresponding *anti*-product *anti*-**6** (R′=*t*-Bu) was obtained in good to excellent yield and selectivity (entries 10–12). In general, the reaction with non-C_2-symmetric catalysts (*S*)-**3** and (*S*)-**4** showed higher enantioselectivity than with the C_2-symmetric catalyst (*R*,*R*)-**2**.

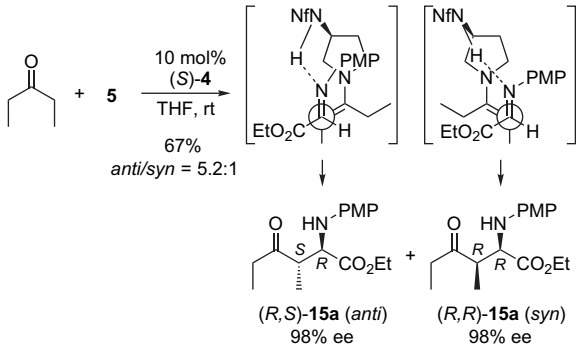
We next turned our attention to the reaction of ketones with α-imino ester **5** (Table 2). With each catalyst, reactions of six-membered cyclic ketones proceeded smoothly to give a satisfactory result in terms of both reactivity and selectivity even at lower catalyst loadings (entries 1–7). In the case of the less reactive acyclic ketone 3-pentanone, moderate yields of the desired *anti*-product *anti*-**15** (R=Et, R′=Me) were obtained with longer reaction time (entries 8–10). When the reaction with (*S*)-**4** was carried out in acetonitrile instead of THF, the yield was improved without loss of stereoselectivity (entry 11). Although the use of 4-heptanone resulted in a significant decrease in yield and diastereoselectivity, the *anti*-isomer was still dominant (entry 12). The reaction with the unsymmetrical ketone 2-butanone gave the branched *anti*-isomer *anti*-**15** (R=R′=Me) predominantly with good enantioselectivity (entry 13). Again, non-C_2-symmetric catalysts (*S*)-**3** and (*S*)-**4** exhibited higher levels of enantioselectivity than the C_2-symmetric analogue (*R*,*R*)-**2**, as observed in the case of aldehydes.

Table 2
anti-Selective Mannich reactions of ketones[a]



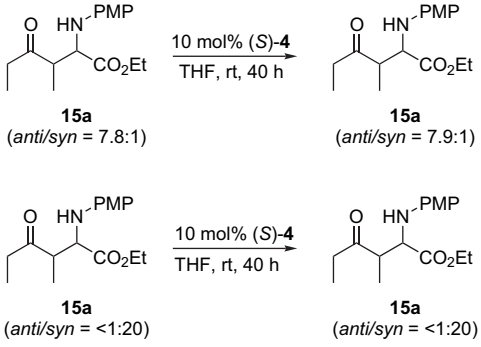
Entry	Substrate	Catalyst	Conditions (°C, h)	% Yield[b] (*anti*/*syn*)[c]	% ee[d]
1		(*R*,*R*)-**2**	rt, 1	99 (>20:1)	95
2[e]			rt, 4	95 (>20:1)	95
3[f]			rt, 35	98 (>20:1)	93
4		(*S*)-**3**	rt, 2	99 (>20:1)	99
5	X = CH_2	(*S*)-**4**	rt, 2	98 (>20:1)	99
6	X=O	(*S*)-**4**	rt, 2	99 (16:1)	94
7	X=S	(*S*)-**4**	rt, 6	99 (>20:1)	97
8	3-Pentanone	(*R*,*R*)-**2**	rt, 70	56 (4.8:1)	92
9		(*S*)-**3**	rt, 90	55 (4.5:1)	98
10		(*S*)-**4**	rt, 43	67 (5.2:1)	98
11[g]			rt, 24	82 (5.8:1)	98
12	4-Heptanone	(*S*)-**4**	rt, 168	22 (1.6:1)	90, 99[h]
13	2-Butanone	(*S*)-**4**	rt, 12	70[i] (4.5:1)	90

[a] The reaction of a ketone (excess) and α-imino ester **5** was carried out in THF in the presence of a catalyst (10 mol %) at room temperature.
[b] Isolated yield.
[c] Determined by ^{1}H NMR.
[d] The enantiomeric excess of the *anti*-isomer *anti*-**15** was determined by HPLC analysis using chiral column (Chiralpak AS and AS-H). The absolute configuration was determined by comparison of the HPLC retention times of *anti*-**15** with the reported data.[3e]
[e] Use of 2 mol % of (*R*,*R*)-**2**.
[f] Use of 0.5 mol % of (*R*,*R*)-**2**.
[g] Acetonitrile was used as a solvent.
[h] The enantiomeric excess of the *syn*-isomer.
[i] Containing 14% of regioisomer.

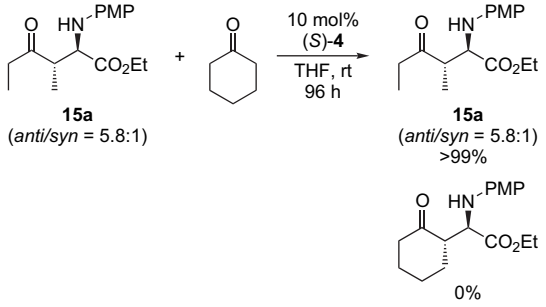


Scheme 4.

In the reaction of 3-pentanone with α-imino ester **5** catalyzed by (*S*)-**4**, both *anti*- and *syn*-product **15a** were found to be obtained with excellent enantioselectivity (Scheme 4). Based on the observed stereochemistry in the reaction, transition state models can be proposed as shown in Scheme 4.[3c,3e] In each case the *Re*-face of the α-imino ester **5** approaches the enamine intermediate as directed by the acidic proton of nonaflamide group, and consequently, the C–C bond forming reaction takes place on both the *Re*- and *Si*-faces of the enamine in highly enantioselective fashion, giving (*R*,*S*)-**15a** (*anti*) and (*R*,*R*)-**15a** (*syn*), respectively. When the diastereomixtures of **15a** (*anti*/*syn*=7.8:1 and <1:20) were treated with 10 mol % of (*S*)-**4** in THF, respectively, no significant change in the diastereomeric ratios was observed in both cases (Scheme 5). These results indicated that the *anti*-selectivity in the present reaction originates not from isomerization between *anti*-**15a** and *syn*-**15a** under the reaction conditions but from the C–C bond forming step. In addition, since the diastereomixture of **15a** was quantitatively recovered from the mixture of **15a**, cyclohexanone, and 10 mol % of (*S*)-**4** under the reaction conditions, the possibility of the retro-Mannich reaction could be ruled out (Scheme 6).



Scheme 5.



Scheme 6.

3. Conclusion

In summary, we have synthesized the pyrrolidine-based amino sulfonamide (*R*,*R*)-**2** from inexpensive and readily available L-tartaric acid, and have shown the efficiency of (*R*,*R*)-**2** for the *anti*-selective direct asymmetric Mannich reaction of even sterically hindered aldehydes and ketones. Furthermore, the newly designed pyrrolidine-based amino sulfonamides (*S*)-**3** and (*S*)-**4** were also found to be effective for the *anti*-selective direct asymmetric Mannich reaction.

4. Experimental

4.1. General information

Infrared (IR) spectra were recorded on a Shimadzu IRPrestige-21 spectrometer. ^{1}H NMR spectra were measured on a JEOL JNM-FX400 (400 MHz) spectrometer. Chemical shifts were reported in parts per million from tetramethylsilane as an internal standard. Data were reported as follows: chemical shift, integration, multiplicity (s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet, br=broad, and app=apparent), coupling constants (Hz), and assignment. ^{13}C NMR spectra were recorded on a JEOL JNM-FX400 (100 MHz) spectrometer with complete proton decoupling. Chemical shifts were reported in parts per million from the residual solvent as an internal standard. High performance liquid chromatography (HPLC) was performed on Shimadzu 10A instruments using a Daicel CHIRALPAK AS-H and AD-H, 4.6 mm×25 cm column. The high-resolution mass spectra (HRMS) were performed on a Bruker microTOF. Optical rotations were measured on a JASCO DIP-1000 digital polarimeter. For thin layer chromatography (TLC) analysis throughout this work, Merck precoated TLC plates (silica gel 60 GF_{254}, 0.25 mm) were used. The products were purified by flash column chromatography on silica gel 60 (Merck 1.09386.9025, 230–400 mesh). In experiments requiring dry solvents, tetrahydrofuran (THF) was purchased from Kanto Chemical Co. Inc. as 'dehydrated'. Acetonitrile was dried over anhydrous K_2CO_3 for 24 h, and dried over 3 Å molecular sieves for 24 h, and then distilled. Aldehydes were distilled and stored under argon atmosphere at −17 °C. Ethyl (4-methoxyphenylimino)acetate **5** was synthesized according to the literature procedure.[6] The following compounds are all known: (3*R*,4*R*)-1-benzyl-3,4-dihydroxypyrrolidine-2,5-dione ((*R*,*R*)-**7**),[7,8] (3*S*,4*S*)-1-benzyl-3,4-bis(methylsulfoxy)pyrrolidine ((*S*,*S*)-**8**),[9] (3*R*,4*R*)-3,4-diazido-1-benzylpyrrolidine ((*R*,*R*)-**9**),[7] (3*R*,4*R*)-3,4-diamino1-benzylpyrrolidine ((*R*,*R*)-**10**).[7] (*S*)-1-Benzyl-3-aminopyrrolidine ((*S*)-**12**) is commercially available from Aldrich, TCI, and several other companies. Other simple chemicals were purchased and used as such.

4.2. Synthesis and characterization of chiral amino sulfonamide (R,R)-2

4.2.1. (3R,4R)-1-Benzyl-3,4-dihydroxypyrrolidine-2,5-dione (R,R)-7

The title compound was synthesized according to the literature procedure.[7]

4.2.2. (3S,4S)-1-Benzyl-3,4-bis(methylsulfoxy)pyrrolidine (S,S)-8

To a solution of (3*R*,4*R*)-1-benzyl-3,4-dihydroxypyrrolidine-2,5-dione (*R*,*R*)-**7** (1.11 g, 5 mmol) in THF (50 mL) was added $LiAlH_4$ (569 mg, 15 mmol) at 0 °C. The reaction mixture was stirred under reflux for 12 h. The reaction was quenched by the sequential treatment with H_2O (0.57 mL), 15%NaOH (0.57 mL), and H_2O (1.7 mL). To the mixture was then added ethyl acetate (100 mL) and stirred under reflux for 4 h. The reaction mixture was filtered through a pad of Celite and the filtrate was concentrated to give a crude (3*S*,4*S*)-1-benzyl-3,4-dihydroxypyrrolidine, which was used for the next step without further purification.

To a stirred solution of (3*S*,4*S*)-1-benzyl-3,4-dihydroxypyrrolidine (1.47 g, 7.6 mmol) in CH_2Cl_2 (38 mL) was added triethylamine (2.54 mL, 18.2 mmol) and methanesulfonic chloride (1.41 mL, 18.2 mmol) at 0 °C. The reaction mixture was stirred at room temperature for 6 h. The mixture was then quenched with saturated $NaHCO_3$ and extracted with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4 and concentrated. The residue was purified by flash column chromatography on silica gel (hexane/ethyl acetate=2:1) to afford (*S*,*S*)-**8** (2.65 g, 7.6 mmol, 95% yield over two steps).

4.2.3. (3R,4R)-3,4-Diazido-1-benzylpyrrolidine (R,R)-9

To a stirred solution of (*S*,*S*)-**8** (3.56 g, 10.2 mmol) in DMF (51 mL) was added sodium azide (1.99 g, 30.6 mmol) at 100 °C. The reaction mixture was stirred at 100 °C overnight. The mixture was then poured into H_2O and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated. The residue was purified by flash column chromatography on silica gel (hexane/ethyl acetate=40:1) to afford (*R*,*R*)-**9** (1.39 mg, 5.7 mmol, 56% yield).

4.2.4. (3R,4R)-3,4-Diamino-1-benzylpyrrolidine (R,R)-10

The title compound was synthesized according to the literature procedure.[7]

4.2.5. (3R,4R)-1-Benzyl-3,4-bis(trifluoromethylsulfonamido)-pyrrolidine (R,R)-**11**

To a stirred solution of triamine (*R*,*R*)-**10** (191 mg, 1.0 mmol) in CH_2Cl_2 (5 mL) was added *N*,*N*-diisopropylethylamine (171 μL, 1.0 mmol) and trifluoromethanesulfonic anhydride (337 μL, 2.0 mmol) at −78 °C. The reaction mixture was stirred at −78 °C for 1 h. The reaction mixture was charged on silica gel directly and purified by flash column chromatography on silica gel (CH_2Cl_2/ethyl acetate=2:1) to afford (*R*,*R*)-**11** (347 mg, 0.76 mmol, 76% yield): $[\alpha]_D^{30}$ −32.2 (*c* 1.0, MeOH); ^{1}H NMR (400 MHz, CD_3OD) δ 7.31−7.23 (5H, m, Ar*H*), 3.93−3.88 (2H, m, TfNHC*H*), 3.68 (1H, d, *J*=12.8 Hz, PhC*H*H), 3.56 (1H, d, *J*=12.8 Hz, PhCH*H*), 2.95 (2H, dd, *J*=9.7, 7.0 Hz, BnNC*H*H), 2.49 (2H, dd, *J*=9.8, 5.9 Hz, BnNCH*H*) ppm; ^{13}C NMR (100 MHz, CD_3OD) δ 138.7, 129.9, 129.4, 128.5, 121.2 (q, J_{C-F} 320 Hz), 61.0, 60.4, 59.7 ppm; IR (neat) 3040, 2922, 1472, 1377, 1196, 1099, 935 cm^{-1}; HRMS (ESI-TOF) calcd for $C_{13}H_{16}F_6N_3O_4S_2$: 456.0481 ($[M+H]^+$), found: 456.0482 ($[M+H]^+$).

4.2.6. (3R,4R)-3,4-Bis(trifluoromethylsulfonamido)-pyrrolidine (R,R)-**2**

A mixture of (*R*,*R*)-**11** (295 mg, 0.65 mmol) and 10% palladium on carbon (30 mg) in acetic acid (5 mL) was stirred under a hydrogen atmosphere at room temperature overnight. The reaction mixture was then filtered through a pad of Celite. The filtrate was concentrated and the acquired residue was purified by using ion exchange resin (Dowex® 50 W-X, supplied by Dow chemical Co. Ltd.) (5% ammonium hydroxide as eluent) to give (*R*,*R*)-**2** (220 mg, 0.60 mmol, 93% yield): $[\alpha]_D^{30}$ −36.5 (*c* 1.0, DMSO); ^{1}H NMR (400 MHz, CD_3OD) δ 3.98−3.95 (2H, m, TfNHC*H*), 3.51 (2H, dd, *J*=12.1, 6.0 Hz, HNC*H*H), 3.11 (2H, dd, *J*=12.1, 5.3 Hz, HNCH*H*) ppm; ^{13}C NMR (100 MHz, CD_3OD) δ 122.1 (q, J_{C-F}=316 Hz), 61.4, 51.5 ppm; IR (neat) 3165, 2351, 1479, 1391, 1202, 1161, 921 cm^{-1}; HRMS (ESI-TOF) calcd for $C_6H_{10}F_6N_3O_4S_2$: 366.0011 ($[M+H]^+$), found: 366.0008 ($[M+H]^+$).

4.3. Synthesis and characterization of chiral amino sulfonamide (S)-**3**

4.3.1. (S)-1-Benzyl-3-(trifluoromethylsulfonamido)-pyrrolidine (S)-**13**

To a stirred solution of (*S*)-1-benzyl-3-aminopyrrolidine ((*S*)-**12**) (353 mg, 2.0 mmol) in CH_2Cl_2 (4 mL) was added *N*,*N*-diisopropylethylamine (348 μL, 2.0 mmol) and trifluoromethanesulfonic anhydride (337 μL, 2.0 mmol) at 0 °C. The reaction mixture was stirred at 0 °C for 2 h. The reaction mixture was charged on silica gel directly and purified by flash column chromatography on silica gel (CH_2Cl_2/ethyl acetate=6:1) to afford (*S*)-**13** (363 mg, 1.2 mmol, 59% yield): $[\alpha]_D^{31}$ −8.6 (*c* 1.0, MeOH); ^{1}H NMR (400 MHz, CD_3OD) δ 7.37−7.28 (5H, m, Ar*H*), 4.12−4.05 (1H, m, TfNHC*H*), 3.81 (1H, d, *J*=12.8 Hz, PhC*H*H), 3.75 (1H, d, *J*=12.8 Hz, PhCH*H*), 2.98 (1H, dd, *J*=10.3, 7.1 Hz, BnNC*H*HCH), 2.86−2.80 (1H, m, BnNC*H*HCH_2), 2.74−2.68 (1H, m, BnNCH*H*CH_2), 2.57 (1H, dd, *J*=10.2, 5.6 Hz, BnNCH*H*CH), 2.32−2.23 (1H, m, BnNCH_2C*H*H), 1.82−1.74 (1H, m, BnNCH_2CH*H*) ppm; ^{13}C NMR (100 MHz, CD_3OD) δ 137.8, 130.4, 129.6, 128.9, 121.8 (q, J_{C-F}=322 Hz), 61.6, 60.8, 54.8, 53.5, 33.4 ppm; IR (neat) 2361, 1647, 1274, 1192, 1176 cm^{-1}; HRMS (ESI-TOF) calcd for $C_{12}H_{16}F_3N_2O_2S$: 309.0879 ($[M+H]^+$), found: 309.0877 ($[M+H]^+$).

4.3.2. (S)-3-(Trifluoromethylsulfonamido)pyrrolidine (S)-**3**

A mixture of (*S*)-**13** (273 mg, 0.88 mmol) and 10% palladium on carbon (100 mg) in ethanol (15 mL) was stirred under a hydrogen atmosphere for 20 h at room temperature. The reaction mixture was then filtered through a pad of Celite and the filtrate was concentrated to give (*S*)-**3** (192 mg, 0.88 mmol, 99% yield): $[\alpha]_D^{30}$ −16.7 (*c* 1.0, MeOH); ^{1}H NMR (400 MHz, CD_3OD) δ 4.13−4.09 (1H, m, TfNHC*H*), 3.40−3.32 (1H, m, HNC*H*HCH_2), 3.25 (1H, dd, *J*=11.5, 5.9 Hz, HNC*H*HCH), 3.25−3.18 (1H, m, HNCH*H*CH_2), 2.97 (1H, dd, *J*=11.4, 4.8 Hz, HNCH*H*CH), 2.14−2.05 (1H, m, HNCH_2C*H*H), 1.89−1.81 (1H, m, HNCH_2CH*H*) ppm; ^{13}C NMR (100 MHz, CD_3OD) δ 123.3 (q, J_{C-F}=326 Hz), 56.1, 54.1, 45.3, 34.7 ppm; IR (neat) 3227, 2970, 2361, 1744, 1622, 1456, 1385, 1279, 1182, 1146, 1101, 941 cm^{-1}; HRMS (ESI-TOF) calcd for $C_5H_9F_3N_2NaO_2S$: 241.0229 ($[M+Na]^+$), found: 241.0233 ($[M+Na]^+$).

4.4. Synthesis and characterization of chiral amino sulfonamide (S)-**4**

4.4.1. (S)-1-Benzyl-3-(nonafluorobutylsulfonamido)-pyrrolidine (S)-**14**

The title compound was prepared in a similar manner as described above using nonafluorobutanesulfonic anhydride instead of trifluoromethanesulfonic anhydride (89% yield): $[\alpha]_D^{30}$ −8.6 (*c* 1.0, MeOH); ^{1}H NMR (400 MHz, CD_3OD) δ 7.37−7.31 (5H, m, Ar*H*), 4.18−4.11 (1H, m, NfNHC*H*), 3.89 (1H, d, *J*=12.8 Hz, PhC*H*H), 3.83 (1H, d, *J*=12.6 Hz, PhCH*H*), 3.07−3.02 (1H, m, BnNC*H*HCH), 2.95−2.89 (1H, m, BnNC*H*HCH_2), 2.81−2.79 (1H, m, BnNCH*H*CH_2), 2.65 (1H, dd, *J*=10.3, 5.4 Hz, BnNCH*H*CH), 2.32−2.23 (1H, m, BnNCH_2C*H*H), 1.85−1.77 (1H, m, BnNCH_2CH*H*) ppm; ^{13}C NMR (100 MHz, DMSO-d_6) δ 136.4, 129.1, 128.3, 127.6, 116.9 (tq, $^2J_{C-F}$=33 Hz, $^1J_{C-F}$=288 Hz), 114.3 (tt, $^2J_{C-F}$=35 Hz, $^1J_{C-F}$=294 Hz), 110.2 (m), 108.3 (m), 60.3, 58.5, 53.7, 52.0, 32.3 ppm; IR (neat) 2980, 2311, 1350, 1277, 1194, 1134, 1026 cm^{-1}; HRMS (ESI-TOF) calcd for $C_{15}H_{16}F_9N_2O_2S$: 459.0783 ($[M+H]^+$), found: 459.0787 ($[M+H]^+$).

4.4.2. (S)-3-(Nonafluorobutylsulfonamido)pyrrolidine (S)-**4**

The title compound was prepared in a similar manner as described above (60% yield): $[\alpha]_D^{29}$ −3.5 (*c* 1.0, DMSO); ^{1}H NMR (400 MHz, DMSO-d_6) δ 4.00−3.97 (1H, m, NfNHC*H*), 3.23−3.16 (1H, m, HNC*H*HCH_2), 3.14−3.08 (1H, m, HNCH*H*CH_2), 3.04 (1H, dd, *J*=10.9, 5.3 Hz, HNC*H*HCH), 2.79 (1H, dd, *J*=10.6, 3.1 Hz, HNCH*H*CH), 1.94−1.85 (1H, m, HNCH_2C*H*H), 1.70−1.63 (1H, m, HNCH_2CH*H*) ppm;

^{13}C NMR (100 MHz, DMSO-d_6) δ 117.3 (tq, $^2J_{C-F}$=34 Hz, $^1J_{C-F}$=288 Hz,), 115.5 (tt, $^2J_{C-F}$=35 Hz, $^1J_{C-F}$=292 Hz,), 110.7 (m), 108.7 (m), 54.7, 53.0, 43.4, 34.1 ppm; IR (neat) 3140, 2936, 2450, 1612, 1352, 1258, 1184, 1140, 1101, 1036 cm^{-1}; HRMS (ESI-TOF) calcd for $C_8H_{10}F_9N_2O_2S$: 369.0314 ([M+H]$^+$), found: 369.0314 ([M+H]$^+$).

4.5. General procedure for the anti-selective direct asymmetric Mannich reaction of aldehydes with a chiral amino sulfonamide catalyst

To a stirred solution of a chiral amino sulfonamide (0.015 mmol) in THF (1.5 mL) were added ethyl (4-methoxyphenylimino)acetate **5** (31 mg, 0.15 mmol) and aldehyde (0.45 mmol) in this order at −20 °C. After stirring at −20 °C for the indicated time in Table 1, the reaction mixture was then quenched with brine and extracted with ethyl acetate. The combined organic layers were dried over Na_2SO_4 and concentrated. The residue was purified by preparative thin layer chromatography on silica gel (hexane/ethyl acetate=2:1) to afford the corresponding Mannich adduct **6**.

4.5.1. Ethyl (2R,3S)-3-formyl-2-(p-methoxyphenylamino)-butanoate

Spectral data were in agreement with those previously reported.[3b,5a] The enantiomeric excess was determined after reduction in accordance with the literature procedure.[2b]

4.5.2. Ethyl (2R,3S)-3-formyl-2-(p-methoxyphenylamino)-pentanoate

Spectral data were in agreement with those previously reported.[3b] HPLC analysis: Daicel Chiralpak AS-H, hexane/*i*-PrOH=99:1, flow rate=1.0 mL/min, retention time: 29 min and 35 min (major).

4.5.3. Ethyl (2R,3S)-3-formyl-2-(p-methoxyphenylamino)-4-methylpentanoate

Spectral data were in agreement with those previously reported.[3a] HPLC analysis: Daicel Chiralpak AS-H, hexane/*i*-PrOH=99:1, flow rate=1.0 mL/min, retention time: 23 min and 43 min (major).

4.5.4. Ethyl (2R,3S)-3-formyl-2-(p-methoxyphenylamino)-4,4-dimethylpentanoate

$[\alpha]_D^{31}$ 44.7 [*c* 1.0, $CHCl_3$ (98% ee)]; spectral data were in agreement with those previously reported.[3a] HPLC analysis: Daicel Chiralpak AS-H, hexane/EtOH=100:1, flow rate=1.0 mL/min, retention time: 11 min and 23 min (major).

4.6. General procedure for the anti-selective direct asymmetric Mannich reaction of ketones with a chiral amino sulfonamide catalyst

To a stirred solution of a chiral amino sulfonamide (0.015 mmol) in THF (1.2 mL) were added ethyl (4-methoxyphenylimino)acetate **5** (31 mg, 0.15 mmol) and ketone (0.3 mL) in this order at room temperature. After stirring at room temperature for the indicated time in Table 2, the reaction mixture was then quenched with brine and extracted with ethyl acetate. The combined organic layers were dried over Na_2SO_4 and concentrated. The residue was purified by preparative thin layer chromatography on silica gel (hexane/ethyl acetate=2:1) to afford the corresponding Mannich adduct **15**.

4.6.1. Ethyl (2R,1′S)-2-(p-methoxyphenylamino)-2-(2′-oxocyclohexyl)acetate

$[\alpha]_D^{29}$ −33.6 [*c* 1.0, $CHCl_3$ (99% ee)]; spectral data were in agreement with those previously reported.[3e] HPLC analysis: Daicel Chiralpak AS, hexane/*i*-PrOH=10:1, flow rate=1.0 mL/min, retention time: 11 min and 14 min (major).

4.6.2. Ethyl (2R,3′R)-2-(p-methoxyphenylamino)-2-(4′-oxotetrahydropyran-3′-yl)acetate

Spectral data were in agreement with those previously reported.[3e] HPLC analysis: Daicel Chiralpak AS-H, hexane/*i*-PrOH=4:1, flow rate=1.0 mL/min, retention time: 15 min and 19 min (major).

4.6.3. Ethyl (2R,3′S)-2-(p-methoxyphenylamino)-2-(4′-oxotetrahydrothiopyran-3′-yl)acetate

$[\alpha]_D^{26}$ −45.9 [*c* 1.0, $CHCl_3$ (97% ee)]; spectral data were in agreement with those previously reported.[3e] HPLC analysis: Daicel Chiralpak AS-H, hexane/EtOH=10:1, flow rate=1.0 mL/min, retention time: 14 min and 19 min (major).

4.6.4. Ethyl (2R,3S)-2-(p-methoxyphenylamino)-3-methyl-4-oxohexanoate

Spectral data were in agreement with those previously reported.[3e] HPLC analysis: Daicel Chiralpak AS-H, hexane/*i*-PrOH=99:1, flow rate=1.0 mL/min, retention time: 20 min and 33 min (major).

4.6.5. Ethyl (2R,3S)-3-ethyl-2-(p-methoxyphenylamino)-4-oxoheptanoate

Spectral data were in agreement with those previously reported.[3e] HPLC analysis: Daicel Chiralpak AD-H, hexane/EtOH=19:1, flow rate=1.0 mL/min, retention time: 8 min (*anti*, major), 12 min (*anti*, minor), 14 min (*syn*, major), and 17 min (*syn*, minor).

4.6.6. Ethyl (2R,3S)-2-(p-methoxyphenylamino)-3-methyl-4-oxopentanoate

$[\alpha]_D^{26}$ 27.6 [*c* 0.5, $CHCl_3$ (99% ee)]; spectral data were in agreement with those previously reported.[3e] HPLC analysis: Daicel Chiralpak AS-H, hexane/*i*-PrOH=100:1, flow rate=1.0 mL/min, retention time: 27 min and 54 min (major).

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