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Bimorpholine-Mediated Enantioselective Intramolecular and Intermolecular Aldol Condensation

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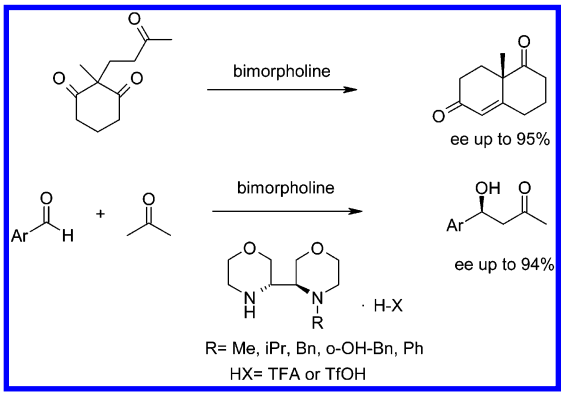
Received March 14, 2007



Monosalts of N-substituted bimorpholine derivatives are efficient organocatalysts in intramolecular and intermolecular aldol reactions. The properties of the catalysts can be tuned either by the selection of an appropriate acid for the salt formation or by the change of a substituent at the nitrogen atom. In aldol condensation, *i*-Pr-substituted bimorpholine is the most stereoselective catalyst affording products in high yield with enantioselectivities up to 95% ee.

Introduction

Aldol condensation is one of the basic reactions for creating a C−C bond.[1] The formation of new stereogenic centers in the course of the reaction makes it a highly valuable tool in asymmetric synthesis. Enantioselective metal-mediated[2] and organocatalytic methods for aldol condensations are both well-documented in the literature.[3] Organocatalysis, where low molecular weight molecules catalyze the reaction without the presence of any metal, has become a very popular tool in the stereoselective aldol reaction over the past few years.[4] Computational and mechanistic studies have revealed that in aldol condensation reaction enamines (carbanion equivalents) are generated in situ from chiral amine and carbonyl compounds followed by an enantioselective nucleophilic attack of the enamine on the electrophilic center.[5] Proline is the first[6] and the most popular organocatalyst in this field.[7] However, because of its limited solubility in common organic solvents, the use of the catalyst has several limitations. Therefore, a number of more soluble and also more stereoselective compounds like the

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10.1021/jo070524i CCC: $37.00
Published on Web 06/13/2007

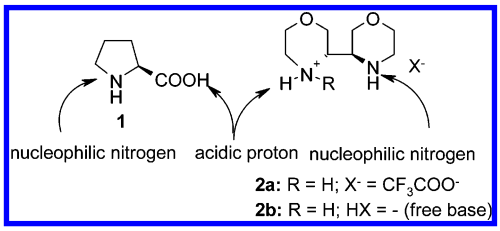


FIGURE 1. Proline **1** and bimorpholine **2** as bifunctional catalysts.

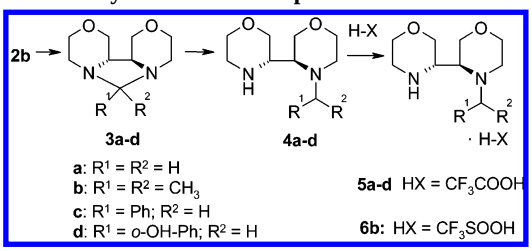
tetrazole analogue of proline,[8] proline amides,[9] dipeptides,[10] and many others[11] have been used as organocatalysts for aldol condensation. We have introduced a new family of organocatalysts, bimorpholines **2**, which are highly soluble in common reaction media and are easily separable from the reaction mixture.[12] The preliminary results demonstrating high efficiency and high stereoselectivity of the catalysts in organocatalytic Michael additions[13] and in intramolecular aldol condensations[14] have been recently published. Furthermore, bimorpholine **2** (or its derivatives) is also useful as a chiral ligand in the transition-metal-catalyzed asymmetric hydrogenation.[15]

One can notice principal similarity between the structures of proline and bimorpholine derivative **2a** (Figure 1).

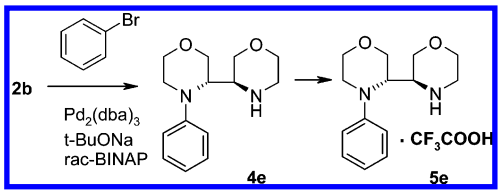
Both compounds are cyclic secondary amines with the chiral center at the α-position of the nitrogen atom. The monosalt of bimorpholine has an acidic proton at a distance of four chemical bonds, like in proline. Additional donor sites in the morpholine rings (O-atoms) may give rise to the formation of a strictly arranged hydrogen-bonded network.

Herein, we describe the synthesis of new bimorpholine derivatives and their use as bifunctional catalysts in aldol reactions.

SCHEME 1. Synthesis of Bimorpholines 5



SCHEME 2



Results and Discussion

Synthesis of Organocatalysts. Our preliminary experiments in the organocatalytic aldol condensation showed that N-monosubstituted bimorpholine derivatives are more selective catalysts than unsubstituted ones.[14] Taking advantage of this fact, we designed new bimorpholine derivatives **4a**−**e**. The C_2 symmetry of compound **2** offers a unique possibility to avoid the regioselectivity problem in monoalkylation. A selective method for the monoalkylation of 1,2-diamines consists of the formation of intermediate aminals from aldehydes or ketones followed by their reduction with sodium borohydride.[16] According to this general procedure several mono-N-alkylated bimorpholines and their monosalts were synthesized starting from bimorpholine **2b** (as a free base) (Scheme 1).

Thus, Me, *i*-Pr, Bn, and 2-hydroxybenzyl substituted bimorpholines **4a**−**d** were obtained in good yields (67−90%) and were converted into the corresponding monosalts **5a**−**d** and **6b** with 1 equiv of trifluoroacetic or trifluoromethanesulfonic acid.

For the synthesis of phenyl-substituted bimorpholine **4e,** Pd-catalyzed coupling of bromobenzene with compound **2b** was employed (Scheme 2). The catalytic system where rac-BINAP is used (according to the ref 17) enables us to preserve the enantiomeric purity of the starting bimorpholine in this reaction.

By applying this method, we obtained phenyl-substituted bimorpholine **4e** in 73% yield and high enantiomeric purity (de 98%, determined as the amide of (*S*)-methoxyphenylacetic acid by NMR). A free base **4e** was converted into the trifluoroacetic acid salt **5e** and was further used in the aldol condensation as an organocatalyst.

Intramolecular Aldol Condensation. We have previously found that the trifluoroacetic acid salt of bimorpholine derivative

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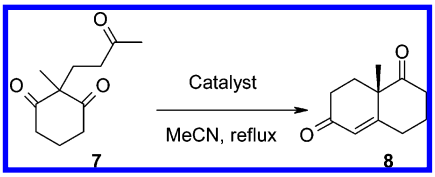
TABLE 1. Bimorpholine-Catalyzed Cyclization of Triketone 7



entry	catalyst (5 mol %)	time (h)	yield [a] (%)	ee[b] (%)
1	**5a**	72	73	82 (*S*)
2	**5b**	69	84	91 (*S*)
3	**5c**	72	75	88 (*S*)
4	**5d**	72	70	74 (*S*)
5	**5e**	120	14	29 (*R*)
6	**2a**	45	92	79 (*S*)
7	**4b**	69	45	*rac*
8	**6b**	96	60	95 (*S*)

[a] Isolated yield. [b] Determined by chiral HPLC.

5b catalyzes the intramolecular cyclization of triketone **7** in various solvents (THF, MeOH, *i*-PrOH, MeCN).[14] Under the optimized conditions (reflux in MeCN for approximately 70 h, catalyst loading 5 mol %) a valuable synthetic intermediate Wieland−Miescher ketone **8**, was obtained in high yield and in enantioselectivity (84% and 91%, respectively) from the cyclic triketone **7** (Table 1 entry 2).

We tested all synthesized new bimorpholine derivatives as organocatalysts in the intramolecular condensation reaction under the same conditions. We found that monosalts of the alkyl-substituted bimorpholines are efficient organocatalysts in the reaction that was chosen as a model. The obtained enantioselectivities are the highest reported so far in the literature, considerably exceeding, in most cases, those selectivities obtained with proline (ee 76%)[18] or with other organocatalysts.[18,19] The highest enantioselectivity was obtained with *i*-Pr-substituted catalyst (Table 1, entries 2, 8). 2-Hydroxybenzyl-substituted bimorpholine **5d** (derived from salicylaldehyde and compound **2b**) and unsubstituted bimorpholine **2a** afforded a product with lower enantiomeric purity (ee 74 and 79%, respectively, Table 1, entries 4 and 6).

It is well recognized that in the proline-catalyzed aldol reactions both the amine functionality and the carboxylic acid functionality play a crucial role in controling stereoselectivity and reactivity.[5] In bimorpholine-catalyzed reactions it is assumed that the acid catalyzes the enamine formation and also controls the level of enantioselectivity. When *i*-Pr-substituted bimorpholine was used as a free base (compound **4b**), a racemic ketone **8** was obtained (Table 1, entry 7). When a stronger acid (trifluoromethanesulfonic acid) salt was used, the reaction became considerably slower but more stereoselective (Table 1, entry 8). We propose a model according to which a preferential staggered conformation (the dihedral angle of 180° between the hydrogens) of bimorpholine is fixed via hydrogen bonding (Figure 2). In this chelated model the nitrogen atom becomes a new stereogenic center.[20]

Substituents at this new stereocenter may also induce additional stereodifferentiation. Therefore, a catalyst with the sterically most demanding alkyl group (*i*-Pr-group of compound **5b**) is also the most stereoselective.

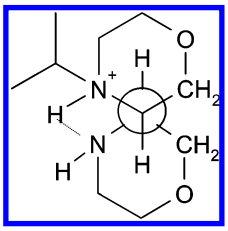


FIGURE 2. Proposed hydrogen-bonded structure of the bimorpholine acid catalyst.

However, the phenyl-substituted bimorpholine **5e** is an expection. The acidity of the secondary and the tertiary ammonium ions is comparable and, therefore, an equilibrium in the protonation of nitrogen atoms in bimorpholines **5a**−**d** exists.[21] The basicity of the substituted and the unsubstituted nitrogens of phenyl-substituted bimorpholine **4e** (as a free base) differs by several orders of magnitude. Protonation takes place favorably at the more basic secondary nitrogen atom, lowering its nucleophilicity and retarding the rate of cyclization. Thus, the isolated yield of ketone **8** was only 14% after the prolonged reaction time of 120 h (Table 1, entry 5). It is noteworthy that the opposite enantiomer of ketone **8** was obtained. Thus, the difference in pK_a of the substituted and the unsubstituted nitrogen atoms can be a switch to the enantioselectivity. It is known that a proper combination of the acid that matches the basicity of the amine is responsible for a high catalytic efficiency.[22] In bimorpholine substitution at the nitrogen atom allows us, via electronic or steric effects, to change the enantiopreference of the reaction. On the basis of these considerations, finely tunable bifunctional organocatalysts can be synthesized from bimorpholines.

Intermolecular Aldol Condensation. To widen the synthetic scope of our new organocatalysts, an intermolecular aldol condensation in the presence of the most efficient bimorpholine salt **6b** was investigated (Table 2). The reaction of acetone with 4-nitrobenzaldehyde **9a** was initially studied as a template to elucidate the influence of the catalyst amount and the reaction time on the stereoselectivity and conversion. 4-Nitrobenzaldehyde **9a** was allowed to react with the acetone in excess at room temperature for 6 days in the presence of 10 mol % of catalyst **6b**. The reaction was selective (only traces of α,*β*-unsaturated ketone were detected) affording mainly the desired product in 87% ee but in low yield (24%). When the amount of catalyst was increased to 30 mol %, the isolated yield improved to 70% without change in enantioselectivity. The following reactions were carried out using this high catalyst loading (30 mol %). The condensation of the substituted aromatic aldehydes **9a**−**g** with acetone in the presence of *i*-Pr-bimorpholine triflic salt **6b** afforded ketols **10a**−**g**; the results are presented in Table 2. The reactivity of the catalyst strongly depends on the electronic effect of the substituent at the phenyl ring. The aldehydes which were activated by electron-withdrawing groups or by electronegative substituents gave products in good to high yields (48−

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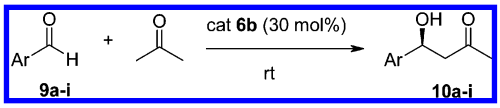
TABLE 2. Intermolecular Aldol Condensation of Various Benzaldehydes with Acetone[a]



entry	Ar	ketol **10**	yield[b] (%)	ee[d,e] (%)
1	4-$NO_2C_6H_4$ (**9a**)	**10a**	70	88
2	2-$NO_2C_6H_4$ (**9b**)	**10b**	77	94
3	4-$CF_3C_6H_4$ (**9c**)	**10c**	48[c]	90
4	4-ClC_6H_4 (**9d**)	**10d**	12[c]	88
5	2-ClC_6H_4 (**9e**)	**10e**	79	89
6	2,4-$Cl_2C_6H_3$ (**9f**)	**10f**	74	88
7	2-Cl-6-FC_6H_3 (**9g**)	**10g**	91	88
8	Ph (**9h**)	**10h**	18[c]	85
9	4-*i*-PrC_6H_4 (**9i**)	**10i**	<10[c]	76[f]

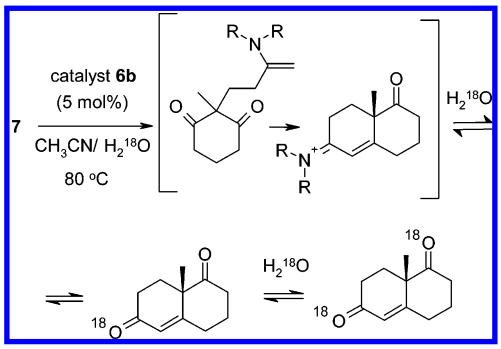
[a] Conditions: 0.3 mmol of aldehyde and 0.09 mmol of catalyst **6b** in 0.6 mL of acetone at room temperature for 6 days. [b] Isolated yield after column chromatography. [c] The reaction time was 10 days. [d] Determined by chiral HPLC analysis. [e] Absolute configuration (*S*) was assigned by comparing the specific rotation with the reference values.[9b,11a,23] [f] Absolute configuration was assigned by analogy.

91%, Table 2, entries 1−3 and 5−7). Nonactivated benzaldehydes were less reactive and gave very poor yields (Table 2, entries 4, 8, and 9). The existence of the electronegative groups at both *ortho*-positions of the phenyl ring causes double activation of aldehyde **9g** and the higher yield of aldol product (91%, Table 2, entry 7).

The enantioselectivities of the condensation are generally either good or high (ee 76−94%). There is no clear dependence between enantioselectivity and the substitution pattern of the aromatic ring. Activated and nonactivated aldehydes gave similarly high enantioselectivity. It is hard to envisage a steric argument since the sterically most crowded 2,6-disubstituted benzaldehyde **9g** gave product **10g** with quite similar enantiomeric purity to that of the unsubstituted benzaldehyde (Table 2, entries 7 and 8). Practically equal enantioselectivities were obtained with *o*-chloro-, *p*-chloro-, and *o*,*p*-dichloro-substituted derivatives (Table 2, entries 4−6). The best selectivity was obtained with *o*-nitrobenzaldehyde (ee 94%, entry 2). The most intriguing is the fact that the *S*-isomer was obtained by the bimorpholine **6b** catalyzed reaction, while the L-proline-catalyzed reaction afforded *R*-isomer. At the same time, in the intramolecular condensation the same handed, not opposite enantiomers, were obtained by using these catalysts. Opposite stereodiscrimination can be rationalized supposing that the environment in bimorpholine salt with fixed conformation is sterically more crowded than that in proline.

Mechanistic Considerations. In order to prove that bimorpholine-catalyzed intramolecular aldol reaction proceeds via iminium ion and enamine intermediates, which is generally accepted as a basic mechanism for the organocatalytic proline-catalyzed aldol reaction,[5] ^{18}O isotope incorporation studies were conducted. Thus, intramolecular cylization of triketone **7** in the mixture of MeCN and ^{18}O-enriched water (in ratio 10:1) was performed. We assumed that if the enamine is formed from a carbonyl group in the acyclic chain of triketone **7** in the course of the reaction, the hydrolysis of it with isotopically labeled water should give a product where ^{18}O atom is incorporated into the conjugated carbonyl moiety (Scheme 3).

SCHEME 3



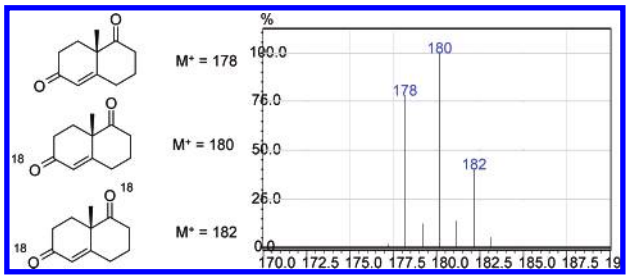


FIGURE 3. Mass spectrum of isotopically labeled ketone **8**.

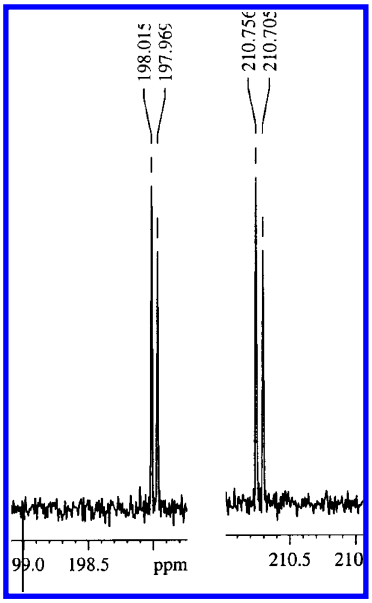


FIGURE 4. ^{13}C NMR spectrum of isotopically labeled ketone **8**.

However, to our surprise we found from MS data that two labeled oxygen atoms were incorporated into the bicyclic product **8**. The M^+ peak at 182 (which is 4 mass units higher than that obtained for the unlabeled compound) clearly indicates it (Figure 3). This was also proved by ^{13}C NMR which revealed ^{18}O isotope shifts for isolated and for conjugated carbonyl moieties (Figure 4). Considering the long reaction time and the high temperature, we suppose that a reversible nucleophilic addition of ^{18}O-labeled water to the isolated carbonyl group affords ketone **8** with two labeled oxygen atoms. In the conjugated carbonyl group a similar reaction takes place only in the presence of a special catalyst rather than with the conventional acid catalysts.[24] Thus, the incorporation of the ^{18}O-

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atom into the conjugated carbonyl group of bicyclic keto−enone **8** strongly supports the existence of enamine intermediate in the bimorpholine-catalyzed aldol reaction.

Conclusions

In this paper we have demonstrated that N-monoalkylated bimorpholine salts are efficient organocatalysts in the intramolecular and the intermolecular aldol reactions affording products with high ee (up to 95%). The formation of an enamine intermediate via one secondary NH group of bimorpholine allows the possibility of the modification of the substituents at the other nitrogen atom. An easy method for substitution is to reduce the aminals obtained from the ketone or the aldehyde and the bimorpholine. The proposed flexible method for the synthesis of organocatalysts makes possible fine-tuning of steric and electronic properties of the organocatalyst. The syntheses of the next generation of bimorpholine-based catalysts and search for their applications are currently underway in our laboratory.

Experimental Section

General Procedure of Organocatalysts 4a−d Preparation. The mixture of bimorpholine **2b** (2 mmol), the corresponding aldehyde (2 mmol) in Et_2O or toluene (10 mL), and molecular sieves (4 Å, ∼500 mg) was stirred overnight, filtered, and evaporated. The obtained aminals **3a−d** were used as crude products in the next step. $NaCNBH_3$ (4 equiv) was added portionwise to the solution of crude aminal in anhydrous MeOH (12 mL) at 0 °C followed by the slow addition of CH_3COOH (10 equiv). The mixture was allowed to warm up to room temperature and was stirred for 3 h. The reaction was quenched with 20% NaOH aqueous solution, and the product was extracted with EtOAc and dried. Concentration in vacuum and purification of the crude product by chromatography on silica gel afforded compounds **4a-d**.

(3*S*,3′*S*)-4-Benzyl-3,3′-bimorpholine (4c). To a solution of (3*S*,3′*S*)-3,3′-bimorpholine (126 mg, 0.73 mmol) and 4 Å molecular sieves (150 mg) in anhydrous toluene (3 mL), benzaldehyde (90 μL, 0.88 mmol) was added under argon atmosphere. The mixture was stirred under reflux for 3 h, filtered through Celite, and concentrated in vacuum affording a pale yellow oil of a crude aminal (204 mg). MS (EI): *m*/*z* (%) = 259 (30), 183 (51), 175 (100), 91 (30).

$NaCNBH_3$ (230 mg, 3.65 mmol) was added portionwise to a solution of crude aminal (204 mg, 0.73 mmol) in anhydrous MeOH (5 mL) at 0 °C followed by slow addition of CH_3COOH (0.42 mL, 7.3 mmol). The mixture was allowed to warm up and was stirred at room temperature for 3 h. The reaction was quenched with 20% NaOH aqueous solution (5 mL) and water (2 mL), extracted with EtOAc (4 × 10 mL), and dried over K_2CO_3. Concentration in vacuum and purification of the crude product by chromatography on silica gel (100:1 mixture of CH_2Cl_2 and 17% solution of NH_3 in MeOH) afforded compound **4c** as a colorless oil, which solidified in the freezer (128 mg, 67% for two steps). mp 60−61 °C. $[\alpha]_D^{21}$ = +34.9 (*c* = 3.29, MeOH). IR (KBr): 3311, 3028, 2957, 2909, 2852, 1633, 1495, 1451, 1314, 1104, 738, 699 cm^{-1}. ^1H NMR ($CDCl_3$, 500 MHz): δ 7.32 (m, 5H, *o*-, *m*-, *p*-), 7.26 (m, 1H, NH), 4.09 and 3.28 (2d, 2H, *J* = 13.2 Hz, Bn), 4.01 (m, 1H, H-2′), 3.96 (dd, 1H, *J* = 3.2 and 12.0 Hz, H-2), 3.79 (td, 1H, *J* = 2 × 2.3 and 11.0 Hz, H-6′), 3.74 (ddd, 1H, *J* = 2.8, 6.8 and 11.5 Hz, H-6), 3.52 (m, 2H, H-2, H-6′), 3.49 (ddd, 1H, *J* = 2.9, 6.8 and 11.5 Hz, H-6), 3.39 (m, 2H, H-2′ and H3′), 2.94 (dt, 1H, *J* = 3.1 and 2 × 11.5 Hz, H-5′), 2.90 (td, 1H, *J* = 2 × 2.3 and 11.5 Hz, H-5′), 2.84 (ddd, 1H, *J* = 2.8, 6.8, and 13.1 Hz, H-5), 2.48 (m, 1H, H-3), 2.29 (ddd, 1H, *J* = 2.8, 6.4, and 13.1 Hz, H-5). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 138.57 (C-*s*), 128.80 (C-*o*), 128.35 (C-*m*), 127.17 (C-*p*), 69.21 (C-2′), 67.56 (C-6′), 64.61 (C-2), 64.35 (C-6), 61.04 (C-3), 57.53 (Bn), 53.11 (C-3′), 48.14 (C-5), 46.38 (C-5′). MS (EI): *m*/*z* (%) = 262 (0.1), 176 (88), 91 (100), 86 (10), 65 (6). HRMS (*m*/*z*): $[M + H^+]$ calcd for $(C_{11}H_{14}NO)^+$, 176.1074; found, 176.1071. Anal. Calcd for $C_{15}H_{21}N_2O_2$ (262.35): C, 68.67; H, 8.45; N, 10.68. Found: C, 68.11; H, 8.45; N, 10.62.

(3*S*,3′*S*)-2-(3,3′-Bimorpholin-4-ylmethyl)phenol (4d). To a solution of (3*S*,3′*S*)-3,3′-bimorpholine (218 mg, 1.27 mmol) and 4 Å molecular sieves (250 mg) in anhydrous toluene (7.5 mL), salicylaldehyde (150 μL, 1.39 mmol) was added under argon atmosphere. The mixture was refluxed for 3 h, filtered through Celite, and concentrated in vacuum affording a pale yellow oil of the crude aminal (408 mg). MS (EI): *m*/*z* (%) = 275 (23), 191 (100), 107 (22), 86 (16).

$NaBH_4$ (193 mg, 5.08 mmol) was added portionwise to a solution of crude aminal (408 mg, 1.27 mmol) in anhydrous MeOH (8 mL) at 0 °C followed by slow addition of CH_3COOH (0.73 mL, 12.7 mmol). The mixture was allowed to warm up and was stirred at room temperature for 2 h. The reaction was quenched with 20% NaOH aqueous solution (7 mL) and water (3 mL), extracted with EtOAc (5 × 10 mL), and dried over Na_2SO_4. Concentration in vacuum and purification of the crude product by chromatography on silica gel (100:1 mixture of CH_2Cl_2 and 17% solution of NH_3 in MeOH) afforded compound **4d** as a colorless oil (316 mg, 90% for two steps). $[\alpha]_D^{21}$ = +40 (*c* = 2.76, CH_2Cl_2). IR (KBr): 3286, 2957, 2854, 1587, 1489,1456, 1253, 1104, 757 cm^{-1}. ^1H NMR ($CDCl_3$, 500 MHz): δ 7.19 (ddd, 1H, *J*=1.6, 7.4 and 8.0 Hz, H-4″), 7.00 (dd, 1H, *J* = 1.6 and 7.4 Hz, H-6″), 6.84 (dd, 1H, *J* = 1.1 and 8.0 Hz, H-3″), 6.79 (dt, 1H, *J* = 1.1 and 2 × 7.4 Hz, H-5″), 4.32 and 3.53 (2d, 2H, *J* = 13.5 Hz, Bn), 3.93 (dd, 1H. *J* = 3.1 and 11.3 Hz, H-2′), 3.87 (dd, 1H, *J* =3 .2 and 11.9 Hz, H-2), 3.80 (td, 1H, *J* = 2 × 2.7 and 11.3 Hz, H-6′), 3.79 (td, 1H, *J* = 2 × 2.3 and 11.0 Hz, H-6′), 3.72 (ddd, 1H, *J* = 3.1, 4.9, and 11.6 Hz, H-6), 3.59 (ddd, 1H, *J* = 2.8, 8.2, and 11.6 Hz, H-6), 3.52 (m, 1H, H-6′), 3.50 (m, 1H, H-2′), 3.21 (ddd, 1H, *J* = 3.1, 5.3, and 9.9 Hz, H3′), 2.98 (m, 2H, H-5′), 2.90 (ddd, 1H, *J* = 2.8, 4.9, and 12.9 Hz, H-5), 2.52 (m, 1H, H-3), 2.42 (ddd, 1H, *J* = 3.1, 8.2, and 12.9 Hz, H-5). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 157.29 (C-2″), 129.54 (C-6″), 129.08 (C-4″), 121.33 (C-1″), 119.17 (C-5″), 116.25 (C-3″), 69.89 (C-2′), 67.54 (C-6′), 66.30 (C-2), 64.65 (C-6), 60.84 (C-3), 56.08 (Bn), 53.72 (C-3′), 49.13 (C-5), 46.02 (C-5′). MS (EI): *m*/*z* (%) = 279 (0.5), 192 (56), 107 (47), 86 (100). HRMS (*m*/*z*): $[M + H^+]$ calcd for $(C_{11}H_{14}NO_2)^+$, 192.1023; found, 192.1019. Anal. Calcd for $C_{15}H_{22}N_2O_3$ (278.35): C, 64.73; H, 7.97; N, 10.06. Found: C, 63.66; H, 8.32; N, 9.40.

(3*S*,3′*S*)-4-Phenyl-3,3′-bimorpholine (4e). A mixture of (3*S*,3′*S*)-3,3′-bimorpholine (406 mg, 2.36 mmol), $Pd_2(dba)_3$ (43 mg, 0.05 mmol), *rac*-BINAP (58 mg, 0.09 mmol), bromobenzene (248 μL, 2.36 mmol), and sodium *tert*-butoxide (317 mg, 3.30 mmol) in toluene (25 mL) was stirred at 70 °C for 20 h under argon atmosphere. The mixture was diluted with Et_2O, filtered through Celite, and concentrated in vacuum. Purification by column chromatography on silica gel using a mixture of methylene chloride and MeOH (saturated with gaseous ammonia) as eluent afforded the target compound as an oil, which solidified in the freezer, (427 mg, yield 73%). mp 70−71 °C, $[\alpha]_D^{23}$ = +31.1 (*c* = 3.29, MeOH). IR (KBr): 3317, 3058, 3022, 2908, 2851, 1597, 1502, 1257, 1103, 752, 694 cm^{-1}. ^1H NMR ($CDCl_3$, 500 MHz): δ 7.25 (m, 2H, *m*-), 6.91 (m, 2H, *o*-), 6.80 (t, 1H, *J* = 2 × 7.4 Hz, *p*-), 3.94 (dd, 1H, *J* = 2.7 and 10.7 Hz, H-2′), 3.87 (m, 1H, H-6), 3.85 (m, 1H, H-2), 3.75 (td, 1H, *J* = 2 × 2.7 and 11.0 Hz, H-6′), 3.70 (m, 1H, H-2), 3.69 (m, 1H, H-6), 3.54 (m, 1H, H-3), 3.53 (m, 1H, H-6′), 3.48 (m, 1H, H-5), 3.46 (m, 1H, H-3′), 3.39 (dd, 1H, *J* = 9.2 and 10.7 Hz, H-2′), 3.38 (m, 1H, H-5), 2.85 and 2.83 (m, 2H, H-5′). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 150.02 (C-*s*), 129.36 (C-*m*), 118.77 (C-*p*), 115.59 (C-*o*), 70.28 (C-2′), 67.29 (C-6′), 66.07 (C-2), 65.98 (C-6), 57.5 (C-3), 53.07 (C-3′), 45.96 (C-5′), 43.53 (C-5). MS (EI): *m*/*z* (%) = 248 (2), 162 (100), 86 (25), 56 (6). HRMS (*m*/*z*): $[M + H^+]$ calcd for $(C_{10}H_{12}NO)^+$, 162.0913; found: 162.0918.

General Procedure of Preparation Bimorpholine Salts 5a−e and 6b. To a solution of substituted bimorpholine (1 mmol) in Et_2O (4 mL), the corresponding acid (1 mmol) was added at 0 °C. The precipitate was collected by filtration and dried in vacuum.

(3*S*,3′*S*)-4-Methyl-3,3′-bimorpholine Trifluoroacetic Acid Salt (5a). mp 104−105 °C. $[\alpha]_D^{21} = +9.8$ (c = 4.21, MeOH). IR (KBr): 3448, 2963, 2761, 1682, 1431, 1207, 1114, 1102, 846, 724 cm^{-1}. ^1H NMR (CD_3OD, 500 MHz): δ 4.84 (bs, OH), 4.08 (dd, 1H, J = 3.3 and 12.7 Hz, H-2′), 3.95 (td, 1H, $J = 2 \times 3.5$ and 12.6 Hz, H-6′), 3.91 (dd, 1H, J = 3.1 and 13.0 Hz, H-2), 3.83 (m, 1H, H-6), 3.78 (m, 1H, H-3′), 3.72 (ddd, 1H, J = 3.3, 9.5 and 12.6 Hz, H-6′), 3.59 (dd, 1H, J = 8.6 and 12.7 Hz, H-2′), 3.52 (m, 2H, H-2,6), 3.24 (m, 1H, H-5′), 3.20 (m, 1H, H-5), 3.19 (m, 1H, H-5′), 2.67 (s, 3H, N−Me), 2.65 (m, 1H, H-3), 2.52 (dm, 1H, J = 14.3 Hz, H-5). ^{13}C NMR (CD_3OD, 125 MHz): δ 67.27 (C-2′), 65.21 (C-6′), 62.88 (C-6), 61.30 (C-2), 58.39 (C-3), 53.03 (C-3′), 49.09 (C-5), 44.07 (C-5′), 41.67 (N−Me). MS (EI): m/z (%) = 100 (100), 86 (16), 70 (19), 69 (14), 45 (17). HRMS (*m/z):* [M + H^+] calcd for $(C_5H_{10}NO)^+$, 100.0762; found: 100.0762. Anal. Calcd for $C_{11}H_{19}F_3N_2O_4$ (300.28): C, 44.00; H, 6.38; N, 9.33. Found: C, 43.61; H, 6.41; N, 9.23.

(3*S*,3′*S*)-4-Isopropyl-3,3′-bimorpholine Trifluoroacetic Acid Salt (5b). mp 113−115 °C. $[\alpha]_D^{21} = +11.7$ (c = 2.24, MeOH). IR (KBr): 3427, 2493, 1672, 1623, 1208, 1129, 1107 cm^{-1}. ^1H NMR ($CDCl_3$, 500 MHz): δ 9.0 (bs, 2H, NH), 4.11 (m, 1H, H-2′), 3.95 (m, 1H, H-6′), 3.84 (m, 2H, H-2,6′), 3.77 (m, 2H, H-2′,3′), 3.65 (m, 1H, H-6), 3.58 (m, 1H, H-6), 3.54 (m, 1H, H-2), 3.31 (m, 1H, H-5′), 3.22 (hept, 1H, J = 6.6 Hz, *i*-Pr), 3.17 (m, 1H, H-5′), 3.04 (m, 2H, H-3,5), 2.73 (m, 1H, H-5), 1.12 and 1.09 (2d, 6H, J = 6.6 Hz, *i*-Pr). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 162.24 (q, J = 35.1 Hz, COO), 116.57 (q, J = 292.8 Hz, CF_3), 65.74 (C-2′), 64.90 (C-6), 63.64 (C-6′), 63.01 (C-2), 53.92 (C-3), 51.98 (C-3), 51.07 (*i*-Pr), 43.26 (C-5′), 41.50 (C-5), 21.66 and 19.97 (*i*-Pr). MS (EI): m/z (%) = 128 (100), 86 (68), 69 (30), 45 (51). HRMS (m/z): [M + H^+] calcd for $(C_7H_{14}NO)^+$, 128.1081; found: 128.1079. HRMS (m/z): [M + H^+] calcd for $(C_4H_8NO)^+$, 86.0611; found: 86.0604.

(3*S*,3′*S*)-4-Isopropyl-3,3′-bimorpholine Trifluoromethanesulfonic Acid Salt (6b). mp 104−105 °C. $[\alpha]_D^{21} = +13.4$ (c = 2.50, MeOH). IR (KBr): 3437, 2860, 2525, 1279, 1245, 1153, 1103, 1031, 641, 519 cm^{-1}. ^1H NMR ($CDCl_3$, 500 MHz): δ 6.8 (bs, 2H, NH), 4.10 (m, 1H, H-2′), 3.98 (m, 1H, H-6′), 3.91 (m, 1H, H-6′), 3.80 (m, 2H, H-2,3′), 3.74 (m, 1H, H-2′), 3.60 (m, 2H, H-6), 3.58 (m, 1H, H-2), 3.34 (m, 1H, H-5′), 3.28 (m, 2H, H-5′, and *i*-Pr), 3.02 (m, 1H, H-3), 3.01 (m, 1H, H-5), 2.86 (m, 1H, H-5), 1.20 and 1.19 (2d, 6H, J =6 .5 Hz, *i*-Pr). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 120.09 (q, J = 318.9 Hz, CF_3), 65.16 (C-2′), 64.46 (C-6), 63.57 (C-6′), 62.18 (C-2), 52.31 (C-3), 52.21 (*i*-Pr), 50.99 (C-3′), 42.35 (C-5′), 40.99 (C-5), 21.95 and 21.68 (*i*-Pr). MS (EI): m/z (%) = 215 (2), 128 (100), 86 (54), 69 (12). HRMS (*m/z):* [M + H^+] calcd for $(C_7H_{14}NO)^+$, 128.1081; found: 128.1086. HRMS (*m/z):* [M + H^+] calcd for $(C_4H_8NO)^+$, 86.0611; found: 86.0612.

(3*S*,3′*S*)-4-Benzyl-3,3′-bimorpholine Trifluoroacetic Acid Salt (5c). mp 105−108 °C. $[\alpha]_D^{21} = +6.9$ (c = 2.24, MeOH). IR (KBr): 3428, 2850, 2518, 1668, 1454, 1198, 1175, 1138, 800, 724 cm^{-1}. ^1H NMR ($CDCl_3$, 500 MHz): δ 7.33 (m, 4H, Bn *o*-, *m*-), 7.29 (m, 1H, Bn *p*-), 4.10 (dd, 1H, J = 2.9 and 12.8 Hz, H-2′), 4.01 (dd, 1H, J = 2.8, 12.9 Hz, H-2), 3.99 and 3.92 (both d, 2H, J = 13.3 Hz, Bn), 3.87 (m, 1H, H-3′), 3.81 (m, 1H, H-2′), 3.80 (m, 1H, H-6′), 3.79 (m, 1H, H-6), 3.67 (m, 1H, H-6′), 3.59 (m, 1H, H-2), 3.53 (m, 1H, H-6), 3.18 (m, 1H, H-5), 2.95 (m, 1H, H-3), 2.94 (m, 1H, H-5′), 2.68 (m, 1H, H-5′), 2.56 (dm, J = 14.6 Hz, H-5). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 162.51 (q, J = 35.0 Hz, COO), 116.67 (q, J = 292.8 Hz, CF_3), 65.08 (C-2′), 63.72 (C-6′), 62.79 (C-6), 60.85 (C-2), 57.32 (Bn), 53.70 (C-3), 50.71 (C-3′), 45.85 (C-5), 41.33 (C-5′). MS (EI): m/z (%) = 176 (49), 91 (100), 86 (12), 69 (12), 45 (30). HRMS (*m/z):* [M + H^+] calcd for $(C_{11}H_{14}NO)^+$, 176.1075; found: 176.1079. Anal. Calcd for $C_{17}H_{23}F_3N_2O_4$ (376.38): C, 54.25; H, 6.16; N, 7.44. Found: C, 54.58; H, 6.16; N, 7.49.

(3*S*,3′*S*)-2-(3,3′-Bimorpholin-4-ylmethyl)phenol Trifluoroacetic Acid Salt (5d). mp 147−149 °C. $[\alpha]_D^{21} = +11.0$ (c = 1.84, MeOH). IR (KBr): 3079, 2959, 2867, 2778, 2463, 1671, 1607, 1463, 1208, 1184, 1143, 1116, 995, 802, 762 cm^{-1}. ^1H NMR (CD_3-OD, 500 MHz): δ 7.25 (dd, 1H, J = 1.2 and 7.4 Hz, H-6″), 7.15 (ddd, 1H, J = 1.2, 7.4, and 8.0 Hz, H-4″), 6.84 (dt, 1H, J = 1.0 and 2 × 7.4 Hz, H-5″), 6.83 (dd, 1H, J = 1.0 and 8.0 Hz, H-3″), 4.11 and 4.04 (both d, 2H, J = 12.5 Hz, Bn), 4.03 (m, 1H, H-2), 4.00 (m, 1H, H-2′), 3.90 (dt, 1H, J = 2.4 and 2 × 11.8 Hz, H-6), 3.82 (m, 1H, H-6′), 3.80 (m, 1H, H-3′), 3.75 (m, 1H, H-2′), 3.70 (m, 1H, H-6′), 3.65 (dm, 1H, J = 13.0 Hz, H-2), 3.55 (dm, 1H, J = 11.3 Hz, H-6), 3.12 (ddd, 1H, J = 3.7, 12.2, and 15.1 Hz, H-5), 3.02 (m, 1H, H-5′), 2.99 (m, 1H, H-3), 2.94 (ddd, 1H, J = 3.2, 6.2, and 13.2 Hz, H-5′), 2.67 (dm, J = 14.5 Hz, H-5). ^{13}C NMR (CD_3OD, 125 MHz): δ 163.07 (q, J = 34.7 Hz, COO), 157.25 (C-2″), 133.03 (C-6″), 130.46 (C-4″), 124.92 (C-1″), 120.89 (C-5″), 118.26 (q, J = 293.2 Hz, CF_3), 116.54 (C-3″), 66.41 (C-2′), 65.08 (C-6′), 63.02 (C-6), 61.43 (C-2), 55.29 (C-3), 52.99 (Bn), 52.03 (C-3′), 45.59 (C-5), 42.46 (C-5′). MS (EI): m/z (%) = 192 (32), 107 (38), 86 (100), 77 (11), 69 (14), 45 (17). HRMS (*m/z):* [M + H^+] calcd for $(C_{11}H_{14}NO_2)^+$, 192.1023; found: 192.1020. Anal. Calcd for $C_{17}H_{23}F_3N_2O_5$ (392.38): C, 52.04; H, 5.91; N, 7.14. Found: C, 51.67; H, 5.92; N, 6.99.

(3*S*,3′*S*)-4-Phenyl-3,3′-Bimorpholine Trifluoroacetic Acid Salt (5e). mp 189−191 °C. $[\alpha]_D^{21} = +44.5$ (c = 2.2, MeOH). IR (KBr): 2981, 2861, 2496, 1682, 1599, 1501, 1200, 1131, 1107, 760, 720. ^1H NMR ($CDCl_3$, 500 MHz): δ 9.54 (bs, 1H, NH), 9.26 (bs, 1H, NH), 7.18 (m, 2H, *m*-), 6.85 (m, 2H, *o*-), 6.75 (t, 1H, $J = 2 \times 7.3$ Hz, *p*-), 4.06 (dd, 1H, J = 2.5 and 12.0 Hz, H-2′), 3.88 (m, 1H, H-3′), 3.83 (m, 1H, H-3), 3.70 (m, 1H, H-6′), 3.69 (m, 1H, H-2′), 3.63 and 3.61 (m, 2H, H-2), 3.52 and 3.50 (m, 2H, H-5′), 3.49 and 3.27 (m, 2H, H-6), 2.65 and 1.98 (m, 2H, H-5). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 161.29 (q, J = 35.5 Hz, COO), 148.25 (C-*s*), 129.49 (C-*m*), 119.27 (C-*p*), 116.03 (q, J = 293.1 Hz, CF_3), 115.93 (C-*o*), 66.12 (C-2′), 65.14 (C-6′), 63.51 (C-2), 63.12 (C-6), 54.06 (C-3), 51.74 (C-3′), 43.52 (C-5′), 43.19 (C-5). MS (EI): m/z (%) = 248 (4), 162 (100), 132 (28), 119 (26), 86 (38), 69 (37). HRMS (*m/z):* [M + H^+] calcd for $(C_{10}H_{12}NO)^+$, 162.0913; found: 162.0911. Anal. Calcd for $C_{16}H_{21}F_3N_2O_4$ (362.34): C, 53.04; H, 5.84; N, 7.73. Found: C, 53.11; H, 5.87; N, 7.67.

General Procedure for the Organocatalytic Intramolecular Aldol Condensation. Organocatalyst **5** (0.05 mmol) was added to the stirred solution of triketone **7** (1.0 mmol) in anhydrous MeCN (2.0 mL). The reaction mixture was refluxed for an appropriate time. The reaction was monitored by capillary GC. After completion of the reaction, toluene was added, the mixture was concentrated in vacuum, and a crude product was purified by chromatography on silica gel (30% EtOAc in petroleum ether).

General Procedure for the Organocatalytic Intermolecular Aldol Condensation of Aromatic Aldehyde and Acetone. Organocatalyst **6b** (0.09 mmol) was added to the solution of the corresponding aromatic aldehyde **9a−i** (0.3 mmol) in acetone (0.6 mL), and the mixture was stirred at room temperature for an appropriate time (6−10 days). The reaction mixture was treated with saturated NaCl solution and extracted with EtOAc or Et_2O, and the combined organic layers were dried. After filtration and concentration in vacuum, the crude product **10a−i** was purified by chromatography on silica gel.

Acknowledgment. The authors thank Estonian Science Foundation (Grant Nos. 6662, 5628, and 6778) and the Ministry of Education and Research (GrantNo. 0142725s06) for financial support.

Supporting Information Available: Experimental details, product characterization, and chromatographic data. This material is available free of charge via the Internet at http://pubs.acs.org.

JO070524I