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Structural constraints for C_2-symmetric heterocyclic organocatalysts in asymmetric aldol reactions

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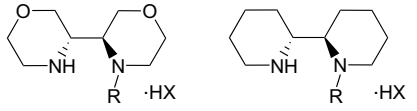
Abstract—Asymmetric aldol reactions were studied in the presence of heterocyclic bimorpholine- and bipiperidine-type organocatalysts. Bimorpholine derivatives were found to be more reactive and more selective in intramolecular, as well as intermolecular, reactions.

1. Introduction

Until the turn of the century, metal catalysis had been dominant, in contrast to the little attention that has been paid to organocatalysis. Over the past few years, it has become evident that simple organic molecules could be highly effective and remarkably enantioselective catalysts in a variety of important transformations. This rediscovery has initiated a growth in the whole area of organocatalysis, particularly in asymmetric aminocatalysis.[1]

Without doubt, L-proline has a special place in the field of organocatalysis, with it being used in a wide variety of asymmetric reactions, among them being the aldol reaction.[2] In this important C–C bond forming reaction, new stereogenic centres are formed. Although the high efficiency of proline has been clearly demonstrated in the enantioselective direct aldol reaction,[3] its shortcoming is a poor solubility in other solvents other than water, DMF and DMSO. We have designed and synthesised organocatalysts, which are 3,3′-bimorpholines (BM)[4] **1**, which are highly soluble in many organic solvents (Fig. 1). These heterocyclic 1,2-diamines are efficient organocatalysts for the direct asymmetric Michael addition of aldehydes to nitroolefines with enantioselectivities up to 90%.[5] Moreover, they catalyse intramolecular and intermolecular aldol condensation with an ee up to 95%.[6]



1a R=H
1b R=$(CH_3)_2CH_2$
1c R=$(CH_3)_2CH_2$ HX=CF_3COOH
1d R=$(CH_3)_2CH_2$ HX=CF_3SO_3H

2 R=H
3a R=$(CH_3)_2CH_2$
3b R=$(CH_3)_2CH_2$ HX=CF_3COOH
3c R=$(CH_3)_2CH_2$ HX=CF_3SO_3H

Figure 1.

The synthesis of compound **1a** is relatively simple, however, it consists of 7 steps (starting from commercially available 2,3-*O*-isopropylidene-D-threitol), with 46% overall yield. Looking for a simpler synthetic analogue to bimorpholines, we proposed that a replacement of the oxygen atom in the morpholine ring with methylene group should not considerably influence the organocatalytic properties of the compound. Such a replacement leads to a bipiperidine (BP) **2** skeleton, which can be characterised by the same chemical and stereochemical features as bimorpholines **1**. Both compounds are six-membered heterocyclic bridged 1,2-diamines bearing the stereogenic centres in the α-position to the nitrogen atom. Due to the more basic nature of the piperidine N-atom than that of the morpholine, a higher reactivity of the piperidine catalyst was also expected. Furthermore, the synthesis of bipiperidine is only a one-step procedure starting from a commercially available 2,2′-dipyridyl.[7] The separation of stereoisomeric salts of **2** with tartaric acid by crystallisation gives easy access

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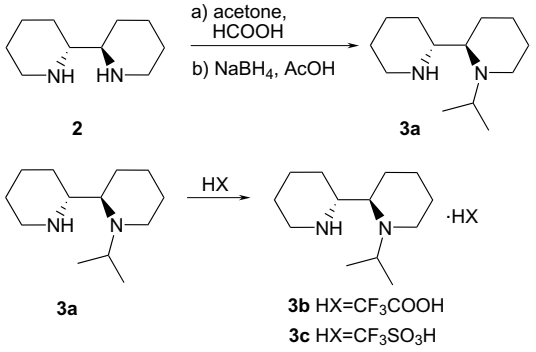
to the enantiomerically pure compound **2**, which, due to its C_2-symmetry, can be easily monoalkylated.

Herein we report the synthesis and derivatisation of enantiomeric 2,2′-bipiperidine **2** and the results when using bimorpholine and bipiperidine in the asymmetric aldol reaction.

2. Results and discussion

2,2′-Bipiperidine **2** was synthesised from 2,2′-dipyridyl by reduction with an excess of metallic sodium in the mixture of *sec*-BuOH and toluene. Alicyclic diamine **2** was obtained in 90% yield as a 1:1 mixture of meso (*R*,*S*) and racemic isomers (*S*,*S* and *R*,*R*). The literature data concerning the separation of *meso*- and *rac*-isomers are contradictory. Although their separation as hydrochloric acid salt via crystallisation is described,[8] we and others have failed[9] in this separation procedure. However, the resolution was successfully achieved by using hydrobromic acid salt according to the procedure described by Herrmann et al.[9] The *meso*-bipiperidine hydrobromic salt crystallised first from the hot ethanol solution and was then separated by filtration. The filter cake was washed with hot ethanol and the combined ethanol washings were cooled causing the precipitation of the racemic bishydrobromide. The enantiomers of the free amine were then resolved with L-tartaric acid.[10] The enantiomeric purity, that was measured on the dibenzoyl derivative of **2** by chiral HPLC, was found to be high (ee >99%).

We had previously found that mono N-substituted bimorpholines are more selective catalysts than unsubstituted ones.[6] In order to obtain monoalkylated bipiperidines, a simple methodology based on aminal formation, followed by reduction, was used.[11] Thus, we introduced the *i*Pr-moiety into bipiperidine **2** as presented in Scheme 1.

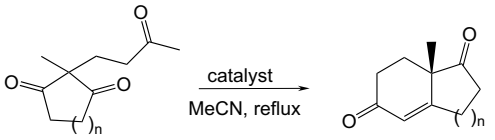


Scheme 1. Synthesis of bipiperidine derivatives.

First, starting from diamine **2**, aminal is formed with acetone in the presence of formic acid. The following reduction of the crude aminal with sodium borohydride in methanol gave *N*-*i*Pr-bipiperidine **3a** in 73% overall yield after chromatographic purification. Finally, diamine **3a** was converted into the corresponding monosalts **3b** and **3c** with 1 equiv of trifluoroacetic acid and trifluoromethanesulfonic acid, respectively, in quantitative yield.

We tested new organocatalysts **3a**–**c** in an asymmetric intramolecular aldol reaction with triketones **4** and **5**. The obtained Wieland–Miescher ketone **6** and its nor analogue **7** are versatile synthons in the natural product synthesis.[12] We had previously shown that bimorpholine derivatives catalyse this reaction with ee up to 95% (Table 1, entry 6).[6] It is well known from proline-catalysed reactions that an acidic carboxylic acid proton is an essential feature for determining reactivity and high stereoselectivity of the reaction.[13] In bimorpholine-catalysed reactions, a similar trend was observed. Only the monosalts of *i*Pr-bimorpholine (**1c** and **1d**) are highly selective catalysts (Table 1, entries 4 and 6), contrary to the free base compound **1b**, which afforded a racemic product (Table 1, entry 2). The acidic proton is needed for the acceleration of the condensation as well as for formation of a fixed conformation of the catalyst via hydrogen bonding, thus providing higher stereoselectivity.

Table 1. Diamine-catalysed cyclisation of triketones **4** and **5**



Entry	Product	Catalyst[a,b]	Time (d)	Yield[c] (%)	ee[d] (%)
1	**6**	*i*PrBP	8	7	43
2	**6**	*i*PrBM	3	45	*rac*
3	**6**	*i*PrBP·TFA	8	38	78
4	**6**	*i*PrBM·TFA	3	84	91
5	**6**	*i*PrBP·TfOH	8	55	52
6	**6**	*i*PrBM·TfOH	4	60	95
7	**7**	*i*PrBP·TFA	8	12	74
8	**7**	*i*PrBM·TFA	3	83	80
9	**7**	*i*PrBP·TfOH	7	7	42
10	**7**	*i*PrBM·TfOH	9	68	87

[a] BP catalyst loading 10 mol %.
[b] BM catalyst loading 5 mol %.
[c] Isolated yield.
[d] Determined by chiral HPLC.

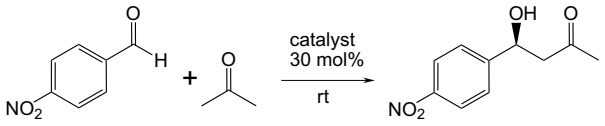
Our preliminary experiments showed that *i*Pr-bipiperidine acting as a free base had a very low reactivity towards the cyclisation reaction, and it forced us to use higher catalyst loadings (10 mol %) than in the case of bimorpholine (5 mol %). To our disappointment, substituted bipiperidine **3a** (free base) and its salts with trifluoroacetic and trifluoromethanesulfonic acids **3b** and **3c**, respectively, are much less efficient catalysts than the corresponding bimorpholine derivatives (Table 1).

Although the beneficial effect of the acid is evident (Table 1, entries 3, 4 vs 1), the reactivity and selectivity are lower than in the case of bimorpholine (Table 1, entries 2 and 4.) For the piperidine derivatives, the salt of a weaker acid (trifluoroacetic acid **3b**) promoted the reaction with higher selectivity but with lower reactivity (Table 1, entry 3) than the salt of a stronger acid (trifluoromethanesulfonic acid **3c**) (entry 5), which is less selective and more active. This

result is opposite to that when compared with bimorpholines. In the case of bis-nor Wieland–Miescher ketone **7** the reactivity of the salts was very low; even after 7–8 days refluxing, ketone **5** in acetonitrile conversion was only 7–12% (Table 1, entries 7 and 9).

The intermolecular aldol reaction between *p*-nitrobenzaldehyde **8** and acetone in the presence of our new catalysts **3a**–**c** was also investigated (Table 2). Similarly to the intramolecular reaction, with, *i*Pr-bimorpholine again as a free base gave a racemic product. However, *i*Pr-bipiperidine did not lead to a selective reaction either (Table 2, entries 1 and 2). Different salts of bimorpholine gave aldol product **9** in almost equally high selectivities (Table 2, entries 4 and 6). Although tendencies in the case of the bipiperidine salts were the same in the intramolecular aldol reaction as in the intermolecular reaction, they were more distinct. Again, catalyst **3b** was more selective and less reactive (ee 81%, yield 18%) than catalyst **3c** (ee 68%, yield 83%) (Table 2, entries 3 and 5).

Table 2. Intermolecular aldol condensation



8 **9**

Entry	Catalyst	Time (d)	Yield[a] (%)	ee[b] (%)
1	*i*PrBP	6	<10	*rac*
2	*i*PrBM	7	n.d.	*rac*
3	*i*PrBP·TFA	6	18	81
4	*i*PrBM·TFA	9	38	85
5	*i*PrBP·TfOH	6	83	68
6	*i*PrBM·TfOH	6	70	88

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

Moreover, in order to achieve acceptable conversion a higher amount of the catalyst than in the case of intramolecular condensation was required (30 mol %).

The different reactivities of the bimorpholine and bipiperidine catalysts could be explained by considering different nucleophilicity of these compounds.

It is generally accepted that the organocatalytic proline-catalysed aldol reaction proceeds through an enamine intermediate.[13] We have proven that the same occurs in the case of bimorpholine-catalysed reaction.[6] The enamine is formed from the carbonyl component and the catalyst amine group, generating 1 equiv of water. The nucleophilic enamine attacks an electrophilic carbonyl compound affording an iminium intermediate. Its hydrolysis recovers the amine and affords the condensation product. Hence, the nucleophilicity of the catalyst amine and the intermediate enamine is an important factor that determines the reactivity.

Generally, the correlation between basicity and nucleophilicity of amines is poor.[14] It is known that morpholine (pK_{aH} in acetonitrile 16.0) is less basic than piperidine (pK_{aH} in acetonitrile 18.8).[15] At the same time, piperidine is more nucleophilic.[16] On the other hand, enamines derived from morpholine are more reactive than those obtained from piperidine.[17] Thus, the morpholine-based catalyst should be more reactive. This is in good accordance with our results.

Differences in stereoselectivity rely on different conformations of the bridged cyclic organocatalysts. The general similarity of the conformations of these structures leads to relatively insignificant differences in the selectivity of the reaction. This is supported by quite complicated nature of protonation effects on ^{1}H and ^{13}C chemical shifts and ^{1}H–^{1}H spin spin coupling constants in **3a**–**c**. High field NMR studies of these combined charge and steric effects are currently in progress.

3. Conclusion

We have synthesised a new organocatalyst—(*R*,*R*)-*N*-*i*Pr-2,2′-bipiperidine and used it in intermolecular and intramolecular aldol reactions. Subtle changes in the structure of a stereoselective and efficient bimorpholine catalyst, however, led to a considerable loss of activity and some decrease in selectivity when compared to the parent compound.

4. Experimental

4.1. General

Chemicals were purchased from Aldrich Chemical Co. or Alfa Aesar and used as received. MeOH was dried by distillation over Na, acetone over P_2O_5, MeCN over CaH_2, Et_2O over $LiAlH_4$. Precoated silica gel 60 F_{254} plates from Merck were used for TLC, whereas for column chromatography silica gel KSK40–100 μm was used. The full assignment of ^{1}H and ^{13}C chemical shifts is based on the 1D and 2D FT NMR spectra on a Bruker AMX500 and AVANCE III 800 MHz instruments. Solvent peaks ($CHCl_3$ $\delta = 7.27$, $CDCl_3$ $\delta = 77.00$) were used as chemical shift references. IR spectra were measured on a Perkin–Elmer Spectrum BX FTIR spectrometer. Mass spectra were recorded on a Shimadzu GCMS-QP2010 spectrometer using EI (70 eV). Elemental analyses were performed on a Perkin–Elmer C, H, N, S-Analyzer 2400. Optical rotations were obtained using a Krüss Optronic GmbH Polarimeter P 3002. Chiral HPLC was performed using Chiralcel OD-H (250 × 4.6 mm) and Chiralpak AS-H (250 × 4.6 mm) column. All reactions sensitive to moisture or oxygen were carried out under an Ar atmosphere in oven-dried glassware.

4.2. (*R*,*R*)-*N*-*i*Pr-2,2′-Bipiperidine (*i*PrBP) 3a

To a solution of (2*R*,2′*R*)-bipiperidine **2** (1.07 g, 6.33 mmol) in Et_2O (18 mL) were added molecular sieves (4 Å, ~0.5 g), acetone (4.3 mL) and formic acid (60 μL). The mixture was stirred overnight, then K_2CO_3 was added

and stirred for 30 min and filtered. The solvent was removed to give the crude aminal (1.26 g), which was dissolved in MeOH (22 mL). $NaBH_4$ (451 mg, 12.0 mmol) was then added in portions followed by acetic acid (1.36 mL, 23.8 mmol) at 0 °C. The mixture was stirred overnight. The additional amount of $NaBH_4$ (157 mg, 4.2 mmol) was required to complete the reaction. Et_2O (30 mL) and 10 M aq NaOH (7 mL) were added and the organic layer was separated. The aqueous phase was extracted with EtOAc (4 × 25 mL). The combined organic phase was dried over K_2CO_3, filtered and concentrated. Purification by column chromatography on silica gel (30:1 mixture of CH_2Cl_2 and 17% solution of NH_3 in MeOH) afforded a yellow oil (0.95 g, 76%). $[\alpha]_D^{18} = +45$ (*c* 7.0, MeOH). ^{1}H NMR (800 MHz, $CDCl_3$): δ substituted ring 3.08 (hp, $J = 6.5$ Hz, 1H, *i*Pr CH), 2.82 (ddd, $J = 13.4$, 9.0, 3.4 Hz, 1H, H-6), 2.51 (ddd, $J = 13.4$, 6.3, 3.4 Hz, 1H, H-6), 2.42 (m, 1H, H-2), 1.62 (m, 1H, H-3), 1.59 (m, 1H, H-4), 1.53 (m, 1H, H-5), 1.40 (m, 1H, H-3), 1.39 (m, 1H, H-4), 1.26 (m, 1H, H-5), 1.05 and 0.98 (2d, $J = 6.5$ Hz; 6H, *i*Pr), δ unsubstituted ring 3.11 (dddd, $J = 11.9$, 4.2, 2.3, 1.7 Hz, 1H, H-6eq), 2.78 (ddd, $J = 11.1$, 7.6, 2.3 Hz, 1H, H-2ax), 2.61 (ddd, $J = 12.3$, 11.9, 2.8 Hz, 1H, H-6ax), 1.82 (m, $J = 13.0$, 4.0, 4.0, 2.8, 2.8, 1.7 Hz, 1H, H-4eq), 1.64 (m, 1H, H-3eq), 1.57 (m, 1H, H-5eq), 1.42 (m, $J = 2 \times 13.0$, 12.3, 2 × 4.0 Hz, 1H, H-5ax), 1.31 (m, $J = 3 \times 13.0$, 2 × 4.0 Hz, 1H, H-4ax), 1.05 (m, 2 × 13.0, 11.1, 4.0 Hz, 1H, H-3ax); ^{13}C NMR (200 MHz, $CDCl_3$): δ substituted ring 60.46 (C-2), 48.68 (*i*Pr), 42.49 (C-6), 23.53 (C-5), 22.64 (C-3), 22.50 (*i*Pr), 22.08 (C-4), 18.44 (*i*Pr), δ unsubstituted ring 55.37 (C-2), 47.69 (C-6), 28.09 (C-3), 26.69 (C-5), 25.17 (C-4). IR: $\nu = 3327$, 2931, 2855, 2795, 1381, 1360 cm^{-1}. MS (EI): *m*/*z* (%) = 126 (100), 110 (3), 84(55), 56 (13), 41 (6). Anal. Calcd for $C_{13}H_{26}N_2$ (210.37): C, 74.23; H, 12.46; N, 13.32. Found: C, 74.16; H, 12.44; N, 13.42.

4.3. (*R*,*R*)-N-*i*Pr-2,2′-Bipiperidine trifluoroacetic acid salt 3b

To a solution of *i*Pr-bipiperidine **3a** (330 mg, 1.57 mmol) in Et_2O (3 mL) trifluoroacetic acid (121 μL, 1.57 mmol) was added at 0 °C. The precipitate was collected and dried under vacuum. Mp 165–167 °C. $[\alpha]_D^{20} = -4.2$ (*c* 5.6, MeOH). ^{1}H NMR (500 MHz, $CDCl_3$): δ substituted ring 3.09 (hp, $J = 6.4$ Hz, 1H, *i*Pr), 3.04 (m, 1H, H-2), 2.77 (m, 2H, H-6), 1.76 (m, 1H, H-3), 1.58 (m, 1H, H-4), 1.53 (m, 1H, H-5), 1.52 (m, 1H, H-3), 1.48 (m, 1H, H-4), 1.36 (m, 1H, H-5), 1.09 and 1.06 (2d, $J = 6.4$ Hz, 6H, *i*Pr), δ unsubstituted ring 3.54 (m, 1H, H-6), 3.28 (m, 1H, H-2), 2.86 (dt, $J = 2 \times 12.0$, 4.2 Hz, 1H, H-6), 1.94 (m, 1H, H-4), 1.91 (m, 1H, H-3), 1.82 (m, 2H, H-5), 1.70 (m, 1H, H-3), ^{13}C NMR (125 MHz, $CDCl_3$): δ 161.99 (q, $J = 34.5$ Hz, COO), 116.81 (q, $J = 293.7$ Hz, CF_3), δ substituted ring 56.22 (C-2), 50.45 (*i*Pr), 42.01 (C-6), 22.16 (C-5), 22.03 (*i*Pr), 21.37 (C-3), 20.26 (2C, C-4 and *i*Pr), δ unsubstituted ring 55.51 (C-2), 45.16 (C-6), 24.80 (C-3), 22.55 (C4), 22.36 (C-5). IR: $\nu = 2974$, 2868, 1674, 1456, 1422, 1203, 1167, 1128, 829, 797, 721 cm^{-1}. MS (EI): *m*/*z* (%) = 126 (100), 112 (5), 110 (5), 84 (52), 82 (5), 69 (13), 56 (14), 45 (16). Anal. Calcd for $C_{15}H_{27}F_3N_2O_2$ (324.38): C, 55.54; H, 8.39; N, 8.64. Found: C, 55.54; H, 8.64; N, 8.61.

4.4. (*R*,*R*)-*N*-*i*Pr-2,2′-Bipiperidine trifluoromethane-sulfonic acid salt 3c

To a solution of *i*Pr-bipiperidine **3a** (92 mg, 0.44 mmol) in Et_2O (1.4 mL) trifluoromethanesulfonic acid (39 μL) was added at 0 °C. The precipitate was collected and dried in vacuum. Mp 143–147 °C. $[\alpha]_D^{23} = -3.6$ (*c* 5.2, MeOH). ^{1}H NMR (500 MHz, $CDCl_3$): δ substituted ring 3.15 (hp, $J = 6.4$ Hz, 1H, *i*Pr), 3.01 (ddd, $J = 10.6$, 5.0, 2.5 Hz, 1H, H-2), 2.93 (m, 1H, H-6), 2.76 (ddd, $J = 15.0$, 12.2, 3.1 Hz, 1H, H-6), 1.76 (m, $J = 14.4$, 13.0, 5.0, 4.0 Hz, 1H, H-3), 1.62 (m, $J = 13.0$, 3 × 4.0, 1.4 Hz, 1H, H-4), 1.57 (m, 1H, H-5), 1.55 (m, 1H, H-3), 1.44 (m, 1H, H-4), 1.38 (m, 1H, H-5), 1.18 and 1.15 (2d, $J = 6.4$ Hz, 6H, *i*Pr), δ unsubstituted ring 3.56 (m, 1H, H-6), 3.27 (dt, $J = 2 \times 10.6$, 2.6 Hz, 1H, H-2), 2.93 (m, 1H, H-6), 1.94 (m, 2H, H-3,4), 1.90 (m, 1H, H-5), 1.83 (m, 1H, H-5), 1.58 (m, 1H, H-3). ^{13}C NMR (125 MHz, $CDCl_3$): δ 120.40 (q, $J = 319.9$ Hz, CF_3), δ substituted ring 56.57 (C-2), 51.72 (*i*Pr), 41.84 (C-6), 22.06 (*i*Pr), 21.76 (C-5), 21.20 (*i*Pr), 21.12 (C-3), 19.55 (C-4), δ unsubstituted ring 55.83 (C-2), 45.81 (C-6), 25.39 (C-3), 22.44 (C-5), 22.30 (C4). IR: $\nu = 3065$, 2973, 2875, 1614, 1294, 1271, 1234, 1160 cm^{-1}. MS (EI): *m*/*z* (%) = 127 (10), 126 (100), 111 (6), 84 (30), 56 (12), 55 (5), 41 (6). Anal. Calcd for $C_{14}H_{27}F_3N_2O_3S$ (360.44): C, 46.65; H, 7.55; N, 7.77. Found: C, 46.70; H, 7.52; N, 7.84.

4.5. General procedure for the organocatalytic intramolecular aldol reaction with catalysts 3a–c

Organocatalyst was added to the stirred solution of triketone **4** or **5** (0.5 mmol) in MeCN (1 mL). The reaction mixture was then refluxed for the indicated time (Table 1). After the completion of the reaction, toluene was added, the mixture concentrated and crude product purified by column chromatography on silica gel (30% EtOAc in petroleum ether). Ee was determined by HPLC (Chiralcel OD-H column, hexane/*i*PrOH 96:4, flow rate 1 mL/min, $\lambda = 254$ nm).

4.6. General procedure for the organocatalytic intermolecular aldol reaction with catalysts 3a–c

The organocatalyst (0.09 mmol) was added to a solution of *p*-nitrobenzaldehyde **8** (0.3 mmol) in acetone (0.6 mL), and the mixture was stirred at rt for 6 days. The reaction mixture was treated with water and extracted with EtOAc. The extracts were dried, filtered and concentrated. The pure aldol product was obtained by column chromatography on silica gel (17–33% EtOAc in petroleum ether). The ee of the product was determined by HPLC (Chiralpak AS-H column, hexane/*i*PrOH 70:30, flow rate 0.75 mL/min, $\lambda = 254$ nm).

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