Enantioselective Synthesis of Wieland–Miescher Ketone through Bimorpholine-Catalyzed Organocatalytic Aldol Condensation

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Abstract: Novel bimorpholine-derived organocatalysts have been used for highly enantioselective intramolecular aldol reaction affording Wieland–Miescher ketone in high yield and enantioselectivity (up to 92% and 95%, respectively).

Key words: asymmetric catalysis, organocatalysis, diamines, stereoselective synthesis, aldol reactions

Proline-catalyzed asymmetric intramolecular aldol condensation of triketones was one of the first reactions where organocatalysis was used.[1] It took several decades to rediscover the concept of organocatalysis. Today biomimetic metal-free reactions catalyzed by small enantiomeric molecules have become a powerful tool for creating of the C–C and the C–heteroatom bond in an asymmetric way.[2] Enamine-based catalysis is a specific example of this strategy.[3] The five-membered ring natural amino acid proline is still the most widely used catalyst in organocatalysis.[4]

Wieland–Miescher ketone (**1**) and its nor-analogue **2** have proven to be remarkably important starting compounds for numerous targeted syntheses.[5] The first published asymmetric synthesis protocol of these compounds[1] is still a landmark, and only a few improvements that involve a modest modification of the main procedure have been reported.[6] Under optimized conditions, enantiomerically pure ketone **1** was obtained in 57% yield after three recrystallizations.[6a] The one-pot reaction starting from 2-methyl 1,3-cyclohexanedione and methyl vinyl ketone (35 °C, 89 h, 35 mol% of proline was used) afforded ketone **1** in 49% yield with 76% of ee.[7a] The synthesis of diketone **2** was more selective as only 3 mol% of catalyst was sufficient to achieve ee of 93% with the quantitative yield of the intermediate bicyclic hydroxy diketone (Scheme 1).[1b]

Proline derivatives or other amino acids were found to be less efficient in this reaction.[7,8] There are only two reports that describe a more enantioselective cyclization reaction. Barbas has used the antibody-catalyzed Robinson annulation that affords ketone **1** in >95% of ee.[9] Davies has obtained ketone **1** in 86% of ee in the presence of β-amino acid cispentacin.[10]

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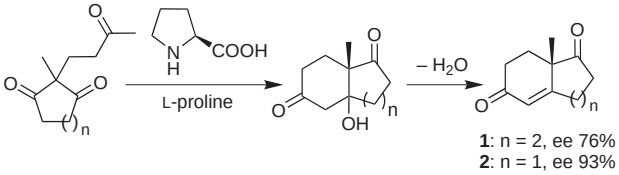
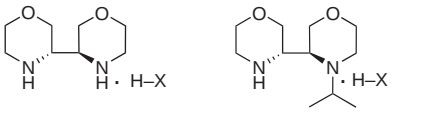


Scheme 1 Proline-catalyzed synthesis of Wieland–Miescher ketone (**1**) and its nor-analogue **2**

It is well recognized that amine functionality and carboxylic acid functionality both play a crucial role in proline-catalyzed aldol reactions to control stereoselectivity and reactivity.[11] Substitution of the carboxylic group with another acidic group (like tetrazole)[12] has led to a principally new approach to acid–base catalyzed aldol reactions.[13] We assumed that mono salts of bimorpholine **3**[14] or its derivative **4** would act similarly to proline possessing both basic and acidic properties (Figure 1). Additional donor sites in the morpholine rings (O-atoms) may give rise to the formation of a strictly arranged hydrogen bond network. These C_2-symmetric compounds represent a new class of bifunctional organocatalysts, which might provide high enantioselectivity toward aldol reaction.



3a: H–X = – (free base)
3b: H–X = CF_3COOH

4a: H–X = – (free base)
4b: H–X = CF_3COOH
4c: H–X = CF_3SO_3H

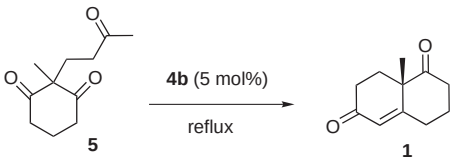
Figure 1

So far, the C_2-symmetric 1,2-diamine **3a** has been used only as a chiral ligand in the transition metal-mediated hydrogenation reactions.[15] Herein we describe the use of bimorpholines **3** and **4** in the highly stereoselective synthesis of Wieland–Miescher ketone (**1**) and its analogue **2**.

High solubility of the bimorpholine salt **4b** (as compared to proline) allows us to use various solvents for the intramolecular cyclization of triketone **5**. The results are presented in Table 1.

The bimorpholine salt was found to be an efficient catalyst of aldol condensation. Under reflux conditions, high conversion of the starting ketone was achieved in almost

Table 1 Cyclization of Triketone **5** in Different Solvents[a]



Entry	Solvent	Time (h)	Ratio of **1**:**5**[c]	ee of **1**[d,e]
1	THF	70	77:17	74
2	MeOH	70	56:32	85
3	*i*-PrOH	66	83:11	85
4	CH_3CN	68	91:6	91
5	MeCN–H_2O[f]	45	79:14	87
6	DMF[b]	144	43:21	*rac*
7	Toluene	5	82:9	36

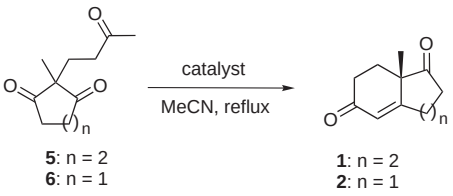
[a] In a typical experiment 0.5 mmol of triketone was refluxed in 1 mL of solvent.
[b] Reaction temperature 100 °C.
[c] Chromatographic ratio was determined by GC.
[d] The ee was determined by chiral HPLC (column Chiralcel OD-H).
[e] The absolute configuration of the main enantiomer was determined by the (+) sign of the optical rotation of the isolated product corresponding to *S*-enantiomer.
[f] H_2O (10 equiv) was used as a co-solvent.

every solvent screened and only a trace of intermediate hydroxy diketone (depicted in Scheme 1) was detected by GC. Most intriguingly, in the majority of cases, the enantioselectivity of the reaction exceeds considerably the selectivity obtained with proline (Table 1, entries 2–5). There are two exceptions: these were the cases when DMF and toluene were used as solvents (entries 6, 7). The reaction in DMF at 100 °C was sluggish and the obtained product was racemic. We assume that too high reaction temperature (boiling toluene) is probably responsible for the low selectivity when the reaction is carried out in toluene. The highest conversion and enantioselectivity (91%) were obtained in MeCN (entry 4). It has been reported that water has unique properties in the organocatalytic aldol reaction.[12,16] In our case, water decreased the stereoselectivity of the reaction (from 91% to 87%, entry 5).

According to the results obtained, MeCN was the solvent for the following reactions carried out under reflux using various bimorpholine derivatives as organocatalysts (Table 2).[17]

We assumed that acid has a dual role in this reaction. Firstly, acid catalyzes the enamine formation and accelerates the following cyclization. Secondly, in a preferential staggered conformation (the dihedral angle of 180° between the hydrogens), the fixed conformation of bimorpholine is formed via hydrogen bonding (Figure 2).

Table 2 Organocatalytic Cyclization of Ketones **5** and **6**[a]



Entry	Ketone	Catalyst (mol%)	Time (h)	Yield[b] (%)	ee[c] (%)
1	**5**	**4a** (5)	69	45[d]	*rac*
2	**5**	**4b** (1)	188	55	87
3	**5**	**4b** (5)	69	84	91
4	**5**	**4b** (10)	48	86	90
5	**5**	**4c** (5)	96	60	95
6	**5**	**4c** (20)	94	82	95
7	**5**	**3a** (5)	94	<10	n.d.
8	**5**	**3b** (5)	45	92	79
9	**6**	**3b** (5)	24	87	58[e]
10	**6**	**4b** (5)	71	83	80
11	**6**	**4c** (5)	216	68	87

[a] In a typical experiment 1 mmol of triketone was refluxed in 2 mL of MeCN.
[b] Isolated yield after column chromatography.
[c] The ee was determined by chiral HPLC (column Chiralcel OD-H).
[d] The reaction stopped at ca. 60% conversion.
[e] The absolute configuration of the main enantiomer was determined by the (+) sign of the optical rotation of the isolated product corresponding to *S*-enantiomer.

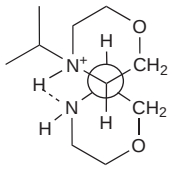
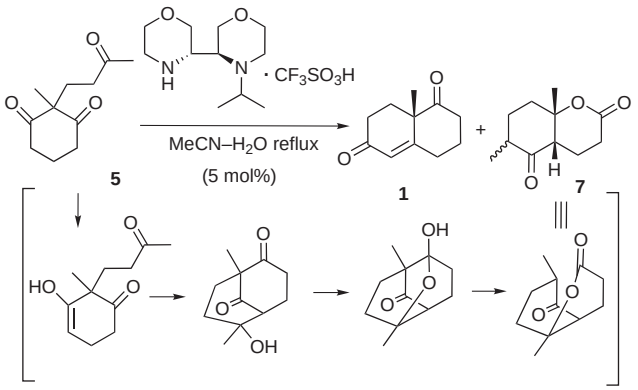


Figure 2 Proposed hydrogen-bonded structure of the bimorpholine–acid catalyst

In this chelated intermediate, the N atom becomes a stereogenic center and an additional stereodiscrimination takes place.[18] The hypothesis is supported by the fact that catalysts **3a** and **4a** (free base of unsubstituted and *i*-Pr-bimorpholine) gave either a racemic product or revealed a very low activity (entries 1, 7). The influence of the isopropyl group attached to the nitrogen atom is also evident. *i*-Pr-bimorpholine-catalyzed (**4b**) reaction afforded ketone **1** with much higher ee than unsubstituted catalyst **3b**, (ee 91% and 79% and isolated yields of ketone **1** 84% and 92%, respectively; entries 3, 8).

The strength of the acid used for the preparation of the catalyst salt is also an important factor that determines the stereoselectivity of the reaction and the reactivity of the

catalyst. A comparison of triflic acid salt **4c** and trifluoroacetic acid salt **4b** showed that the former was a more selective but less reactive catalyst than was the latter (entries 3, 5). A stronger acid reduces the nucleophilicity of amine via protonation and probably retards the formation of enamine. At the same time, a more strongly chelated structure of bimorpholine favors higher enantioselectivity. Indeed, the highest ee (95%, entries 5, 6) was obtained when the reaction was catalyzed with triflic salt **4c** although the reaction time was longer than in the case of trifluoroacetic acid salt **4b**. The prolonged reaction time led to the formation of side-product **7** as 2:1 mixture of diastereoisomers (Scheme 2).[19] When water was used as an additive (10 equiv), Wieland–Miescher ketone (**1**) and lactone **7** were formed in almost equal amounts. In the trifluoroacetic acid salt catalyzed (**4b**) reactions the formation of lactone **7** was not detected.



Scheme 2 Formation of side-product **7**

The formation of the by-product **7** can be explained according to Coates et al., who found that similar δ-lactones are formed via the enolization of the carbonyl group in the ring, giving bridged ketol by aldol condensation followed by intramolecular hemiacetal formation and retro-Claisen transformation.[20]

We obtained optimal results while using 5–10 mol% of the trifluoroacetic acid salt **4b** of bimorfoline (entries 3, 4). The reaction with 5 mol% of the catalyst was completed within 69 hours, affording ketone **1** in 84% of isolated yield and 91% of ee (entry 3). The reduction of the amount of the catalyst to 1 mol% resulted in the prolonged reaction time and in the lower stereoselectivity (entry 2).

The same tendencies were observed in the case of triketone **6**. Triflic acid salt **4c** was found to be the most selective but the least reactive organocatalyst. Also, *i*-Pr-substituted derivatives **4b** and **4c** were more selective catalysts than unsubstituted bimorpholine salt **3b** (entries 9–11). Unfortunately, in these cases the enantioselectivity was lower than with ketone **5**, reaching 87% at most.

We may conclude that a new class of organocatalysts – *i*-Pr-substituted bimorpholine mono salts – for highly enantioselective intramolecular aldol reactions have been introduced. The efficiency of the organocatalyst has been demonstrated on the important synthetic intermediate Wieland–Miescher ketone (**1**), which was synthesized in high yield and ee (up to 92% and 95%, respectively). Further investigation of the scope of the aldol reaction and other possible applications of the novel organocatalysts **4** is under way.[21]

Acknowledgment

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(17) **General Method for the Organocatalytic Aldol Condensation of Ketones 5 and 6.**
Organocatalyst **3** or **4** (0.05 mmol) was added to a stirred solution of triketone **5** or **6** (1.0 mmol) in anhyd 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 (5 mL) was added, the mixture was concentrated under vacuum and the crude product was purified by chromatography on silica gel (30% EtOAc in PE). The obtained ketones **1** and **2** are known compounds and our spectroscopic and chromatographic data are in agreement with published data. The ee was determined by HPLC (Daicel Chiralcel OD-H (250 × 4.6 mm), detection at λ = 254 nm, eluent: 4% of *i*-PrOH in hexane, flow rate 0.8 mL/min); t_R (*S*)-**1** = 19.4 min, t_R (*R*)-**1** = 21.6 min, t_R (*S*)-**2** = 25.6 min, t_R (*R*)-**2** = 28.3 min.

(18) Converting stereogenic N atoms via chelation is described by: Kizirian, J.-C.; Caille, J.-C.; Alexakis, A. *Tetrahedron Lett.* **2003**, *44*, 8893.

(19) **(4a*S**,8a*S**)-6,8a-Dimethylhexahydro-2*H*-chromene-2,5(3*H*)-dione (7).**
A 2:1 mixture of two isomers with differing orientations of the 6-methyl group. Main isomer with 6*R** configuration: ^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.73 (m, 1 H, H-3), 2.54 (m, 1 H, H-4a), 2.49 (m, 1 H, H-3), 2.43 (m, 1 H, H-6), 2.42 (m, 1 H, H-4), 2.15 (m, 1 H, H-8), 1.97 (m, 1 H, H-8), 1.94 (m, 1 H, H-7), 1.93 (m, 1 H, H-4), 1.71 (m, 1 H, H-7), 1.54 (s, 3 H, 8a-Me), 1.03 (d, *J* = 6.5 Hz, 3 H, 6-Me). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 209.33 (C-5), 171.24 (C-2), 86.19 (C-8a), 49.52 (C-4a), 44.32 (C-6), 37.48 (C-8), 29.83 (C-7), 28.39 (C-8a-Me), 25.54 (C-3), 15.69 (C-4), 14.19 (C-6 Me). Minor isomer with 6*S** configuration: ^{1}H NMR (500 MHz, $CDCl_3$,): δ = 2.68 (m, 1 H, H-3), 2.66 (m, 1 H, H-4a), 2.57 (m, 1 H, H-6), 2.45 (m, 1 H, H-3), 2.27 (m, 1 H, H-4), 2.10 (m, 2 H, H-7), 2.08 (m, 2 H, H-8), 1.95 (m, 1 H, H-4), 1.44 (s, 3 H, 8a-Me), 1.13 (d, *J* = 6.5 Hz, 3 H, 6-Me). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 211.33 (C-5), 169.97 (C-2), 85.27 (C-8a), 51.49 (C-4a), 41.53 (C-6), 33.14 (C-8), 27.90 (C-7), 27.81 (C-8a-Me), 27.56 (C-3), 19.53 (C-4), 15.23 (C-6 Me). MS (EI): *m/z* (%) = 196 (3) [M^+], 181 (2), 168 (4), 112 (86), 84 (29), 43 (100).

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