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Bimorpholines as Alternative Organocatalysts in Asymmetric Aldol Reactions

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Abstract: Asymmetric organocatalytic aldol condensation is discussed on the basis of intramolecular and intermolecular reactions. In addition to the widely used proline and its derivatives an application of the new type of the organocatalyst – bimorpholines in the above-mentioned reactions is described. The new catalyst has a unique C_2-symmetric skeleton with four acceptor sites that makes it stereoselective and efficient. Small changes in the structure of the catalyst lead to a remarkable loss of selectivity.

Keywords: Aldol condensation · Bimorpholine · Organocatalysis · Stereoselective

1. Introduction

The aldol reaction is one of the basic C–C bond forming reactions.[1] To perform stereoselective aldol condensation both metal-catalyzed and organocatalytic reactions are used. It was in an aldol reaction that proline was first used as an organocatalyst and which subsequently became a benchmark in the field of organocatalytic reactions.[2] However, it took several decades to rediscover this concept and now it has definitely matured to a widely used methodology.[3] Among a wide variety of organocatalysts, proline and its derivatives or other amino acids are still of importance. Synthesis of new organocatalysts focuses on the specific properties of the target molecule and enables the development of sterically and electronically tunable catalysts. We have designed and synthesized a new catalyst – bimorpholine – and here we will describe its use in the aldol reaction and compare it with other aminocatalysts.

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2. Aminocatalyzed Aldol Reaction

It is generally accepted that the amine-catalyzed aldol reaction proceeds *via* the following catalytic cycle (Fig. 1).[4]

First, enamine is formed from the carbonyl component of the condensation and the amine to generate one equivalent of water. The nucleophilic enamine attacks the electrophilic carbonyl compound affording an iminium intermediate. Its hydrolysis recovers the amine and the condensation product is obtained. If the amine used is chiral, a stereoselective reaction is expected.

2.1. *Enantioselective Aminocatalysis in the Aldol Reaction*

Intramolecular condensation of triketones **1** and **2** is the most investigated organocatalytic aldol reaction, affording the Wieland-Miescher ketone **3** and its *nor*-analog **4**, which are valuable synthetic intermediates (Fig. 2).

Starting from the pioneering work by the groups of Eder and Hajos[2] several models have been proposed to rationalize the mechanism and the factors determining stereoselectivity of the reaction.[5–8] The Houk model[9] is the only one supported both by theoretical calculations and experimental ^{18}O-labeled studies.[10] According to this model, enamine is formed from the side chain carbonyl group and it reacts with the electrophile in the cycle. The reaction proceeds through a six-membered cyclic transition state in the most stable chair conformation. The presence of the acidic proton is essential to catalyze enamine formation

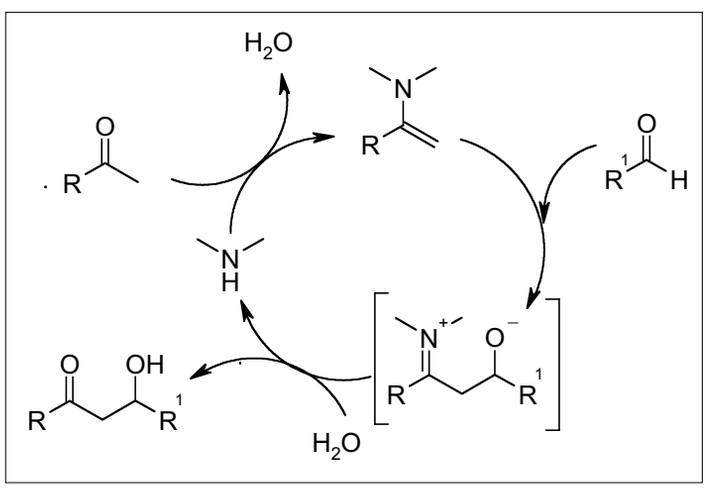


Fig. 1. A general scheme of the catalytic cycle of the amine-catalyzed aldol reaction

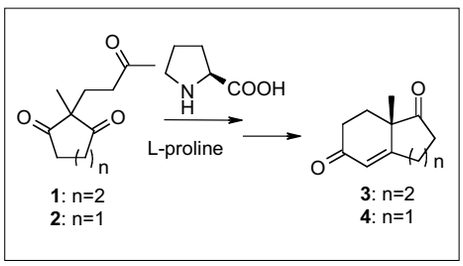


Fig. 2. Synthesis of the Wieland-Mischer ketone and its *nor*-analog through the Hajos-Parrish-Eder-Sauer-Wiechert reaction

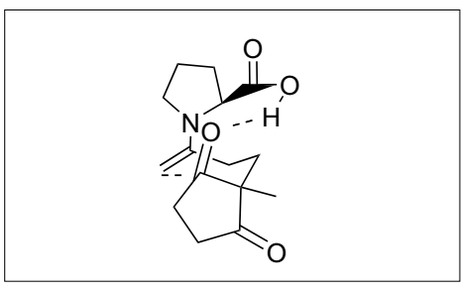


Fig. 3. The Houk model for the cyclic transition state

and stereoselective C–C bond formation supported by hydrogen bonding (Fig. 3).

However, acidity is far from the only and decisive feature of an efficient catalyst. Several other less acidic aminocatalysts like proline amides,[11] dipeptides,[12] catalysts with similar acidity like other amino acids or their derivatives[13] or more acidic compounds like pyrrolidine-2-yl tetrazols[14] have successfully been used in asymmetric aldol reactions (Fig. 4).

Our contribution to this chemistry is the enantiomeric bimorpholine (**5**) and its derivatives.[15,16] In addition to the aldol reaction, bimorpholines have been used as organocatalysts in the stereoselective Michael reaction[17] and as chiral phase transfer catalysts.[18] Bimorpholine **5** is a 1,2-diamine that has a unique C_2-symmetric skeleton with four acceptor sites. Because of the molecule's symmetry, mono-N-alkylation is easy to perform and mono salts of it can be considered as α-amino acid analogs possessing an acidic proton four chemical bonds away from the amino group. The second amino group acts in catalysis *via* enamine formation. Additionally, bimorpholine **5** has two other acceptor sites (oxygen atoms) which may support organocatalysis. Thus, bimorpholines and their derivatives should demonstrate high activity in the aldol reaction.

2.2. *Intramolecular Condensation*

Intramolecular aldol condensation will be discussed on the example of the cyclization of triketones **1** and **2**. The reaction proceeds *via* hydroxyketones **6** and **7**, affording the target compounds **3** and **4**, respectively, after dehydration. Comparative data of this organocatalytic cyclization are presented in Table 1.

Not all used catalysts led directly to the dehydrated products **3** and **4**. In most cases (Table entries 2–9), an extra acid-catalyzed step is needed for the dehydration. Generally, the cyclization of cyclopentane derivatives is more selective than the cyclization of the corresponding cyclohexanes. For a long time, proline (**8**) was most efficient catalyst for both triketones (entries 1, 2). Other amino acids (like phenyl alanine (**13**)) were found to be much less efficient, although the chemical yield of the cyclization was high (entries 8, 9). The catalytic properties of *cis*- and *trans*-methanoprolines (compounds **10** and **11**, respectively) differ from each other (entries 5, 6): the former being comparable with proline and the latter is less selective. Differences in the configurations are responsible for the different catalytic behavior of the compounds. From the various β-amino acids investigated by Limbach, homoproline (**12**) catalyzed reaction gave the bicyclic product in almost quantitative yield but with low enantioselectivity (entry 7). Another β-amino acid – cispentacin (**9**) revealed high selectivity in respect to both triketones, affording the Wieland-Mischer ketone with higher enantiomeric purity than in the case of proline (entries 3, 4). So far it has been clear that a carboxylic group and the rigid pyrrolidine ring of proline are the most important structural units of an enantioselective catalyst. In bimorpholine (**5**), the conformationally more flexible six-membered ring and a less acidic ammonium proton are present. However, enantioselectivities using catalyst **14** were very high and for the Wieland-Mischer ketone the highest ever obtained in organocatalysis (entries 10, 11). (Only in the antibody-catalyzed Robinson annulation was the *ee* of the product **3** >95%[25]).

In our detailed study we have shown that acid is essential for the enantioselection as the free base of *i*Pr-bimorpholine affords a racemic product.[16] In addition to conventional acid catalysis in the formation of enamine, a protonated chiral catalyst[26] with a fixed conformation of bimorpholine rings is formed. We assumed that changing the morpholine ring with the piperidine ring will increase the nucleophilicity of the secondary amine as well as the reactivity of the catalyst. The stereoselectivity was expected to remain unchanged. However, to our surprise, both the reactivity of the corresponding isopropyl bipiperidine (**15**) and the stereoselectivity of the cyclization were lower (entry 12) than that of bimorpholine. Thus, the morpholine ring is essential to achieve high selectivity. Not only that: the catalyst with a bridge between the morpholine rings in the β-position to the nitrogen atom (2,2'-bimorpholine (**16**)) led to a totally nonselective reaction affording the racemic product (entry 13). It is assumed that O-atoms in the morpholine rings enable the formation of a strictly arranged hydrogen bond network providing high enantioselectivity of the cyclization.

From the experimental point of view it is important that the bimorpholine derivatives are soluble in a variety of common organic solvents (THF, MeOH, *i*PrOH, CH_3CN) and they all can be used as reaction media without significant loss of selectivity. Use of proline or other amino acids is limited to polar solvents like DMSO, DMF and water.

2.3. *Intermolecular Condensation*

The very broad topic of intermolecular condensation is well documented by List and Berkessel.[27] Here some examples are given to compare our recent results with those of other authors. The topic will be discussed using the example of the archetypal aldol condensation between *p*-nitrobenzaldehyde and acetone. Proline is a benchmark also in this reaction[28] (Table 2, entry 1).

It is evident that the acidity of the catalyst is important. Catalyst activity is dras-

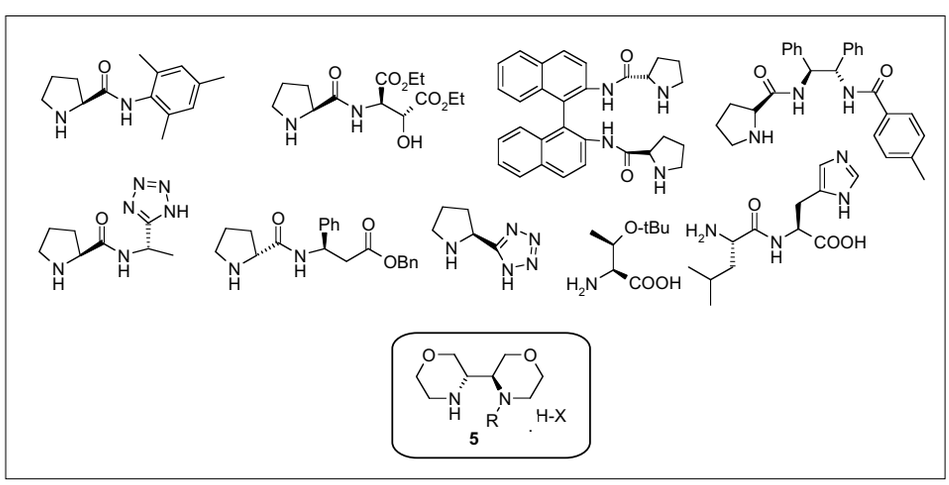
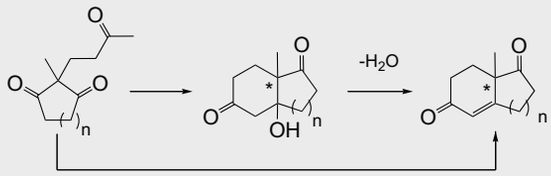
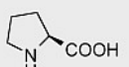
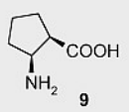
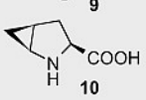
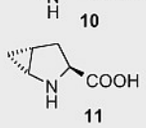
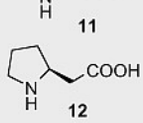
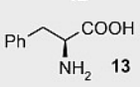
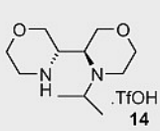
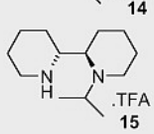
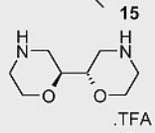


Fig. 4. Some efficient organocatalysts used in the aldol reaction[11–15]

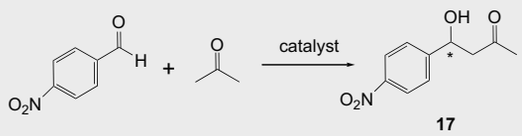
Table 1. Organocatalytic cyclization of triketones **1** and **2**

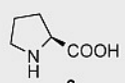
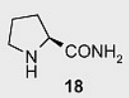
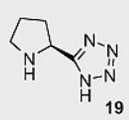
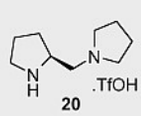
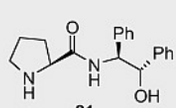
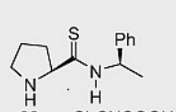
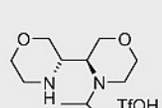
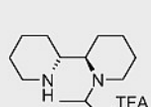


Entry	Catalyst	Triketone / product	Equiv of cat. [mol%]	Yield [%]	*ee* [%]	Ref.
1	 **8**	**1 / 3**	5	81	70	[19]
2		**2 / 7**	3	quant	93[a]	[2b]
3	 **9**	**1 / 6**	30		86[a]	[20]
4		**2 / 7**	30	94	90[a]	[20]
5	 **10**	**2 / 7**	3	86	93[b]	[21]
6	 **11**	**2 / 7**	3	67	83[b]	[21]
7	 **12**	**2 / 7**	20	99	58[a]	[22]
8	 **13**	**1 / 3**	30	75	9[c]	[23]
9		**2 / 4**		73	11[c]	
10	 **14**	**1 / 3**	5	60	95	
11		**2 / 4**	5	68	87	
12	 **15**	**1 / 3**	10	38	78	[24]
13	 **16**	**1 / 3**	5	quant	*rac*	[24]

[a]determined after acid-catalyzed dehydration; [b]*ee* of compound **7**; [c]50 mol% of pyridinium *p*-toluenesulfonate was added to the reaction mixture to enforce dehydration

Table 2. Organocatalytic aldol condensation between *p*-nitrobenzaldehyde and acetone



Entry	Catalyst	Conditions	Yield of **17**	*ee* of **17**	Ref.
1	 **8**	30 mol%, DMSO/acetone, 2h, rt	68%	76%	[28]
2	 **18**	Same conditions	< 10%	Nd	[28]
3	 **19**	20 mol%, DMSO/ acetone, 10 min, rt	82%	79%	[14b]
4	 **20**	3 mol%, acetone, 2 h, 30 °C	60%	88%	[29]
5	 **21**	20 mol%, acetone, 24 h, -25 °C	66%	93%	[30]
6	 **22**	2.5 mol%, acetone, 60 h, 4 °C	99%	93%	[32]
7	 **14**	30 mol%, acetone, 144 h, rt	70%	88%	[24]
8	 **15**	30 mol%, acetone, 144 h, rt	18%	81%	[24]

tically decreased by substituting proline with proline amide (**18**) (entry 2). Using tetrazole derivative **19**, which is a stronger acid than proline, led to the increase of the reaction rate as well as the enantioselectivity (entry 3). An alternative acid–base catalysis approach was proposed by Saito and Yamamoto.[31] Changing a carboxylic moiety with a less acidic diamine-Brønsted acid salt enables one to create a cooperatively arranged hydrogen-bond network, enabling high reactivity and enantioselectivity. Thus, in the presence of only 3 mol% of catalyst **20** an aldol condensation product was obtained in good yield and high *ee* (entry 4). Another example of the significance of the hydrogen bonding is given by the catalyst **21** with the terminal hydroxyl group and without any carboxylic or ammonium protons. It is assumed that stereodiscrimination is caused by the hydrogen bond donor properties of the catalyst (entry 5). In the case of prolinethioamide derivative **22**, again acid is needed to activate the catalyst. In the recent detailed study by Gryko *et al.*[32] it was found that catalyst activity as well as selectivity strongly depend on the pK_a value of the acid. The optimal value of this particular catalyst is ~1.3 and the best results were obtained by using dichloroacetic acid salt (entry 6). The structure of the bimorpholine derivative **14** differs significantly from that of the above-mentioned catalysts. It is a six-membered ring diamine-Brønsted acid salt with additional hydrogen bonding acceptor centers. In spite of that, the catalyst selectivity is high, albeit its reactivity is low (entry 7). High catalyst loading (30 mol%) and a long reaction time is needed to obtain a practically acceptable yield. Replacing of O-atoms in the heterocyclic rings with methylene groups (corresponding bipiperidine derivative **15**), *i.e.* eliminating hydrogen donor acceptors, led to the decrease of the selectivity and reactivity (entry 8).

3. Conclusions

Organocatalysis is undoubtedly a very attractive method to perform the stereoselective aldol reaction. Its mechanism and the factors that determine enantioselectivity are well established for proline-catalyzed reactions. However, every new organocatalyst is an individual compound with a unique set of properties. Acidity, conformation and hydrogen bonding abilities are the key features that are responsible for the stereodiscrimination. On the examples of bimorpholines and bipiperidines we have shown that small changes in the catalyst structure will lead to remarkable changes in stereoselectivities. Considerable improvements in the field of organocatalysis can be achieved in particular by increasing the efficiency of the catalysts. Bimorpholines can be easily derivatized *via* selective mono N-alkylation. Protonation of the catalyst with various acids changes also its catalytic properties. This makes bimorpholines a tunable bifunctional organocatalyst that can hopefully be used in various enantioselective transformations.

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