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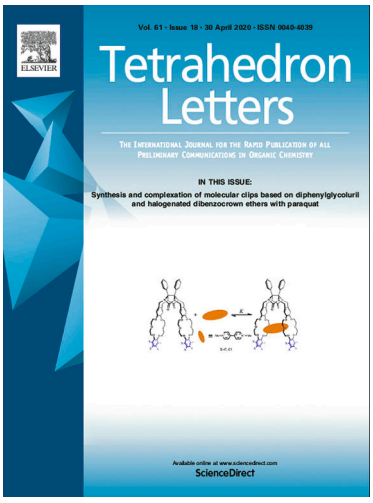

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PII: S0040-4039(20)30762-0
DOI: https://doi.org/10.1016/j.tetlet.2020.152295
Reference: TETL 152295

To appear in: *Tetrahedron Letters*

Received Date: 3 June 2020
Revised Date: 19 July 2020
Accepted Date: 23 July 2020

Please cite this article as: Shim, J.H., Kim, M-J., Lee, J.Y., Kim, K.H., Ha, D-C., Organocatalytic asymmetric aldol reaction using protonated chiral 1,2-diamines, *Tetrahedron Letters* (2020), doi: https://doi.org/10.1016/j.tetlet.2020.152295

Graphical Abstract

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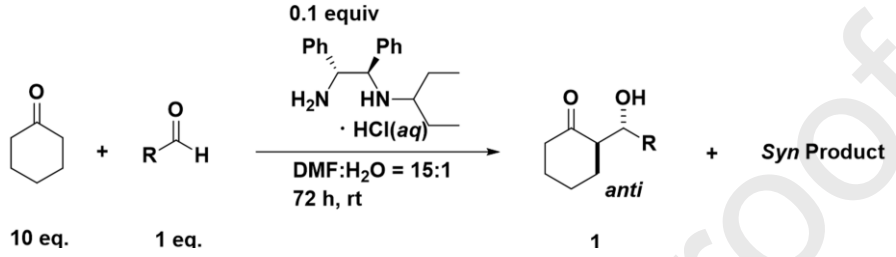

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Organocatalytic asymmetric aldol reaction using protonated chiral 1,2-diamines

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ARTICLE INFO

Article history:
Received
Received in revised form
Accepted
Available online

Keywords:
Aldol reaction
Organocatalyst
N-alkylated DPEN catalyst
Proline
Asymmetric reactions

ABSTRACT

Organic-catalyzed stereoselective reactions have gained attention because they avoid the problems associated with metal catalysts, but existing catalysts based on proline have limitations. Therefore, (*R*,*R*)-(+)-1,2-diphenylethylenediamine (DPEN) was selectively mono-*N*-alkylated through reductive alkylation and used as an organic catalyst for the aldol reaction. Using a variety of aldehydes in the catalytic aldol reaction, the *N*-alkylated DPEN catalyst proceeded from primary amine to enamine and iminium intermediates and achieved both a high yield (80%) and enantioselectivity (90%). It was found that the steric hindrance of the *N*-alkyl substituent of the chiral diamine and the hydrogen bond between the ammonium moiety and the oxygen of the aromatic aldehyde determine the enantioselectivity. Various aromatic aldehydes were tested, and electron-withdrawing substituents led to good yields, whereas electron-donating substituents led to poor yields via the deactivation of the carbonyl group of the aldehyde. Further, ortho substituents resulted in higher stereoselectivities than para substituents because the stereoscopic effect was enhanced.

1. Introduction

Recently, studies on metal-free stereoselective organic catalysts have gained much attention. Previous studies have shown that stereoselective reactions using a metal catalyst with a chiral ligand lead to better results than when using organic-only catalysts. However, the metal to which chiral ligands are coordinated can cause problems because of its cost, the risk of causing environmental pollution and contaminating the final product, and its instability under aerobic and moist conditions. Consequently, asymmetric synthesis using metal-free organic catalysts has drawn significant attention [1]. Thus, we have conducted studies on organic catalysts and investigated stereoselective Diels–Alder reactions using chiral diamine catalysts. Here, we report an organic-catalyzed aldol reaction, which, like the Diels-Alder reaction, is a representative organic reaction [2].

The aldol reaction is a key C-C bond forming reaction, and a number of enantioselective aldol reactions using organic catalysts has been reported; key examples include the works of List[1], Barbas[6], Macmillan [3], and Yamamoto [4]; in these reactions, typically, proline and its derivatives have been used as catalysts. These studies represent an important step forward in organic catalysis, and enantioselective aldol reactions using proline derivatives continue to be developed. However, the reaction is limited because of its dependency on the proline structural unit and the need for the formation of an iminium intermediate via the secondary amine of proline. In this study, we developed a novel asymmetric organic catalyst by introducing simple alkyl substituents to chiral (*R*,*R*)-(+)-1,2-diphenylethylenediamine (DPEN). Conventional organic catalysts utilize chiral iminium intermediates formed through the secondary amine of proline. In contrast, in our catalytic system, an imine is first formed by reacting the primary amine of secondary-alkyl-modified DPEN with a ketone; this is followed by the reaction of a hydrogen-bonded aldehyde, which is guided by the steric hindrance of the ammonium salt of the alkyl-substituted amine with the iminium, and, finally, the reaction of the enamine and aldehyde forms a new C-C bond, thus yielding aldol products. Thus, the purpose of this study is to understand the catalytic cycle via imine formation and hydrolysis using the ammonium salt of the diamine, as well as the efficient use of the chiral structure of DPEN.

Enantioselective intramolecular aldol reactions through the formation of enamines and hydrogen bonds using proline were reported 30 years ago by Hoffman-La-Roche and Schering AG [5]. Those experiments utilized the double activation of both nucleophile and electrophile by the amino group and carboxylic group of proline. The proline-catalyzed aldol reactions did not immediately gain much attention, and List reported the use of a proline organic catalyst for aldol reactions for the first time in 2000. This reaction has since attracted attention because of the general applicability of proline and its derivatives [6].List assumed that the mechanism involves the reaction of acetone with proline to form an enamine intermediate, as well as the formation of a

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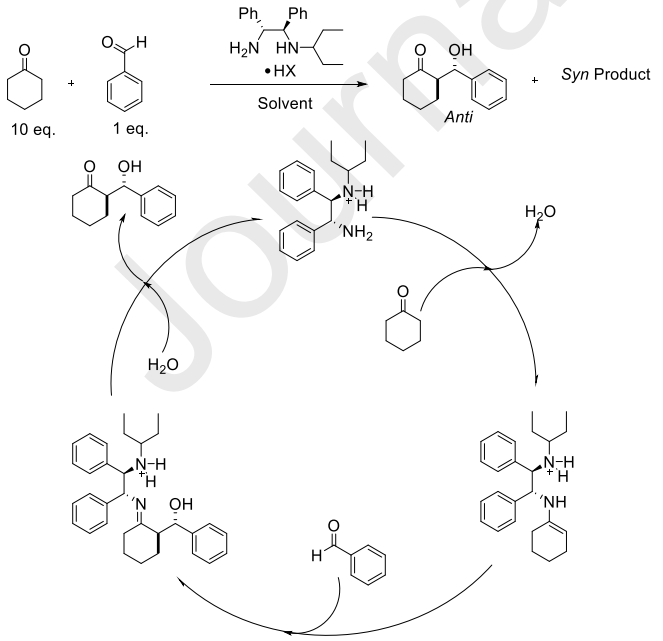
hydr on acid, resulting in activation. Subsequently, List tested aldol reactions with a range of proline derivatives having various ring sizes. Thus, aldol reactions with acetone were performed with various substituents on the aromatic aldehyde. The experimental results for the aldol reaction showed that there were differences between the aromatic aldehyde types and some degree of selectivity in the reaction when proline was used as the catalyst. List's aldol reaction has several advantages, such as the use of non-toxic and inexpensive proline, the ability to produce enantiomeric products, and the reaction's insensitivity to H_2O, which simplifies the reaction conditions. In addition, the aldol reactions can be carried out without modifying the carbonyl groups. In 2005, Barbas achieved a high yield and good enantioselectivity using acid additives and organic catalysts based on the proline structure; further, good results were obtained when H_2O was used as the solvent [7]. Instead of utilizing the hydrogen bonding of the carboxylic acid of proline as previously reported, the carboxylic acid is transformed into a tertiary amine, which forms a new hydrogen bond with the aldehyde in the presence of an acid catalyst. Notably, in this reaction, the poor yield and stereoselectivity of various aldol reactions using water as the solvent were resolved, and good yields were afforded when ketones, which are often used in excess, were used. Recently, a reaction with high yields and high selectivities in water was reported. In this reaction, the carboxylic acid of proline is changed for a sulfonamide and the terminal group is changed to a dendrimer [8]. This reaction using modified proline as an organic catalyst resulted in not only the enantioselectivity of the *anti*-product but also *anti/syn* selectivity. Further, conventional proline derivatives have a poor recovery rate, but this was overcome when using L-proline sulfonamide derivatives, and the catalytic activity was maintained on reuse [9]. Crucially, in the aldol reactions using an organic catalyst described above, high efficiency is obtained when chiral amine catalysts are used. However, previously reported studies of aldol reactions mostly use proline derivatives, which limits the applicable reactions. Previously, we developed a new asymmetric organic catalyst by incorporating a simple alkyl substituent onto the chiral skeleton of DPEN and performed efficient Diels–Alder reactions using these chiral diamines [10].



Scheme 1. Catalytic cycle for chiral-DPEN-catalyzed aldol reaction.

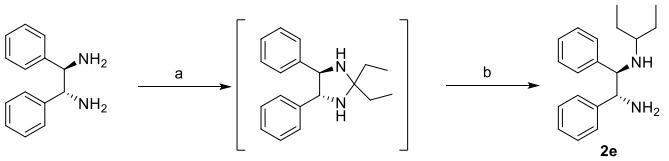
In the reaction (Scheme 1), the added aldehyde reacts with the primary amine to form an (*E*)-imine that minimizes non-bonding and becomes further activated by intramolecular hydrogen bonding with the neighboring ammonium proton to form an iminium intermediate. Here, the incorporated alkyl substituent is present on the opposite side of the adjacent phenyl group, thus blocking the *re* face of the dienophile in the iminium intermediate, along with the phenyl group of the carbon bonded to the iminium. Consequently, the diene is limited to approach the *si* face, and endo products are produced selectively. These are capable of secondary orbital interactions with the iminium. Similarly, aldol reactions using chiral diamine organic catalysts selectively alkylated on one side have been designed based on Scheme 1.

In this catalytic cycle, the added ketone reacts with the primary amine to form an enamine in the direction in which the steric hindrance of the phenyl group of the adjacent carbon is minimized, and the secondary ammonium proton and aromatic aldehyde form a hydrogen bond while avoiding steric hindrance, leading to the double activation of both enamine nucleophile and the aldehyde electrophile [10]. Then, a new C-C bond is formed between the enamine and approaching aldehyde. Finally, the aldol reaction is completed and *anti*-products are afforded in high stereoselectivity by the hydrolysis of the iminium by the H_2O produced in the reaction of the ketone and primary amine, as well as the added H_2O.

2. Results and Discussion

2.1. Synthesis of the chiral diamine

In this study, we chose DPEN, a chiral amine, for use in the aldol reaction as an organic catalyst. The catalyst was used to form an enamine intermediate through the reaction of its primary amine on one side with a ketone, as well as to provide a dual activation environment that can achieve stereoselectivity by introducing an alkyl group on the opposite side. The desired catalyst (**2**) was first obtained in low yield using conventional reductive *N*-alkylation. Therefore, the reaction conditions for the preparation of *N*-alkylated DPEN were modified. For the *N*-pentyl-modified catalyst, DPEN was dissolved in toluene and 3-pentanone was added. The mixture was heated to reflux and $MgSO_4$ was added. The solvent and $MgSO_4$ were removed, and the crude diaminoacetal was reduced with excess $NaBH_4$ in ethanol to afford the desired product (**2e**, Table 1) in a relatively high yield. The prepared catalysts are listed in Table 1. Using the synthesized organic catalyst, we investigated the solvent and anion effects on the aldol reaction, as well as the effects of different aromatic aldehydes. The synthesis of mono-*N*-alkyl-DPEN is shown in Scheme 2.



Scheme 2. *N*-Alkylation of DPEN. Reagents and conditions: a) 1.0 eq. 3-pentanone, $MgSO_4$, toluene (0.1 M), reflux, 48 h. b) EtOH (0.1 M), excess $NaBH_4$, 3 h (overall yield 81%).

Tab nd this study.

entry	R1, R2	entry	R1, R2
2a	R1 = H, R2= isopropyl	**2e**	R1 = H, R2 = 3-pentane
2b	R1 = H, R2 = cyclohexyl	**2f**	R1 = H, R2 = acetyl
2c	R1 = H, R2 = 4-heptane	**2g**	R1 = acetyl, R2 = 3-pentyl
2d	R1 = H, R2 = 5-nonane	**2h**	R1 = 3-pentyl, R2 = 3-pentyl

2.2. Aldol reaction between aromatic aldehydes and cyclohexanone using chiral DPEN

2.2.1. Aldol reaction using chiral amine

2.2.1.1. Solvent effects

To examine the solvent effects in the reaction between an aromatic aldehyde and a cyclohexanone using a chiral amine, we performed the aldol reaction using benzaldehyde, which is highly reactive, and cyclohexanone, as shown in Table 2.

To investigate the effect of the reaction solvent on the stereoselectivity, a number of organic solvents were tested: dimethylformamide (DMF), tetrahydrofuran (THF), water, and no solvent (neat conditions) (Table 2). The highest yield and the highest enantioselectivity of the *anti*-product were obtained when DMF was used, although the *anti/syn* selectivity was not good. Thus, concerning the enantioselectivity of the *anti*-product, DMF is the best solvent. However, because benzaldehyde shows excellent reactivity, similar yields were obtained in most solvents.

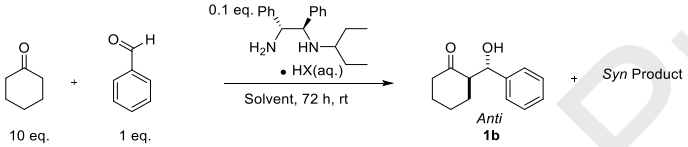


Table 2. Effects of acid additives and solvents on the organic-catalyzed aldol reaction.

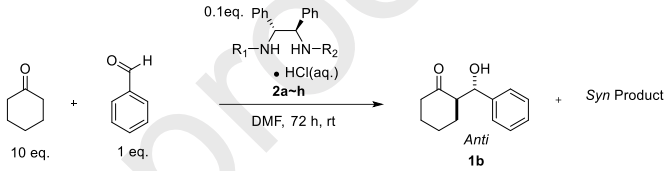
	Solvent (0.5 M)	Additive (aq.)	Solvent:H_2O	Yield[a] (%)	*Anti/Syn*[b]	ee (anti)[c] (%)
1	DMF	TfOH[d] (0.1)	15:1	65	9.0/1.0	94
2	DMF	HCl (0.1)	15:1	78	5.0/1.0	92
3	DMF	HCl (0.15)	15:1	64	3.4/1/0	85
4	DMF	HCl (0.2)	15:1	56	3.4/1.0	79
5	THF	HCl (0.1)	15:1	81	3.1/1.0	40
6	H_2O	TfOH (0.1)	-	87	1.8/1.0	80
7	H_2O	HCl (0.1)	-	88	2.5/1.0	44
8	neat	TfOH (0.1)	-	82	1.2/1.0	60

[a]Combined yield of isolated diastereomers. [b]Determined from the ^{1}H-NMR of the crude product. [c]Enantiomeric excess (ee) determined from chiral-phase high-performance liquid chromatography analysis of the *anti*-product. [d]Triflic acid (TfOH).

enantioselectivity of the *anti*-product were the highest when DMF was used as the solvent. When pure H_2O was used as the solvent, the yield was higher than that when using DMF. This may be due to the important role that H_2O plays in promoting the reaction and the catalytic cycle. Although DMF afforded a lower yield than when using H_2O, the stereoselectivity was better. Entry 2 – 4 of Table 2, an aldol reaction under DMF organic solvent conditions, showed *syn/anti* ratio and ee increased when adjusting the ratio content of additives (HCl). However, the yield was not as good as when using water as the solvent. And in Entry 5 of SI Table 1, when water is used as single solvent, the yield was good, but ee was not as good as when using other organic solvents.

2.2.2. Aldol reactions between benzaldehyde and cyclohexanone using chiral amine derivatives

Table 3. Effects of different *N*-alkyl substituents on chiral catalyst **2**.



Chiral Cat*.	Ketone:aldehyde	Yield[a] (%)	*Anti/Syn*[b]	ee (anti)[c] (%)
2a	10:1	80	3.0:1.	34
2b	10:1	76	2.2:1	82
2c	10:1	82	3.4:1	86
2d	10:1	77	3.0:1	84
2e	10:1	78	5.0:1	92
2e	5:1	55	2.2/1	87
2e	1:1	45	2.0/1	75
2e	1:5	47	1.4/1	66
2e	1:10	58	1.5/1	57
2f	10:1	No rxn	-	-
2g	10:1	No rxn	-	-
2h	10:1	5	-	-
2h[d]	10:1	No rxn	-	-

[a]Combined yield of isolated diastereomers. [b]Determined from ^{1}H-NMR spectrum of the crude product. [c]Enantiomeric excess (ee) Determined by chiral-phase high-performance liquid chromatography analysis of the *anti*-product [d]0.2 eq HCl used.

Chiral catalyst **2a** contains an isopropyl group (Table 1), which has a small steric effect, leading to a reduced stereoselectivity for the *anti*-product (Table 3). However, when catalyst **2e** was used, there was greater steric hindrance, and this is thought to play an essential role in increasing the selectivity of the reaction. When catalysts **2f** and **2g** were used, the reaction did not proceed at all. Based on these results, the aldol reaction proceeds from a primary

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found that the activation of the aldehyde by hydrogen bonding with the proton of the ammonium plays a significant role in the reaction. Furthermore, based on the low yield obtained using catalyst **2h**, we deduced that enamine and iminium intermediates are formed from primary rather than secondary amines.

Also, in the case of ketone and aldehyde, we experimented with aldehyde cases where substrate is benzyl and cyclohexyl, but the reaction did not proceed (Supporting information Table 1). However, in the case of aromatic aldehyde, the reaction went well.

2.2.1. Effects of the H_2O ratio and anions of DPEN salts formed with different acid additives

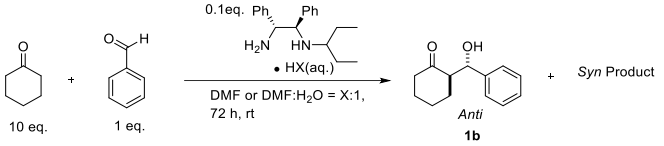

Table 4. Effects of acids on the organic-catalyzed aldol reaction of cyclohexanone and benzaldehyde in the presence of **2a**.

Entry	Additive (0.1 eq)	Solvent:H_2O	Yield[a] (%)	*Anti*/*Syn*[b]	ee (*anti*/*syn*)[c] (%)
1	HCl	30:1	77	5.0/1	90/10
2	HCl	15:1	78	5.0/1	92/20
3	HCl	10:1	80	4.7/1	90/30
4	HCl	5:1	77	5.0/1	92/26
5	TfOH	30:1	70	6.2/1	92/8
6	TfOH	15:1	71	4.7/1	90/8
7	TfOH	10:1	77	5.0/1	90/20
8	TfOH	5:1	75	4.0/1	88/42
9	TFA[e]	-	8	-	-
10	TFA	30:1	70	5.0/1	90/32
11	TFA	15:1	66	5.0/1	90/34
12	TFA	10:1	72	4.5/1	90/40
13	TFA	5:1	72	4.2/1	90/42
14	*p*-DBSA[f]	30:1	70	3.4/1	60/10
15	*p*-DBSA	15:1	74	3.7/1	60/14
16	*p*-DBSA	10:1	69	3.4/1	60/12
17	*p*-DBSA	5:1	75	3.3/1	60/18

[a]Combined yield of isolated diastereomers. [b]Determined from ^{1}H-NMR spectrum of the crude product. [c]Enantiomeric excess (ee) determined by chiral-phase high-performance liquid chromatography analysis of the *anti*-product. [d]Trific acid (TfOH). [e]Trifluoroacetic acid (TFA). [f]*p*-Dodecylbenzenesulfonic acid.

The proposed reaction mechanism suggests that H_2O plays a significant role in the catalytic cycle. The results shown in Table 4 reveal that H_2O plays an important role in these aldol reactions [11]. In the absence of H_2O (entries 5 and 10), the reaction yields were low. In particular, the reaction proceeded slowly in the absence of H_2O, as shown by the low product yield, because of the slow catalytic cycle. Also, when HCl was used as an acid additive, compared to those obtained with other acid additives, the highest yield was obtained. However, as long as H_2O was added to promote the catalytic cycle, the *anti/syn* selectivity and the enantioselectivity of the *anti*-product with different acid additives were similar.

different aromatic aldehyde substituents

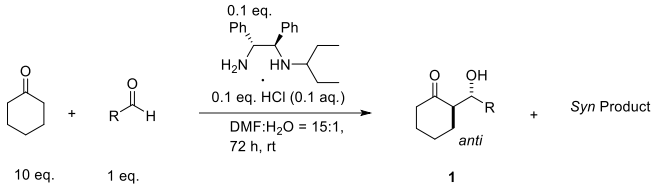

Table 5. Effects of different aldehyde substituents on the reaction products.

Entry	R	Product	Yield[a] (%)	*Anti*/*Syn*[b]	ee (anti)[c] (%)
1	4-ClC_6H_4	**1c**	93	2.9/1	72
2	3-ClC_6H_4	**1d**	98	3.8/1	80
3	2-ClC_6H_4	**1e**	99	4.1/1	88
4	4-$F_3CC_6H_4$	**1f**	92	2.5/1	76
5	3-$F_3CC_6H_4$	**1g**	99	3.6/1	58
6	2-$F_3CC_6H_4$	**1h**	87	10/1	94
7	4-$MeOC_6H_4$	**1i**	31	2.9/1	48
8	3- $MeOC_6H_4$	**1j**	73	3.7/1	52
9	2- $MeOC_6H_4$	**1k**	78	5.5/1	84
10	4-MeC_6H_4	**1l**	63	3.8/1	>99
11	4-$O_2NC_6H_4$	**1a**	97	2.7/1	81
12	2-$O_2NC_6H_4$	**1m**	99	4.0/1	92
13	1-naphtyl	**1n**	72	10.0/1	70
14	2-naphthyl	**1o**	75	3.5/1	76
15	4-$BnOC_6H_4$	**1p**	36	2.7/1	58

[a]Combined yield of isolated diastereomers. [b]Determined from the ^{1}H-NMR spectrum of the crude product. [c]Enantiomeric excess (ee) determined by chiral-phase high-performance liquid chromatography analysis of the *anti*-product.

Table 5 reveals that the use of electron-withdrawing substituents on the aromatic aldehyde led to high reaction yields [12]. However, when electron-donating methoxy and benzyloxy groups were used as the substituents, the reaction yield decreased significantly, indicating that the aldehyde carbonyl group plays an important role in the reaction. For electron-donating substituents, such as methoxy or benzyloxy groups, the polarity of the carbonyl group on the aromatic aldehyde is reduced, leading to the decreased reactivity of the aldehyde and poor yield or stereoselectivity. In addition, it was also found that the position of the substituent greatly affected the selectivity of the reaction [13]. No effects were observed for different substituents on the meta-position of the aldehyde. However, when the position of the substituent was changed from the para-position to the ortho-position of the aldehyde, the stereoselectivity and *anti/syn* selectivity of the *anti*-product improved. Thus, as the aldehyde is converted into an iminium intermediate, the higher steric hindrance at the ortho-position is more effective than that at the para-position. Moreover, as shown by entry 10 in Table 5 the stereoselectivity for the *anti*-product was very high, despite the lower yield compared to the reaction of benzaldehyde. Although *p*-methylbenzaldehyde may not be significantly different from benzaldehyde regarding electrostatic interactions, the effect of the steric hindrance of the methyl substituent is important in determining the selectivity. This suggests that the electrostatic

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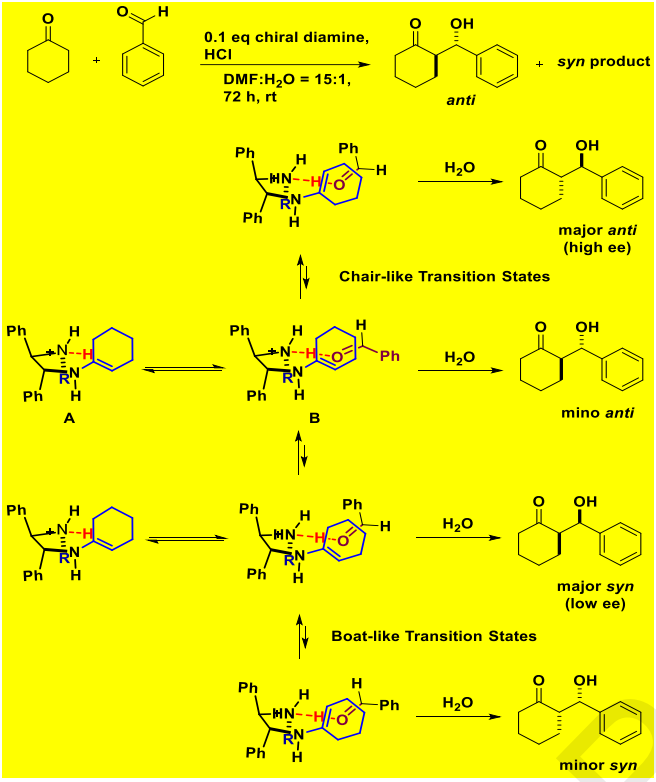
determining the stereoselectivity for the product.

2.3. Proposed reaction mechanism

The proposed reaction mechanism for the aldol reaction is shown in Scheme 3.



Scheme 3. Proposed reaction cycle.

As shown in Scheme 3, in our proposed reaction cycle, cyclohexanone reacts with the primary amine to form an enamine, which forms a transition structure (denoted A) to minimize steric hindrance, and the aromatic aldehyde hydrogen bonds with the ammonium salt and forms a new C-C bond via structure B while minimizing the steric hindrance of the alkyl group. Finally, the aldol products are formed by the hydrolysis of the iminium by the H_2O generated in the enamine formation and the H_2O added in the reaction. Water can help to form a product. However, the syn/anti ratio and ee ratio were found to be good under the conditions of DMF:H_2O = 15:1.

3. Conclusion

Good reactivity and enantioselectivity were achieved in the organic-catalyzed enantioselective reaction of cyclohexanone and benzaldehyde using the mono-alkylated diamine derivative (*R*, *R*)-(+)-1,2-diphenylethylenediamine (DPEN). Importantly, the used catalysts could be recovered after the reaction. In addition, the experimental results demonstrate that H_2O is an essential component of the catalytic cycle. By varying the substituents of the aromatic aldehyde substrate, we found that the substituent has a strong effect on the yield and stereoselectivity of the aldol reaction. In addition, high stereoselectivity was obtained by controlling the steric factors of the DPEN derivatives and the hydrogen bonding between the ammonium salt and aromatic aldehyde. It is expected that even better stereoselectivity could be achieved by designing a new catalyst with larger substituents than the phenyl group, as well as introducing other substituents to the phenyl group.

This work was supported by a Ministry of SMEs and Startups [MSS-2019R10251604]. We thank Dr. Yeonsun Hong for providing assistance.

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Supplementary Material

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HIGHLIGHTS

Organocatalytic asymmetric aldol reaction using protonated chiral 1,2-diamines

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- *N*-Alkylated chiral 1,2-diphenylethylenediamine used as aldol reaction catalyst.
- Range of aldehydes tested; high yield (99%) and enantioselectivity (>99%) obtained.
- Steric hindrance and hydrogen bonding determine enantioselectivity.
- Aromatic aldehydes with electron-withdrawing substituents led to good yields
- Ortho substituents gave higher stereoselectivities than para substituents