

Highly Diastereo- and Enantioselective Direct Aldol Reactions Promoted by Water-Compatible Organocatalysts Bearing Central and Axial Chiral Elements

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Abstract: Two novel bifunctional primary amine catalysts **1** (R_A,S,S) and **2** (R_A,R,R), which bear both central and axial chiral elements, have been developed to promote highly diastereoselective and enantioselective aldol reactions of arylaldehydes with cyclic and acyclic ketones in the presence of water at room temperature. The catalyst **2** (R_A,R,R) afforded the desired products with high levels of *anti* diastereoselectivity (up to 99:1) and enantioselectivity (up to 98%), showing that the two chiral elements of catalyst **2** (R_A,R,R) are matched, and enhance the stereochemical control. In addition, the catalyst **2** (R_A,R,R) was found to catalyze the direct aldol reaction of 4-nitrobenzaldehyde with 2-cyclohexanone under neat reaction conditions at room temperature with the high *anti* diastereoselectivity (98:2) and enantioselectivity (98%).

Keywords: aldol reaction; asymmetric catalysis; catalyst design; central and axial chirality; water

The asymmetric aldol reaction is one of the most important carbon-carbon bond forming reactions in organic synthesis.^[1] Asymmetric organocatalysis has grown explosively to become the main focus of research in asymmetric synthesis in recent years.^[2] Since the pioneering findings by List,^[3] Barbas,^[4] and their co-workers that L-proline could work as an active organocatalyst in intermolecular direct aldol reactions, numerous organocatalysts have been developed for the direct asymmetric aldol reactions.^[5]

Water is an ideal solvent for chemical reactions due to its low cost, safety and environmentally benign nature.^[6] The development of highly stereoselective organocatalysts that promote direct asymmetric aldol

reactions in aqueous medium remains an important but challenging goal^[7] as water often inhibits the catalyst's activity or alters enantioselectivity by interrupting ionic interactions and hydrogen bonds critical for stabilizing the transition states of the reactions. Early studies with small organic molecules in an aqueous medium had limited success.^[8] Recently Hayashi,^[9] Barbas III and Takabe^[10] independently reported proline-derived chiral catalysts for highly enantioselective aldol reactions in the presence of water. Following these seminal reports, a number of organocatalysts have been designed for the direct asymmetric aldol reactions in aqueous medium.^[11–13] However, only a few organocatalysts among them really seem to work in the presence of a large excess of water,^[9,10,11a–c] while other catalysts have different drawbacks. Some of them work in aqueous organic mixed solvents^[12] or require the use of a large excess of ketones^[11f–i] and others are supported or dendritic systems.^[13] On the other hand, the catalysts which really seem to work in the presence of a large excess of water are often suffering from limitations such as the requirement of low temperature^[9b,11a,c] and the high catalyst loading.^[11e] Therefore, from the practical viewpoint, the development of new chiral organocatalysts with appropriate catalyst loading for the direct asymmetric aldol reactions in the presence of a large excess of water at room temperature is still highly desirable.

As part of our interest in asymmetric organocatalysis based on chiral primary amines,^[14] we report a novel type of organocatalyst for promoting the direct aldol reaction in water at room temperature with high diastereoselectivity and enantioselectivity.

For the design of novel chiral catalysts, we are interested in organocatalysts bearing two different types of stereogenic structure in the same molecule as this would facilitate catalyst tunability. On the other hand, to achieve a catalytic asymmetric aldol reaction in

water, the incorporation of an appropriate hydrophobic group into the organic catalyst may be feasible as it would generate a hydrophobic organocatalyst. Given these considerations, we designed bifunctional organocatalysts **1** and **2** (Figure 1) possessing the ax-

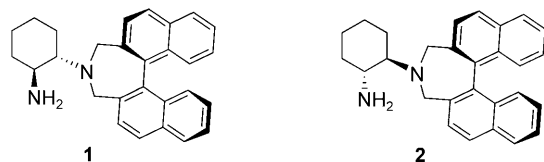


Figure 1. Designed bifunctional catalysts **1** and **2**.

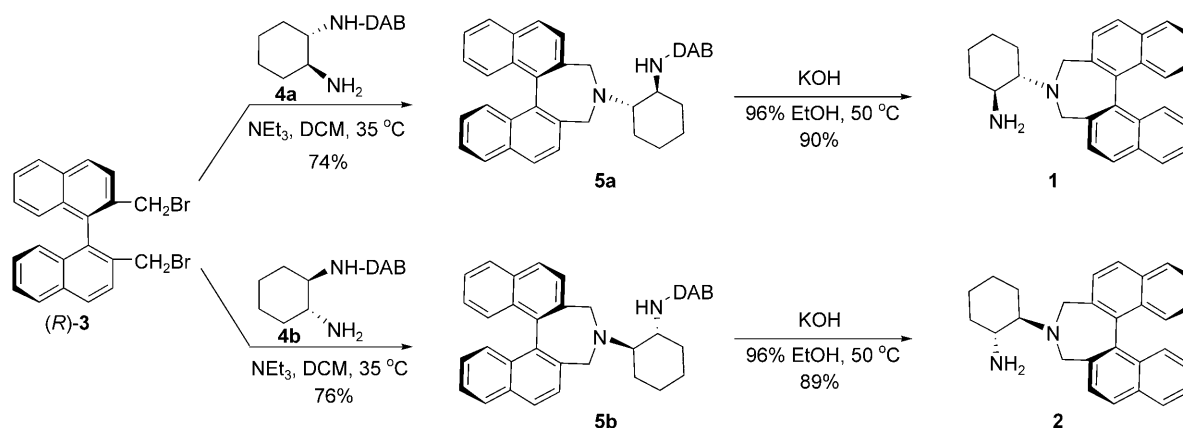
ially chiral binaphthyl unit. It was hypothesized that the axially chiral binaphthyl group of the catalysts would play a double role in the catalytic process. One role is to act as the second chiral element to facilitate catalyst tunability, and another role is to act as a hydrophobic group to enhance the hydrophobic hydration of the catalysts and assembly with organic substrates in water. As a result, water can be sequestered from the transition state and high stereocontrol may be expected. To the best of our knowledge, this is the first highly diastereoselective and enantioselective direct aldol reaction in the presence of a large excess of water promoted by a primary amine catalyst with both central and axial chiral elements.

The two bifunctional chiral organocatalysts **1** and **2**, carrying the same absolute configuration of the binaphthyl unit, but differing in the two stereogenic centers of the cyclohexyl scaffold, were easily synthesized by following the procedure described in Scheme 1. The reaction of (*R*)-2,2'-di(bromomethyl)-1,1'-binaphthyl **3**^[15] with DAB (1,3-dimethyl-5-acetylbarbituric acid)-mono-protected (1*S*,2*S*)- and (1*R*,2*R*)-cyclohexyldiamine **4a** and **4b** in CH₂Cl₂ in the presence of Et₃N as the base gave the correspond-

ing tertiary amines **5a** and **5b** in 74% and 76% yield, respectively.^[16] Subsequent deprotection of **5a** and **5b** with KOH in 96% EtOH solution at 50 °C afforded primary amines **1** and **2** in 90% and 89% yield, respectively.

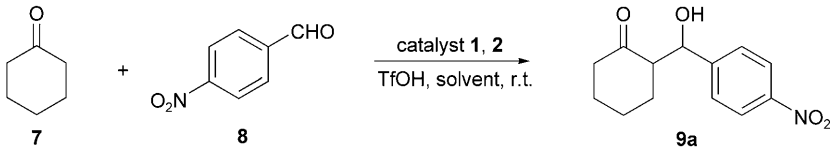
The efficacy of bifunctional primary amines **1** and **2** as chiral organocatalysts was initially evaluated using the reaction of cyclohexanone **7** with 4-nitrobenzaldehyde **8** in the presence of 7 mol% of the bifunctional primary amines and TfOH in water at room temperature (Table 1). Under the same conditions, the catalyst **2** (*R_A*,*R_R*) gave the desired product **9a** in higher diastereoselectivity (98:2) and enantioselectivity (98%) (entry 2), whereas the catalyst **1** (*R_A*,*S_S*) afforded the product **9a** in lower diastereoselectivity (79:21) and enantioselectivity (85%) (entry 1). These results seem to indicate that the two chiral elements in the primary amine catalyst **2** (*R_A*,*R_R*) are matched, enhancing the stereochemical control, whereas two chiral elements in the chiral primary amine catalyst **1** (*R_A*,*S_S*) are mismatched. Interestingly, very recently we^[17] developed two bifunctional amine-thiourea organocatalysts **6a** and **6b** possessing both central and axial chiral elements for the enantioselective Michael reaction between 1,3-dicarbonyl compounds and nitro-olefins in which two chiral elements of the amine-thiourea catalyst **6b** (*R_A*,*S_S*) was matched, whereas two chiral elements of the amine-thiourea catalysts **6a** (*R_A*,*R_R*) was mismatched (Figure 2).

Additionally, the reaction became very sluggish in the absence of TfOH (entry 3). This experiment indicated that strong acidic additive such as TfOH was essential for catalytic activity. As shown in the Table 1, although the central chiral element of the primary amine catalysts predominates the absolute configuration of the product **9a**, the axial chirality significantly influences the diastereoselectivity and enantioselectivity of this reaction. Next, the primary amine **2** was taken as the catalyst of choice and evaluated for the same reaction in neat reaction conditions. To our de-



Scheme 1. Synthesis of bifunctional organocatalysts **1** and **2**.

Table 1. Direct aldol reaction of 2-cyclohexanone **7** with 4-nitrobenzaldehyde **8** catalyzed by primary amines **1** and **2**.^[a]

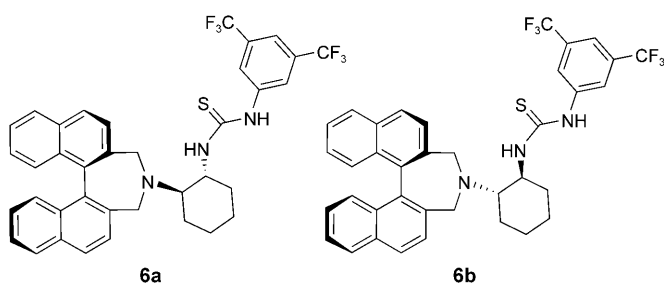
						
Entry	Catalyst (mol%)	TfOH (mol%)	Solvent	Yield ^[b] [%]	<i>anti/syn</i> ^[c]	<i>ee</i> ^[d] [%]
1	1 (7)	7	H ₂ O	81	79:21	85
2	2 (7)	7	H ₂ O	96	> 98:2	98
3	2 (7)	0	H ₂ O	trace	–	–
4	2 (7)	7	Neat	97	98:2	98
5	2 (3.5)	3.5	H ₂ O	96	98:2	98

^[a] The reaction was performed with cyclohexanone **7** (0.6 mmol) and 4-nitrobenzaldehyde **8** (0.2 mmol) in the presence of catalysts **1** and **2** with specified catalyst loading at room temperature.

^[b] Combined yields of diastereomers.

^[c] Diastereoselectivities were determined by ¹H NMR analysis of the products.

^[d] The *ees* of the *anti* product were determined by HPLC using a Chiralpak AD-H column.

**Figure 2.** Bifunctional amine-thiourea organocatalysts **6a** and **6b**.

light, the same level of diastereoselectivity (98:2) and enantioselectivity (98%) was achieved (entry 4). It should be noted that few universal catalysts give high diastereoselectivity and enantioselectivity for this reaction, both in the presence of water and under neat

conditions.^[11] Since we got high diastereoselectivity (98:2) and enantioselectivity (98%) on performing the aldol reaction in water by using 7 mol% of **2**/TfOH, the possibility of decreasing the catalyst loading was evaluated with the hope to improve the catalyst efficiency. Fortunately, by using water as the solvent, 3.5 mol% of **2**/TfOH was efficient enough to mediate the aldol reaction in a good yield (96%) with an excellent diastereomeric ratio of 98:2 as well as high enantioselectivity of 98% *ee* (entry 5).

To examine the generality of the reaction, the aldol reactions between aryl aldehydes with ketones including cyclic and acyclic ketones were tested by using catalyst **2**/TfOH. The results are summarized in Table 2. The aldol reactions of aryl aldehydes with ketones proceeded smoothly to give the desired adducts in water. With 2-cyclohexanone, high diastereoselectivities (94:6~99:1) and enantioselectivities (90–98%)

Table 2. **2**/TfOH-catalyzed direct aldol reactions in water.^[a]

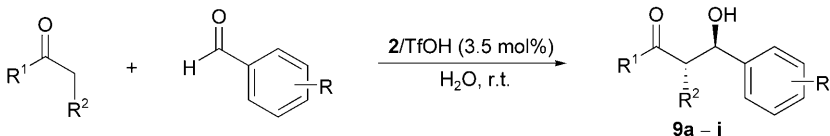
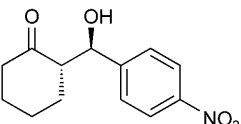
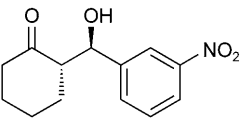
					
Entry	Product	Time [h]	Yield [%] ^[b]	<i>anti/syn</i> ^[c]	<i>ee</i> [%] ^[d]
1		10	96	> 98:2	98
2		16	93	98:2	97

Table 2. (Continued)

Entry	Product	Time [h]	Yield [%] ^[b]	<i>anti/syn</i> ^[c]	<i>ee</i> [%] ^[d]
3		18	94	99:1	96
4		30	83	98:2	95
5		21	80	97:3	95
6		17	93	98:2	96
7 ^[e]		60	61 ^[f]	94:6	94
8 ^[e]		72	23 ^[g]	95:5	90
9		12	94	80:20	86
10 ^[h]		18	91	90:10	92
11 ^[i]		48	71 ^[j]	—	87

^[a] The reaction was performed with arylaldehydes (0.2 mmol), ketones (0.6 mmol), **2**/TfOH (3.5 mol%) and water (0.5 mL) at room temperature.

^[b] Combined yields of diastereomers.

^[c] Diastereoselectivities were determined by ¹H NMR analysis of the products.

^[d] The *ees* were determined by chiral-phase HPLC analysis of the *anti* product.

^[e] The reaction was performed with 7 mol% catalyst **2**.

^[f] 35% benzaldehyde was recovered.

^[g] 72% 4-methoxybenzaldehyde was recovered.

^[h] The reaction was run at 12 °C.

^[i] 20 equiv. of acetone was used in this reaction.

^[j] 23% 4-nitrobenzaldehyde was recovered.

were obtained (entries 1–8). In the case of 2-cyclopentanone with 4-nitrobenzaldehyde, lower diastereoselectivity (80:20) and enantioselectivity (86%) were achieved at room temperature compared to 2-cyclo-

hexanone in our catalytic system. However, the diastereoselectivity and enantioselectivity were increased to 90:10 *dr* and 92% *ee*, respectively, when the reaction was conducted at 12 °C. It should be noted that

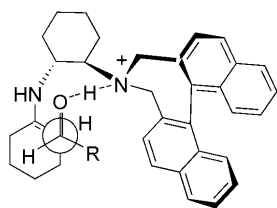


Figure 3. Proposed transition state model.

the diastereoselectivity in this reaction represents the best result so far. In addition to cyclic ketones, an acyclic ketone was also evaluated as the substrate. For example, acetone gave the desired product with 87% *ee*.^[18] Absolute configurations of **9a–i** were determined by comparing the retention time on HPLC of the products with literature data.^[11g,13a,19]

To account for the stereochemical outcome of the current reaction, we propose that the primary amine-catalyzed aldol reaction occurs via the transition state as depicted in Figure 3, where the enamine attacks the aldehyde from the *Si* face, leading to the formation of the major stereoisomer. In this model, the protonated tertiary amine serves as a directing hydrogen bonding donor.^[19] We believe that chiral binaphthyl group of the organocatalyst facilitates the formation of a hydrophobic core with substrates in water, thus promoting the aldol reaction in water. This may be supported by the observation that the catalyst (1*R*,2*R*)-*N*¹,*N*¹-dimethylcyclohexane-1,2-diamine (3.5 mol%) with decreased hydrophobicity affords only a very small amount of product in the reaction of cyclohexanone (0.6 mmol) and 4-nitrobenzaldehyde (0.2 mmol) in water (0.5 mL) at room temperature after 10 h.

In summary, we have developed two novel bifunctional enamine catalysts **1** (*R*_A,*S*,*S*) and **2** (*R*_A,*R*,*R*), which bear both central and axial chiral elements, for promoting the diastereoselective and enantioselective aldol reaction in water between aryl aldehydes with cyclic and acyclic ketones. The catalyst **2** (*R*_A,*R*,*R*) afforded the desired products with high levels of diastereoselectivity (up to 99:1) and enantioselectivity (up to 98%), showing that two chiral elements of **2** are matched, and enhance the stereochemical control. In addition, the catalyst **2** was found to catalyze the direct aldol reaction of 4-nitrobenzaldehyde with 2-cyclohexanone under neat reaction conditions at room temperature with the high *anti* diastereoselectivity (98:2) and enantioselectivity (98%). Mechanistic studies and applications of these bifunctional enamine organocatalysts in other asymmetric reactions are under examination in our laboratory.

Experimental Section

Typical Procedure for the Direct Asymmetric Aldol Reaction Catalyzed by Bifunctional Catalyst **2**

To a stirred suspension of **2**/TfOH (3.5 mol%) and ketone (0.6 mmol) in water (0.5 mL) at room temperature after 20 min, the aryl aldehyde (0.2 mmol) was added. The mixture was allowed to stir for the stated time, then the reaction mixture was quenched with saturated NH₄Cl solution, extracted with EtOAc and dried over Na₂SO₄. The crude product was purified by flash silica gel chromatography.

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