Enantioselective aldol reaction of cyclic ketones with aryl aldehydes catalyzed by a cyclohexanediamine derived salt in the presence of water†

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Water was found to be a suitable reaction medium for the direct asymmetric aldol reaction of various cyclic ketones with aryl aldehydes catalyzed by a primary-tertiary diamine-Brønsted acid.

The aldol reaction is recognized as one of the most efficient methods for the formation of carbon-carbon bonds in modern organic synthesis. It provides an atom-economic approach to synthesize β-hydroxy carbonyl compounds. Since L-proline was found by List in 2000 to be able to mimic the catalytic behavior of type I aldolase in intermolecular aldol reactions,[1] much progress has been made in the development of organocatalysis.[2] However, the donors of these aldol reactions are usually used in a large excess amount, which hampers its practical application. Therefore, it is necessary to develop more effective ways to lower the amount of donors.

Water as a reaction medium has attracted both academic and industrial interests because of its special properties such as safety, nontoxicity, inflammability, cheapness and environmental friendliness. While the advantages of water are obvious from the perspective of green chemistry, there are still many challenges in the field of organocatalysis in which water is involved. Water interferes with organocatalysts and disrupts hydrogen bonds and other polar interactions, accordingly in many cases deteriorating catalytic activity and stereoselectivity. Even so, the aldol reaction involving water has developed significantly over the past several years.[3] Interestingly, a hot debate has arisen recently on the role of water in aldol reactions.[4] On the one hand, Janda didn't agree that these reactions were truly carried out "in water" because the reaction system is biphasic.[4a] As for the accurate description of the reaction system, Hayashi proposed that the terminology "in the presence of water" would best convey the effect of water in these reactions.[4b] On the other hand, both Janda and Blackmond didn't consider that the aldol reactions carried out in the presence of water were so green because the donor cyclohexanone was used in a large amount, even in excess over water, and much organic solvent was required for extraction work-up.[4a,4c] Furthermore, cosolvents were usually employed to improve the stereoselectivity in these
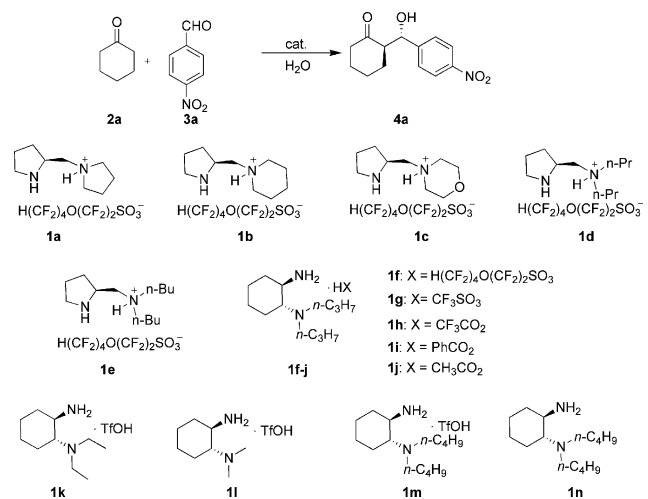
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reactions.[3h,5] In such situations, it is interesting to investigate further organocatalytic aldol reactions in the presence of water.

Recently, we found that an ionic liquid derived from the 1,1,2,2-tetrafluoro-2-(1,1,2,2,3,3,4,4-octafluorobutoxy)-ethanesulfonate anion can act as both the recyclable solvent and catalyst for Friedel–Crafts alkylations of indoles with nitroalkenes.[6] The good solubility of this kind of ionic liquid in water and organic solvent prompted us to presume that organic salts containing this sulfonate might be used as surfactant-type organocatalysts.[7] Thus, a series of salts having such a sulfonate anion (**1a–1f**) were synthesized by direct neutralization of amines with the sulfonic acid or by neutralization with hydrochloric acid first and then metathesis with the sulfonate (see ESI).† When these salts were used as catalysts (10 mol%) for the aldol reaction between cyclohexanone (1 mmol) and 4-nitrobenzaldehyde (0.5 mmol) in the presence of water (2 mL), it was found that they exhibited low stereoselectivity for the transformation (Table 1, entries 1–6). This phenomenon might be ascribed to the large steric hindrance of the long chain sulfonate anions, which hampered the hydrogen bonding between catalysts and the substrate. It seemed that catalysts based on the large sulfonate anion were not suitable for this reaction. Among the catalysts tested, **1f** exhibited higher stereoselectivity for the transformation. Therefore, 1,2-cyclohexanediamine-derived salts were chosen as the catalyst for the above aldol condensation (Table 1, entries 7–10). It can be seen that the stereoselectivity was greatly improved while decreasing the size of the anion. The salts with fluorinated anions gave better results (entries 7 and 8) than those nonfluorinated analogues (entries 9 and 10). Comparatively, the triflate salt **1g** showed the highest stereoselectivity (entry 7). Other triflates **1k–1m** (entries 11–13) with different lengths of alkyl group on the nitrogen demonstrated similar stereoselectivity but different catalytic activity. For those triflates with shorter alkyl chains on the nitrogen, the reaction proceeded relatively slowly (entries 11 and 12). **1g** and **1m** exhibited comparable activities (entries 7 and 13). But **1g** is viscous liquid while **1m** is solid at room temperature. Thus, the operation of **1m** is more convenient. In addition, the salt form of the 1,2-cyclohexanediamine is essential for the catalysis. When **1n**, the free base form of **1m**, was used as the catalyst, the reaction became so sluggish that only a trace amount of the desired product was formed (entry 16). Based on a comprehensive consideration of catalytic activity, stereoselectivity and operational convenience, **1m** was chosen as the catalyst (entry 13).

Table 1 Screening of reaction conditions in the direct asymmetric aldol reaction of cyclohexanone (**2a**) with 4-nitrobenzaldehyde (**3a**) in the presence of water[a]

Entry	Catalyst	Time (h)	Yield (%)	anti/syn[b]	ee (%)[c]
1	**1a**	50	62	64/36	−35
2	**1b**	50	85	57/43	−48
3	**1c**	60	NR	—	—
4	**1d**	30	96	69/31	−71
5	**1e**	24	92	57/43	−26
6	**1f**	40	88	83/17	61
7	**1g**	60	95	94/6	96
8	**1h**	70	93	93/7	95
9[d]	**1i**	36	96	78/22	95
10[d]	**1j**	70	92	88/12	93
11	**1k**	90	98	94/6	97
12	**1l**	90	43	86/14	97
13	**1m**	60	95	95/5	95
14	**1m** (2nd cycle)	60	92	95/5	96
15	**1m** (3rd cycle)	60	91	93/7	93
16	**1n**	30	Trace	—	—
17[e]	**1m**	12	97	96/4	92
18[f]	**1m**	12	96	98/2	96
19[g]	**1m**	12	96	> 99/1	98
20[h]	**1m**	80	95	80/20	85
21[i]	**1m**	24	98	97/3	98

[a] Reaction conditions: **2a** (1 mmol), **3a** (0.5 mmol) and catalyst (0.05 mmol) in the presence of water (2 mL) at room temperature. [b] Determined by ^{1}H NMR of the crude product. [c] Determined by chiral-phase HPLC analysis of the *anti* product. [d] The catalyst was generated *in situ* in the reaction system. [e] Cyclohexanone (2 mL) was used as the solvent without water. [f] Cyclohexanone (2 mL) was used as the solvent with the addition of water (0.5 mmol). [g] Cyclohexanone (2 mL) was used as the solvent with the addition of water (5 mmol). [h] Cyclohexanone (3 mmol) was used in the presence of water (2 mL). [i] Cyclohexanone (5 mmol) was used in the presence of water (2 mL).

After the completion of the reaction, the organic product could be readily separated from the reaction mixture by simple filtration. Further column chromatography afforded the pure product. In the case of triflate **1m**, it was found that a small amount of catalyst (0.012 mmol) and unreacted cyclohexanone (0.27 mmol) was left in the filtrate, as determined by ^{1}H and ^{19}F NMR spectroscopy. After cyclohexanone and catalyst was supplemented to the original amount, the filtrate can be reused in the next run, showing no significant decrease in catalytic performance (entries 14 and 15).

Water played an important role in the reaction. Using cyclohexanone as the solvent, although the reaction proceeded smoothly without water (entry 17), the stereoselectivity was slightly improved by the addition of one equivalent of water (entry 18). Increasing the amount of water to 10 equiv. markedly enhanced the stereoselectivity (entry 19). On the other hand, the amount of cyclohexanone also affected the selectivity. When the reaction was performed in the presence of water, the stereoselectivity was considerably improved by using a large excess of cyclohexanone (entries 20 and 21). From the green chemistry perspective, 2 : 1 of donor (ketone) to acceptor (aldehyde) was adopted as the optimum reactant ratio.

The important feature of this catalytic system is that organic solvents are not necessary for either the reaction or the extraction. Since cyclohexanone was used in slight excess over aryl aldehyde in the presence of water, the reaction system was biphasic, thus leading to easy separation of the organic product. Similar work done by Cheng and Luo revealed that large excess of ketone was used both as the starting material and as the solvent,[2g] and an acidic additive was needed to obtain good stereoselectivity. Therefore, this procedure for aldol reactions catalyzed by triflate **1m** in the presence of water seems very attractive from a green chemistry perspective.

A series of aryl aldehydes and cyclic ketones were then subjected to the optimal reaction conditions described above. As summarized in Table 2, the reaction of cyclohexanone with aryl aldehydes bearing various substituents afforded high selectivities of *anti*-aldol products (entries 1–9). When this procedure was applied to cyclopentanone (entry 10), the diastereoselectivities and enantioselectivities became significantly lower. However, in the case of water miscible tetrahydro-4*H*-pyran-4-one, excellent selectivities were obtained (entries 11 and 12).

The effectiveness of triflate **1m** for the aldol reaction aroused our interest in this catalyst. The precursor of the catalyst, **1n**, has

Table 2 Asymmetric aldol reaction in the presence of water[a]

Entry	X	n	Y	Time (d)	**4**, %	anti/syn[b]	ee (%)[c]
1	C	1	4-NO₂	2.5	**4a**, 95	95/5	95
2	C	1	3-NO₂	3	**4b**, 94	94/6	96
3	C	1	4-CF₃	2	**4c**, 94	93/7	96
4	C	1	4-CN	7	**4d**, 82	90/10	86
5	C	1	4-Br	4	**4e**, 99	95/5	98
6	C	1	4-Cl	4	**4f**, 96	88/12	93
7	C	1	2,4-Cl₂	5.5	**4g**, 84	99/1	97
8	C	1	3,4-Cl₂	7	**4h**, 94	93/7	96
9	C	1	4-Ph	7.5	**4i**, 56	96/4	93
10	—	0	4-NO₂	2	**4j**, 34	79/21	84
11	O	1	4-NO₂	7	**4k**, 57	95/5	98
12	O	1	4-CF₃	7	**4l**, 75	94/6	95

[a] Reaction condition: **2** (1 mmol), **3** (0.5 mmol) and catalyst (0.05 mmol) in the presence of water (2 mL) at room temperature. [b] Determined by ^{1}H NMR of the crude product. [c] Determined by chiral-phase HPLC analysis of the *anti* product.

a primary and a tertiary amino group. Generally, the basicity of primary amines is stronger than that of tertiary amines.[8] The reaction of **1n** with trifluoromethanesulfonic acid should happen preferentially at the primary amine. However, there has been little investigation into the protonated structure of diamines containing both primary and tertiary amino groups. Hine once suggested that the monoprotonated forms of such diamines exist as internally hydrogen-bonded species.[9] Fortunately, single crystals of **1m** suitable for X-ray diffraction studies were obtained. It was thus proved that the proton is located at the primary amino group in its solid state.[10]

Nevertheless, we tend to think that the solvated triflate **1m** would take an internally hydrogen-bonded structure **A** (Scheme 1), which is very similar to that proposed by Hine.[9] A proton is situated between two N atoms, forming a proton transfer equilibrium between **1m** and **B**. Accordingly, **B** initiated the catalytic cycle *via* nucleophilic addition to the ketone to give an enamine intermediate **C**. Hydrogen bonding interaction between tertiary amino group of **C** and aldehyde led to the formation of intermediate **D**. The cyclic ring of the ketone effectively screened the Re face of the aryl aldehyde from attack by enamine. Enamine–aldehyde condensation and subsequent hydrolysis afforded asymmetrically the aldol product, simultaneously generating **B** for next cycle.
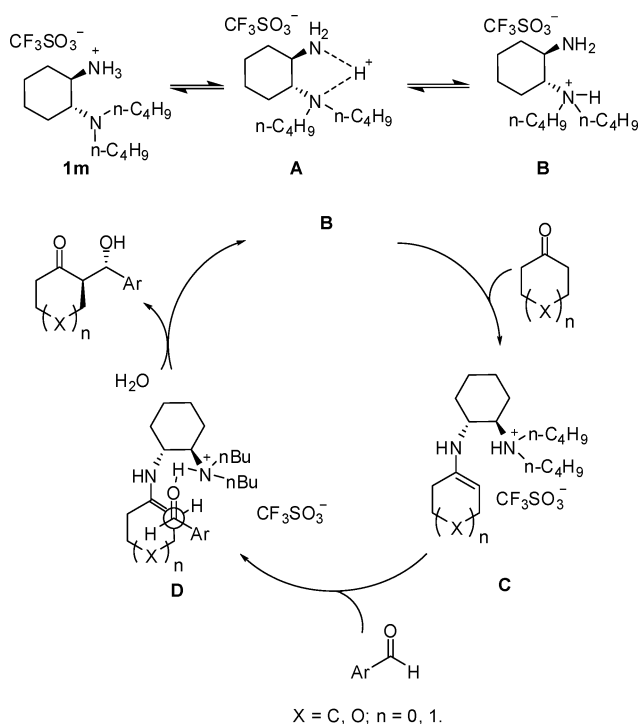
Scheme 1 Proposed mechanism for the aldol reaction catalyzed by **1m**.

In summary, water was found to be a suitable reaction medium for the direct asymmetric aldol reaction of various cyclic ketones with aryl aldehydes catalyzed by a primary-tertiary diamine-Brønsted acid. No organic solvents are necessary for either the reaction or the extraction. The advantages are clear from a green chemistry perspective. The protonated structure of 1,2-cyclohexanediamine was elucidated by single crystal X-ray analysis. A possible mechanism involving an internally

hydrogen-bonded structure of the catalyst was proposed to explain this direct aldol reaction. Further studies on the catalytic system to other reactions are currently underway.

Experimental

Typical procedure for the aldol reaction: to a suspension of catalyst **1m** (18.8 mg, 0.05 mmol) in water (2 mL) was added cyclic ketone (1 mmol). After stirring for one minute, aryl aldehyde (0.5 mmol) was introduced. Then the reaction was kept at room temperature for the time indicated in Table 2. After completion of the reaction, the product precipitated as a solid. The crude product was collected by filtration. Diastereoselectivity was determined by ^{1}H NMR analysis of the crude product. Further column chromatography gave the pure product.

Acknowledgements

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