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Research Article

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Cooperating β-CD with (4R)-4-phenyl-oxazolidin-2-one to catalyze aldol reactions on/in phosphate buffer

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ABSTRACT

It was amazed that the catalytic system was combined β -cyclodextrin (β -CD, 10 mol%) with (4R)-4-phenyl-oxazolidin-2-one (2mol%) in phosphate buffer, which can catalyzed aldol reactions. The optimal catalytic condition of (4R)-4-phenyl-oxazolidin-2-one for the aldol reaction was investigated by performing a model reaction using stoichiometric of various aryl aldehydes and cyclohexanone respectively in three kinds of phosphate buffer (pH 3.8, 7.0, 10.5). To compare the catalytic effect of (4R)-4-phenyl-oxazolidin-2-one that three comparing experiments were carried out at the optimal condition (pH 10.5 and p-nitrobenzaldehyde). Although the catalytic effect is lower than L-proline at same condition (reaction time, yield and ee), it has been expended the application of (4R)-4-phenyl-oxazolidin-2-one only as chiral auxiliary in asymmetric synthesis.

Key words: Inclusion complex, Chiral auxiliary, β-cyclodextrin, Aldol reaction, Catalyst.

INTRODUCTION

The work of Evans in development of chiral oxazolidin-2-ones as chiral auxiliaries, namely Evans auxiliaries has proved to be an effective methodology in asymmetric synthesis. Such chiral auxiliaries have been utilized in a variety of highly diastereoselective reactions of the attached N-acyl groups including alkylation, amination, azidation, bromination, hydroxylation, aldol additions, Diels-Alder cycloadditions and conjungate additions [1-4]. Although oxazolidinones serve as chiral auxiliaries for a wide array of reactions, the limited of these compounds are the equal of chiral auxiliary as reactant to attach of the acyl fragment, at less three stages in the use of chiral auxiliary, and unwanted endocyclic cleavage of the acyl fragment[5]. Asymmetric catalytic reactions can produce large quantities of chiral products with a very high efficiency using small amounts of chiral catalysts.

Supramolecular catalysts offer chemists precise spatial control over chemical transformations. Cyclodextrins (CDs), which possess a hydrophobic cavity for substrate binding, have been recognized as versatile enzyme mimics. The astounding catalytic efficiency and substrate specificity have been observed by mimetic enzymes for specific reactions and substrates. CDs' host-guest recognition via noncovalent interactions have been employed in hydrolysis reactions,[6, 7] C-H bond activation,[8, 9] epoxidation of olefins,[10, 11] Diels-Alder reactions,[12, 13] 1,3-dipole cycloadditions,[14, 15] etc .

The asymmetric direct aldol reaction is one of the most powerful methods of forming C-C bonds. Proline is regarded as an effective and versatile small-molecule "enzyme" that catalyzes a wide range of organic transformations, such as the asymmetric direct aldol reactions. There are a few examples describing organocatalysts that combine the catalytic properties of proline with the ability of cyclodextrin to form inclusion complexes.[16-18] However, in most of these examples an inclusion complex between a cyclodextrin and a hydrophobic proline is formed with capacity of catalyze aldol reactions in water.[16-18] Zhang reported the direct asymmetric aldol reactions through the

β -CD-immobilized (4S)-phenoxy-(S)-prolie.[16] Fernandez-Mayoralas reported that the utility of pendant copolymers bearing proline and permethylated β -CD also could catalyze the asymmetric aldol reactions.[18] Armstron reported that using L-prline as the catalyst and sulated β-CD as an inverse phase-transfer reagent in water to afford the aldol product in good yields and with both high enantioselectivity and diastereoselectivity.[17] In this work, we wanted to expand the utility of (4*R*)-4-phenyl-oxazolidin-2-one in water for the aldol reactions under environmentally benign conditions.

EXPERIMENTAL SECTION

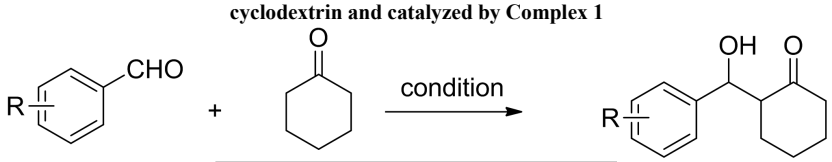
Materials and general methods

β-CD (average substitution degree = 1135) was purchased from ABCR GmbH & Co. KG and used without further purification. Other chemicals and reagents were obtained from commercial sources and used as received. NMR spectra were conducted on a Bruker Avance DRX spectrometer at 500 MHz and 298 K in D_2O or $CDCl_3$. The one-dimensional spectra of both solutions were run with FID resolution of 0.18 Hz/point. The residual HDO line had a line width at a half-height of 2.59 Hz. Two-dimensional (2D) ROESY spectra were acquired at 298 K with presaturation of the residual water resonance and a mixing (spin-lock) time of 350 ms at a field of ~2 kHz, using the TPPI method, with a 1024 K time domain in F2 (FID resolution 5.87 Hz) and 460 experiments in F1. Processing was carried out with zero-filling to 2K in both dimensions using sine (F2) and qsine (F1) window functions, respectively. Diastereomeric and enantiomeric excess were calculated by NMR and chiral HPLC (chiralpark AD-H, lecture at 254 nm).

General procedure for asymmetric aldol reaction

Cyclohexanone (0.52 mL, 5 mmol) and aryl aldehyde (5 mmol) were added to a solution of (4*R*)-4-phenyl-oxazolidin-2-one (2 mol%, 0.1 mmol) and β-cyclodextrin (10 mol%) in phosphate buffer (15 mL, pH 3.8, 7.0 or 10.5), and the reaction mixture was stirred at room temperature. The different reaction conditions and results were summarized in Table 1. The catalytic activity of (4*R*)-4-phenyl-oxazolidin-2-one for the asymmetric direct aldol reaction were evaluated in Table 2. After the specified time elapsed, the mixture was extracted with dichloromethane. The organic phase was concentrated under reduced pressure.

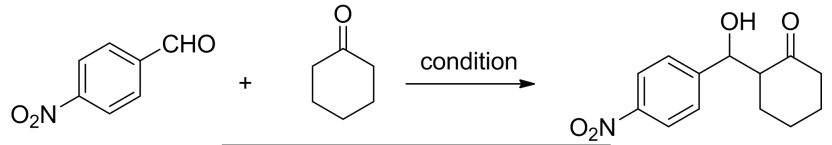
Table 1 The asymmetric aldol reactions of cyclohexanone with various aryl aldehydes in various phosphate buffer mediated by cyclodextrin and catalyzed by Complex 1



Entry	R	pH	yield %
1	*p*-NO_2	3.8	0
		7.0	0
		10.5	89
2	*p*-OCH_3	3.8	0
		7.0	0
		10.5	0
3	*p*-Cl	3.8	0
		7.0	0
		10.5	8
4	2,4-dimethoxy	3.8	0
		7.0	0
		10.5	0

Reactin condition: benzaldehyde (5.0 mmol), cyclohexanone (5.0 mmol), (4R)-4-phenyl-oxazolidin -2-one (2 mol%), β-CD (10 mol%), and phosphate buffer (15 ml), at room temperature .

Table 2 The catalytic activity of (4*R*)-4-phenyl-oxazolidin-2-one for the asymmetric direct aldol reaction were evaluated



Entry	condition	Time h	yield %
1	a	20	89
2	b	42	20
3	c	42	90

Reaction condion: a) benzaldehyde (5.0 mmol), cyclohexanone (5.0 mmol), L-proline (2 mol%), β-CD (10 mol%), and phosphate buffer (pH = 10.5, 15 ml); b) benzaldehyde (5.0 mmol), cyclohexanone (5.0 mmol), β-CD (10 mol%), and phosphate buffer (pH = 10.5, 15 ml); c) benzaldehyde (5.0 mmol), cyclohexanone (5.0 mmol), (4R)-4-phenyl-oxazolidin -2-one (2 mol%), β-CD (10 mol%), and phosphate buffer (pH = 10.5, 15 ml). All of above reactions were stirred at room temperature.

Synthesis of inclusion complex (1)

(4*R*)-4-phenyl-oxazolidin-2-one (0.01 mM, 9.9 mg) and β-CD (0.01 mM) were completely dissolved in a mixed solution of ethanol and water (ca. 7mL, V:V = 1:5, given the poor water solubility of GA-13316, ethanol was used), and the mixture was stirred for 5 days at room temperature. After evaporating the ethanol from the reaction mixture, the uncomplexed (4*R*)-4-phenyl-oxazolidin-2-one was removed by filtration. The filtrate was evaporated under reduced pressure at 45 °C to remove the solvent and dried in vacuum to produce the (4*R*)-4-phenyl-oxazolidin-2-one /CD complexe. (4*R*)-4-phenyl-oxazolidin-2-one/β-CD inclusion complex (**1**) (yield 92%): ^{1}H NMR (500 MHz, D_2O, TMS): δ 7.30–7.37 (m, 5H, aromatic protons for (4*R*)-4-phenyl-oxazolidin-2-one), 4.99–5.02 (m, 3H, H-3, H-4 of (4*R*)-4-phenyl-oxazolidin -2-one), 4.99 (s, 7H, H-1 of β-CD), 3.45–3.78 (m, 35H, H-2–6 of β-CD).

RESULTS AND DISCUSSION

Many highly efficient aldol reactions followed the so-called "enamine catalysis" to design catalytic systems. Considering the structure of (4*R*)-4-phenyl-oxazolidin-2-one, which could generated the enamine intermediate at some condition. Because (4*R*)-4-phenyl-oxazolidin-2-one contains a phenyl group, we evoke that β-CD can be employed as a carrier to include the chiral auxiliary into a hydrophobic cavity in water for the assembly of aldol reactions under environmentally benign conditions. It is reassuring that the use of cyclohexanone in equal for the aldol reaction with atom economical "green" credentials. The catalytic condition of (4*R*)-4-phenyl-oxazolidin-2-one for the aldol reaction was investigated by performing a model reaction using stoichiometric of various aryl aldehydes and cyclohexanone respectively in three kinds of phosphate buffer (pH 3.8, 7.0, 10.5), and the results are listed in Table 1. At pH 10.5 the reaction occurs while it is facile only aromatic aldehydes with electron-withdrawing group, it reaches a yield of 89% especially for 4-nitrobenzaldehyde (entry 1) and 8% for 4-chloro benzaldehyde (entry 3) after 42 h. It is in opposite that the reaction does not occur while aromatic aldehydes with electron-donating group as 4-methoxybenzaldehyde (entry 2) and 2,4-dimethoxybenzaldehyde (entry 4). It is implied that the enamine intermediate is facile to generate with electron-withdrawing group and at pH 10.5. Unfortunately, the enantioselectivity of (4*R*)-4-phenyl-oxazolidin-2-one was not determined by chiral HPLC.

According to the above, the optimal condition is gotten. Comparing to the catalytic effect of the chiral auxiliary, the tests were carried out using β-CD in phosphate buffer at pH 10.5, in the aldol reaction between *p*-nitrobenzaldehyde and cyclohexanone as a model reaction (Table 2). Table 2 shows the results obtained at the optimal condition respectively using *L*-proline (entry 1), none (entry 2), and (4*R*)-4-phenyl-oxazolidin- 2-one (entry 3). Using *L*-proline as catalyst (entry 1), the reaction is obviously faster with 90% conversion after 20 h. When neither *L*-proline nor (4*R*)-4-phenyl-oxazolidin-2-one was added, the reaction is evidently slower with 20% after 42 h. Through the comparing experiment, it is showed that the (4*R*)-4-phenyl-oxazolidin-2-one cooperating with β-CD could catalyze the aldol reaction in water.

To find the effect of β -CD in the aldol reaction, a new inclusion complex (**1**) was formed by (4*R*)-4-phenyl-oxazolidin-2-one and β-CD. The β-CD/(4*R*)-4-phenyl-oxazolidin-2-one inclusion complex (**1**) was conveniently prepared by simply stirred a mixture of (4*R*)-4-phenyl-oxazolidin -2-one and β-CD in ethanol-water (1:5). Evidence for the formation of the complex of β-CD/(4*R*)-4-phenyl-oxazolidin-2-one was obtained from ^{1} H NMR. The ^{1}H NMR spectrum of the inclusion complex (**1**) is shown, where the signals of β-CD and solvent are indicated and the rest are signals of the (4*R*)-4-phenyl-oxazolidin-2-one. Although the formation of the complex (**1**) could catalyze the aldol reaction in water, it only could bind benzaldehyde to generate the possible enamine, and the cyclohexanone mobilizes around the enamine resulting to product without enantioselectivity.

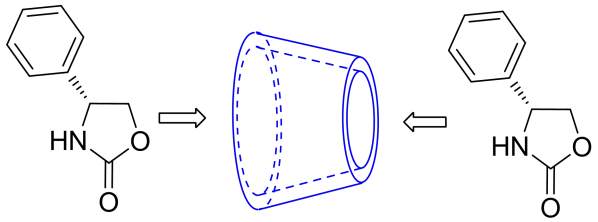


Fig. 1 The β-CD/(4*R*)-4-phenyl-oxazolidin-2-one inclusion complex (1)

CONCLUSION

In conclusion, we have developed a catalytic system in water mediated by β-CD which can cooperate with a chiral auxiliary of (4*R*)-4-phenyl-oxazolidin-2-one. When the strong electron -withdrawing substituted aryl aldehydes were subjected to the catalytic system, simple filtration or phase separation afforded the aldol products in good yields.

Herein, it suggested that the high enantioselcetivity of the reaction is to graft the chiral auxiliary to β-CD forming immobilized catalyst.

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