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Direct asymmetric α-hydroxymethylation of ketones in homogeneous aqueous solvents

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ABSTRACT

A chiral prolinamide-based zinc complex promotes the aldol reaction of ketones with aqueous formaldehyde, giving the corresponding adducts in good yields and high ees. The efficient direct aldol reaction of formaldehyde with ketones in homogeneous aqueous solution is presented for the first time.

The direct catalytic asymmetric aldol reaction is a powerful and leading methodology,[1] even for the synthesis of chiral β-carbonyl compounds.[2] Following the pioneering work of Shibasaki,[3] considerable attention has been paid to in situ activation of carbonyl compounds as nucleophiles, and direct aldol reactions represent the current state of art in the area.[4] Although many chiral catalysts have been developed for the reactions of various donors and acceptors, their application to the direct aldol reaction of formaldehyde is still limited to only a few examples.[5]

Hydroxymethylation reactions represent one of the most useful one-carbon extension methods,[6] but the use of formaldehyde as a C_1-unit in direct catalytic asymmetric aldol reactions of ketones is surprisingly neglected, possibly due to its high reactivity and small and symmetrical structure. The direct use of commercially available aqueous formaldehyde (formalin) solution gives the safest and most economically attractive reaction conditions. This is another important issue, as an aqueous medium is not compatible with most of the known chiral metal complexes and organocatalysts.

Several interesting reactions with unique reactivity and selectivity have been demonstrated to proceed in water or water–organic solvents,[7] but the development of an asymmetric aqueous aldol reaction is still ongoing.[8] Most published examples using water as a solvent are carried out 'in the presence of water', and the organic substrates (aromatic ketones and cyclohexanone) and catalyst are not dissolved in water, the reaction proceeding in the organic phase.[8b,9]

Recent progress in the area has initiated constructive discussion on the role and practical merits of water as a solvent.[10] Water and water-based reactions were debated with regard to terminology (i.e., whether a reaction is carried out 'in water', 'in the presence of water', or 'in the presence of a large excess of water').[9] Given the synthetic utility of the asymmetric aldol reaction, there has been increased interest in the search for better-defined organic catalysts that can promote effectively this reaction in homogeneous water solution.[11–13] Understanding such a process is an important issue.

Formaldehyde, having a high affinity for water, was beyond the reach of known water-compatible chiral catalysts for a long time. Whereas asymmetric aqueous hydroxymethylation of an enolate component with formaldehyde is known,[14] the direct use of ketones instead of silicon enolates in water still needs further investigations. Recently, two examples of organocatalytic asymmetric hydroxymethylation using formalin in the presence of a small amount of water were reported.[5a,15] In both cases, the chemical yields were moderate, and the substrate scope was limited to a single example, cyclohexanone, which is insoluble in water.

We recently demonstrated that zinc triflate and the chiral C_2-symmetrical prolinamide ligand **1** presented in Figure 1 was an efficient catalyst system for asymmetric aldol reactions of acetone and cyclic ketones in water, and in the presence of water.[11] The protonated ligand **1** (with trifluoroacetic acid) also catalyzed direct aldol reactions, as an organocatalyst with excellent diastereo- and enantiocontrol. Thus, this study reveals an interesting overlap in aqueous asymmetric aldol reactions between the application of metal complexes and organocatalysis.

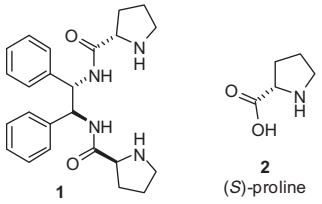

Figure 1. Structure of the proline-based ligand **1** used in this study.

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To improve the flexibility of the previously elaborated catalytic system and to highlight the discussion on homogeneous aqueous catalysis, we herein communicate our recent research on the direct aldol reaction of formaldehyde promoted by a Zn complex of prolinamide **1** in a homogeneous aqueous environment.

Initial optimization studies using cyclohexanone and formalin as model substrates are summarized in Table 1. Both molecules are of different hydrophobic/hydrophilic nature and are symmetrical thereby making the desired asymmetric reaction even more challenging.

In an initial experiment, cyclohexanone (1.5 mmol), aqueous formaldehyde (0.75 mmol), and 10 mol % of (*S*)-proline were mixed in DMSO following a literature protocol (Table 1, entry 1).[5b] After stirring for 20 h, α-hydroxymethyl ketone was isolated in 15% yield and 84% ee. Although not as promising as in the published example (47% yield, 99% ee), this aldol reaction in our hands afforded the product with a good level of enantioselectivity. At the outset, several aqueous solvents were examined for the proline–catalyzed reaction of cyclohexanone and formalin, but the reaction product was not detected or was present in only a trace amount (5%) in the reaction mixture (Table 1, entries 2 and 3).

This confirms our knowledge that proline catalyzes direct aldol reactions with high enantioselectivity in polar organic solvents such as DMSO and DMF, but water or an aqueous solution is not acceptable as reaction media.[16]

Next, we tested the catalytic activity of the bis(prolinamide) catalyst **1** for the same reaction. Only a trace amount of the product was obtained in DMSO while brine was more promising (entries 4 and 5). Unfortunately, the use of a homogeneous aqueous solution affected the enantioselectivity. Although the reaction proceeded sluggishly in the absence of an additive (entries 4–6), the use of a catalytic amount of zinc triflate resulted in an improved yield and enantioselectivity (entry 7).

As far as we are aware, there are no other examples in which this reaction proceeds with high enantioselectivity in aqueous solution, with all the reagents and catalyst dissolved homogeneously in the reaction mixture. For the present catalytic system the same level of enantioselectivity can be reached with 10–50% of water present in the reaction mixture (entries 7 and 8). The reaction in brine or in water is less efficient, but still compares well with previously published results in aqueous systems.[17] Only a twofold excess of ketone was necessary for good substrate conversion.

The use of an ethanol–water solution instead of THF–water mixtures improved the reaction further (Table 1, entry 11), and finally, at higher concentration and still at room temperature, the reaction proceeded in higher yield and with high selectivity (Table 2, entry 1).

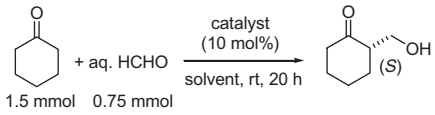
Comparison of the HPLC analysis, on a chiral stationary phase, of the benzoyl derivative of the product with that reported in the literature[14a] revealed that both (*S*)-proline and catalyst **1** provided (*S*)-2-hydroxymethyl cyclohexanone.

The new catalyst incorporates a metal center that can act as a Lewis acid in water and mimics the mode of action of type II aldolases. On the other hand, the complex could also form an enamine intermediate, in analogy to type I aldolases. The fact that proline alone is not an efficient catalyst supports only the expectation that enamine formation is unfavorable under the aqueous reaction conditions.[9a] The zinc complex gave the *S* enantiomer of the aldol product in excess, and with proline alone, the same *S* enantiomer was also predominant. Thus we postulate a mechanism involving organocatalytic enamine formation, where zinc complexation only stabilizes the formation of an enamine intermediate in water.

Using the optimized conditions, we next examined other substrates and were delighted to find that various ketones could be successfully employed (Table 2). Again, the same level of enantioselectivity could be reached with 10% and 50% of water in the homogeneous reaction mixture (Table 2, entry 1).[18]

The Zn-prolinamide-catalyzed α-hydroxymethylation afforded products with excellent enantioselectivity (entries 1–5). High stereocontrol was maintained with five- and seven-membered rings. With 2-methylcyclohexanone we observed high regioselectivity but the yield of the product was low because of the formation of a sterically hindered product (entry 4). The predominance of one stereoisomer in the reaction of 4-methylcyclohexanone resulted from a match and mismatch interaction between the chiral catalyst and substrate (entry 5).[19]

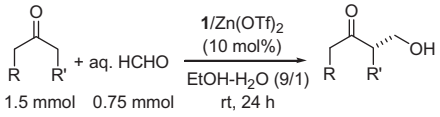
Table 1
Optimization of the reaction conditions[a]

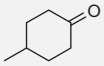


Entry	Cat.	Additive	Solvent	% Yield[b]	% ee[c]
1	**2**	—	DMSO	15	84
2	**2**	—	H_2O	0	—
3	**2**	—	THF–H_2O (9:1)	5	Racemic
4	**1**	—	DMSO	10	42
5	**1**	—	Brine	19	81
6	**1**	—	THF–H_2O (9:1)	25	20
7	**1**	$Zn(OTf)_2$	THF–H_2O (9:1)	39	92
8	**1**	$Zn(OTf)_2$	THF–H_2O (1:1)	40	92
9	**1**	$Zn(OTf)_2$	Brine	25	90
10	**1**	$Zn(OTf)_2$	H_2O	25	95
11	**1**	$Zn(OTf)_2$	EtOH–H_2O (9:1)	55	94
12	**1**	$Zn(OTf)_2$	EtOH–H_2O (1:1)	45	94
13	**1**	TFA	THF–H_2O (9:1)	23	Racemic

[a] The reaction was performed employing formalin (0.75 mmol, 37% in water), cyclohexanone (1.5 mmol), catalyst (10 mol %), and solvent (1 mL). Additives: $Zn(OTf)_2$ (10 mol %), TFA (20 mol %).
[b] Isolated yield.
[c] Ee determined by HPLC analysis of the benzoate ester on a chiral phase (Daicel OD-H column).

Table 2
Direct catalytic asymmetric aldol reaction of various ketones with formaldehyde[a]



Entry	Ketone	% Yield	% ee[b]
1		60 52	94[18] 94[c]
2		58	98
3		59	93
4		<10	95
5		63	94 (dr 3/2)
6		n.d.	—

[a] The reaction was performed employing formalin (0.75 mmol, 37% in water), ketone (1.5 mmol), catalyst (10 mol %), and EtOH/H_2O (9:1, 0.5 mL).
[b] Isolated yield. Ee determined by HPLC analysis of the benzoate ester on a chiral phase (Daicel AD-H and OD-H columns).
[c] Reaction performed in EtOH/H_2O (1:1, 0.5 mL).

In conclusion, we have reported the novel direct catalytic asymmetric α-hydroxymethylation of unmodified ketones in wet solvents. It is not *yet another aldol reaction in water*—to date these are the best results reported for the direct aqueous reaction of formaldehyde catalyzed by a small synthetic metal complex.[20] Though there is still room for improvement in terms of yield and generality, the present reaction is the first example of the direct asymmetric hydroxymethylation in homogeneous aqueous solvents.

Further studies to clarify the mechanism of the present system and to expand the substrate scope by modifying the chiral catalyst are now in progress in our laboratory.

Acknowledgment

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17. For comparison, see Ref. 15: 37% yield, 96% ee, reaction medium: ketone with 18 equiv of water, 90 h; and Ref. 5a: 40% yield, 99% ee, reaction medium MeCN, and buffer.
18. (*S*)-2-(Hydroxymethyl)cyclohexanone (Table 2, entry 2): Prolinamide **1** (30.5 mg, 0.075 mmol, 10 mol %) and $Zn(OTf)_2$ (27.3 mg, 0.075 mmol, 10 mol %) were stirred for 5 min in the EtOH–H_2O (9/1, 0.5 mL). To the resulting solution cyclohexanone (1.5 mmol, or the same amount of another ketone) and formaldehyde (0.75 mmol, 37% in water) were added at room temperature and the mixture was stirred for 20 h. The mixture was extracted with CH_2Cl_2, and the combined organic layer was dried over anhydrous Mg_2SO_4. The solvents were evaporated, and the residue was purified by chromatography (silica gel, hexane/EtOAc (1/1)) to give the product in 60% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.50–2.10 (m, 6H), 2.22–2.52 (m, 3H), 2.56 (s, 1H), 3.50–3.60 (m, 1H), 3.62–3.72 (m, 1H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 25.4, 28.2, 30.7, 42.9, 52.9, 63.5, 215.4. The enantiomeric excess of the product was determined by chiral HPLC analysis of the corresponding benzoate derivative. [(*S*)-2-Oxocyclohexyl]methyl benzoate:[14a] to a solution of (*S*)-2-(hydroxymethyl)cyclohexanone (12 mg, 0.094 mmol) in CH_2Cl_2 (1 mL) were added benzoyl chloride (22 μL, 0.187 mmol) and pyridine (38 μL, 0.47 mmol) at room temperature. After stirring for 2 h, the reaction was quenched with H_2O. The mixture was extracted with CH_2Cl_2, and the combined organic layer was washed with brine and dried over anhydrous Na_2SO_4. The solvents were evaporated, and the residue was purified by short column chromatography (silica gel, hexane/EtOAc (4:1)) to give the desired product in 34% yield: ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.50–1.60 (m, 1H), 1.65–1.78 (m, 2H), 1.86–2.00 (m, 1H), 2.07–2.16 (m, 1H), 2.26–2.40 (m, 2H), 2.44–2.49 (m, 1H), 2.79–2.87 (m, 1H), 4.32 (dd, 1H, J = 11.6, 6.7 Hz), 4.66 (dd, 1H, J = 11.6, 5.8 Hz), 7.41–7.45 (m, 2H), 7.53–7.57 (m, 1H), 8.01–8.03 (m, 2H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 25.3, 28.3, 31.7, 42.7, 50.3, 64.5, 129.0, 129.1, 130.3, 130.9, 172.1, 210.9 ppm; HPLC (Daicel Chiralcel OD-H, hexane/*i*-PrOH = 98:2, flow rate = 1.0 mL/min, λ = 254 nm), t_R = 11.9 min (major, *S*), t_R = 14.0 min (minor, *R*).
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