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Asymmetric direct aldol reactions catalyzed by chiral amine macrocycle–metal(II) complexes under solvent-free conditions†

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Solvent-free asymmetric aldol reactions between cyclohexanone and 4-nitrobenzaldehyde using chiral amine macrocycle–metal(II) complexes as catalysts in a ball mill afforded the *anti*-aldol product as the major isomer with up to 93% ee.

Introduction

Aldol condensation is a key carbon-carbon bond forming reaction for creating a β-hydroxy carbonyl structural unit found in many natural products and drugs.¹ Several excellent asymmetric aldol reactions have been developed using organic solvents.² The application of solvent-free reaction conditions to perform the aldol reaction has allowed reduction of the excess use of starting aldehydes and ketones to perform this reaction more greener.³ However, the aldol reactions under solvent-free conditions have been studied scarcely to date.⁴⁻⁶ For example, Bolm and co-workers reported the asymmetric aldol reactions under solvent-free conditions catalyzed by (S)-proline in a ball mill. The anti-aldol products were obtained in high ee.⁴ Najera and co-workers reported the solvent-free asymmetric aldol reactions catalyzed by (S)-binam-L-prolinamide with high ee (up to 88%).⁵ In more recent work, Juaristi and co-workers reported a similar reaction using (S)-proline-containing thiodipeptides as catalysts with high ee (up to 96%).⁶ Metal complexes with chiral ligands are widely used as asymmetric catalysts for Henry reactions. However, the metal complexes with macrocyclic chiral ligands have been scarcely developed. For example, the trianglamines 1-3 are effective ligands in Cu(OAc)₂-catalyzed Henry reactions of nitromethane with aromatic aldehydes (up to 87% ee) and aliphatic aldehydes (up to 93% ee) under solvent-free conditions.⁷ Hexamethyl-substituted macrocycles 5 revealed a lesser degree of asymmetric induction as compared to ligand 3 in the Cu-catalyzed

Henry reaction.⁸ 75% ee was obtained in the zinc-catalyzed Henry reaction in THF using ligand **6**.⁹ Moreover, the condensation of

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⁽R,R,R,R,R,R)-7

nitromethane and aromatic and aliphatic aldehydes in the presence of catalytic amounts of copper diacetate and pyrrole macrocyclic ligand 7 in ethanol provided products with up to 95% ee.¹⁰ Herein, we report asymmetric aldol reactions under solvent-free conditions using a ball mill, catalyzed by chiral amine macrocycle(1-4)-metal(π) complexes.

Results and discussion

A series of chiral amine macrocycles (1-4) were prepared by treating enantiomerically pure (S,S)-1,2-cyclohexanediamine with the corresponding dialdehydes followed by reduction of NaBH₄ of the intermediate imine macrocycles.¹¹

The chiral macrocyclic ligand was tested as a chiral catalyst for the asymmetric aldol reaction of 4-nitrobenzaldehyde and cyclohexanone in a ball mill. A mixture of (S,S,S,S,S,S)-1 (0.1 mmol), CuCl₂ (0.1 mmol), cyclohexanone 8 (2.0 mmol), and 4-nitrobenzaldehyde 9 (1.0 mmol) was milled by a planetary ball mill for 24 h at 100 rpm and at room temperature. The crude reaction mixture was purified using column chromatography (silica gel, hexane–EtOAc = 2:1) to afford a mixture of *syn*- and *anti*-aldol reaction products (1'R, 2S)-10 (*anti–syn* = 67:33) in 11% yield with an enantioselectivity of 67% ee (Table 1, entry 1).

Initially, we examined the effects of varying catalyst amounts. Ratios for the ligand/CuCl₂ and reaction time are shown in Table 1, entries 2–5. This analysis revealed that the best results were obtained when the reaction was carried out using the ligand (0.2 mmol) and CuCl₂ (0.4 mmol) for 48 h, affording (1'*R*, 2*S*)-10 (*anti–syn* = 71:29) in 85% yield with an enantioselectivity of 83% ee (Table 1, entry 5). Next, the effectiveness of the size of various ligands 1–4 for the catalyst was explored. Ligands 2 and 4 gave good enantioselectivity (80% ee) with lower yield and diastereoselectivity (Table 1, entries 6 and 8), while ligand 3 gave a poor result under the same reaction conditions (Table 1, entry 7). However, in the MeOH solution the reaction resulted in a very low yield (13%) with good enantio- and diastereo-selectivities (Table 1, entry 9).

In order to determine the effect of ball milling on the aldol reaction, a comparative study using conventional magnetic stirring was carried out. For example, conventional magnetic stirring afforded (1'R, 2S)-**10** (*anti–syn* = 60:40) in only 4% yield with an enantioselectivity of 63% ee (Table 1, entry 10). Thus, the solvent-free aldol reaction of 4-nitrobenzaldehyde and cyclohexanone was faster under ball-milling conditions than in a solution or neat liquid.

Next, we screened Cu salts for the aldol reaction. By using CuBr₂, (1'R, 2S)-10 was obtained in 90% ee, and the use of Cu(OAc)₂ resulted in poor enantioselectivity (63% ee) (Table 2, runs 1 and 3). The type of metal ion used was also an important parameter in this reaction. The use of Co ions resulted in the best ee (93%) (Table 2, entries 10–12), followed by Cu ions (Table 2, entries 1–3), Zn ions (Table 2, entries 4–6), and Ni ions (Table 2, entries 7–9).

Under the optimal reaction conditions, the scope of the reaction was studied varying the ketone and aldehyde (Table 3). Several cyclic ketones were used as nucleophiles in the reaction with *p*-nitrobenzaldehyde. As expected cyclopentanone and cycloheptanone gave the *anti*-products (**13**, **14**) as the major isomers with lower enantioselectivities (Table 3, entries 4 and 5). Other cyclic ketones such as tetrahydropyran-4-one or tetrahydrothiapyran-4-one gave moderate enantioselectivities (Table 3, entries 6 and 7).

Different aldehydes were used in the reaction with cyclohexanone giving the expected products. Both the yield and enantioselectivity of the product decreased in the order of p - > m - > o-nitrobenzaldehyde (Table 3, entries 1–3). Between p- and o-nitrobenzaldehyde, more steric crowding at the *ortho* position may lead to lower conversion for the *ortho* variety. In the case of chloro-substituted benzaldehyde, a similar trend in both activity and stereo-selectivity was observed (Table 3, entries 8–10). Whereas the lower electronegativity of the bromo variety compared to the

 Table 1
 Asymmetric aldol reaction of 4-nitrobenzaldehyde with cyclohexanone catalyzed by the chiral amine macrocycle–CuCl₂ complex in a ball mill^a

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Table 2	Asymmetric aldol reaction of 4-nitrobenzaldehyde with cyclohexanone
catalvzed	by the (S.S.S.S.S.S.S)-1-metal complex in a ball mill ^a

(*S*,*S*,*S*,*S*,*S*,*S*)-1

8	+ H		ball-milling 100 rpm	10 anti-ison	+ syn NO ₂	n-isomer
Entry	Time (h)	Ligand (mmol)	CuCl ₂ (mmol)	Yield (%)	anti–syn	ee (%)
1	24	1 (0.1)	0.1	11	67:33	67
2	24	1 (0.1)	0.2	12	54:46	69
3	24	1(0.1)	0.3	7	54:46	45
4	24	1 (0.2)	0.4	45	70:30	75
5	48	1(0.2)	0.4	85	71:29	83
6	48	2(0.2)	0.4	73	61:39	80
7	48	3 (0.2)	0.4	43	49:51	17
8	48	4 (0.2)	0.4	59	63:37	80
9^b	48	1 (0.2)	0.4	13	70:30	79
10^{c}	48	1 (0.2)	0.4	4	60:40	63
11	48	1 (0.2)	0	17	68:32	59

^a Reaction conditions: ketone 8 (2.0 mmol), aldehyde 9 (1.0 mmol), rt.
 ^b Reaction was carried out in MeOH. ^c Reaction was carried out in neat liquid.

8	$\begin{array}{c} H \\ 9 \\ \hline \\ 9 \\ \hline \\ 100 \text{ rpm, } 48 \text{ h} \\ anti-isomer \\ \hline \\ anti-isomer \\ \hline \\ \end{array}$					
Entry	MX_2	Yield (%)	anti–syn	ee (%)		
1	$Cu(OAc)_2$	63	53:47	63		
2	CuCl ₂	85	71:29	83		
3	CuBr ₂	30	75:25	90		
4	$Zn(OAc)_2$	44	67:33	79		
5	ZnCl ₂	52	72:28	52		
6	ZnBr ₂	22	38:62	56		
7	$Ni(OAc)_2$	14	51:49	60		
8	NiCl ₂	21	50:50	75		
9	NiBr ₂	26	54:46	73		
10	$Co(OAc)_2$	63	53:47	63		
11	CoCl ₂	83	73:27	91		
12	CoBr ₂	82	71:29	93		
<i>.</i> .				-		

^{*a*} Reaction conditions: ketone 8 (2.0 mmol), aldehyde 9 (1.0 mmol), (S,S,S,S,S,S)-1 (0.2 mmol), MX₂(0.4 mmol), rt.

 $\label{eq:table_state} \begin{array}{l} \mbox{Table 3} & \mbox{Asymmetric aldol reaction of 4-nitrobenzaldehyde with ketone catalyzed} \\ \mbox{by the ($$,$,$,$,$,$)-1-metal complex in a ball mill^3 } \end{array}$

Entry	Product	Yield (%)	anti–syn	ee (%)
1		82	71:29	93
2		72	69:31	87
3		52	77:23	86
4		51	74:26	75
5		42	52:48	26
6		55	61:39	69
7		54	50:50	60
8		14	51:49	22
9		35	57:43	65
10		42	51:49	75
11		12	50:50	88
12	O OH Br	20	64:36	85
13		44	69:31	75
14	O OH	49	50.50	56
14		48	50:50	30
15	24 OMe	4	54:46	n.d.
16		23	—	20

^{*a*} Reaction conditions: ketone (2.0 mmol), aldehyde (1.0 mmol), (*S*,*S*,*S*,*S*,*S*,*S*)-1 (0.2 mmol), CoBr₂ (0.4 mmol), rt.

chloro one causes a higher enantioselectivity in the case of o- and m-bromobenzaldehydes (Table 3, entries 11–13). More electronrich groups lowered both the reactivity and stereoselectivity (Table 3, entries 14 and 15). In contrast, acetone afforded a product with only 20% ee (Table 3, entry 16).

In order to investigate the effect of the ball-milling, both the reaction of neat-liquid using conventional magnetic stirring and the reaction in MeOH solution were examined. For example, while under conventional stirring the reaction between cyclohexanone and 4-nitrobenzaldehyde in the neat-liquid afforded the aldol product in only 4% yield with 63% ee, ball-milling led to the same product in 82% yield with 93% ee. Reaction in CH_2Cl_2 solution also showed poor reactivity (9% yield) and lower enantioselectivities (63% ee).

The ligand (*S*,*S*,*S*,*S*,*S*,*S*)-1 could easily be recovered using column chromatography, and was recycled as a catalyst.

To gain insight into the mechanism within the enantioselective aldol reaction of 4-nitrobenzaldehyde and cyclohexanone in the presence of a chiral amine macrocycle-(S, S, S, S, S, S)-1-metal(II) complex, we tried synthesis of complex crystals. When a 1:2 mixture of (S, S, S, S, S)-1 and Cu(OAc)₂ was dissolved in MeOH, and the solution was kept at room temperature for several days, an accidental formation of a 1:3 complex between (S, S, S, S, S, S)-1 and Cu(OAc)₂ was observed as a dark green crystal.

X-ray structure of a 1:3 complex between (S,S,S,S,S,S,S)-1 and $Cu(OAc)_2$ was analysed at 100 K. In the solid state, the (S,S,S,S,S,S)-1· $Cu_3(CH_3CO_2)_6$ ·11H₂O complex has triangular capsule-like structure (Fig. 1). The two Cu^{2+} ions (Cu1, Cu2) have a distorted square planar N, O coordination sphere involving close contacts with both oxygen atoms of the acetates, whereas the Cu3 is coordinated in the apical position with an extra water molecule O13, displaying more perfect square-pyramidal geometry. Typically, each acetate group has one short distance to the copper atom: Cu1 ... O1 1.944(5), Cu1 ... O3 2.012(3), Cu2 ... O5 1.983(4),



Fig. 1 Ortep diagram showing structure of the 1:3 complex between (*S*,*S*,*S*,*S*,*S*)-1 and Cu(OAc)₂ at 100 K. Thermal ellipsoids are shown at the 30% probability level; 8 water molecules of crystallization were omitted for clarity.

Cu2 ... O7 1.963(4), and Cu3 ... O9 1.959(4), Cu3 ... O11 1.953(4) Å. The two out of remaining 10 water molecules are located inside of the capsule due to hydrogen bonding with amino groups of the organic ligand [N4 ... O18 3.080(6) Å, N4-H4N 0.91 Å, H4N ... O18 2.21 Å, angle 160° ; N5 ... O20 2.998(7) Å, N5-H5N 0.91 Å, H5N ... O20 2.13 Å, angle 159°]. The remaining 8 water molecules are located in the crystal around the acetate anions.

The possible solid state host-guest interactions allowing migration of the substrate molecules into the catalytic sites located inside of the capsule might be due to their planar structure and relatively small size. The distance between Cu1 and Cu2 atoms in a wider part of the capsule is 8.864(2) Å. The only possible coordination places are located in triplicate inside of this capsule.

Conclusions

In summary, a 1:2 complex of (S,S,S,S,S,S)-1 with CoBr₂ was an excellent catalyst for the asymmetric aldol reaction between cyclohexanone and 4-nitrobenzaldehyde under solvent-free conditions using a planetary ball mill. The *anti*-aldol adduct (1'R, 2S)-10 was obtained with high enantioselectivity (up to 93% ee), relative to the same reaction in the solution or in neat liquid with traditional magnetic stirring. Further studies using this catalytic system in environmentally friendly asymmetric transformations are underway.

Experimental section

General

All reagents were purchased from commercial suppliers. ¹H-NMR spectra were recorded on a JEOL JNM-AL 400 spectrometer with tetramethylsilane as the internal standard. The diastereoselectivity of the reaction was determined by 1H-NMR spectroscopy of the crude product. Enantiomeric excesses were determined by high-performance liquid chromatography (HPLC) either on a Chiralpak OD or a Chiralpak AD-H column (Daisel). The absolute configuration of aldol products was determined by comparison with published HPLC retention times. Reactions in the ball mill were conducted using a Fritsch Planetary Micro Mill model "Pulverisette 7". In the planetary mill grinding bowls rotate around their own axes while also orbiting around a central axis.

Typical procedure for the solvent-free asymmetric aldol reaction between cyclohexanone and 4-nitrobenzaldehyde in a ball mill

A mixture of (S, S, S, S, S, S)-1 (0.13 g, 0.02 mmol), CoBr₂ (0.087 g, 0.04 mmol), cyclohexanone 8 (2.0 mmol) and 4-nitrobenzaldehyde 9 (0.151 g, 1.0 mmol) was milled for 24 h at 100 rpm and at room temperature using a planetary ball mill (Fritsch P-7). The crude reaction mixture was purified using column chromatography (silica gel, hexane–EtOAc = 2:1) to afford a mixture of *syn*- and *anti*-aldol reaction products (1'*R*, 2*S*)-10 (*anti–syn* = 71:29) in 82% yield with an enantioselectivity of 93% ee. The diastereoselectivity was determined using ¹H NMR of the crude product. The ee was determined by chiral HPLC using a Chiralpak AD-H column (hexane:2-PrOH (90:10), 1 mL min⁻¹).

X-ray crystal data for the complex

C₅₄ H₁₀₀ Cu₃ N₆ O₂₃, *M* = 1392.02, orthorhombic, space group *P*2₁2₁2₁, (no. 19), *a* = 11.6000(2) Å, *b* = 16.6558(3) Å, *c* = 35.0297(7) Å, *V* = 6768.0(2) Å³, *Z* = 4, *d*_{calc} = 1.366 mg M⁻³, *F*(000) = 2948, *T* = 100 K, 36 640 reflections were collected on a Bruker Apex II diffractometer using MoKα radiation (λ = 0.7107 Å), 10 630 unique reflections with *I* > 2 σ_I (R_{int} = 0.0587) were used for structure solution and refinement. Final *R*₁ = 0.0561, w*R*₂ = 0.1530, goodness of fit = 1.162. All hydrogen atoms were placed in calculated positions and refined as riding on their parent atoms with U_{iso} = 1.2 U_{eq} (N, C). Hydrogen atoms from 11 water molecules could not be found from difference maps. Absolute configuration of the (*S*,*S*)-1,2-cyclohexanediamine substrate; Flack parameter = 0.261(12). CCDC 894524.†

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