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Enantioselective Henry reaction catalyzed by trianglamine–$Cu(OAc)_2$ complex under solvent-free conditions

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Abstract

Chiral trianglamine–$Cu(OAc)_2$ complex was found to be an efficient catalyst for enantioselective Henry reaction between nitromethane and various aldehydes to provide β-hydroxynitoroalkanes with high enantiomeric excesses under solvent-free conditions.

The Henry (nitroaldol) reaction is one of the versatile C–C bond forming reaction in organic synthesis for the formation of β-hydroxynitroalkanes.[1] Optically active β-hydroxynitroalkanes are useful intermediates in the synthesis of several pharmacologically important compounds, such as chloroamphenicol, ephedrine, propranolol, and sphingosine.[2] Recently, much attention has been paid for the development of catalytic asymmetric Henry reactions. For example, metal complexes with chiral ligands, such as BINOL–metal complex,[3] Zn amino alcohol complex,[4] Co salen complex,[5] and some Cu chiral amine complexes[6] have been developed. However, these catalysts still have some limitations such as moisture or air sensitivity, need for bases and low temperature, low enantioselectivity, and difficult preparation of the catalysts. As a part of our research on chiral recognition study of optically active trianglamines,[7] we explored the potential application of their $Cu(OAc)_2$ complexes for enantioselective Henry reaction between nitromethane and aromatic and aliphatic aldehydes under solvent-free conditions.

A series of chiral trianglamines (**1**–**4**) were prepared by treating enantiomerically pure (*S*,*S*)-1,2-cyclohexanediamine with the corresponding dialdehydes followed by $NaBH_4$ reduction of the intermediate trianglimines.[8] Equimolar amounts of trianglamines (**1**–**4**) and $Cu(OAc)_2$ were stirred at room temperature in CH_2Cl_2, furnishing the desired chiral Cu complexes as pale green solids.[9] The enantiomeric nature of (*S*,*S*,*S*,*S*,*S*,*S*)-(+)- and (*R*,*R*,*R*,*R*,*R*,*R*)-(−)-**1** and their complex with $Cu(OAc)_2$ were demonstrated by the CD spectra, which showed almost the mirror images of each other (Fig. 1).

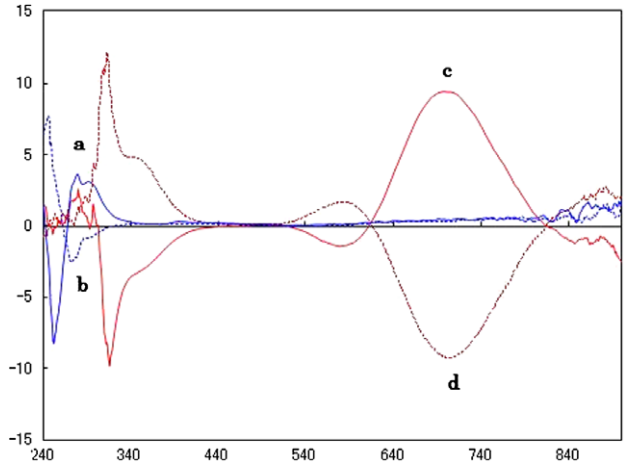

Fig. 1. CD spectra of (a) (+)-**1**, (b) (−)-**1**, (c) (+)-**1**–$Cu(OAc)_2$ complex, and (d) (−)-**1**–$Cu(OAc)_2$ complex in EtOH.

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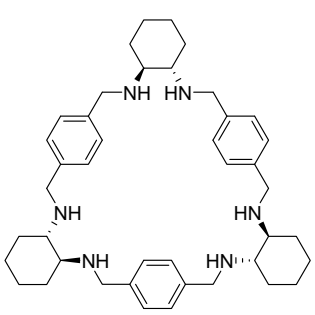
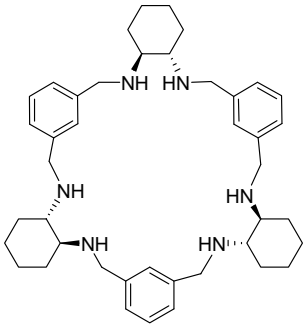
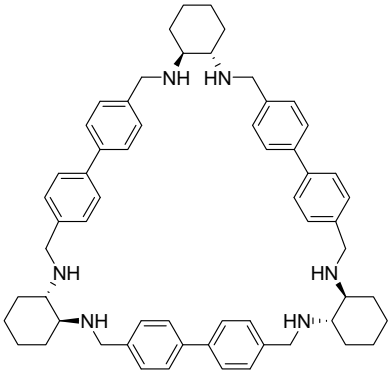


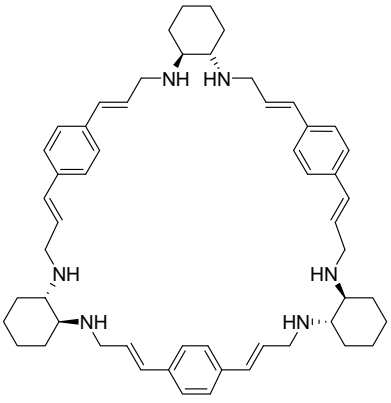
(*S*,*S*,*S*,*S*,*S*,*S*)-(+)-**1**



(*S*,*S*,*S*,*S*,*S*,*S*)-(+)-**2**



(*S*,*S*,*S*,*S*,*S*,*S*)-(+)-**3**

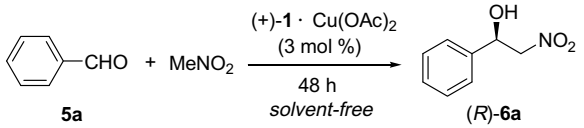


(*S*,*S*,*S*,*S*,*S*,*S*)-(+)-**4**

The complex of (*S*,*S*,*S*,*S*,*S*,*S*)-(+)-**1** with $Cu(OAc)_2$ was evaluated as a catalyst (3 mol %) by using benzaldehyde (**5a**) and 10 equiv of nitromethane in an open air without using any solvents (Table 1). From the results of Table 1, best result in both enantioselectivity and reactivity was obtained when the reaction was carried out at 0 °C for 48 h using a catalyst loading of 3 mol %.[10] We next explore the effectiveness of the size of the various ligands (**1**–**4**) for the catalyst.

Ligands **1** and **2** (Table 2, entries 1 and 2) gave good chemical yield and high enantioselectivity (82–86% ee), while both yield and enantioselectivity decreased using larger ligands in size **3** and **4** (Table 2, entries 3 and 4).

Table 1
Optimization of reaction conditions for the enantioselective Henry reaction of **5a** and $MeNO_2$ using 3 mol % of (+)-**1**–$Cu(OAc)_2$

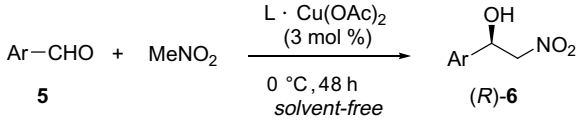


5a (*R*)-**6a**

Entry	Temp (°C)	Conv.[a] (%)	Yield[a] (%)	ee[b] (%)
1	25	93	54	42
2	10	97	76	73
3	0	96	78	82
4	−10	86	49	85

[a] Determined by GC and ^1H NMR.
[b] Determined by chiral HPLC.

Table 2
Enantioselective Henry reaction of $MeNO_2$ and aromatic aldehydes under solvent-free conditions



5 (*R*)-**6**

a: Ar = Ph
b: Ar = 2-$NO_2C_6H_4$
c: Ar = 4-$NO_2C_6H_4$
d: Ar = 4-ClC_6H_4
e: Ar = 4-$MeOC_6H_4$

Entry	Ar	L	Conv.[a] (%)	Yield[a] (%)	ee[b] (%)
1	Ph	(+)-**1**	96	78	82
2	Ph	(+)-**2**	91	62	86
3	Ph	(+)-**3**	90	40	79
4	Ph	(+)-**4**	87	15	58
5	2-$NO_2C_6H_4$	(+)-**1**	93	48	56
6	2-$NO_2C_6H_4$	(+)-**2**	97	75	74
7	2-$NO_2C_6H_4$	(+)-**3**	97	84	72
8	2-$NO_2C_6H_4$	(+)-**4**	95	82	63
9	4-$NO_2C_6H_4$	(+)-**1**	86	65	62
10	4-$NO_2C_6H_4$	(+)-**2**	88	66	77
11	4-$NO_2C_6H_4$	(+)-**3**	79	74	39
12	4-$NO_2C_6H_4$	(+)-**4**	75	75	16
13	4-ClC_6H_4	(+)-**1**	82	48	73
14	4-ClC_6H_4	(+)-**2**	67	39	87
15	4-ClC_6H_4	(+)-**3**	77	53	63
16	4-ClC_6H_4	(+)-**4**	74	45	46
17	4-$MeOC_6H_4$	(+)-**1**	65	52	84
18	4-$MeOC_6H_4$	(+)-**2**	57	55	79
19	4-$MeOC_6H_4$	(+)-**3**	69	56	83
20	4-$MeOC_6H_4$	(+)-**4**	48	38	75

[a] Determined by GC and ^1H NMR.
[b] Determined by chiral HPLC.

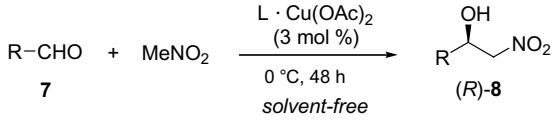
To explore the generality of this method, we examined wide variety of aromatic aldehydes listed in Table 1 under the optimal conditions in the presence of $Cu(OAc)_2$ complex with chiral ligands (**1**–**4**). In all the cases, the reactions proceeded smoothly to give the desired products. The presence of either electron-withdrawing (entries 5–16) or electron-donating (entries 17–20) substitution at the *para*- or *ortho*-positions of the aromatic ring of the aldehydes was well tolerated and furnished the corresponding nitroaldol products in moderate to good yields with high enantioselectivities (Table 2).

More interestingly, aliphatic (cyclic, linear, and branched) aldehydes were smoothly converted to nitroaldols in good yields with excellent enantioselectivity (83–93% ee) especially using ligand **1** (Table 3, entries 1, 5, 9, 13, 17, 21, 25, and 29). For example, the reaction of 1-octanal provided the corresponding nitroaldol (**8b**) in 74% yield with 93% ee. Pivaldehyde was also applicable in the Henry reaction, providing the corresponding nitroaldol (**8f**) with 90% ee in 88% yield (entry 21).

It is noteworthy that the products were obtained in the (*R*)-form in all the reactions examined in Tables 1–3, showing the nucleophilic addition of nitromethane at the *si*-face of the aldehyde. The mechanistic details of the reaction are still under investigation.

In conclusion, the $Cu(OAc)_2$ complex with chiral trianglamine was found to be efficient for the catalytic enantioselective Henry reaction under solvent-free conditions. It showed broad substrate applicability, good product yield, and high enantioselectivity under the mild and solvent-free conditions. Further studies using this catalytic system in environmentally friendly asymmetric transformation are underway.

Table 3
Enantioselective Henry reaction of $MeNO_2$ and aliphatic aldehydes under solvent-free conditions



a: R = Cyclohexyl
b: R = *n*-C_7H_{15}
c: R = *n*-C_6H_{13}
d: R = *n*-C_5H_{11}
e: R = *n*-C_4H_9
f: R = *t*-C_4H_9
g: R = *i*-C_3H_7
h: R = C_2H_5
i: R = CH_3

Entry	R	L	Conv.[a] (%)	Yield[a] (%)	ee[b] (%)
1	Cyclohexyl	(+)-**1**	57	57	92
2	Cyclohexyl	(+)-**2**	75	63	81
3	Cyclohexyl	(+)-**3**	60	25	80
4	Cyclohexyl	(+)-**4**	53	36	71
5	*n*-C_7H_{15}	(+)-**1**	95	74	93
6	*n*-C_7H_{15}	(+)-**2**	97	22	80
7	*n*-C_7H_{15}	(+)-**3**	89	49	89
8	*n*-C_7H_{15}	(+)-**4**	90	68	80
9	*n*-C_6H_{13}	(+)-**1**	97	60	91
10	*n*-C_6H_{13}	(+)-**2**	85	34	83
11	*n*-C_6H_{13}	(+)-**3**	97	17	83
12	*n*-C_6H_{13}	(+)-**4**	89	35	75
13	*n*-C_5H_{11}	(+)-**1**	—[c]	73	88
14	*n*-C_5H_{11}	(+)-**2**	—	82	78
15	*n*-C_5H_{11}	(+)-**3**	—	32	82
16	*n*-C_5H_{11}	(+)-**4**	—	46	70
17	*n*-C_4H_9	(+)-**1**	—	88	89
18	*n*-C_4H_9	(+)-**2**	—	48	83
19	*n*-C_4H_9	(+)-**3**	—	46	83
20	*n*-C_4H_9	(+)-**4**	—	61	73
21	*t*-C_4H_9	(+)-**1**	—	88	90
22	*t*-C_4H_9	(+)-**2**	—	12	93
23	*t*-C_4H_9	(+)-**3**	—	7	88
24	*t*-C_4H_9	(+)-**4**	—	13	76
25	*i*-C_3H_7	(+)-**1**	—	67	83
26	*i*-C_3H_7	(+)-**2**	—	56	81
27	*i*-C_3H_7	(+)-**3**	—	49	81
28	*i*-C_3H_7	(+)-**4**	—	43	63
29	C_2H_5	(+)-**1**	—	83	84
30	C_2H_5	(+)-**2**	—	72	79
31	C_2H_5	(+)-**3**	—	12	78
32	C_2H_5	(+)-**4**	—	43	66

[a] Determined by GC and ^1H NMR.
[b] Determined by chiral HPLC.
[c] Not determined.

Acknowledgments

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9. *Synthesis of trianglamine–Cu(OAc)$_2$ complex*: $Cu(OAc)_2$–H_2O (0.03 g, 0.15 mmol) was added to a solution of ligand **1** (0.1 g, 0.15 mmol) in CH_2Cl_2 (40 ml) and the mixture stirred for 4 h. Then, the solvent was evaporated under reduced pressure. The crude product obtained was washed with dry Et_2O (40 ml), and the pale blue solid was collected by filtration and dried under vacuum. 0.074 g (60% yield); mp 175 °C (decomposition); IR (Nujol): 3107, 1573, 1378 cm^{-1}.
10. *Representative enantioselective Henry reaction (Table 2, entry 1)*: A mixture of nitromethane (0.57 g, 9.4 mmol), (+)-**1**–$Cu(OAc)_2$ complex (0.023 g, 0.028 mmol), and benzaldehyde (0.1 g, 0.94 mmol) was stirred at 0 °C for 48 h. Then, the volatiles were removed under reduced pressure and the residue chromatographed on a short silica gel to give nitoalkanol (*R*)-**6a**[6f] (0.13 g, 78% yield) in 82% ee. The optical purity was determined by HPLC (Chiralcel OD, Detection: UV 254 nm; eluent: *n*-hexane–2-propanol = 90:10, flow rate: 1.0 ml/min; $t_R = 14.0$ min; $t_S = 16.9$ min).