DOI: 10.1002/chem.200601262

A New Copper(I)–Tetrahydrosalen-Catalyzed Asymmetric Henry Reaction and Its Extension to the Synthesis of (*S*)-Norphenylephrine

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Abstract: A new chiral hydrogenated salen catalyst has been developed for the asymmetric Henry reaction which produces the expected products in moderate to high yields (up to 98%) with excellent enantioselectivities (up to 96% *ee*). A variety of aromatic, heteroaromatic, enal, and aliphatic aldehydes were found to be suitable substrates in the presence of hydrogenated salen **1f** (10 mol%), $(CuOTf)_2{\cdot}C_7H_8$ (5 mol%), and 4 Å molecular sieves. This process is air-tolerant and easily manipulated with readily available reagents, and has been successfully extended to the synthesis of (*S*)-norphenylephrine in 67% overall yield, starting from commercially available *m*-hydroxybenzaldehyde. Based on experimental investigations and MM+ calculations, a possible catalytic cycle including a transition state (**8** or **A**) has been proposed to explain the origin of reactivity and asymmetric inductivity.

Keywords: asymmetric catalysis · copper · Henry reaction · norphenylephrine · salen

Introduction

The nitroaldol (Henry) reaction is one of the most powerful reactions in constructing C–C bonds in organic chemistry,[1] providing efficient access to valuable functionalized structural motifs, such as 1,2-amino alcohols and α-hydroxy carboxylic acids.[2,3] In the last few years, great efforts have been devoted towards the implementation of asymmetric versions of the Henry reaction and significant progress has been achieved.[4–10] Along a similar principle of cooperative activation, Shibasaki reported the first efficient method by making use of the two-center catalysis,[7] and Trost revealed a novel family of dinuclear zinc complexes,[8] catalyzing the reaction between nitromethane and aldehydes. Subsequently, Evans's copper acetate–bis(oxazoline) catalyst[9] and Palomo's zinc triflate–amino alcohol complex[10] were both found to effectively catalyze the Henry reaction by concurrent activation, realized by the combined use of discrete Lewis acid and base as structurally independent entities.

Meanwhile, of recent interest are the hydrogenated derivatives of the Schiff base-type ligands and their complexes with transition-metal ions.[11] Comparing the properties of salen and tetrahydrosalen ($[H_4]$salen), the latter has increased N basicity and framework flexibility to more easily in a folded fashion,[12] which might produce strong asymmetric inductivity in some reactions. However, they have been much less developed to date. In our previous study, hydrogenated Schiff base ligand has been successfully employed in the asymmetric cyanosilylation of aldehydes.[11c]

Herein, we wish to report a new Cu^I–$[H_4]$salen-catalyzed asymmetric Henry reaction, which delivers excellent enantioselectivities for aromatic, heteroaromatic, enal, and aliphatic aldehydes. In addition, this method provides several practical advantages: 1) chiral $[H_4]$salen ligand **1f** is readily modifiable and can be easily synthesized in two simple steps and in 94% overall yield, 2) in contrast to the instability of the salen ligand in acid medium, chiral $[H_4]$salen ligand can be recovered in near quantitative yield after the reaction by simple aqueous acid/base workup and thus can be reused (see Experimental Section), and 3) *m*-hydroxybenzaldehyde **4d** was directly employed as a starting material for the synthesis of (*S*)-norphenylephrine which has therapeutic applications in a variety of diseases, for example, in the treatment of hypertension, pain, and depression.[13]

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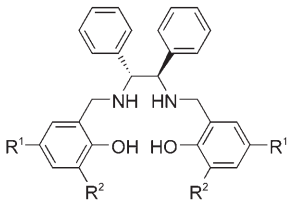
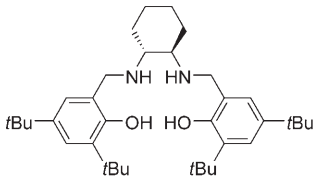
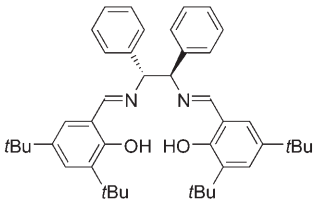


1a: R^1 = H, R^2 = H
1b: R^1 = H, R^2 = Ph
1c: R^1 = Ph, R^2 = H
1d: R^1 = *t*Bu, R^2 = adamantanyl
1e: R^1 = Cl, R^2 = H
1f: R^1 = *t*Bu, R^2 = *t*Bu



2a



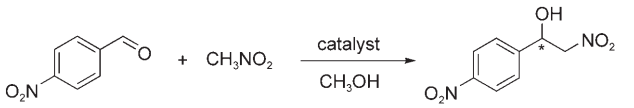
3a

Results and Discussion

Initially, building on the $[H_4]$salen–$Cu(OAc)_2$ complex, tetradentate *R*,*R* ligands (**1a–f**) were examined by using the Henry reaction of 4-nitrobenzaldehyde with nitromethane as the model reaction (Table 1). Moderate bulky *t*Bu groups at the 3′,5′-position of the phenolic ring of ligand **1f** were beneficial to the enantioselectivity (Table 1, entry 6 versus 1–5). To find an effective metal complex for the catalytic addition, we conducted systematic screening studies[14] and established that chiral ligand **1f** and $(CuOTf)_2{\cdot}C_7H_8$ could effectively promote the enantioselective addition (Table 1, entry 8). Complexed with $(CuOTf)_2{\cdot}C_7H_8$, $[H_4]$salen ligand **2a**, based on the cyclohexane-1,2-diamine moiety and salen ligand **3a**, gave poor enantioselectivities (Table 1, entries 11 and 12). These studies also included examinations of various additives and the reaction temperature, which led us to determine that the combined use of 4 Å molecular sieves and a temperature of 45 °C were both crucial to reactivity and enantioselectivity (Table 1, entry 9 versus 8 and entry 10 versus 9). Thus, we found that treatment of 4-nitrobenzaldehyde with nitromethane in the presence of $[H_4]$salen **1f** (10 mol %), $(CuOTf)_2{\cdot}C_7H_8$ (5 mol %), and 4 Å molecular sieves enabled the excellent and efficient formation of product in 95 % yield with 91 % *ee* (Table 1, entry 10).

Under the optimal reaction conditions, a variety of aromatic, heteroaromatic, aliphatic, and enal aldehydes were found to be suitable substrates, with the Henry reaction giving the corresponding nitroaldol adducts in moderate to good yields with excellent enantioselectivities (Table 2). It is

Table 1. Asymmetric Henry reaction of 4-nitrobenzaldehyde with nitromethane under indicated conditions.

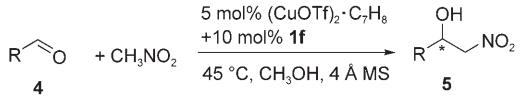


4a **5a**

Entry[a]	Ligand	Catalyst [mol %]	Metal	*T* [°C]	*t* [h]	Yield [%][b]	*ee* [%][c]
1	**1a**	20	$Cu(OAc)_2$	13	9	37	41
2	**1b**	20	$Cu(OAc)_2$	13	9	43	46
3	**1c**	20	$Cu(OAc)_2$	13	9	28	52
4	**1d**	20	$Cu(OAc)_2$	13	9	41	62
5	**1e**	20	$Cu(OAc)_2$	13	9	34	52
6	**1f**	20	$Cu(OAc)_2$	13	9	40	67
7	**1f**	20	$Cu(OTf)_2$	13	9	trace	n.d.
8	**1f**	10	$(CuOTf)_2{\cdot}C_7H_8$	13	9	21	83
9[d]	**1f**	10	$(CuOTf)_2{\cdot}C_7H_8$	13	9	33	93
10[d]	**1f**	5	$(CuOTf)_2{\cdot}C_7H_8$	45	30	95	91
11[d]	**2a**	5	$(CuOTf)_2{\cdot}C_7H_8$	45	30	88	71
12[d]	**3a**	5	$(CuOTf)_2{\cdot}C_7H_8$	45	30	20	2

[a] All reactions were run on a 0.2 mmol scale of 4-nitrobenzaldehyde in the mixture of 0.8 mL of methanol and 0.6 mL of nitromethane. [b] Isolated yield. [c] Determined by HPLC analysis. [d] In the presence of 10 mg of 4 Å MS.

Table 2. Asymmetric Henry reaction of aldehydes with nitro compound under optimum conditions.



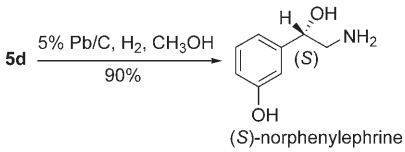
4 **5**

Entry[a]	Aldehyde	*t* [h]	Yield [%][b]	*ee* [%][c]
1	4-nitrobenzaldehyde (**4a**)	30	95	91 (*S*)
			93	90 (*S*)[d]
2	3-nitrobenzaldehyde (**4b**)	24	93	91
3	2-nitrobenzaldehyde (**4c**)	30	95	93 (*S*)
4[e]	3-hydroxybenzaldehyde (**4d**)	30	75	90
5	3-phenoxybenzaldehyde (**4e**)	60	61	94
6	4-chlorobenzaldehyde (**4f**)	19	77	94 (*S*)
7	3-chlorobenzaldehyde (**4g**)	48	73	94
8	2-chlorobenzaldehyde (**4h**)	30	92	96 (*S*)
9	2,4-dichlorobenzaldehyde (**4i**)	13	96	92
10	benzaldehyde (**4j**)	60	64	92 (*S*)
11	1-naphthaldehyde (**4k**)	60	66	93 (*S*)
12[f]	2-naphthaldehyde (**4l**)	72	84	90
13	4-phenylbenzaldehyde (**4m**)	56	63	91 (*S*)
14	furan-2-carbaldehyde (**4n**)	60	86	91
15[e]	thiophene-2-carbaldehyde (**4o**)	60	38	91
16	cinnamaldehyde (**4p**)	56	44	92
17[g]	hexanal (**4q**)	72	74	90
18[e]	isobutyraldehyde (**4r**)	60	57	88 (*S*)
19[h]	4-nitrobenzaldehyde (**4a**)	20	98	91

[a] Reactions were carried out on a 0.2 mmol scale of aldehydes in the mixture of 0.8 mL of methanol and 0.6 mL of nitromethane in the presence of 10 mg of 4 Å MS. [b] Isolated yield. [c] Determined by HPLC analysis. The absolute configurations were established as *S* by comparison of the sign of the optical rotation values with that in the literature (see reference [9]). [d] In the presence of 50 μL of water. For the detailed experimental procedure see the Supporting Information. [e] In the mixture of 0.4 mL of *t*BuOH and 0.3 mL of nitromethane. [f] *t*BuOH as the solvent. [g] In the mixture of 0.2 mL of methanol and 0.15 mL of nitromethane. [h] Reactions were carried out on a 0.2 mmol scale of 4-nitrobenzaldehyde in the mixture of 0.8 mL of methanol and 0.6 mL of nitroethane in the presence of 10 mg of 4 Å MS; *syn*/*anti* 15:85 was determined by HPLC and ^{1}H NMR spectroscopy.

noteworthy that not only the steric hindrance of the substitution at the aromatic ring, but also its electronic nature has no obvious effect on enantioselectivity (Table 2, entries 1–3, 6–9 and 11–12). 4-Nitrobenzaldehyde could also react smoothly with nitroethane with high diastereoselectivity (*syn*/*anti* 15:85) and excellent enantioselectivity (91% *ee*) (Table 2, entry 19). Interestingly, even in the presence of additional water (50 μL), the chemical efficiency and enantioselectivity of the model reaction were maintained (Table 2, entry 1). When using the enantiomer of **1f** as a ligand, the model reaction afforded the *R* product **5a** in 95% yield with 90% *ee*.

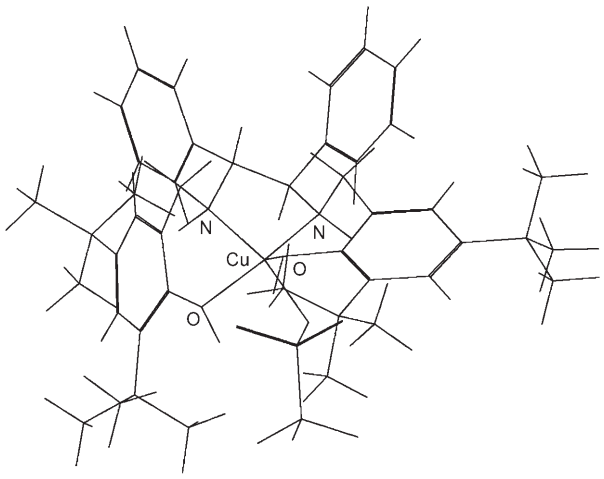
As an interesting synthetic utility of this method, *m*-hydroxybenzaldehyde **4d** was directly used as the starting material for the synthesis of (*S*)-norphenylephrine with the Henry reaction giving the nitroaldol adduct (*S*)-**5d** in 75% yield with 90% *ee* (Table 2, entry 4). By catalytic hydrogenation, nitro compound **5d** was readily converted into (*S*)-norphenylephrine in 90% yield (Scheme 1, $[\alpha]_D^{20} = -1.75$ ($c = 0.4$ in CH_3OH); lit.[15] $[\alpha]_D^{20} = -1.7$ ($c = 5.8$ in CH_3OH, 98% *ee*)). When 3-phenoxybenzaldehyde **4e** was employed as a substrate, the reaction also provided the corresponding product **5e** in moderate yield with excellent enantioselectivity (Table 2, entry 5).



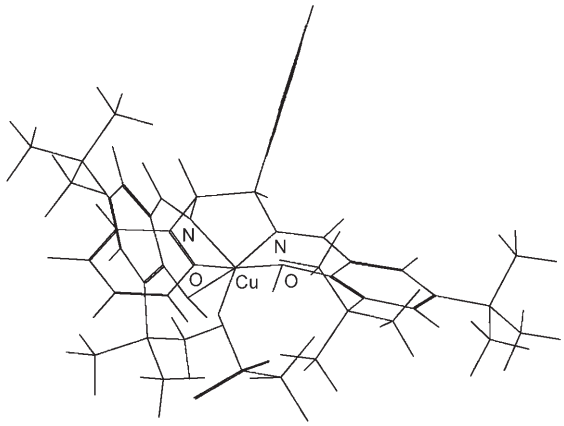
Scheme 1. Synthesis of (*S*)-norphenylephrine.

In this paper, the Henry reaction was simple in operation with readily available reagents and no special precautions were taken to exclude water or air from the reaction vessel. By using the HyperChem program package, the geometries of [H_4]salen **1f**-CuOTf (**I**) and salen **3a**-CuOTf (**II**) complexes were optimized at the MM+ level (Figure 1). The CuO_2N_2 plane in the former shows a heavier tetrahedral distortion and the two phenolic rings are bent upwards and downwards, respectively.

Based on our preliminary experimental investigations, modeled complex **I** and the previously reported steric and electronic considerations,[9] the explanation of the asymmetric induction mechanism can be correctly predicted (Figure 2). In the catalytic cycle, due to the strong coordination ability of the nitro group to soft metal, nitromethane is activated and deprotonated to generate the active nucleophile through a possible complex **7**. Once the nitroaldol reaction proceeds from the transition-state model **8** to **6**, the intermediate **6** again works as a chiral Brönsted base catalyst for the second cycle. On the basis of the observed absolute configuration of 2-nitro-1-(4-nitrophenyl)ethanol (Table 2, entry 1), a possible transition state (**8** or **A**) has been proposed. In transition state **A**, the *Re* face of the carbonyl of 4-nitrobenzaldehyde is much more accessible to a nucleophilic group than the *Si* face as the interaction of the *Si* face and the attacking group will strongly increase repulsion between phenyl subunits as in transition state **B**.



I



II

Figure 1. MM+ optimized geometries for [H_4]salen **1f**-CuOTf (**I**) and salen **3a**-CuOTf (**II**) complexes.

Conclusion

We have developed a new chiral Cu^I–[H_4]salen catalyst for the asymmetric Henry reaction with good substrate generality. The products from this reaction are produced in moderate to high yields with excellent enantioselectivities. This pathway is air-tolerant and easily manipulated with readily available reagents. Furthermore, this method has been successfully applied to the synthesis of (*S*)-norphenylephrine, starting from commercially available *m*-hydroxybenzaldehyde. Further efforts will be devoted to improve the reactivity and enantioselectivity as well as to synthesize norepinephrine and epinephrine analogues.

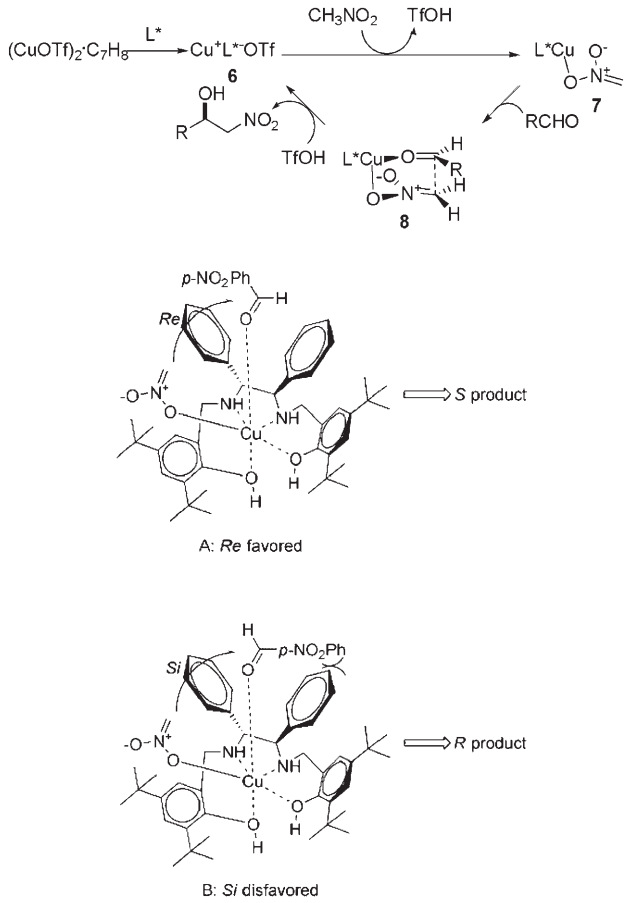


Figure 2. Proposed reaction pathway and transition state (**A** or **B**) for the catalytic asymmetric Henry reaction. L* = [H_4]salen **1f**.

Experimental Section

Typical experimental procedure: Ligand **1f** (13.0 mg, 0.02 mmol), 4 Å molecular sieves (10 mg), and $(CuOTf)_2{\cdot}C_7H_8$ (5.2 mg, 0.01 mmol) were added to methanol (0.8 mL) at ambient temperature. Stirring continued for 10 min and then 4-nitrobenzaldehyde (30.2 mg, 0.2 mmol) and nitromethane (0.6 mL) were added to the resulting green solution. After heating the mixture to 45 °C, stirring continued for 30 h. The mixture was concentrated in vacuo to give a glutinous phase. CH_2Cl_2 (2 mL) and HCl (1 M, 5 mL) were added and stirring continued until the green color disappeared. The mixture was then extracted with CH_2Cl_2 (3×10 mL) and the organic extracts were combined, washed with brine, dried over anhydrous Na_2SO_4, and evaporated in vacuo. The residue was purified by flash chromatography by using EtOAc/PE (1:4; PE = petroleum ether b.p. 60–90 °C) as the eluent to afford **5a** as an off-white solid (40.3 mg, 95% yield, 91% *ee*; Chiralcel OD, hexane/*i*PrOH 85:15, 0.8 mL min^{-1}, *R*: t_R(minor) = 19.70 min, *S*: t_R(major) = 24.23 min; $[\alpha]_D^{25} = +31.6°$ ($c = 0.14$ in CH_2Cl_2, 91% *ee*) (lit.[10b] $[\alpha]_D^{25} = -38.4°$ ($c = 1.3$ in CH_2Cl_2, 84% *ee*)). To recover the [H_4]salen ligand **1f** from the aqueous phase, saturated $NaHCO_3$ was added dropwise to the aqueous phase until pH ≈10. The mixture was extracted with CH_2Cl_2 (3×10 mL), and the organic layer was dried over Na_2SO_4 and filtered. The solvent was evaporated to afford chemically and optically pure [H_4]salen ligand **1f** (12.5 mg, 96% recovered).

Acknowledgements

We thank the National Natural Science Foundation of China (Nos. 20225206, 20390055 and 20372050) and the Ministry of Education, P R China (No. 104209 and others) for financial support.

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Received: September 2, 2006
Published online: October 27, 2006

