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Efficient and enantioselective nitroaldol reaction catalyzed by copper Schiff-base complexes

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Abstract—Mild and efficient enantioselective nitroaldol reactions of nitromethane with various aldehydes were catalyzed by chiral copper Schiff-base complexes, which can be readily prepared from amino acid, yielding the corresponding adducts with high yields and good enantiometric excess (ee).

1. Introduction

The nitroaldol reaction (or Henry reaction) is one of the most important and atom-economical reactions[1] for carbon–carbon bond formation to generate β-nitroalkanols. The diversity of the transformation of adducts, such as reduction to amines, Nef reaction to carbonyl compounds, or dehydration to nitroalkenes, offers a variety of applications for this reaction.[2] Recent efforts have been focused on the development of catalytic enantioselective reaction variants. In these processes, different chiral catalysts were developed, such as those based upon BINOL by Shibasaki,[3] Bis(oxazoline) by Evans and Jørgensen,[4] cinchona alkaloid by Corey,[5] dinuclear zinc complexes by Trost,[6] Salen–Co complexes by Yamada,[7] and amino alcohols by Palomo.[8,9] Often these reactions are required to be performed at low temperature and sometimes under airproof conditions. A chiral Schiff-base is one of the frequently used catalysts, especially in asymmetric cyclopropanation.[10,11] However, it has not yet been used in the asymmetric nitroaldol reaction. We herein report a novel, efficient and mild enantioselective nitroaldol reaction catalyzed by chiral copper Schiff-base complexes **1**, which can be prepared from phenylalanine.[10a–d] The absolute configuration of **1a** was identified by its crystal structure (Fig. 1).

2. Results and discussion

The two enantiomers of phenylalanine (D and L) were used, and catalysts of different configurations were prepared and utilized in the reaction. It was found that absolute configuration of the product can be controlled by the configuration of the catalyst in a Henry reaction. Initially, the nitroaldol reaction of nitromethane with 4-nitro-benzaldehyde was explored in order to search for the optimal conditions, as shown in Scheme 1. Table 1 summarized the results of the initial studies. In each instance, the reaction was carried out at ambient temperature within the given reaction time. With 10 mol % of **1a**, the corresponding product was obtained in a high yield and with a good ee (Table 1, entry 1). A decrease of **1a** resulted in reduction of the reaction yield and little variation in ee while an increase of **1a** from 10 to 20 mol % led to a reduction either in yield or ee value (Table 1, entries 1 and 2). Generally, the amount of the catalyst could be decreased to 5% without a marked loss in enantioselectivity (Table 1, entry 3). Increasing the amount of nitromethane can remarkably enhance both reaction yield and rate, but slightly reduces enantioselectivity (Table 1, entry 11). The reaction solvent also has a great influence on the reaction. When the reaction solvent was changed from toluene to methylene chloride

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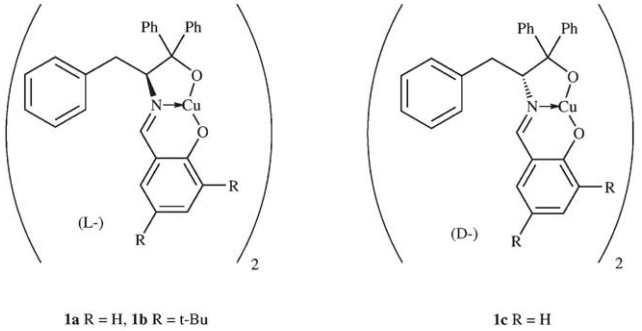


1a R = H, **1b** R = t-Bu **1c** R = H

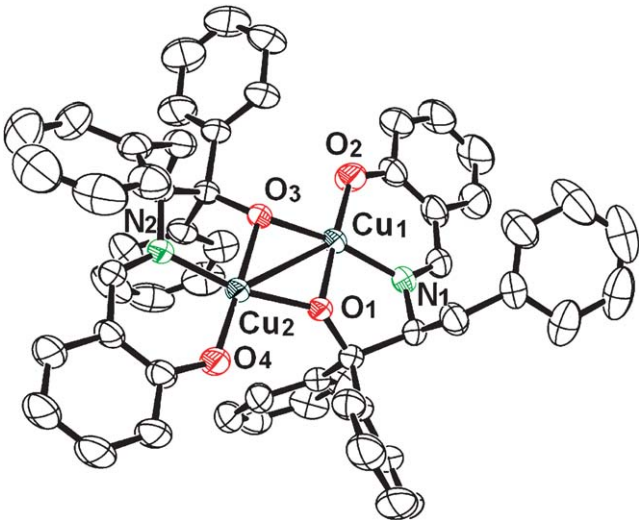
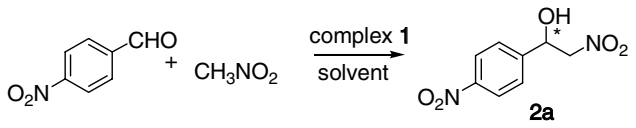


Figure 1. Two opposite configurations of complex **1** and the crystal structure of **1a**.[12]



Scheme 1.

or THF, the reaction yield or ee was decreased. Especially, the ee was reduced to 7% when toluene was replaced by methylene chloride (Table 1, entries 4 and 5). When methanol or ethanol was used as a solvent, the corresponding reaction rate and yield were enhanced markedly (Table 1, entries 8–11). As for ee, ethanol favored the enantioselectivity, while methanol was deleterious (Table 1, entries 9 and 10). Since the catalyst is very stable in water, we attempted to carry out this asymmetric reaction in aqueous media. However, the addition of water disfavored this reaction, resulting in a decrease in yield, as well as a large decrease in ee (Table 1, entries 14 and 15).

All the experimental data demonstrated EtOH as a superior solvent in terms of yield and ee, consistent with the report by Evans.[4a] On the other hand, the organic base has an important influence on this reaction. The addition of triethylamine markedly decreased enantioselectivities although it can improve the reaction yield (Table 1, entries 6, 7, and 17). Additionally, reaction temperature has a great influence on the reaction rate, yield and the ee value. When the reaction was carried at or below 0 °C, the corresponding yield was lower and the reaction took a longer time. The sacrifice in

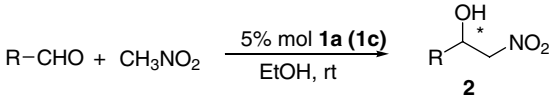
Table 1. Studies on the asymmetric nitroaldol reactions with chiral copper Schiff-base complexes[a]

Entry	Catalyst (loading)	Solvent	Reaction time (h)	Yield (%)[b]	ee (%)[c]	Config[d]
1	**1a** (10%)	PhMe	48	65	51	*S*
2	**1a** (20%)	PhMe	48	62	45	*S*
3	**1a** (5%)	PhMe	48	45	50	*S*
4	**1a** (10%)	CH_2Cl_2	48	48	7	*S*
5	**1a** (10%)	THF	48	56	43	*S*
6[e]	**1a** (10%)	PhMe	48	91	17	*S*
7[f]	**1a** (10%)	PhMe	24	95	9	*S*
8	**1a** (10%)	EtOH	24	87	80	*S*
9	**1a** (5%)	EtOH	24	85	78	*S*
10	**1a** (5%)	MeOH	24	86	28	*S*
11[g]	**1a** (5%)	EtOH	24	91	70	*S*
12[h]	**1a** (5%)	EtOH	6	80	56	*S*
13[i]	**1a** (5%)	EtOH	24	52	70	*S*
14	**1a** (5%)	EtOH/H_2O (10:1)	24	82	23	*S*
15	**1a** (5%)	EtOH/H_2O (1:1)	24	78	17	*S*
16	**1b** (10%)	PhMe	48	61	34	*S*
17[f]	**1b** (10%)	PhMe	48	80	15	*S*
18	**1b** (5%)	EtOH	24	85	64	*S*
19	**1c** (5%)	EtOH	24	83	76	*R*

[a] All reactions were performed with 0.5 mmol of 4-nitrobenzaldehyde and 2.5 mmol nitromethane in the presence of catalyst **1** at room temperature, unless specified. The reaction procedure is described in Ref. 13.
[b] Isolated yield.
[c] Determined by chiral HPLC using a OD-H column.
[d] Determined by comparing the HPLC elution order of the enantiomers with an authentic sample according to the literature.[4a,6]
[e] 10 mol % triethylamine was added to the reaction system.
[f] 20 mol % triethylamine was added to the reaction system.
[g] 1 mL nitromethane was used instead of 2.5 mmol nitromethane.
[h] The reaction was performed at 50 °C.
[i] The reaction was performed at 0 °C.

the yield and rate did not affect the significant enhancement of the ee value (Table 1, entry 13). When the reaction was carried out at 50 °C, the reaction rate was enhanced remarkably while the corresponding ee value was reduced. Synthetically, room temperature should be the optimized temperature for this reaction. When we added an organic base to prompt the reaction, however, the corresponding ee decreased dramatically. Finally, the structure of complex **1** played a crucial role in this enantioselective reaction. By comparison, a less bulky complex **1a** was proved to be a better ligand for this asymmetric reaction while the complex **1b** bearing *tert*-butyl group disfavored the enantioselectivity (Table 1, entries 1 and 16). Catalyst **1c** derived from D-phenylalanine yielded the corresponding product with high enantioselectivity, however, the absolute configuration of the main product was *R* in contrary to that of the reaction product catalyzed by **1a** (entry 19).

Under the optimized reaction conditions, different aldehydes were tested in order to extend the substrate scope, as shown in Scheme 2. Firstly, when **1a** was used to catalyze this nitroaldol reaction (entries 1–11), it was found that this catalyst worked well for various aromatic aldehydes, regardless of the substituents on the aromatic rings, either electron-withdrawing or donating group (Table 2), although the yield in entry 5 of Table 2 was low. It seems that aromatic aldehydes with ortho-substituted groups (entries 6, 7, and 17) favor slightly the stereoselectivity. Benzaldehyde, without any substituents, however, gave the product with moderate yield and ee (Table 2, entry 4), attributed to its lesser steric hindrance. Similarly, phenylethyl aldehyde, a type of aliphatic aldehyde, gave a moderate yield and poor ee value (Table 2, entry 9). The other aliphatic aldehydes tested gave moderate yields and low ee values (Table 2, entries 10 and 11). When this secondary alkyl group was replaced by a corresponding primary alkyl group, it was hard to observe an ee value under the experimental condition. When the catalyst **1c** was employed under the same conditions, similar results were obtained. These phenomena indicate that steric hindrance plays an important role in the enantioselectivity.



Scheme 2.

Table 2. Henry reaction of nitromethane with various aldehydes[a]

Entry	R	Product	Time (h)	Yield (%)[b]	ee (%)[c]	Config
1	4-NO_2Ph	**2a**	24	85	78	*S*
2	4-ClPh	**2b**	48	86	82	*S*
3	1-Naphthyl	**2c**	48	73	81	*S*
4	Ph	**2d**	48	65	67	*S*
5	4-MeOPh	**2e**	72	43	75	*S*
6	2-ClPh	**2f**	48	90	86	*S*
7	2-MeOPh	**2g**	60	71	77	*S*
8	4-MePh	**2h**	48	75	80	*S*
9	$PhCH_2$	**2i**	60	61	45	—[d]
10	*i*-Pr	**2j**	48	68	52	*S*
11	*i*-Bu	**2k**	48	72	61	*S*
12	4-NO_2Ph	**2a**	24	83	76	*R*
13	4-ClPh	**2b**	48	81	81	*R*
14	1-Naphthyl	**2c**	48	72	86	*R*
15	Ph	**2d**	48	67	51	*R*
16	4-MeOPh	**2e**	72	48	62	*R*
17	2-ClPh	**2f**	48	88	85	*R*
18	2-MeOPh	**2g**	60	75	78	*R*
19	4-MePh	**2h**	48	69	81	*R*
20	$PhCH_2$	**2i**	60	64	52	—[d]
21	*i*-Pr	**2j**	48	64	54	*R*
22	*i*-Bu	**2k**	48	69	64	*R*

[a] All reactions were performed on a 0.5 mmol scale with 5 mol % of complex **1a** or **1c** in the presence of 2.5 mmol of nitromethane in ethanol. For entries 1–11, **1a** was used, while for entries 12–22, **1c** was used.

[b] Isolated yields after chromatographic purification.

[c] Enantiomeric excess was determined by HPLC using Chiracel OD-H or OJ-H column.

[d] Configurations in entries 9 and 20 were not determined but they were reversed with respect to each other.

3. Conclusion

In summary, a new and facile enantioselective nitroaldol reaction was realized at room temperature by the employment of complex **1**, yielding β-nitroalkanols with good yield and a high ee value. Also, the product configuration can be adjusted by alteration of the configuration of **1**, which can be controlled by choosing L- or D-phenylalanine, as this complex was prepared from the derivatives of phenylalanine and copper acetate. On the other hand, the catalyst is very stable in air and water at room temperature, so it does have potential in industrial applications. Further study is currently in progress to improve the yield and enantiomeric excess and to elucidate the reaction mechanism.

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References

1. Trost, B. M. *Science* **1991**, *254*, 1471–1477.
2. (a) Rosini, G. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Heathcock, C. H., Eds.; Pergamon: New York, 1991; Vol. 2, pp 321–340; (b) Luzio, F. A. *Tetrahedron* **2001**, *57*, 915–945; (c) Ono, N. *The Nitro Group in Organic Synthesis*; Wiley-VCH: New York, 2001.
3. (a) Sasai, H.; Suzuki, T.; Arai, S.; Arai, T.; Shibasaki, M. *J. Am. Chem. Soc.* **1992**, *114*, 4418–4420; (b) Arai, T.; Yamada, Y. M. A.; Yamamoto, N.; Sasai, H.; Shibasaki, M. *Chem. Eur. J.* **1996**, *2*, 1368–1372.
4. (a) Evans, D. A.; Seidel, D.; Rueping, M.; Lam, H. W.; Shaw, J. T.; Downey, C. W. *J. Am. Chem. Soc.* **2003**, *125*, 12692–12693; (b) Christensen, C.; Juhl, K.; Hazell, R. G.;

Jørgensen, K. A. *J. Org. Chem.* **2002**, *67*, 4875–4881; (c) Christensen, C.; Juhl, K.; Jørgensen, K. A. *Chem. Commun.* **2001**, 2222–2223; (d) Du, D. M.; Lu, S. F.; Fang, T.; Xu, J. X. *J. Org. Chem.* **2005**, *70*, 3712–3715; (e) Lu, S. F.; Du, D. M.; Zhang, S. W.; Xu, J. X. *Tetrahedron: Asymmetry* **2004**, *15*, 3433–3441.

5. Corey, E. J.; Zhang, F.-Y. *Angew. Chem., Int. Ed.* **1999**, *38*, 1931–1934.
6. (a) Trost, B. M.; Yeh, V. S. C. *Angew. Chem., Int. Ed.* **2002**, *41*, 861–863; (b) Trost, B. M.; Yeh, V. S. C.; Ito, H.; Bremeyer, N. *Org. Lett.* **2002**, *4*, 2621–2623.
7. (a) Yamada, T. *Synthesis-Stuttgart* **2004**, *12*, 1947–1950; (b) Kogami, Y.; Nakajima, T.; Ashizawa, T.; Kezuka, S.; Ikeno, T.; Yamada, T. *Chem. Lett.* **2004**, *33*, 614–615.
8. (a) Palomo, C.; Oiarbide, M.; Laso, A. *Angew. Chem., Int. Ed.* **2005**, *44*, 3881–3884; (b) Zhong, Y.-W.; Tian, P.; Lin, G.-Q. *Tetrahedron: Asymmetry* **2004**, *15*, 771–776.
9. (a) Palomo, C.; Oiarbide, M.; Mielgo, A. *Angew. Chem., Int. Ed.* **2004**, *43*, 5442–5444; (b) Klein, G.; Pandiaraju, S.; Reiser, O. *Tetrahedron Lett.* **2002**, *43*, 7503–7506; (c) Köhn, U.; Schulz, M.; Görls, H.; Anders, E. *Tetrahedron: Asymmetry* **2005**, *16*, 2125–2131.
10. (a) Li, Z.-N.; Zheng, Z.; Chen, H. *Tetrahedron: Asymmetry* **2000**, *11*, 1157–1163; (b) Cai, L.; Mahmoud, H.; Han, Y. *Tetrahedron: Asymmetry* **1999**, *10*, 411–427; (c) Aratani, T.; Yoneyoshi, Y.; Nagase, T. *Tetrahedron Lett.* **1982**, *23*, 685–688; (d) Aratani, T. *Pure Appl. Chem.* **1985**, *57*, 1839–1844; (e) Itagaki, M.; Hagiya, K.; Kamitamari, M.; Masumoto, K.; Suenobu, K.; Yamamoto, Y. *Tetrahedron* **2004**, *60*, 7835–7843.
11. (a) Jarvo, E. R.; Lawrence, B. M.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **2005**, *44*, 6043–6046; (b) Gademann, K.; Chavez, D. E.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **2002**, *41*, 3059–3061; (c) Dossetter, A. G.; Jamison, T. F.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **1999**, *38*, 2398–2400; (d) Ruck, R. T.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **2003**, *42*, 4771–4774; (e) Ruck, R. T.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2002**, *124*, 2882–2883; (f) Gama, Á.; Flores-López, L. Z.; Aguirre, G.; Parra-Hake, M.; Somanathan, R.; Cole, T. *Tetrahedron: Asymmetry* **2005**, *16*, 1167–1174.
12. Crystal data for **1a**: $C_{56}H_{46}Cu_2N_2O_4$, $fw = 938.03$, grey prism crystal, $0.7 \times 0.45 \times 0.2$ mm, monoclinic, space group $P2_1$, $a = 10.705(2)$ Å, $b = 12.738(3)$ Å, $c = 34.184(7)$ Å, $\beta = 93.56(3)°$, $V = 4652.3(16)$ Å^3, $Z = 2$, $D_{calcd} = 1.339$ g cm^{-3}, $\mu = 0.963$ mm^{-1}, $T = 293(2)$ K, $F_{000} = 1944$, MoKα radiation, $\lambda = 0.71073$ Å. Refinement of 1153 parameters and 1 restrains on 15,995 independent reflections out of 27,419 measured reflections ($R_{int} = 0.0204$) led to $R1 = 0.0351$ ($I > 2\sigma(I)$, 15,259 reflections), $wR2 = 0.0856$ (all data) and $S = 1.081$. Bruker SMART CCD diffractometer, structure solution by direct method, refinement on F^2. Crystallographic data for the structure reported in this letter have been deposited with the Cambridge Crystallographic Data Centre and allocated the deposition numbers: CCDC 297115. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EW, UK (Fax: Int code+(1223) 336-033; E-mail: deposit@ccdc.cam.ac.uk).
13. Typical procedure: To a solution of complex **1a** (0.025 mmol) in ethanol was added nitromethane (2.5 mmol) and the mixture was stirred for 2 h. Aldehyde (0.5 mmol) was added and reacted for the indicated time. The volatile components were removed in vacuo and the crude product purified by column chromatography.