Asymmetric nitroaldol reaction with a chiral copper complex derived from D-tartaric acid

Changsheng Gan

Abstract: A novel catalytic enantioselective Henry reaction has been developed using a tetradentate copper complex derived from D-tartaric acid to give β-nitroalkanols in moderate to high enantioselectivities.

Key words: Henry reaction, D-tartaric acid, enantioselective, β-nitroalkanols.

Résumé : On a développé le champ d'application de la nouvelle réaction catalytique énantiosélective d'Henry en utilisant le complexe tétradentate de cuivre de l'acide D-tartrique pour préparer des β-nitroalcanols avec des énantiosélectivités allant de modérées à élevées.

Mots-clés : réaction d'Henry, acide D-tartrique, énantiosélective, β-nitroalcanols.

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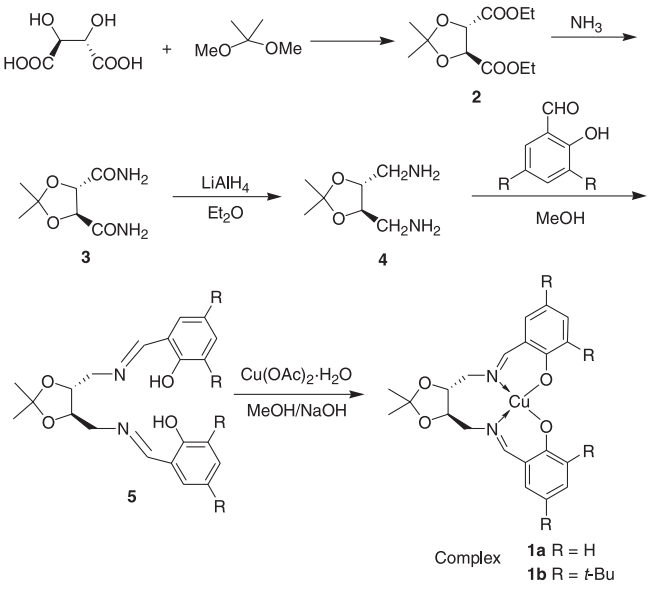
Introduction

The nitroaldol reaction (or Henry reaction) constitutes an important class of C–C bond-forming reactions that provide straightforward access to important synthetic intermediates from readily accessible nitroalkanes and carbonyl compounds (1). Because of its significance in organic synthesis, considerable efforts have been devoted to the development of catalytic asymmetric nitroaldol reactions (2). Several efficient catalysts have been developed, such as BINOL by Shibasaki (3), bis(oxazoline) by Evans and Jørgensen (4), cinchona alkaloid by Deng (5), dinuclear zinc complex by Trost (6), amino alcohol (7), thiourea (8), and Schiff base catalysts (9). Because D-tartaric acid is available very cheaply from natural chiral sources, it has been widely studied in asymmetric catalysis, and different catalysts have been developed for a series of asymmetric reactions (10). We have been studying it for some time. In this article, we report a novel enantioselective Henry reaction catalyzed by a C_2-symmetric tetradentate catalyst **1** derived from D-tartaric acid, which is similar in structure to the salen derivative (11).

Scheme 1 summarizes the synthesis of complex **1** from D-tartaric acid. (4*S*, 5*S*)-(–)-Diethyl 2, 3-*O*-isopropylidene-D-tartarate (**2**) was prepared from D-(–)-tartaric acid using a reported procedure (12, 13). Dropping 25% ammonia into **2** in the presence of ammonium chloride in an ice-salt bath, then stirring overnight, gave diamide **3** in 85% yield. Reduction of the diamide moiety of **3** to diamine **4** with $LiAlH_4$ in refluxing ether for 18 h, followed by condensation with corresponding salicylaldehyde, provided chiral ligand **5**. Finally, mixing **5** and $Cu(OAc)_2 \cdot H_2O$ in methanol followed by the addition of excess sodium hydroxide produced the tetradentate copper complex **1**.

Scheme 1. The synthetic route of complex **1**.



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[2]Supplementary data for this article are available on the journal Web site (canjchem.nrc.ca) or may be purchased from the Depository of Unpublished Data, Document Delivery, CISTI, National Research Council Canada, Ottawa, ON K1A 0R6, Canada. DUD 3715. For more information on obtaining material refer to cisti-icist.nrc-cnrc.gc.ca/irm/unpub_e.shtml.

Results and discussions[2]

The complex **1** was added to a mixture of 4-nitrobenzaldehyde and nitromethane (Scheme 2). The results are shown in Table 1. Entries 1 and 2 show that the tetradentate complex **1b**, with a bulky *tert*-butyl substituent,

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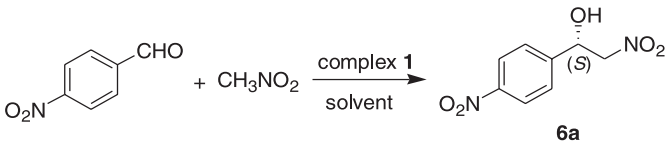
Table 1. Studies on the asymmetric nitroaldol reactions with chiral copper complexes.

Entry	Cat.	Solvent	CH_3NO_2	Time (h)	Yield[a] (%)	Ee[b] (%)
1	**1a**	Tol	2.5 mmol	80	38	12
2	**1b**	Tol	2.5 mmol	80	39	63
3	**1b**	CH_2Cl_2	2.5 mmol	80	42	34
4	**1b**	CH_3CN	2.5 mmol	80	36	23
5	**1b**	THF	0.5 mL	80	75	52
6	**1b**	Tol	0.5 mL	80	67	68
7	**1b**	Tol	1 mL	60	77	44
8	**1b**	EtOH	1 mL	60	79	26
9[c]	**1b**	Tol	0.5 mL	72	68	69
10[d]	**1b**	Tol	0.5 mL	72	66	59
11[e]	**1b**	Tol	1 mL	72	65	72
12[f]	**1b**	Tol	0.5 mL	24	95	11
13[g]	**1b**	Tol	0.5 mL	48	98	25

Note: All reactions were performed with 0.5 mmol 4-nitrobenzaldehyde, nitromethane, and 10 mol% of catalyst **1** in 2 mL solvent at room temperature unless otherwise specified.
[a]Isolated yield.
[b]Determined by chiral HPLC using an OD-H column.
[c]20 mol% of catalyst **1b** was used.
[d]100 mg 4A molecular sieve was added to the reaction mixture.
[e]4 mL toluene and 1 mL nitromethane were used.
[f]20 mol% Et_3N was added to the reaction mixture.
[g]The reaction was carried out at –20 °C in the presence of 20 mol% Et_3N.

Scheme 2. Asymmetric nitroaldol reaction of 4-nitrobenzaldehyde and nitromethane.



catalyzed the reaction much better than **1a**. Then different solvents were screened. Toluene proved the best, followed by THF, whereas EtOH, CH_2Cl_2, and CH_3CN gave only poor enantioselectivities (entries 2–5, 8). Increasing the amount of CH_3NO_2 to 0.5 mL promoted both the yield and the enantioselectivity (entry 6), but when 1 mL of CH_3NO_2 was used, the enantioselectivity was significantly decreased (entry 7). Neither increasing the amount of catalyst nor adding a molecular sieve to the reaction mixture was effective in improving the enantioselectivity (entries 9 and 10). But diluting the catalyst concentration by doubling the amount of solvent and nitromethane did further improve the enantioselectivity without significant loss of yield (entry 11). Conducting the reaction under lower temperature was then examined. However, very low enantioselectivity was obtained (entry 13). The absolute configuration of the product in Table 1 was determined as *S* by comparing the HPLC elution order of the enantiomers and the optical rotations reported in the literature (4*a*).

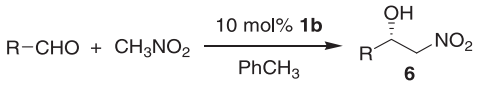
With the optimized reaction conditions, the complex **1b** was used to catalyze the addition of nitromethane to a variety of aldehydes (Scheme 3). The results are summarized in Table 2. Moderate enantioselectivities were obtained for the *para*-substituted aromatic aldehydes, such as 4-chlorobenzaldehyde (entry 2), 4-methoxybenzaldehyde (entry 5), and 4-methylbenzaldehyde (entry 8). 2-Chlorobenzaldehyde (entry 6) was shown to produce the highest enantioselectivity among all the substrates examined. When it came to the sterically less-encumbered benzaldehyde (entry 4), the ee value diminished to 48%. As far as aliphatic aldehydes were concerned, the enantioselectivities were only moderate (entries 9–11). The absolute configurations of the products in Table 2 were assigned as *S* based on the data reported in the literature (4, 9, 14), except for **6i**, whose configuration was not determined.

Table 2. Studies on the asymmetric nitroaldol reactions of nitromethane with various aldehydes.

Entry	R	Product	Time (h)	Yield (%)[a]	Ee (%)[b]
1	4-NO_2Ph	**6a**	72	65	72
2	4-ClPh	**6b**	72	64	58
3	1-naphthyl	**6c**	72	66	80
4	Ph	**6d**	72	61	48
5	4-MeOPh	**6e**	84	40	52
6	2-ClPh	**6f**	72	79	84
7	2-MeOPh	**6g**	72	71	70
8	4-MePh	**6h**	72	60	57
9	$PhCH_2$	**6i**	72	59	45[c]
10	*i*-Pr	**6j**	72	56	57
11	*i*-Bu	**6k**	72	60	61

Note: All reactions were performed on a 0.5 mmol scale with 10 mol% of complex **1b** using 1 mL nitromethane in 4 mL toluene. Reactions were run at room temperature for the indicated time.
[a]Isolated yields.
[b]Enantiomeric excess was determined by HPLC using a Chiracel OD-H or OJ-H column.
[c]The absolute configuration was not determined.

Scheme 3. Asymmetric nitroaldol reactions of nitromethane with various aldehydes.



Conclusions

In summary, we have developed a novel and facile enantioselective nitroaldol reaction. It is the first reported use of tartaric acid derivatives in the catalytic enantioselective Henry reaction. Moderate to high enantioselectivities were obtained for the *ortho*-substituted aromatic aldehydes. This reaction works quite well at room temperature, avoiding the use of low temperature. Since the catalyst is very stable in the air, airproof conditions in N_2 or Ar are also unnecessary. Considering that the chiral catalyst can be readily prepared from naturally abundant tartaric acid, this method provides a practical and convenient way to prepare optically active nitroalkanols. Further study is currently in progress to improve the yield and enantiomeric excess and to elucidate the reaction mechanism.

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