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Hydrogen-Bonding Directed Reversal of Enantioselectivity

Wei Zeng,[†] Guo-Ying Chen,[†] Yong-Gui Zhou,*[,†,‡] and Yu-Xue Li*[,‡]

Dalian Institute of Chemical Physics, CAS, 457 Zhongshan Lu, Dalian 116023, China, and State Key Laboratory of Organometallic Chemistry, Shanghai Institute of Organic Chemistry, CAS, 354 Fenglin Lu, Shanghai 200032, China

Received October 12, 2006; E-mail: ygzhou@dicp.ac.cn; liyuxue@mail.sioc.ac.cn

The preparation of both enantiomers of a chiral compound is still a vital task in pharmaceutical and bioorganic chemistry.[1] Basically, it can be achieved with the use of both enantiomers of a chiral ligand, respectively, in a catalytic asymmetric process. However, the two enantiomers of a chiral ligand are not always easily available from natural chiral sources, such as amino acids, carbohydrates, and alkaloids. Alternatively, the enantioselectivity can be reversed by using different metals[2] in the presence of the same ligands, including additives,[3] or changing the reaction parameters (temperature[4] and solvents[5]) or other methods.[6] Although the use of hydrogen bonding to accelerate or catalyze certain reactions has been well documented recently,[7] reversal of enantioselectivity directed by hydrogen bonding is still rare.[8] We envisage that the formation of hydrogen bonds may reverse the enantioselectivity if ligands were properly designed. The reversal could be caused by the variation of reaction transition states (Figure 1), in which transition state A is common. Both substrates SM1 and SM2 coordinate with the central metal M, but in transition state B, SM2 can coordinate with the central metal M, while the other substrate SM1 has an interaction with NH_2 of the ligand through hydrogen bonding. Thus, different enantiofacial attack was afforded, leading to the reversal of enantioselectivity. In this Communication, we present a hydrogen-bond-directed reversal of enantioselectivity in AgOAc-catalyzed [3+2] cycloaddition of azomethine ylides.

In our initial study, we chose the cycloaddition of iminoester **2a** with dimethyl maleate as the model reaction, which is a useful way to form highly substituted pyrrolidine rings[9] (Table 1). Ligands **1a**−**e** could be conveniently synthesized according to the known literature method.[10] The reaction proceeded smoothly in the presence of AgOAc/**1a** in Et_2O, and only endo cycloaddition product was detected with 76% ee. To our delight, the opposite absolute configuration of adduct **3a** was obtained with 83% ee when ligand **1b** was used, whose substituents on the N atom are H atoms. To achieve better enantioselectivity, we replaced phenyl groups in **1a**/**1b** with 3,5-dimethylphenyl (**1c**/**1d**). Both enantiomers of adduct **3a** were obtained with 84% and −84% ees, respectively (entries 3 and 4). The ee was improved to 92% using **1c** when the reaction was run at −25 °C. Adduct **3a** with 92% ee and opposite absolute configuration was obtained using ligand **1d** at −25 °C. Thus, both enantiomers of adduct **3a** can be obtained with excellent enantioselectivity using AgOAc/**1c**/−25 °C and AgOAc/**1d**/−25 °C, respectively.

To explore the scope of the hydrogen bond-directed reversal of enantioselectivity in cycloaddition of azomethine ylides, a variety of iminoester substrates derived from aldehydes with different steric and electronic properties were examined (Table 2). All reactions went to completion within 4 h in high isolated yields (91−98%). Reversal of the absolute configuration was realized in the reactions of various iminoesters **2a**−**f** and dimethyl maleate regardless of the steric hindrance and electronic properties of the benzene ring of iminoester **2**. Other dipolarophiles such as *tert*-butylacrylate and *N*-phenylmaleimide were also tested; successful reversal of the absolute configuration was observed (entries 11−16).

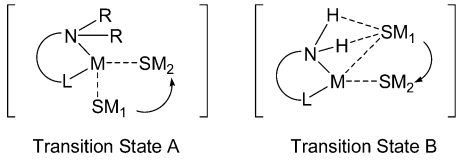
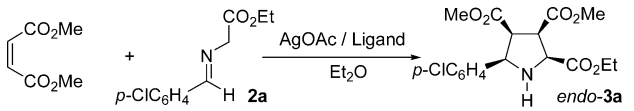
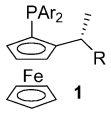


Figure 1. Proposed variation of transition states.

Table 1. AgOAc-Catalyzed Asymmetric Cycloaddition of **2a**[a]





(*S*,*R*$_P$)-**1a**: Ar = Ph, R = NMe_2
(*S*,*R*$_P$)-**1b**: Ar = Ph, R = NH_2
(*S*,*R*$_P$)-**1c**: Ar = 3,5-$Me_2C_6H_3$, R = NMe_2
(*S*,*R*$_P$)-**1d**: Ar = 3,5-$Me_2C_6H_3$, R = NH_2
(*S*,*R*$_P$)-**1e**: Ar = Ph, R = NHMe

entry	ligand	*T* (°C)	yield[b] (%)	ee[c] (%)
1	**1a**	0	95	−76
2	**1b**	0	91	83
3	**1c**	0	95	−84
4	**1d**	0	94	84
5	**1e**	0	71	−19
6	**1c**	−25	95	−92
7	**1d**	−25	90	92

[a] Conditions: iminoester **2a** (1.0 equiv), dimethyl maleate (1.5 equiv), AgOAc (3 mol %), ligand (3.3 mol %), concentration = 0.12 M. [b] Isolated yields based on **2a**. [c] Determined by HPLC.

To further understand the role of hydrogen bonding, a computational study was performed. As shown in Figure 2, the complexes formed by **2b** and Ag-**1a**/**1b** have four possible types of structures (**C1** to **C4**). Eight structures for **1a** (R = Me) and **1b** (R = H) of **C1** to **C4** type are fully optimized by B3LYP[11] method with the Gaussian 03 program.[12] For C, H and N, the 6-31G* basis set was used; for Ag, the Lanl2DZ basis set with effective core potential (ECP)[13] was used. The results show that the most stable complexes for both **1a** and **1b** are **C2** type (Figure 3).

Figure 3 shows that there is large space at both sides of the iminoester in **C2**-**1b**. The two carbonyl groups of the dimethyl maleate can coordinate with the Ag center. Furthermore, they may form two hydrogen bonds with the NH_2 group. This interaction can stabilize the negatively charged oxygen atom in the possible zwitterionic intermediate and the transition state.[9h] This indicates that it is favorable for **C2**-**1b** to be attacked from the top face. While in **C2**-**1a**, the dimethylamino group cannot form hydrogen bonds, and the methyl groups will cause steric repulsion. Therefore the dimethyl maleate will attack from the bottom face of **C2**-**1a**,

[†] Dalian Institute of Chemical Physics.
[‡] Shanghai Institute of Organic Chemistry.

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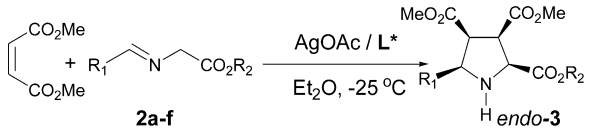
Table 2. AgOAc-Catalyzed Asymmetric Cycloaddition[a]



entry	R_1/R_2 in **2**	ligand	yield[b]/**3**	ee (%)[c]
1	Ph/Me (**2b**)	**1d**	95 (**3b**)	90
2	Ph/Me (**2b**)	**1c**	96 (**3b**)	−85
3	*p*-anisyl/Me (**2c**)	**1d**	93 (**3c**)	90
4	*p*-anisyl/Me (**2c**)	**1c**	98 (**3c**)	−87
5	4-chlorophenyl/Me (**2d**)	**1d**	96 (**3d**)	88
6	4-chlorophenyl/Me (**2d**)	**1c**	91 (**3d**)	−91
7	*o*-toluyl/Me (**2e**)	**1d**	95 (**3e**)	88
8	*o*-toluyl/Me (**2e**)	**1c**	95 (**3e**)	−85
9	2-naphthyl/Me (**2f**)	**1d**	98 (**3f**)	91
10	2-naphthyl/Me (**2f**)	**1c**	91 (**3f**)	−87
11[d]	Ph/Me (**2b**)	**1d**	90 (**3g**)	97
12[d]	Ph/Me (**2b**)	**1c**	90 (**3g**)	−78
13[d]	*o*-toluyl/Me (**2e**)	**1d**	96 (**3h**)	94
14[d]	*o*-toluyl/Me (**2e**)	**1c**	89 (**3h**)	−79
15[e]	Ph/Me (**2b**)	**1d**	98 (**3i**)	36
16[e]	Ph/Me (**2b**)	**1c**	98 (**3i**)	−92

[a] Conditions: iminoesters **2** (1.0 equiv), dimethyl maleate (1.5 equiv), AgOAc (3 mol %), ligand (3.3 mol %), concentration = 0.12 M, at −25 °C. [b] Isolated yields. [c] Determined by HPLC. [d] *t*-Butylacrylate was used. [e] *N*-phenylmaleimide was used.

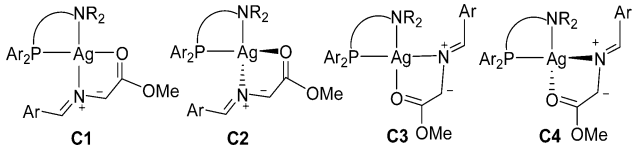


Figure 2. The four types of complexes formed by **2b** and Ag-**1a**/**1b**.

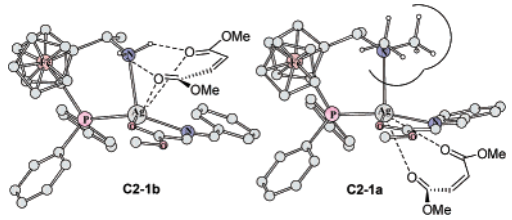


Figure 3. The optimized structures of **C2-1b** and **C2-1a**. The hydrogen atoms that are not involved in the reactions are omitted for clarity. Calculated at B3LYP/6-31*/Lanl2DZ level.

hence, the enantioselectivity is reversed. According to the above model, addition of competitive hydrogen-bond donors should destroy the hydrogen binding, decrease of enantioselectivity should be observed, and so, cycloaddition of **2a** and dimethyl maleate was performed using AgOAc-**1b** as catalyst in the presence of additives (*t*-amyl alcohol, EtOH) at 0 °C, enantioselectivity was decreased to 79% and 78% from 83%.[14]

^{1}H NMR titration experiments and Job's method were employed to probe the hydrogen binding between the complex AgOAc-**1b** and dimethyl maleate. A significant change of the N−H chemical shift was observed, and an approximate 1:1 complex was indicated.[14]

In summary, a successful stereochemical reversal was achieved in AgOAc catalyzed [3+2] cycloaddition of azomethine ylides by the formation of hydrogen bonding between ligand and reactant. Density-functional theory studies proposed a reasonable mechanism of the reversal of the enantioselectivity. The strategy may provide some useful hints for ligand design.

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Supporting Information Available: Spectroscopic data, experimental details, computational methods, and complete ref 12. This material is available free of charge via the Internet at http://pubs.acs.org.

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