Bifunctional AgOAc-catalyzed asymmetric reactions

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The discovery and progress of new bifunctional AgOAc-based catalysts for asymmetric reactions is described. In this bifunctional procedure, AgOAc acts as an efficient Lewis acid catalyst as well as a base through the deprotonation of active hydrogen promoted by acetate. The bifunctional strategy offers a great opportunity to establish new fundamentals for stereoselective construction of C–C as well as C–N bonds.

1. Introduction

Over the past decade, a variety of asymmetric catalysts have been developed and successfully employed in asymmetric catalysis. However, the reactivity and selectivity of most artificial catalysts are still far from satisfactory for practical application. Therefore, many bifunctional catalyst systems have been developed to improve the reaction efficiency and selectivity based on the mechanism of enzyme catalysis.[1] The common definition of bifunctional catalyst in chemistry is a catalyst that contains two functional sites, and is capable of activating two components of a chemical reaction simultaneously. By far, the design of bifunctional catalyst systems was mainly focused on the modification of chiral ligands which required difficult chemical transformation sometimes, heterobimetalic catalysts, some organocatalysts with two different functional groups.[1] Thus, developing a conceptually new bifunctional catalyst system readily realized will be a promising strategy for asymmetric synthesis.

Chiral Lewis acids have emerged as powerful catalysts used in asymmetric synthesis which produce optically active products from achiral starting materials. Nonetheless, for many reactions catalyzed by transition metal complexes, a catalytic or stoichiometric amount of base is usually crucial for achieving full conversion. As far as we know, the counterion accompanying a charged transition metal complex is basic (Fig. 1). When the basicity of the counterion is comparable to the extra base employed in the reaction to facilitate the deprotonation of active hydrogen, the presence of base is not necessary for realizing the catalytic cycle and the metal complex will act as a bifunctional catalyst. Silver acetate bearing a moderate Lewis acidity and basicity is an appealing choice for the realization of this strategy.[2]

In this feature article, we will mainly discuss the recent development and application of asymmetric reactions catalyzed by chiral bifunctional AgOAc complexes.

2. Bifunctional AgOAc-catalyzed asymmetric reactions

2.1 Asymmetric [3 + 2] cycloaddition of azomethine ylides

The cycloaddition of azomethine ylides with electronic-deficient olefins provides an efficient method for synthesizing highly substituted pyrrolidines, which are key chiral building blocks found in various natural products and pharmaceutically important compounds.[2,3] In previous work, the formation of optically active pyrrolidines was mainly induced by chiral auxiliaries.[4] The first truly catalytic asymmetric cycloaddition of azomethine ylides reaction was reported by

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Duo-Sheng Wang was born in 1982 in Hunan province, China. He obtained his BS degree in 2006 from Shanxi University, and subsequently joined Dalian Institute of Chemical Physics, Chinese Academy of Sciences, under the supervision of Prof. Zhou. His PhD research is focused on mechanism elucidation and asymmetric hydrogenation of heteroaromatic compounds.

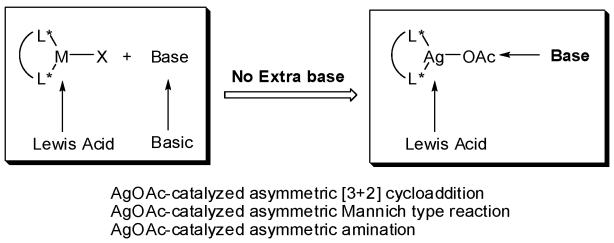
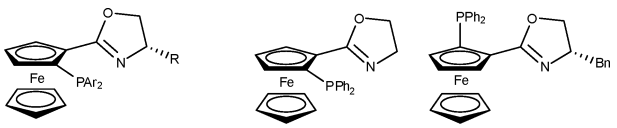


Fig. 1 Bifunctional AgOAc Catalyst.



(S,S_P)-**L1a**: Ar = Ph, R = *i*-Pr
(S,S_P)-**L1b**: Ar = Ph, R = Bn
(S,S_P)-**L1c**: Ar = 4-$CF_3C_6H_4$, R = *i*-Pr
(S,S_P)-**L1d**: Ar = 4-$CF_3C_6H_4$, R = Bn

(S_P)-**L1e**

(S,R_P)-**L1b**

Fig. 2 Some ligands used in this text.

Zhang and co-workers in 2002.[5] Endo products with ee's as high as 97% were obtained for various azomethine ylides using AgOAc/FAP/*i*-Pr_2NEt as the catalyst system. Subsequently, a variety of Lewis acids such as Ag(I), Cu(I), Cu(II) and Zn(II) complexes have been proved to be excellent catalyst precursors for the asymmetric 1,3-dipolar cycloaddition.[2,3]

The generally accepted mechanism for the cycloaddition of azomethine ylides is shown in Scheme 1.[5a,6] In the first step, the iminoester is activated by chiral Ag(I) or other metal complexes, and then undergoes deprotonation through base to form the reactive metal–bound azomethine ylide dipole. This intermediate will react with dipolarophiles, followed by elimination of the cycloadduct to regenerate the chiral catalyst. So, for the above catalyst systems, the addition of external base is necessary for this asymmetric transformation.

By carefully analyzing the above mechanism, we assume that the presence of extra base is not essential for AgOAc-catalyzed cycloaddition of azomethine ylide owing to fact that the deprotonation of iminoesters to generate the azomethine

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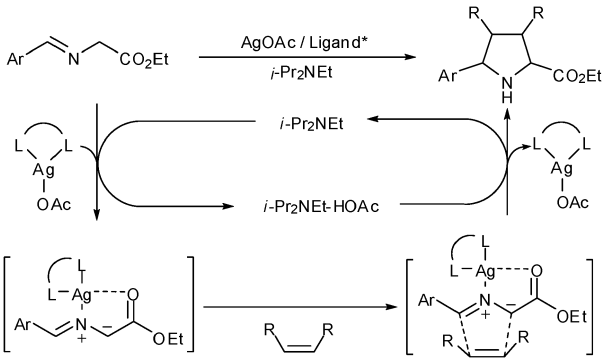
Yong-Gui Zhou was born in 1970 in Hubei Province, China, received his PhD from Shanghai Institute of Organic Chemistry in 1999, working under the direction of Profs. Li-Xin Dai and Xue-Long Hou. He joined Xumu Zhang's group at the Pennsylvania State University as a post-doctoral fellow that same year, and in 2002 he began his independent research career at the Dalian Institute of Chemical Physics, Chinese Academy of Sciences, where currently he is Professor of Chemistry. His research interests include the development of catalytic asymmetric reactions, mechanistic elucidation, and asymmetric synthesis.

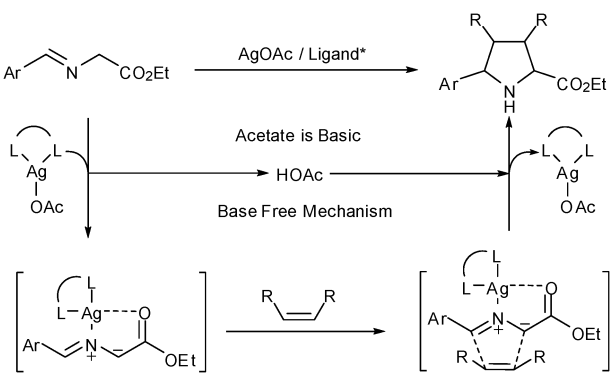


Scheme 1 Mechanism of AgOAc-catalyzed 1,3-dipolar cycloaddition.

ylide could be promoted by acetate which bears a moderate basicity (Scheme 2).[7]

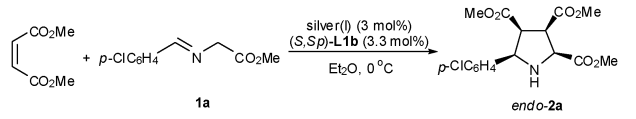
At the outset of our experimental work, the cycloaddition of **1a** with dimethyl maleate could be efficiently catalyzed by AgOAc/**L1a** in toluene with high activity and moderate enantioselectivity (68% ee) without addition of extra base and gave only the *endo* diasteromer. Ligand (S,R_P)-**L1b** with the same central chirality and opposite planar chirality to (S,S_P)-**L1b** was used in this reaction to investigate the effect of planar chirality on enantioselectivity and absolute configuration of the products resulting in opposite absolute configuration and lower enantioselectivity (−78% *vs.* 88% ee). The difference in ee's observed most likely arose from the mismatched nature of the planar chirality with the central chirality of the ligand (Fig. 2).

The role of counterions accompanying the silver was then studied in the cycloaddition of iminoester **1a** with dimethyl maleate using Ag(I)/(S,S_P)-**L1b**/Et_2O system at 0 °C (Table 1). Similar activities and enantioselectivities were achieved when AgOCOPh or silver 4-cyclohexylbutyrate was used as a catalyst precursor, whose anions have similar basicity with acetate (entries 2 and 3). The activity decreased dramatically when using $AgOCOCF_2CF_2CF_3$ as a catalyst precursor probably due to its anion's weak basicity (entry 4). No cyclo-addition adduct was observed under the same condition when AgOTf was used as the metal precursor in the absence of extra base (entry 5). Only 48% yield was obtained even if 10 mol% of (*i*-Pr)$_2$NEt was added (entry 6). According to the above results, it can be inferred that AgOAc is an efficient Lewis acid catalyst



Scheme 2 Base–free mechanism of AgOAc-catalyzed cycloaddition.

Table 1 The effect of silver precursors on enantioselectivity and conversion of cycloaddition of **1a** with dimethyl maleate



1a endo-2a

Entry	Silver(I)	Time/h	Yield (%)	Ee (%)
1	AgOAc	3	93	88
2	AgOCOPh	2	95	89
3	c-$C_6H_{11}(CH_2)_3CO_2Ag$	2	94	87
4	$AgOCOCF_2CF_2CF_3$	24	35	94
5	AgOTf	20	<5	—
6[a]	AgOTf	20	48	91

[a] 10 mol% of i-Pr_2NEt was added.

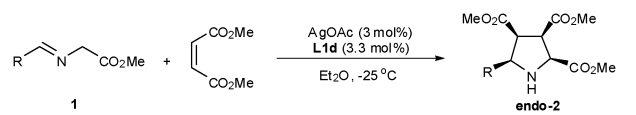
bearing proper basicity and acts as a bifunctional role in this reaction.

The influence of electronic property of substituents of phosphorus in ligand (S,S_P)-**L1b** was also investigated. An improvement in enantioselectivity was obtained when ligand **L1d** bearing a strong electron-withdrawing trifluoromethyl at the *para* position of phenyl ring was used.

Under the optimized conditions, the scope of the AgOAc/**L1d**/Et_2O catalyzed [3 + 2] azomethine ylides cycloaddition was explored (Table 2). In general, α-(arylimino)esters were cyclized in good yields and excellent enantioselectivities (93–98% ee) regardless of the electronic property and steric hindrance of the phenyl ring (entries 1–10). α-(Alkylimino)ester was less reactive, requiring prolonged reaction time and giving cycloaddition product with slightly lower enantioselectivity (entry 11).

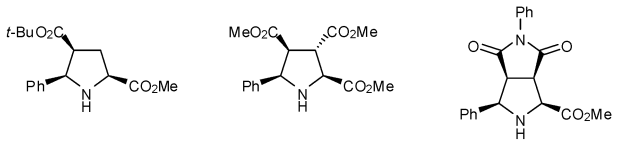
High isolated yields and good enantioselectivities were also obtained for the cycloaddition of α-(phenylimino)ester with other dipolarophiles (Fig. 3). Minor *exo* adducts (*endo*/*exo* = 93/7) were observed when dimethyl fumarate was used as the dipolarophile. For *N*-phenylmaleimide, a fused bicyclic pyrrolidine containing four continuous stereocenters was obtained with excellent enantioselectivity (93% ee) under the optimized condition.

Table 2 AgOAc catalyzed asymmetric cycloaddition of **1** with dimethyl maleate



1 endo-2

Entry	R in **1**	Time/h	Yield (%)	Ee (%)
1	Ph	3	85	97
2	*p*-Anisyl	3	94	98
3	4-Chlorophenyl	3	99	97
4	4-Fluorophenyl	3	96	97
5	4-Cyanophenyl	3	91	97
6	2-Chlorophenyl	3	98	97
7	*o*-Toluyl	3	99	98
8	1-Naphthyl	3.5	85	98
9	2-Naphthyl	3	95	98
10	3-Pyridyl	3.5	76	93
11	*i*-Pr	20	56	88



97% yield
88% ee

96% yield (*endo*/*exo* = 93/7)
89% ee (*endo*)

98% yield
93% ee

Fig. 3 Cycloaddition of α-(phenylimino)ester with other dipolarophiles catalyzed by AgOAc/**L1d**.

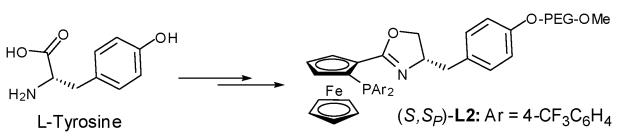
Recently, separation and recycling of the expensive chiral catalysts utilizing soluble PEG (polyethylene glycol) polymer supports have attracted a great of interest.[8] The prominent advantage of PEG-immobilized chiral catalysts lies in that they are soluble in organic solvents, thereby allowing the reaction to proceed homogeneously and display similar activities and enantioselectivities to those of the homogeneous parent systems. The recovery of the PEG-supported catalyst from the reaction mixture can be readily achieved by filtration, precipitation or extraction.

In 2008, our group had prepared a series of tunable axial chiral MeO-PEG-supported bisphosphine ligands and successfully applied them to asymmetric hydrogenation of quinolines with up to 92% ee.[9] Inspired by this achievement, we synthesized PEG-supported ferrocenyl-oxazoline ligands from L-tyrosine and investigated their activities and recovery in the asymmetric [3 + 2] cycloaddition (Scheme 3).[10]

The iminoesters **1** reacted smoothly with *N*-phenyl maleimide in high yields and excellent enantioselectivities (90–98% ee) (*endo*:*exo* > 20 : 1) with AgOAc/**L2** at room temperature. The catalytic activities and enantioselectivities were similar to the homogeneous parent systems (Table 3 and Fig. 3).

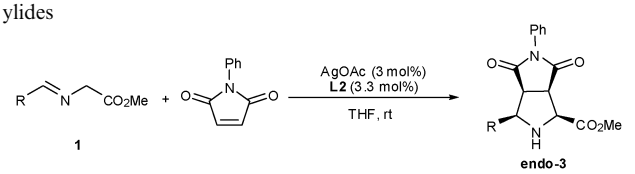
The recyclability of the Ag complex of the PEG-(1900)-supported ligand **L2** was investigated in the cycloaddition of iminoester **1a** with *N*-phenylmaleimide in THF at room temperature (Table 4). After each iteration, elimination of the solvent and repeated washings of the catalyst with Et_2O, until no product was tested, under a rigorously inert atmosphere allowed the catalyst to be recovered and reused in the next run without the need for further additions of silver acetate. The catalyst was reused five times with retention of reactivity and enantioselectivity (98–95% ee, entries 1–5). But when the catalyst was used for the sixth time, the activity and enantioselectivity were reduced probably because of catalyst loss or deactivation (entry 6).

In 2005, Carretero and coworkers demonstrated that Cu(I)-Fesulfos catalyst system showed excellent performance in enantioselective 1,3-dipolar cycloaddition of azomethine ylides with *N*-phenylmaleimide.[11] However, bad *endo*/*exo* selectivity was achieved when the dipolarophile was changed to dimethyl maleate (*endo*/*exo* 67/33). Thus, we prepared a series of ferrocene derived chiral P,S ligands from the commercially available *N*,*N*-dimethyl-(*S*)-α-ferrocenyl ethylamine



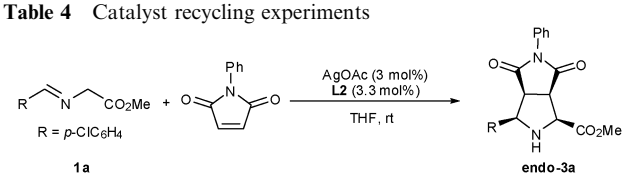
Scheme 3 Synthesis of chiral P,N-ligands with PEG chain.

Table 3 Enantioselective 1,3-dipolar cycloaddition of azomethine ylides



Entry	R in **1**	Time/h	Yield (%)	Ee (%)
1	4-Chlorophenyl	2	95	98
2	Ph	2	90	92
3	*p*-Toluyl	4	84	95
4	4-Fluorophenyl	2	93	92
5	*o*-Toluyl	4	86	94
6	2-Chlorophenyl	4	92	90

Table 4 Catalyst recycling experiments

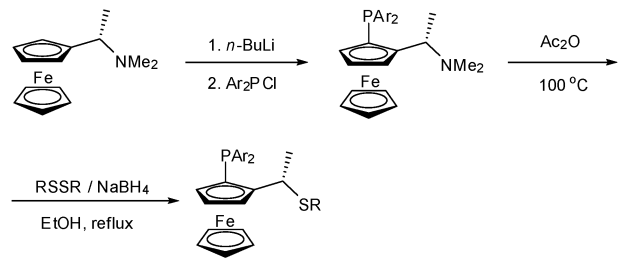


Cycle	Time/h	Yield (%)	Ee (%)
1	4	92	98
2	4	88	95
3	6	92	95
4	6	86	96
5	8	85	95
6	12	74	81

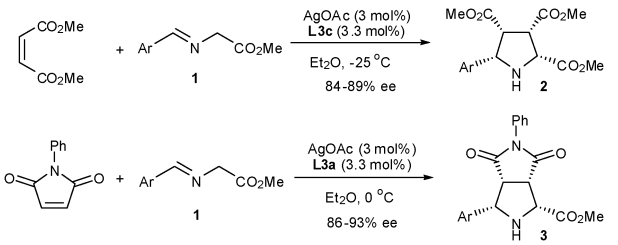
(Scheme 4). The combination of AgOAc and these ferrocene derived P,S-heterodonor ligands resulted in a highly reactive catalyst system, displaying excellent diastereoselectivities and enantioselectivities in the asymmetric 1,3-dipolar cycloaddition of azomethine ylides. [12]

L3a–3c all facilitated the cycloaddition of azomethine ylides and dimethyl maleate smoothly with high *endo* selectivity (*endo*/*exo* > 95/5) (Scheme 5). The best enantioselectivity was obtained when **L3c** was used. Higher enantioselectivities were achieved in the asymmetric cycloaddition of iminoesters **1** and *N*-phenylmaleimide with exclusively *endo*-selectivity using AgOAc/**L3a** as the catalyst.

In 2007, we presented a hydrogen-bond directed reversal of enantioselectivity in the cycloaddition of azomethine ylides employing chiral ferrocene-derived P,N-ligand/AgOAc



Scheme 4 Synthesis of ferrocene derived chiral P,S-ligands.



Scheme 5 AgOAc/**L3** catalyzed asymmetric [3 + 2] cycloaddition.

complexes.[13] We properly designed a series of ligands to regulate the formation of hydrogen bonds between substrates and catalysts by introducing different substituents on the *N* atom of the ligand.

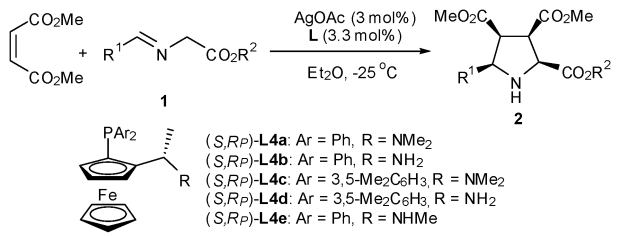
The asymmetric cycloaddition of azomethine ylides with dimethyl maleate proceeded smoothly in the presence of AgOAc/**L4a** in Et_2O and gave only *endo* cycloaddition product with moderate enantioselectivity (−76% ee). The significant reversal of the absolute configuration was realized when ligand **L4c** and **L4d** were used (Table 5). This catalytic asymmetric reaction has a broad substrate generality with respect to activity and enantioselectivity. All reactions went to completion within 4 h in high isolated yields (89–98%). Reversal of the absolute configuration was observed in the reactions of various iminoesters **1** and dimethyl maleate regardless of the steric hindrance or electronic properties of the benzene ring of iminoesters **1** (entries 1–10). Other dipolarophiles such as *tert*-butylacrylate and *N*-phenylmaleimide were also tested resulting in successful reversal of the enantioselectivity (entries 11–16).

The variation of reaction transition states is responsible for the inversion of enantioselectivity in the asymmetric 1,3-dipolar cycloaddition reaction as shown in Fig. 4. Both substrates **SM1** and **SM2** coordinate with the central metal Ag (I) in the transition state **A** which commonly occurs in the general case. But in the transition state **B**, **SM2** coordinates with the central metal Ag (I), while the other substrate **SM1** has an interaction with NH_2 of the ligand owing to the strong hydrogen bonding. Therefore, different enantiofacial attack is afforded and results in the hydrogen-bond directed reversal of enantioselectivity.

The computational study confirmed the above discussion. As shown in Fig. 5, the complexes formed by **1b** and Ag-**L4a**/**L4b** have four possible types of structure (**C1** to **C4**). The results show that the most stable complexes for both **L4a** and **L4b** are **C2** type.

The optimized structures of **C2-L4b** and **C2-L4a** were calculated at B3LYP/6-31*/Lanl2DZ level (Fig. 6). A large space exists at both sides of the iminoester in **C2-L4b**. Thus, the two carbonyl groups of the dimethyl maleate can coordinate with the Ag center. Furthermore, the negatively charged oxygen atom in the possible zwitterionic intermediate can be stabilized by the double hydrogen bond between dimethyl maleate and the NH_2 group at the ligand. This indicates that it is favorable for **C2-L4b** to be attacked from the top face. While in **C2-L4a**, the dimethylamino group cannot form hydrogen bonds, and the methyl groups will cause steric repulsion. Therefore the dimethyl maleate will

Table 5 Hydrogen-bonding directed reversal of enantioselectivity



Entry	R_1, R_2 in **1**	Ligand	Yield (%)	Ee (%)
1	Ph/Me (**1b**)	**L4d**	95	90
2	Ph/Me	**L4c**	96	−85
3	*p*-Anisyl/Me	**L4d**	93	90
4	*p*-Anisyl/Me	**L4c**	98	−87
5	4-Chlorophenyl/Me	**L4d**	96	88
6	4-Chlorophenyl/Me	**L4c**	91	−91
7	*o*-Toluyl/Me	**L4d**	95	88
8	*o*-Toluyl/Me	**L4c**	95	−85
9	2-Naphthyl/Me	**L4d**	98	91
10	2-Naphthyl/Me	**L4c**	91	−87
11[a]	Ph/Me	**L4d**	90	97
12[a]	Ph/Me	**L4c**	90	−78
13[a]	*o*-Toluyl/Me	**L4d**	96	94
14[a]	*o*-Toluyl/Me	**L4c**	89	−79
15[b]	Ph/Me	**L4d**	98	36
16[b]	Ph/Me	**L4c**	98	−92

[a] *t*-Butylacrylate was used. [b] *N*-phenylmaleimide was used.

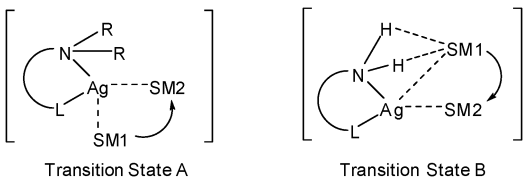


Fig. 4 Proposed variation of transition states.

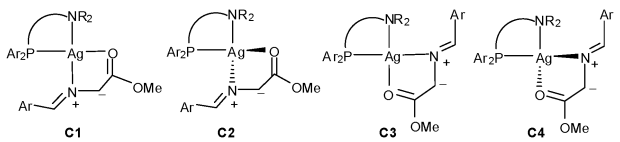


Fig. 5 The four types of complexes formed by **1b** and Ag-**L4a**/**L4b**.

attack from the bottom face of **C2-L4a**; hence, the enantioselectivity is reversed. Based on the above model, the hydrogen binding addition will be weakened by addition of competitive hydrogen-bond donors. In the presence of additives (*t*-Amyl alcohol, EtOH), the enantioselectivity of cycloaddition of **L4a** and dimethyl maleate was decreased to 79% and 78% from 83% using AgOAc-**L4b** as catalyst at 0 °C. These results provided additional evidence to support the hydrogen-bond directed asymmetric induction.

^{1}H-NMR titration experiments and Job's method were employed to probe the hydrogen binding between the complex AgOAc-**L4b** and dimethyl maleate. The significant change of N–H chemical shift indicated a formation of ~1 : 1 complex during the catalytic procedure.

The inversion of enantioselectivity of asymmetric cycloaddition of azomethine ylides could also be obtained through

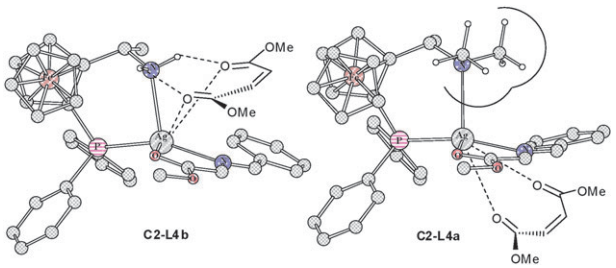


Fig. 6 The optimized structures of **C2-L4b** and **C2-L4a**. The hydrogen atoms that are not involved in the reactions are omitted for clarity. Calculated at B3LYP/6-31*/Lanl2DZ level.

variation of the metal precursors. Recently, Oh and co-workers reported the reversal of enantioselectivity between the copper(I)- and silver(I)-catalyzed 1,3-dipolar cycloaddition reactions using a brucine-derived amino alcohol ligand **L5** (Table 6).[14] Copper(I) and silver(I) salts were chosen as the model catalyst owing to their distinctive ionic radii and impressive versatilities in catalytic cycloaddition of azomethine ylides. Under the optimized conditions, good to excellent inversion of the enantioselectivities were obtained in the asymmetric cycloaddition of iminoesters **1** and *tert*-butyl acrylate using Cu/**L5** or Ag/**L5** as the catalyst system, respectively. It is noteworthy that addition of extra base was not good for improving the activity or enantioselectivity in the presence of silver acetate which acts as a bifunctional catalyst in the cycloaddition addition.

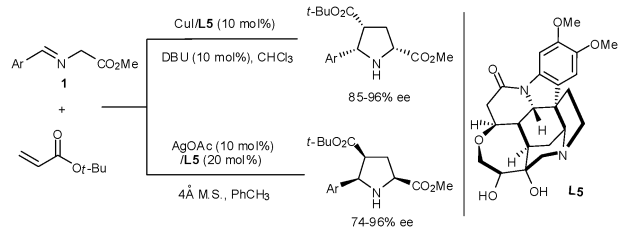
With regard to the mechanism, the pronounced difference in ionic radii of copper(I) and silver(I) may be responsible for the reversal of enantioselectivity through different binding modes among ligand, metal and substrate in the transition state. The existence of two hydroxy groups proximal to the tertiary amine moiety leading to **L5** displayed different binding modes with copper(I) salt and silver(I) salt which have different ionic radii (Fig. 7).

The variation of metal precursor will also result in the improvement of enantioselectivity in the asymmetric 1,3-dipolar cycloaddition. In 2008, Wang group demonstrated that CuI/**L6** complex exhibited excellent enantioselectivity in asymmetric 1,3-dipolar cycloaddition of various azomethine ylides with several dipolarophiles such as dimethyl maleate, methyl and *tert*-butyl acrylate.[15] However, the enantioselectivity decreased dramatically when *N*-phenyl maleimide was used as the dipolarophile. After screening various metal precursors, the same group found AgOAc/TF-BiphamPhos (**L6**) served as a highly efficient catalyst for the asymmetric 1,3-dipolar cycloaddition in the absence of additional base (Scheme 6).[16]

It is notable that the catalyst system also facilitated the asymmetric addition of more sterically hindered azomethine ylides derived from α-substituted α-amino acids with high yields and excellent enantioselectivities (91–98% ee) in despite of the position and electronic property of the substituents on the aromatic ring, affording the corresponding *endo* products exclusively (Table 7).

The asymmetric cycloaddition of azomethine ylides with electronic-deficient olefins catalyzed by bifunctional AgOAc could be well performed in intramolecular. In 2005, Pfaltz

Table 6 Inversion of enantioselectivity caused by variation of metal precursors



Entry	Ar in **1**	Metal	Yield (%)	Ee (%)
1	Ph	Cu^{I}	98	95
2	Ph	Ag^{I}	79	74
3	*p*-Tolyl	Cu^{I}	75	96
4	*p*-Tolyl	Ag^{I}	75	75
5	*p*-ClC_6H_4	Cu^{I}	60	92
6	*p*-ClC_6H_4	Ag^{I}	94	82
7	*p*-Anisyl	Cu^{I}	82	96
8	*p*-Anisyl	Ag^{I}	72	75
9	*o*-Tolyl	Cu^{I}	70	85
10	*o*-Tolyl	Ag^{I}	81	80
11	*m*-ClC_6H_4	Cu^{I}	65	86
12	*m*-ClC_6H_4	Ag^{I}	65	78
13	1-Naphthyl	Cu^{I}	92	92
14	1-Naphthyl	Ag^{I}	86	90
15	2-Naphthyl	Cu^{I}	84	96
16	2-Naphthyl	Ag^{I}	77	96
17	2-Furyl	Cu^{I}	80	85
18	2-Furyl	Ag^{I}	71	77
19	2-Thienyl	Cu^{I}	64	88
20	2-Thienyl	Ag^{I}	74	83

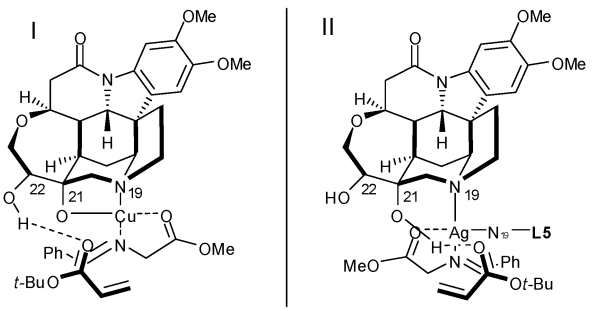
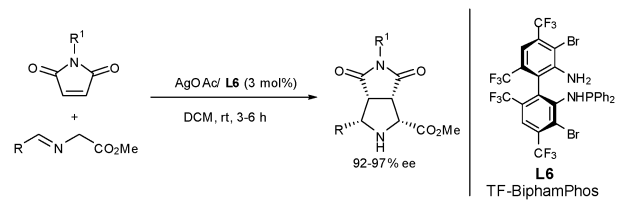


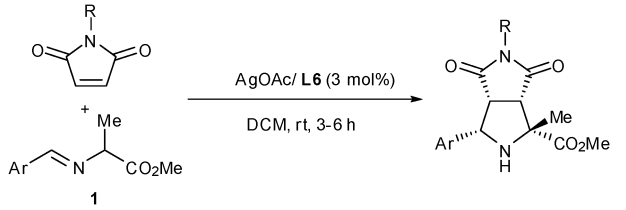
Fig. 7 Proposed binding models for catalyst systems. (a) Binding mode I for the smaller Cu metal center. (b) Binding mode II for Ag metal center.



Scheme 6 AgOAc/**L6** catalyzed asymmetric [3 + 2] cycloaddition.

reported that chiral Ag(I)-PHOX complexes were efficient catalysts for intramolecular cycloadditions of azomethine ylides and α,β-unsaturated carboxylic esters with good yield, excellent diastereoselectivity (*dr* > 95/5) and up to 99% ee (Scheme 7).[17]

Table 7 AgOAc-catalyzed symmetric 1,3-dipolar cycloaddition of azomethine ylides derived from α-substituted-α-amino acids



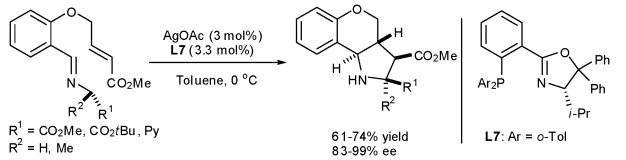
Entry	Ar in **1**	*R*	Yield (%)	Ee (%)
1	Ph	Me	95	98
2	4-$MeOC_6H_4$	Me	92	95
3	4-MeC_6H_4	Me	83	97
4	2-MeC_6H_4	Me	99	97
5	4-ClC_6H_4	Me	87	97
6	2-ClC_6H_4	Me	99	96
7	3-ClC_6H_4	Me	99	95
8	4-BrC_6H_4	Me	97	97
9	4-FC_6H_4	Me	90	98
10	2-Furyl	Me	99	96
11	3-ClC_6H_4	Ph	92	96

2.2 Asymmetric Mannich reaction

Over the past decade, the catalytic asymmetric Mannich reaction[18] has been widely investigated based on either organometallic complexes or organocatalysts and received considerable attention as a valuable synthetic method for the preparation of optically active β-amino carbonyl compounds and their derivatives,[19] which are important synthetic intermediates for the synthesis of drugs and biologically active compounds. Recently, Hoveyda and Snapper groups have reported several enantioselective Mannich reactions catalyzed by amino acid derived phosphine-Ag(I) catalyst system.[20] However, the use of silyl enol ethers as nucleophilic reagents is not ideal from the standpoint of atom-economy. In 2009, we developed a bifunctional AgOAc-catalyzed atom economic direct Mannich reaction of acetyl acetone and *N*-Boc-protected arylimines with up to 91% ee.[21]

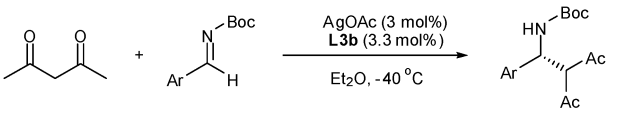
Generally, AgOAc/**L3b** displayed as a highly effective catalyst for the nucleophilic addition of acetyl acetone to *N*-Boc arylimines[22] with high isolated yields and good enantioselectivities regardless of the electronic property and steric hindrance of the phenyl ring of aldimines **4** (Table 8, entries 1–7). For heteroaromatic aldimine **4h**, a slightly lower enantioselectivity was observed (entry 8).

This protocol could be generally applied to some other β-dicarbonyl compounds (Scheme 8). High isolated yields (86 and 90%) and good enantioselectivities (78% ee) were obtained for both malonate and β-ketoester. The low diastereoselectivity (*dr* 2 : 1) obtained in the asymmetric Mannich reaction between β-ketoester and aldimine **4b** is probably attributable to epimerization.



Scheme 7 AgOAc-catalyzed intramolecular [3 + 2] cycloaddition.

Table 8 AgOAc-catalyzed asymmetric Mannich reaction between acetyl acetone and *N*-Boc arylimines



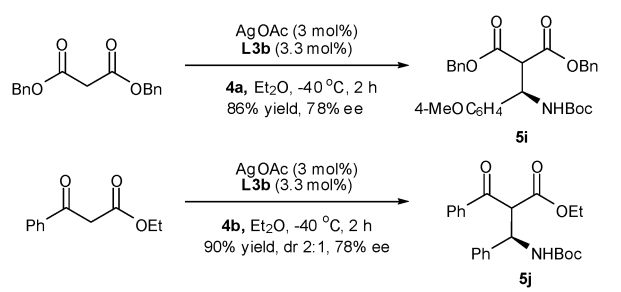
4 5

Entry	Ar in **4**	Time/h	Yield (%)	Ee (%)
1	4-$MeOC_6H_4$ (**4a**)	0.5	92 (**5a**)	88
2	Ph (**4b**)	3	67 (**5b**)	86
3	4-MeC_6H_4 (**4c**)	3	82 (**5c**)	88
4	4-FC_6H_4 (**4d**)	1	99 (**5d**)	91
5	4-BrC_6H_4 (**4e**)	2.5	81 (**5e**)	90
6	2-MeC_6H_4 (**4f**)	3	86 (**5f**)	88
7	1-Naphthyl (**4g**)	5	95 (**5g**)	88
8	2-Furyl (**4h**)	5	88 (**5h**)	80

The bifunctional AgOAc-catalyzed Mannich reaction is also applicable to the asymmetric addition of glycine Schiff base **6a** to *N*-Ts imine **7** (Table 9).[21,23] Aromatic imines with both electron-donating and electron-withdrawing groups at different positions were well tolerated in terms of the activities and enantioselectivities (entries 1–5). However, low diastereoselectivites were observed in this condition. To our delight, a significant improvement of diastereoselectivities (*syn*/*anti* up to 93/7) was observed when aliphatic imines were used (entries 6 and 7).

The asymmetric vinylogous Mannich reaction (AVM), as a variant of the Mannich reaction, has attracted increasing attention owing to its ability to directly deliver complicated and highly functionalized δ-amino compounds.[24] Recently, α,α-dicyanoolefins have been demonstrated as successful vinylogous nucleophiles in asymmetric organic synthesis, such as Mannich and Michael reactions.[25] As part of ongoing studies in our group toward bifunctional AgOAc-catalyzed enantioselective Mannich reactions, we disclosed an enantioselective vinylogous Mannich reaction catalyzed by bifunctional AgOAc employing α,α-dicyanoolefin as the vinylogous donor.[21]

As summarized in Table 10, the aldimines **4** could react smoothly with a variety of α,α-dicyanoolefins in good yields and excellent diastereoselectivities, though with moderate enantioselectivities. The α,α-dicyanoolefin **9a** emerged as the best scaffold for this AVM reaction. The enantioselectivity of this AVM was sensitive to both the steric and electronic properties of the substituents on the phenyl ring of aldimines **4**. Generally, aldimines **4** bearing electron-donating groups at the *para* position of phenyl ring gave a higher ee compared to those having electron-withdrawing groups (entries 5–7).



Scheme 8 AgOAc-catalyzed asymmetric Mannich reactions.

The reaction of α,α-dicyanoolefin **9a** with aldimine **4a** proceeded well and gave the best selectivity (82% ee, dr > 95/5, entry 5). The existence of an *ortho* substituent on aldimine compromised the enantioselectivity but neither the yield nor diastereoselectivity (entry 8). It is noteworthy that this is the first example of metal-based asymmetric catalysis employing α,α-dicyanoolefins as vinylogous nucleophiles.

2.3 Asymmetric amination reaction

The electrophilic amination reaction is a direct and efficient method to stereoselectively construct the C–N bond which is the important fundamental process in organic chemistry and biochemistry. Accordingly, much progress has been achieved in the enantioselective α-amination of aldehydes, ketones, α-keto esters, β-keto esters, α-cyano esters and other compounds using azodicarboxylates as the nitrogen source since the pioneering work of Evans in 1997.[26] Recently, We developed an efficient bifunctional AgOAc-catalyzed enantioselective α-amination of glycine Schiff bases and azodicarboxylates with high yields and up to 98% ee.[27]

The steric property of both substrates is crucial for the enantioselectivity of this reaction (Table 11). With increasing steric hindrance of the substituents in glycine Schiff bases **6**, the stereoselectivity decreased remarkably (from 98% ee to 75% ee) (entries 1–4). In contrast, an improvement of enantioselectivities was observed through increasing the steric hindrance of the substituents in azodicarboxylates **11** (entries 1, 5–7). The best stereoselectivities (98% ee) were obtained in the asymmetric amination reaction of di-*tert*-butyl azodicarboxylate with benzophenone imine glycine methyl ester or ethyl ester (entries 1 and 2).

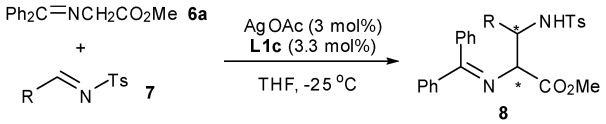
Mechanistically we assume that the first step in the asymmetric amination is the deprotonation of glycine Schiff bases **6** promoted by acetate to generate reactive metal-bound azomethine ylide dipole **A** (Scheme 9). Subsequently, **A** undergoes enantioselective addition to azodicarboxylates **11** that results in the formation of intermediate **B**, which reacts with acetate acid to give the desired amination products **12** as well as regenerate the catalyst.

3. Conclusions

In summary, this feature article has described the recent progress achieved in bifunctional AgOAc-catalyzed asymmetric cycloaddition, Mannich and amination reactions. Extra base is not desirable in the bifunctional catalytic procedure, in which acetate promotes the deprotonation of the active proton. The mild reaction conditions and the simple operation make the predominant advantages of this protocol.

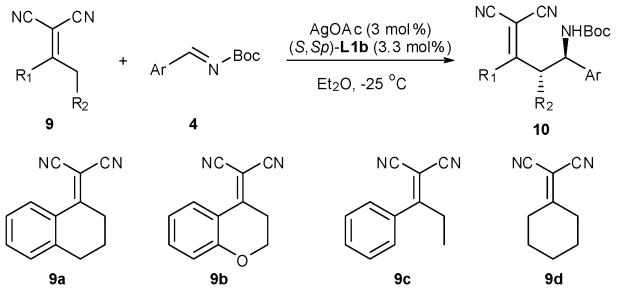
Despite the progress in this field, the reaction type remains limited in asymmetric cycloaddition, Mannich and amination reactions. Thus, further development will be expected in its potential in other asymmetric reaction, such as Michael and Henry reactions. On the other hand, exploration of new bifunctional catalyst systems based on other metal precursor will be another promising strategy.

Table 9 AgOAc-catalyzed asymmetric Mannich reaction of glycine Schiff bases with *N*-Ts aldimines



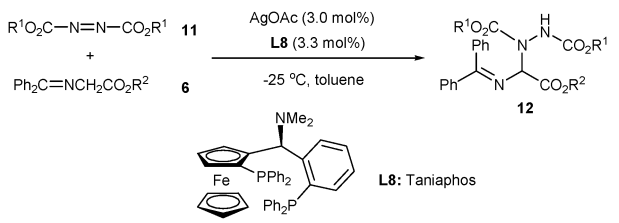
Entry	R in **7**	Yield (%)	Dr (*syn*/*anti*)	Ee (%, *syn*)	Ee (%, *anti*)
1	Ph	93 (**8a**)	44/56	91	96
2	2-BrC_6H_4	97 (**8b**)	39/61	94	97
3	3-ClC_6H_4	92 (**8c**)	51/49	97	95
4	4-$MeOC_6H_4$	98 (**8d**)	48/52	91	82
5	2-Naphthyl	96 (**8e**)	53/47	92	96
6	*i*-Pr	99 (**8f**)	93/7	96	—
7	Cy	97 (**8g**)	90/10	93	91

Table 10 AgOAc-catalyzed asymmetric Mannich reaction of α,α-dicyanoolefins with *N*-Boc aldimines

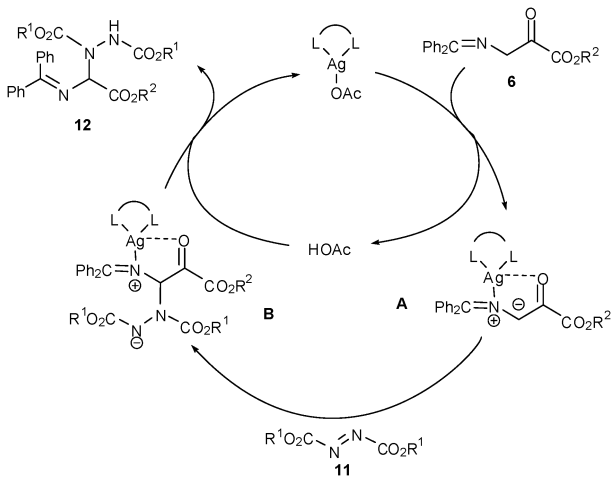


Entry	9	Ar in 4	Time/h	Yield (%)	Dr (*syn*/*anti*)	Ee (%)
1	**9a**	Ph (**4b**)	4	88	93/7	64
2	**9b**	Ph (**4b**)	8	96	>95/5	64
3	**9c**	Ph (**4b**)	30	79	87/13	47
4	**9d**	Ph (**4b**)	23	90	94/6	25
5	**9a**	4-$MeOC_6H_4$ (**4a**)	3	96	>95/5	82
6	**9a**	4-FC_6H_4 (**4d**)	9	91	92/8	70
7	**9a**	4-BrC_6H_4 (**4e**)	21	84	87/13	61
8	**9a**	2-$CH_3C_6H_4$ (**4f**)	4	96	>95/5	59

Table 11 AgOAc-catalyzed asymmetric amination of glycine Schiff bases with azodicarboxylates



Entry	R^1/R^2 in **11** and **6**	Time/h	Yield (%)	Ee (%)
1	*t*-Bu/Me	22	95	98
2	*t*-Bu/Et	21	98	98
3	*t*-Bu/4-$BrC_6H_4CH_2$	6	95	96
4	*t*-Bu/*t*-Bu	51	93	75
5	*i*-Pr/Me	16	98	92
6	Bn/Me	16	98	76
7	Et/Me	21	98	75



Scheme 9 Proposed mechanism for AgOAc-catalyzed asymmetric amination.

Acknowledgements

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