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Chiral Silver Amides as Effective Catalysts for Enantioselective [3+2] Cycloaddition Reactions

Yasuhiro Yamashita, Takaki Imaizumi, Xun-Xiang Guo, and Shū Kobayashi*[a]

Abstract: Asymmetric [3+2] cycloaddition of α-aminoester Schiff bases with substituted olefins is one of the most efficient methods for the preparation of chiral pyrrolidine derivatives in optically pure form. In spite of its potential utility, applicable substrates for this method have been limited to Schiff bases that bear relatively acidic α-hydrogen atoms. Here we report a chiral silver amide complex for asymmetric [3+2] cycloaddition reactions. A silver complex prepared from silver bis(trimethylsilyl)amide (AgHMDS) and (*R*)-DTBM-SEGPHOS worked well in asymmetric [3+2] cycloaddition reactions of α-aminoester Schiff bases with several olefins to afford the corresponding pyrrolidine derivatives in high yields with remarkable *exo*- and enantioselectivities. Furthermore, α-aminophosphonate Schiff bases, which have less acidic α-hydrogen atoms, also reacted with olefins with high *exo*- and enantioselectivities. The stereoselectivities of the [3+2] cycloadditions with maleate and fumarate suggested that the reaction proceeded by means of a concerted mechanism. An NMR spectroscopic study indicated that complexation of AgHMDS with the bisphosphine ligand was not complete, and that free AgHMDS, which did not show any significant catalytic activity, existed in the catalyst solution. This means that significant ligand acceleration occurred in the current reaction system.

Keywords: amides · asymmetric synthesis · cycloaddition · Lewis acids · silver

Introduction

Metal, including metalloid, catalysts (MX) have played key roles in synthetic organic chemistry. While many catalysts based on many metals and metalloids have been developed in this field, acid/base catalysis has been one of the major targets in the past two decades.[1] Among them, Lewis acid catalysis has been of great interest because unique reactivity and selectivities, especially enantioselectivities, have been attained under mild reaction conditions.[2] To pursue higher reactivity and selectivities, a target is stronger Lewis acids, which are prepared by combining more Lewis acidic metals or metalloids with less nucleophilic centers. According to this approach, ligands (counteranions) have evolved from halides to perchlorate, triflate, triflimide, and so on, thus leading to stronger Lewis acids.

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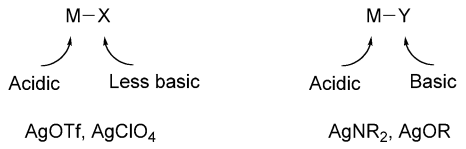
However, strong Lewis acids are sometimes not suitable for catalytic reactions. In Lewis acid catalysis, electrophile/Lewis acid complexes are formed in transition states, and if the complexes are too stable, Lewis acid catalysts might be trapped by electrophiles to suppress the catalyst turnover. Furthermore, atom-economical reactions have recently become desirable from environmental viewpoints in organic transformations, and addition reactions (including cycloaddition) accompanied by proton transfer are preferable.[3] In carbon–carbon bond-forming reactions, proton transfer usually starts from carbanion generation using a catalytic amount of base. In those cases, external bases have often been added in the presence of Lewis acids.[2] We envisioned that if metal or metalloid catalysts with both acidic and basic characters were developed, more efficient catalytic systems would be created.[4] Because a simple catalyst structure is desirable, metal or metalloid catalysts that bear basic ligands (counteranions) such as metal amides or alkoxides are candidates (acid/base catalyst in Scheme 1). However, typical metal amides or alkoxides, such as alkaline metal amides or alkoxides, are too basic. Obviously, the choice of metals or metalloids is a key to achieving this concept.

For such catalysts, we focused on silver bis(trimethylsilyl)amide (AgHMDS). Silver is in group 11 between copper



Scheme 1. Lewis acid catalyst and acid/base catalyst.

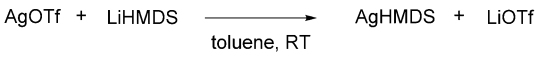
(Cu) and gold (Au). Except for cases that require an exchange of counteranions (AgCl forms in most cases), silver salts have mainly been used as Lewis acid catalysts to activate carbonyls, imines, and carbon–carbon multiple bonds.[5] When silver salts are combined with chiral ligands, excellent asymmetric environments can be created; AgOTf with chiral bidentate ligands such as 2,2′-bis(diphenylphosphino)-1,1′-binaphthyl (BINAP) has been successfully used in asymmetric catalysis.[6] On the other hand, silver species as chiral Brønsted bases are very limited. Until now, chiral silver Brønsted bases have mostly been prepared by silver acetate or the combination of an appropriate silver salt with an external tertiary amine base, which could show high stereoselectivities in some asymmetric reactions; however, activity as a base has been insufficient.[7] Based on this background, we focused on the use of a chiral silver amide, in particular AgHMDS with chiral ligands, as a strong silver base catalyst in asymmetric reactions. If the silver cation worked as an effective Lewis acid and at the same time the amide anion worked as a strong Brønsted base, the silver amide might work as an efficient catalyst even to achieve asymmetric catalysis with appropriate ligands.

Here we describe a detailed study of a chiral silver bis(trimethylsilyl)amide-catalyzed asymmetric [3+2] cycloaddition reaction of Schiff bases of α-amino esters or α-aminophosphonates with olefins. The desired reactions proceeded smoothly to afford the desired cycloadducts in high yields with high diastereo- and enantioselectivities.[8]

Results and Discussion

Preparation of Silver Bis(trimethylsilyl)amide (AgHMDS)

In 1996, Hitchcock, Lappert, and Pierssens reported the synthesis of AgHMDS from silver isocyanate (AgCNO) and dimethyltin di[bis(trimethylsilyl)amide] ($Me_2Sn(HMDS)_2$), and showed that it formed a tetrameric complex in crystals.[9] Since then, however, no report on AgHMDS has appeared that involves catalysis. We anticipated unique catalytic activity of silver amides as mentioned above and tried to prepare AgHMDS. First, we conducted the preparation according to the literature method; however, the starting materials were found to be uncommon. Therefore, we decided to develop a new preparation method for AgHMDS and found that AgHMDS can be readily prepared from AgOTf and LiHMDS (Scheme 2). AgHMDS thus prepared is a colorless powder, is fully characterized, and can be stored at room temperature.[10]



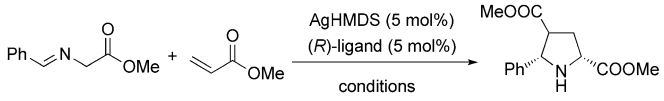
Scheme 2. Preparation of AgHMDSs.

A Chiral Silver Amide-Catalyzed [3+2] Cycloaddition of α-Amino Esters to Olefins

Synthesis of highly substituted pyrrolidine derivatives is very important in bioorganic and medicinal chemistry because they are useful building blocks of biologically active molecules and also sometimes show interesting biological activity.[11] Asymmetric [3+2] cycloaddition of α-aminoester Schiff bases with substituted olefins is one of the most efficient methods for their preparation in optically pure form,[12] thus making it possible to introduce various substituents on the pyrrolidine skeleton stereoselectively. From pioneering work of Grigg et al., chiral catalyst systems based on a combination of chiral metal Lewis acids and tertiary amine bases have been reported, and excellent diastereo- and enantioselectivities have been attained in some cases;[13] however, applicable substrates for this method are still limited. For example, Schiff bases that bear less acidic α-hydrogen atoms cannot be used in this reaction. A new catalyst that allows efficient deprotonation of less acidic α-hydrogen atoms of Schiff bases is desired, and we decided to employ AgHMDS in this reaction.

First, we investigated a [3+2] cycloaddition reaction of the benzaldehyde Schiff base of glycine methyl ester (**1a**) with methyl acrylate (**2a**) in the presence of a chiral complex (10 mol%) prepared from AgHMDS and (*R*)-BINAP (**L1**) in toluene at 30°C. The desired reaction proceeded in 82% yield with moderate enantioselectivities (Table 1, entry 1). In this catalyst system, the *endo* adduct was obtained as the major diastereomer (*endo*/*exo* = 72:18). On the other hand, during our investigation on the ligand structures, interestingly, we found that use of SEGPHOS-type ligands afforded the *exo* adduct preferentially (Table 1, entries 3 and 4); (*R*)-DTBM-SEGPHOS (**L4**) in particular showed high *exo* selectivity (*endo*/*exo* = 4:96) and good enantioselectivity (84% *ee*, Table 1, entry 4). Whereas typical chiral silver catalysts showed *endo* selectivity, it is remarkable that the *exo* product was obtained selectively.[14] With these promising results in hand, we optimized the reaction conditions for further improvement of the selectivities. Although the effect of the ester parts of the substrates was investigated, bulky substrates such as *tert*-butyl acrylate (**2b**) and the Schiff base of glycine *tert*-butyl ester (**1b**) did not give any improved result (Table 1, entries 5 and 6). Even when the reaction was conducted in the presence of 5 mol% of the silver catalyst, the reaction proceeded smoothly in good yield with slight loss of the selectivities (Table 1, entry 7). When the reaction was conducted at 0°C for 24 hours using 5 mol% of the silver catalyst, the desired product was obtained in only 37% yield but with excellent *exo* selectivity and very high enantioselectivity (Table 1, entry 8). Several solvents were then examined, and it was found that a less

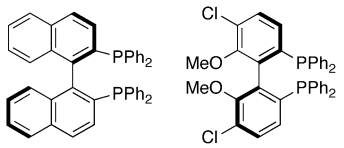
Table 1. Asymmetric [3+2] cycloaddition reaction of glycine Schiff base **1a** with methyl acrylate **2a**.[a]



1a **2a** **3aa**

Entry	(*R*)-**L**	Solvent	*T* [°C]	*t* [h]	Yield [%]	*endo*/*exo*	*ee* [%] (*endo*/*exo*)
1[b]	**L1**	toluene	30	2	82	72:18	45:52
2[b]	**L2**	toluene	30	2	90	40:60	17:30
3[b]	**L3**	toluene	30	2	91	18:82	–:77
4[b]	**L4**	toluene	30	2	90	4:96	–:84
5[b,c]	**L4**	toluene	30	2	92	2:98	–:77
6[b,d]	**L4**	toluene	30	2	89	18:82	–:78
7	**L4**	toluene	30	2	87	9:91	–:79
8	**L4**	toluene	0	24	37	1:99	–:94
9	**L4**	CH_2Cl_2	0	24	34	4:96	–:79
10	**L4**	THF	0	24	38	10:90	–:88
11	**L4**	Et_2O	0	24	40	<1:>99	–:98
12	**L4**	*t*BuOMe	0	24	41	20:80	–:91
13	**L4**	Et_2O	0	72	78	<1:>99	–:98
14	**L4**	Et_2O	10	24	78	8:92	–:95
15[e]	**L4**	Et_2O	0	24	71	<1:>99	–:97
16[f]	**L4**	Et_2O	0	24	91	1:99	–:98
17[f,g]	**L4**	Et_2O	0	48	76	<1:>99	–:97
18[f]	–	Et_2O	0	72	6	>99:<1	–

[a] Asymmetric [3+2] cycloaddition of **1a** with **2a** in the presence of 5 mol% of the catalyst prepared from AgHMDS or AgOTf and KHMDS, and the chiral phosphine ligand at 0.2 M unless otherwise noted. [b] 10 mol% AgHMDS and the ligand were used. [c] *t*Butyl acrylate (**2b**) was used instead of **2a**. [d] The Schiff base of glycine *tert*-butyl ester (**1b**) was used instead of **1a**. [e] 0.4 M. [f] 0.6 M. [g] 1 mol% of the catalyst was used.



(*R*)-BINAP (**L1**) (*R*)-ClMeOBIPHEP (**L2**) Ar = 3,5-$Me_2C_6H_3$: (*R*)-DM-SEGPHOS (**L3**) Ar = 3,5-*t*Bu_2-4-$MeOC_6H_2$: (*R*)-DTBM-SEGPHOS (**L4**)

Table 2. Asymmetric [3+2] cycloaddition of **1** with olefin **2a**.[a]

1 **2a** **3**

Entry	R^1	R^2	**1**	**3**	Yield [%]	*exo*/*endo*	*ee* [%] (*exo*)
1	4-MeC_6H_4	H	**1c**	**3ca**	90	>99:<1	99
2	2-MeC_6H_4	H	**1d**	**3da**	91	>99:<1	99
3	4-$MeOC_6H_4$	H	**1e**	**3ea**	93	>99:<1	98
4	4-FC_6H_4	H	**1f**	**3fa**	82	>99:<1	95
5	4-ClC_6H_4	H	**1g**	**3ga**	86	>99:<1	90
6	4-BrC_6H_4	H	**1h**	**3ha**	88	97:3	92
7	4-$CF_3C_6H_4$	H	**1i**	**3ia**	90	>99:<1	91
8	4-NCC_6H_4	H	**1j**	**3ja**	98	>99:<1	96
9	3-pyridyl	H	**1k**	**3ka**	92	>99:<1	90
10	2-furyl	H	**1l**	**3la**	90	>99:<1	94
11	2-thiophenyl	H	**1m**	**3ma**	88	>99:<1	82
12	1-naphthyl	H	**1n**	**3na**	97	94:6	99
13	2-naphthyl	H	**1o**	**3oa**	96	>99:<1	92
14	cinnamyl	H	**1p**	**3pa**	90	>99:<1	98
15	Ph	Me[b]	**1q**	**3qa**	78	>99:<1	97
16	Ph	*i*Bu[b]	**1r**	**3ra**	87	97:3	94
17	Ph	Bn[b]	**1s**	**3sa**	81	94:6	90
18	*c*C_6H_{11}	H	**1t**	**3ta**	71	>99:<1	97
19	$(CH_3)_2CH$	H	**1u**	**3ua**	43	>99:<1	80
20	$(CH_3)_2CHCH_2$	H	**1v**	**3va**	64	>99:<1	88
21	$PhCH_2CH_2$	H	**1w**	**3wa**	70	>99:<1	92
22	$CH_3(CH_2)_2$	H	**1x**	**3xa**	60	>99:<1	79
23	$CH_3(CH_2)_5$	H	**1y**	**3ya**	62	>99:<1	82
24	$CH_3(CH_2)_9$	H	**1z**	**3za**	36	>99:<1	84

[a] The reaction of **1** with **2a** was conducted in the presence of the Ag catalyst (5 mol%) at 0°C for 24 h at 0.6 M unless otherwise noted. [b] L-Amino acid ester was used.

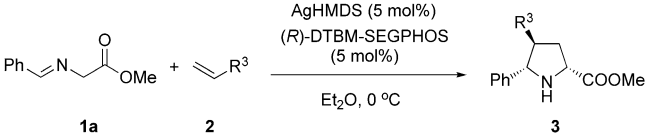
polar solvent, dichloromethane, did not give a promising result (Table 1, entry 9). On the other hand, ether solvents gave better selectivities (Table 1, entries 10–12), and use of diethyl ether (Et_2O) was finally found to be the best. Excellent diastereo- and enantioselectivities (*endo*/*exo* = <1/>99, 98% *ee* (*exo*)) were obtained (Table 1, entry 11). We further optimized the reaction time and temperature to improve the yield; however, no conclusive improvement of the reactivity was observed (Table 1, entries 13 and 14). Finally, we found that the reactions at higher concentrations were effective in improving the yield without significant loss of selectivities (Table 1, entries 15 and 16), and high yield and high stereoselectivities were attained in the reaction at 0.6 M (Table 1, entry 16). Under these conditions, 1 mol% of the catalyst also worked well to afford the desired product (Table 1, entry 17). Interestingly, AgHMDS itself showed very low catalytic activity in the absence of the phosphine ligand (Table 1, entry 18).

With the optimal reaction conditions in hand, we then examined the scope of the substrates (Table 2). First, several Schiff bases of the glycine ester were tested in the reaction of methyl acrylate **2a** in the presence of the silver complex. The [3+2] reactions using the Schiff base with electron-donating groups such as methyl and methoxy groups on the aromatic ring gave almost identical results to the Schiff base from benzaldehyde, and the desired products were obtained in high yields with high stereoselectivities (Table 2, entries 1–3). Not only the Schiff bases with electron-donating groups but also the Schiff bases with electron-withdrawing groups reacted with **2a** to afford the desired products in good yields with excellent *exo* selectivities and over 90% enantiomeric excesses (Table 2, entries 4–8). The Schiff bases that contained hetero atoms in their aromatic rings also worked well without significant loss of selectivities (Table 2, entries 9–11). Bulky aromatics, 1-naphthyl and 2-naphthyl, did not affect the asymmetric environment, and good to high *exo* selectivities and high enantiomeric excesses were observed (Table 2, entries 12 and 13). The Schiff base with an alkenyl substituent also reacted in high yield

with high diastereo- and enantioselectivities (Table 2, entry 14). It is noteworthy that the Schiff bases prepared from other amino acid esters worked well and that the cycloadducts with quaternary carbon centers were obtained with high stereoselectivities (Table 2, entries 15–17). Next, we tried to expand our methodology to reactions of Schiff bases prepared from aliphatic aldehydes. Usually, [3+2] cycloaddition reactions that use aliphatic Schiff bases are recognized to be difficult because the α-hydrogen is not acidic enough for deprotonation by amine bases. Furthermore, aliphatic imines, especially primary alkyl imines, are easily converted into enamines in the presence of bases, which lead to undesired side reactions such as self-condensation, and so on. In fact, successful examples of asymmetric [3+2] cycloadditions of aliphatic Schiff bases of glycine esters are quite limited, and high enantioselectivities were obtained only in the cases of secondary alkyl Schiff bases.[15] On the other hand, we envisioned that the current silver amide system could be applied to aliphatic Schiff bases, because the system has a unique acid/base character. We tested the reaction of cyclohexylcarboxyaldehyde Schiff base **1t** and were delighted to find that the reaction proceeded well in the presence of the AgHMDS catalyst to afford the desired cycloadduct in good yield with high enantioselectivity under the same reaction conditions as for the Schiff base prepared from benzaldehyde (Table 2, entry 18). The isopropylaldehyde Schiff base **1u** also reacted with **2a** in moderate yield with high diastereo- and good enantioselectivities (Table 2, entry 19). We then tried to use the most challenging primary alkylaldehyde Schiff bases (Table 2, entries 20–24) and found that the desired reactions also proceeded well to give the adducts in moderate to good yields with good to high enantioselectivities. In contrast, the [3+2] cycloaddition of **1y** with **2a** using typical silver catalyst systems (AgOTf+Et_3N or 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), AgOAc) with (*R*)-DTBM-SEGPHOS did not proceed at all under the same reaction conditions. It is worth noting that, to the best of our knowledge, this is the first successful example of asymmetric [3+2] cycloaddition of primary alkyl Schiff bases.

The current catalyst system was also successfully applied to asymmetric [3+2] cycloadditions with other olefins **2** (Table 3). Methyl acrylate **2a** as well as acryl amides (**2c** and **2d**) reacted with **1a** in high yields with high diastereo- and enantioselectivities (Table 3, entries 1 and 2). The reaction of methyl vinyl ketone (**2e**) also gave the desired product with high selectivities (Table 3, entry 3). These results indicated that the coordination ability of the carbonyl oxygen of the olefins did not affect asymmetric environments in the transition states. Other olefins with electron-withdrawing groups were also examined, and the olefins that bear sulfonyl, phosphonyl, and cyano groups reacted with **1a** to afford the corresponding pyrrolidine derivatives in high yields with high selectivities. Thus, the wide scope of both substrates, Schiff bases, and olefins in this chiral silver amide system is remarkable. In addition, it is noteworthy that the reactions proceeded smoothly without addition of any external bases.

Table 3. Asymmetric [3+2] cycloaddition of **1a** with olefins **2**.[a]



1a **2** **3**

Entry	R^3	**2**	**3**	Yield [%]	*exo*/*endo*	*ee* [%] (*exo*)
1	$CO[N(CH_2)_2O(CH_2)_2$-]	**2c**	**3ac**	92	>99:<1	96
2	$CONMe_2$	**2d**	**3ad**	97	>99:<1	95
3	COMe	**2e**	**3ae**	82	>99:<1	97
4	SO_2Ph	**2f**	**3af**	83	>99:<1	97
5	$P(O)(OEt)_2$	**2g**	**3ag**	80	>99:<1	98
6	CN	**2h**	**3ah**	96	>99:<1	99

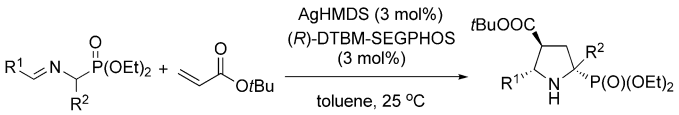
[a] The reaction of **1a** with **2** was conducted in the presence of the Ag catalyst (5 mol%) at 0 °C for 24 h in 0.6 M.

Asymmetric [3+2] Cycloaddition of Imines of α-Aminophosphonate with Olefins

Next, we focused on the asymmetric [3+2] cycloaddition of a Schiff base that bore less acidic α-hydrogen atoms. The phosphonic analogues of α-aminoesters, α-aminophosphonates, are interesting compounds as chiral building blocks for constructing structures that mimic peptides. However, application of the [3+2] cycloaddition methodology to α-aminophosphonate Schiff bases is difficult because the acidity of their α-hydrogen is not high enough to be deprotonated.[16] To the best of our knowledge, all previous methods use more than stoichiometric amounts of bases to conduct stereoselective [3+2] cycloaddition of Schiff bases of α-aminophosphonates.[17]

First, we applied the AgHMDS–(*R*)-DTBM-SEGPHOS catalyst system to the reaction of Schiff bases of α-aminophosphonates **4** with acrylates. It was found that the reaction of **4a** with *tert*-butyl acrylate **2b** gave excellent diastereo- and enantioselectivities in the presence of 3 mol% of the silver catalyst (Table 4, entry 1). In this reaction, only 1 mol% silver catalyst worked well to afford the desired product in high yield with high diastereo- and enantioselectivities (Table 4, entry 2). It is noted that the reaction of an α-aminophosphonate Schiff base proceeded well in the presence of a catalytic amount of the silver complex. Schiff bases **4** with electron-donating or electron-withdrawing groups on their aromatic rings reacted with **2b** smoothly to afford the desired cycloadducts in high yields with high *exo* selectivities and enantioselectivities (Table 4, entries 3–7). Bulkiness of the aromatic group was found to affect the reaction slightly, and the reaction of 1-naphthyl Schiff base **4g** required further optimal reaction conditions, whereas 2-naphthyl Schiff base **4e** showed similar reactivity to other aromatic Schiff bases (Table 4, entries 8 and 9). The heteroaromatic moiety, 3-pyridyl, also did not affect the results through some extra coordination to the silver atom (Table 4, entry 10). The sterically less-hindered alkenyl group also gave high reactivity and selectivity (Table 4, entry 11). When the Schiff bases with alkyl substituents, isopropyl, cyclohexyl, and isobutyl groups were employed, the reactions also

Table 4. Asymmetric [3+2] cycloaddition of Schiff bases of α-aminophosphonate **4** with **2b**.[a]

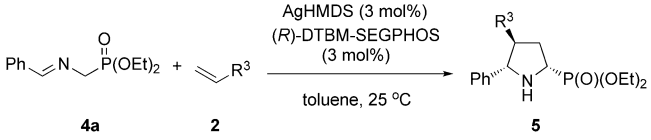


4 **2b** **5**

Entry	R^1	R^2	**4**	**5**	Yield [%]	*exo*/*endo*	*ee* [%] (*exo*)
1	Ph	H	**4a**	**5ab**	94	>99:<1	96
2[b]	Ph	H	**4a**	**5ab**	94	>99:<1	96
3	4-MeC_6H_4	H	**4b**	**5bb**	99	>99:<1	94
4[c,e]	4-$MeOC_6H_4$	H	**4c**	**5cb**	91	>99:<1	96
5	4-FC_6H_4	H	**4d**	**5db**	94	>99:<1	97
6	4-BrC_6H_4	H	**4e**	**5eb**	93	>99:<1	95
7	4-$CF_3C_6H_4$	H	**4f**	**5fb**	91	>99:<1	95
8[c,f]	1-naphthyl	H	**4g**	**5gb**	80	94:6	>99
9	2-naphthyl	H	**4h**	**5hb**	85	>99:<1	97
10	3-pyridyl	H	**4i**	**5ib**	74	>99:<1	90
11[c,f]	cinnamyl	H	**4j**	**5jb**	77	>99:<1	97
12[d,g]	*i*Pr	H	**4k**	**5kb**	56	>99:<1	82
13[d,g]	*c*C_6H_{11}	H	**4l**	**5lb**	73	>99:<1	86
14[d,g]	*i*Bu	H	**4m**	**5mb**	43	97:3	90
15[c,h]	Ph	Me	**4n**	**5nb**	81	>99:<1	98
16[c,h]	Ph	*i*Bu	**4o**	**5ob**	80	>99:<1	91
17[c,h]	Ph	Bn	**4p**	**5pb**	72	>99:<1	90

[a] The reaction of **4** with **2b** was conducted in the presence of the Ag catalyst (3 mol%) in toluene at 25°C for 2 h at 0.2 M unless otherwise noted. [b] The Ag complex (1 mol%) was used. [c] The Ag complex (5 mol%) was used. [d] The Ag complex (10 mol%) was used. [e] 20 h. [f] 4 h. [g] 0°C for four days. [h] 15 h.

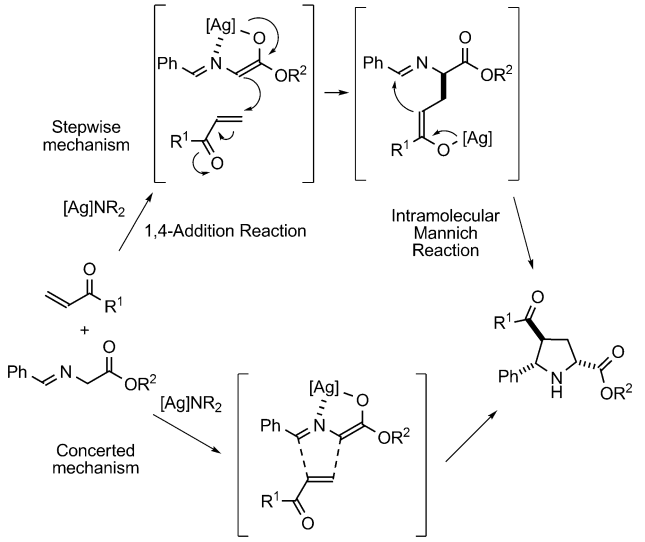
Table 5. Asymmetric [3+2] cycloaddition of **4a** with olefins **2**.[a]



4a **2** **5**

Entry	R^3	**2**	**5**	Yield [%]	*exo*/*endo*	*ee* [%] (*exo*)
1	CO_2Et	**2i**	**5ai**	95	>99:<1	97
2	$CO(N(CH_2)_2O(CH_2)_2$-)	**2c**	**5ac**	93	>99:<1	99
3	$CONMe_2$	**2d**	**5ad**	97	>99:<1	98
4	COMe	**2e**	**5ae**	81	>99:<1	99
5	SO_2Ph	**2f**	**5af**	98	>99:<1	99
6	$P(O)(OEt)_2$	**2g**	**5ag**	85	>99:<1	98
7	CN	**2h**	**5ah**	91	>99:<1	97

[a] The reaction of **4** with **2b** was conducted in the presence of the Ag catalyst (3 mol%) in toluene at 25°C for 2 h in 0.2 M unless otherwise noted.



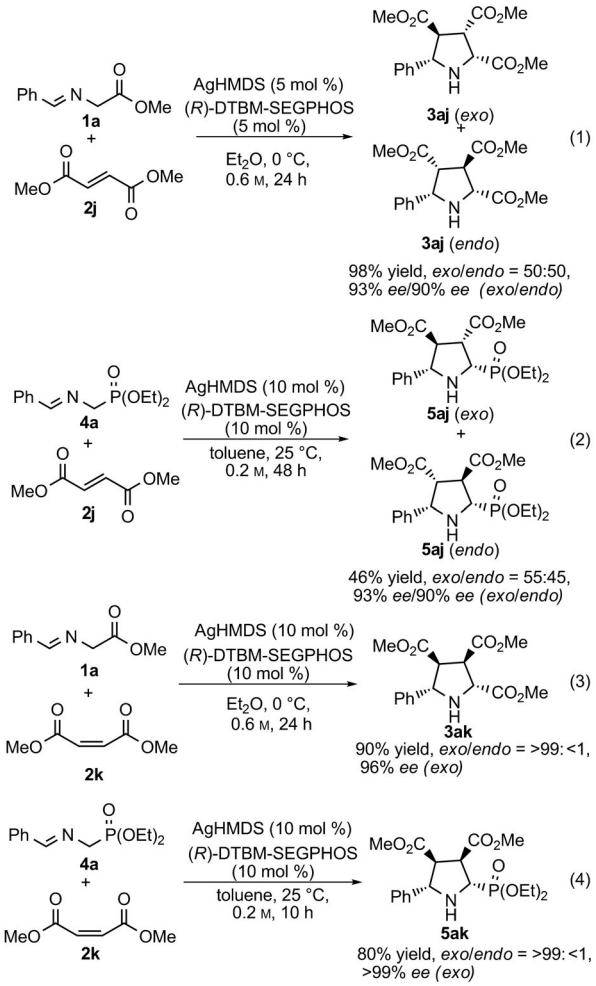
Scheme 3. Possible mechanisms for the [3+2] cycloaddition reaction.

proceeded to afford the desired pyrrolidine derivatives with high diastereo- and good to high enantioselectivities (Table 4, entries 12–14). Moreover, it is worth noting that Schiff bases prepared from α-alkyl-α-aminophosphonates also worked well and that the desired cycloadducts with quaternary carbon centers were obtained in high diastereo- and enantioselectivities (Table 4, entries 15–17). To the best of our knowledge, this is the first example of catalytic asymmetric [3+2] cycloaddition of α-aminophosphonate Schiff bases with olefins.

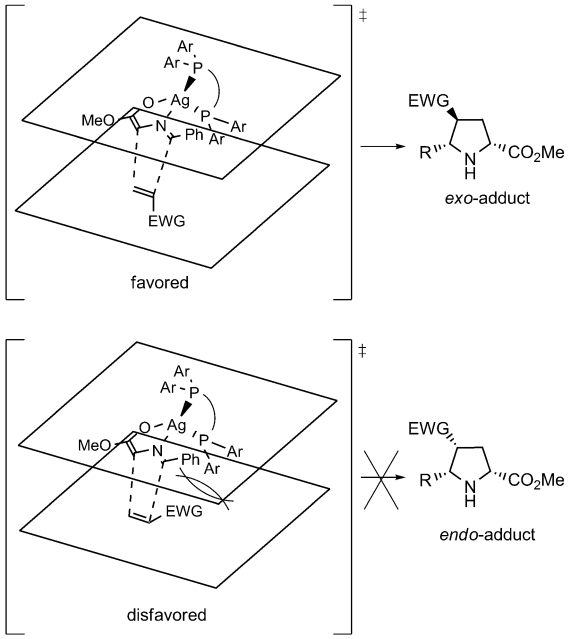
Furthermore, we tested the [3+2] cycloaddition with other olefins **2** (Table 5). Similar to the case of Schiff bases of glycine ester **1**, the reactions of olefins substituted with carbonyl, sulfonyl, phosphonyl, and cyano groups proceeded smoothly to afford the desired products in high yields with high enantioselectivities. These results indicated that the chiral silver amide catalyst was also effective for the [3+2] cycloadditions of various Schiff bases of the α-aminophosphonate, and the wide substrate scope was confirmed.

Reaction Mechanism

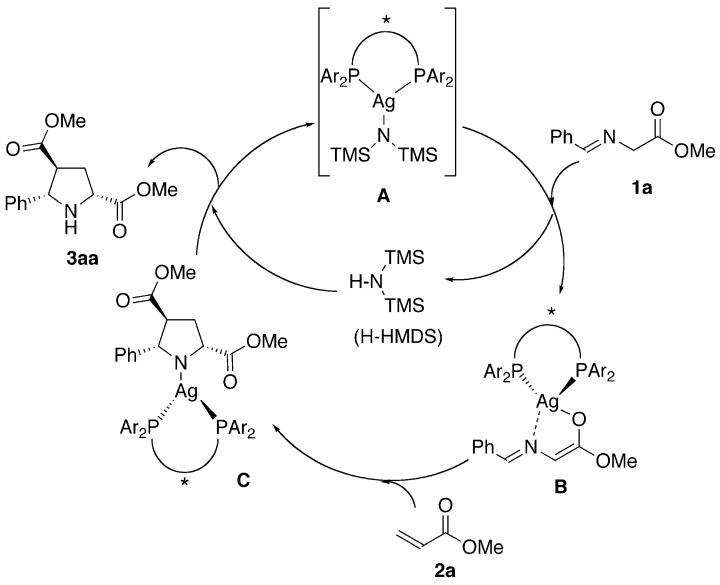
We then investigated the reaction pathways of the present chiral silver-catalyzed [3+2] cycloadditions. There are two typical mechanisms for the [3+2] cycloaddition of azomethine ylides with olefins (Scheme 3). One is a stepwise mechanism, which consists of an initial 1,4-addition of the anion species of the Schiff base to an olefin double bond, followed by an intramolecular Mannich reaction of the formed enolate with the imine part of the Schiff base. This mechanism has been supported by experimental or theoretical calculation in some cases.[18] The other possibility is a concerted mechanism, in which the 1,3-dipole formed in situ reacts with the olefin at two positions simultaneously. To obtain information on the mechanism, we carried out the [3+2] cycloaddition reactions of the Schiff base of glycine ester **1** or α-aminophosphonate **4** in the presence of the chiral silver catalyst (Scheme 4). Interestingly, the reaction using dimethyl fumarate gave a 1:1 mixture of *exo* and *endo* adducts with high enantioselectivities, and no other diastereomers were observed in the reaction systems, which means that no epimerization of the stereocenters occurred [Eqs. (1) and (2)]. In contrast, the reactions with dimethyl maleate gave single *exo* isomers with high enantioselectivities [Eqs. (3) and (4)]. These results clearly indicated that the current [3+2] cycloaddition reactions proceeded by



Scheme 4. The [3+2] cycloaddition reactions with dimethyl fumarate (**2j**) and dimethyl maleate (**2k**).



Scheme 5. Proposed transition states.



Scheme 6. Proposed catalytic cycle.

means of the concerted mechanism under control of the silver catalyst. On the basis of the concerted mechanism, we assumed the transition states of the [3+2] cycloaddition reactions (Scheme 5). The azomethine ylide prepared from the chiral silver amide and the Schiff base interacts with the olefin at two positions simultaneously in the transition state, and carbon–carbon bond formation occurred at the same time. Large steric bulkiness on the phosphine atom might control the orientation of the olefin substituent, and the azomethine ylide would react with the olefin without any significant chelation control, thereby avoiding large steric repulsion between the ligand substituents and the olefin substituent.

A proposed catalytic cycle for the reaction of Schiff base **1a** with **2a** is shown in Scheme 6. First, the chiral silver amide species (**A**) deprotonates the active α-hydrogen of the Schiff base to form the azomethine ylide with chiral silver complex **B** and free H-HMDS. The silver complex **A** further reacts with olefin **2a** to form silver amide species **C**, which is then protonated by H-HMDS to release the product **3aa** along with regeneration of the silver amide complex **A**.

Catalyst Structure

The structure of the chiral silver amide complex was investigated by ^{31}P NMR spectroscopic experiments (Figures 1 and 2). When AgHMDS and DTBM-SEGPHOS were mixed in [D_8]toluene in 1:1 molar ratio, two double doublet peaks were newly observed ($\delta = 0.3$ and 2.7 ppm) and accompanied a peak of free DTBM-SEGPHOS ($\delta = -12.3$ ppm)

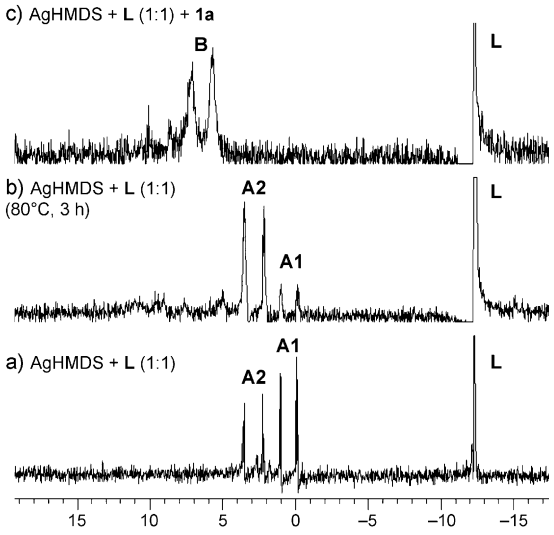


Figure 1. ^{31}P NMR spectroscopic study of an AgHMDS–(*R*)-DTBM-SEGPHOS complex in [D_8]toluene (1). Methods: a) AgHMDS+DTBM-SEGPHOS (1:1) were mixed in [D_8]toluene; b) the sample prepared in a) was heated at 80°C for 3 h; c) AgHMDS+DTBM-SEGPHOS (1:1) were mixed in [D_8]toluene, then **1a** was added. **L** = DTBM-SEGPHOS.

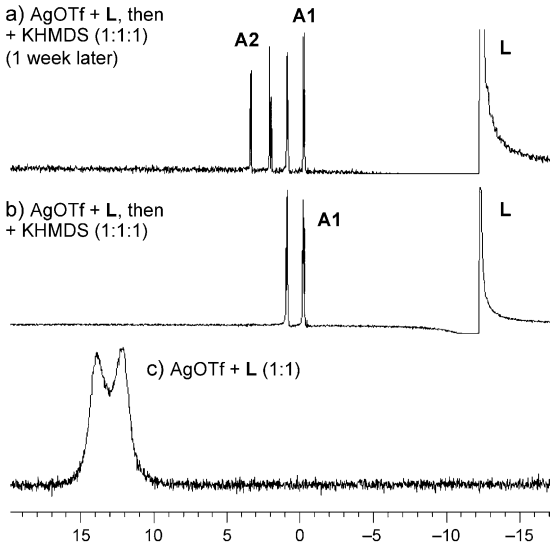


Figure 2. ^{31}P NMR spectroscopic study of an AgHMDS–(*R*)-DTBM-SEGPHOS complex in [D_8]toluene (2). Methods: a) AgOTf+DTBM-SEGPHOS (1:1) were mixed in [D_8]toluene; b) AgOTf+DTBM-SEGPHOS (1:1) were mixed in [D_8]toluene, then KHMDS (1 equiv) was added after 30 min stirring; c) the sample prepared in b) was stored under Ar for one week at room temperature. **L** = DTBM-SEGPHOS.

(Figure 1a). We assumed that these two peaks might be derived from two Ag–DTBM-SEGPHOS complexes (species **A1** ($\delta = 0.3$ ppm) and species **A2** ($\delta = 2.7$ ppm)), on the basis of observation of ^{31}P,^{107}Ag or ^{31}P,^{109}Ag coupling. Interestingly, the peak ratio changed at 80°C (Figure 1b). We added the glycine Schiff base **1a** to the complex solution and found the peaks moved to another position (Figure 1c). The newly appeared peak might be derived from a reactive Ag–DTBM-SEGPHOS–**1a** complex (complex **B** in Scheme 3). It is interesting that in all cases, large amounts of the free ligand still existed in the reaction solution even after addition of **1a**. This fact indicated that free AgHMDS existed in the catalyst solution but did not show any significant effects on the asymmetric reactions (see Table 1, entry 18), and that significant reaction rate acceleration occurred by the ligand. Moreover, it was also suggested that the amount of the actual active chiral silver catalyst in the reaction solutions was much less than we expected.

At this stage, we assumed that the species **A1** is the AgHMDS–DTBM-SEGPHOS 1:1 complex and that **A2** is a higher aggregation state of **A1** (e.g., tetramer).[9] When we prepared the catalyst species from the AgOTf–DTBM-SEGPHOS complex (Figure 2a) and KHMDS, only a peak of species **A1** was observed at $\delta = 0.3$ ppm (Figure 2b), and species **A2** appeared after one week (Figure 2c). These results indicated that the species **A2** was much more thermodynamically stable than species **A1**, and the species **A1** was formed under kinetic conditions. To obtain further information on the actual AgHMDS species, we conducted many trials using mass spectrometry analysis and ^{109}Ag NMR spectroscopic analysis of the complex, and so on; however, no useful result was obtained. One reason for these disappointing results may be the low population of the active catalyst complex.

We also examined the relationship between *ee* value of the ligand and *ee* value of the product, which could provide information on the complex aggregation in the catalyst solution (NLE study).[19] As a result, we observed an almost perfect linear relationship between the *ee* values (Table 6 and Figure 3). This result may indicate that the silver complex does not form any stable heterooligomeric complexes. The result of the NLE study may support the hypothesis that the observed silver species are the AgHMDS–ligand (1:1) complex (**A1**) and its aggregated form (**A2**). The species **A2** could be deaggregated into **A1** and form the active species in the presence of the glycine Schiff base **1a**.

Table 6. NLE study.[a]

Entry	*ee* value of the ligand [%]	Yield [%]	*exo*/*endo*	*ee* [%] (*exo*)
1	29	90	>99:<1	29
2	50	90	>99:<1	50
3	77	92	>99:<1	77
4	>99	91	>99:<1	98

[a] The reactions were conducted using **1a** and **2a** in the presence of the Ag catalyst (5 mol%) at 0°C for 24 h.

Conclusion

We have demonstrated successful asymmetric [3+2] cycloaddition reactions of Schiff bases using a chiral silver amide catalyst. AgHMDS was easily prepared from AgOTf and LiHMDS or KHMDS, and a silver complex prepared from AgHMDS and a chiral phosphine ligand worked as an effi-

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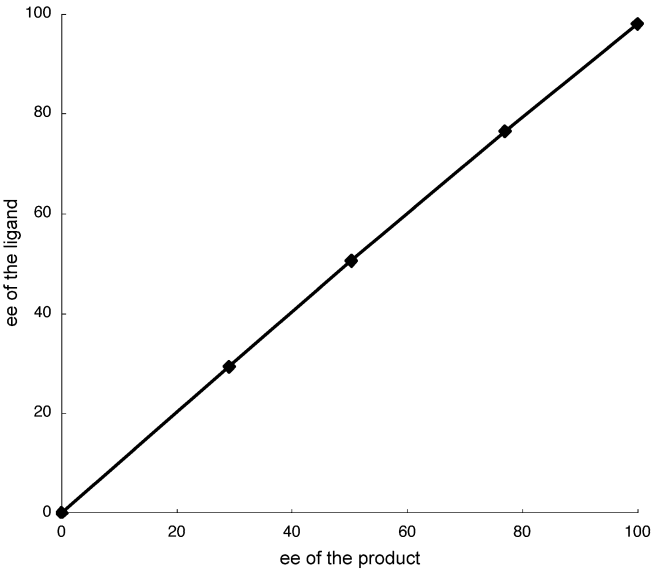

Figure 3. Relationship between the *ee* value of the ligand and the *ee* value of the product.

cient base catalyst without any additional tertiary amine. Examination of the ligand structure has revealed that a large and bulky bidentate phosphine ligand, (*R*)-DTBM-SEGPHOS, was effective in forming excellent asymmetric environments, and α-aminoester Schiff bases including those derived from aliphatic imines successfully reacted with several olefins to afford the corresponding pyrrolidine derivatives in high yields with high *exo* selectivities and high enantioselectivities. Furthermore, α-aminophosphonate Schiff bases, which have less acidic hydrogen atoms at the α positions, also reacted smoothly in the presence of a catalytic amount of the silver amide complex to give the desired cycloadducts in high stereoselectivities. A mechanistic study indicated that the [3+2] cycloaddition proceeded by means of a concerted mechanism, and an NMR spectroscopic study indicated that complexation of AgHMDS and the bisphosphine ligand was not complete and that free AgHMDS, which did not show any significant activity, existed in the catalyst solution. Therefore, significant ligand acceleration occurred in the current reaction system. This is the first example of chiral silver amides as catalysts for asymmetric reactions.

Experimental Section

A Typical Procedure for Silver-Catalyzed [3+2] Cycloaddition of Schiff Bases of α-Aminoglycinate to Vinyl Compounds

Under an Ar atmosphere, a solution of AgHMDS (0.015 mmol) and (*R*)-DTBM-SEGPHOS (0.015 mmol) in Et_2O (0.3 mL) or a solution of AgOTf (0.015 mmol), KHMDS (0.015 mmol), and (*R*)-DTBM-SEGPHOS (10.6 mg, 0.015 mmol) in Et_2O (0.3 mL) in a flame-dried glass tube with aluminum foil was stirred for 30 min at room temperature. Schiff base of α-aminoglycinate **1** (0.30 mmol) and acrylate **2** (0.36 mmol) were added successively at 0 °C, and the mixture was then stirred for 24 h at the same temperature. The reaction mixture was quenched with THF/H_2O (20:1) mixture (1 mL), and the quenched mixture was passed through a silica-celite-Na_2SO_4 pad using a solvent mixture of $CHCl_3$ and methanol (1:1). After concentration under reduced pressure, the residue was purified by preparative thin-layer chromatography (PTLC) with hexane/ethyl acetate (3:1) as an eluent to give the desired product **3**.

A Typical Procedure for Silver-Catalyzed [3+2] Cycloaddition of Schiff Bases of α-Aminomethylphosphnates to Vinyl Compounds

Under an Ar atmosphere, a solution of AgHMDS (0.0090 mmol) and (*R*)-DTBM-SEGPHOS (0.0090 mmol) in toluene (1.0 mL) or a solution of AgOTf (0.0090 mmol), (*R*)-DTBM-SEGPHOS (0.0090 mmol), and KHMDS (0.0090 mmol) in toluene (1.0 mL) in a flame-dried glass tube with aluminum foil was stirred for 15 min at room temperature. Schiff base of α-aminomethylphosphonate **4** (0.30 mmol) and acrylate **2** (0.36 mmol) were added successively, and the reaction mixture was then stirred at 25 °C for 2 h. The reaction mixture was quenched with saturated aqueous NH_4Cl (10 mL) and extracted with CH_2Cl_2 (15 mL × 3). The organic phases were combined and dried over $MgSO_4$. After filtration and concentration under reduced pressure, the residue was purified by preparative thin-layer chromatography (PTLC) with EtOAc/hexane (2:1) as an eluent to give the desired product **5**.

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