Asymmetric Catalysis

DOI: 10.1002/ange.201008272

Chiral Silver Amide Catalyst for the [3+2] Cycloaddition of α-Amino Esters to Olefins**

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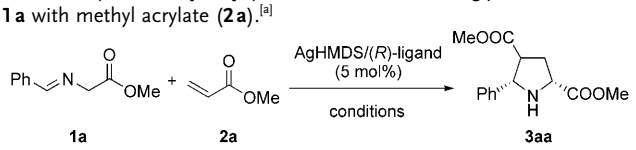
The synthesis of highly substituted pyrrolidine derivatives is very important in bioorganic and medicinal chemistry, because they are useful building blocks for biologically active molecules, and they sometimes show interesting biological activity.[1] The asymmetric [3+2] cycloaddition of α-amino ester Schiff bases with substituted olefins is one of the most efficient methods for pyrrolidine preparation in an optically pure form,[2] thus making it possible to introduce various substituents on the pyrrolidine skeleton stereoselectively. From the pioneering work of Grigg et al.,[3] chiral catalyst systems based on a combination of chiral metal Lewis acids and tertiary amine bases have been reported, and high diastereo- and enantioselectivities have been attained in some cases.[4–7] However, there are some problems that have yet to be solved for this reaction: 1) addition of external amines is needed in most cases; 2) major products of the cycloaddition are *endo*, and there are few examples which provide *exo* adducts selectively; 3) applicable substrates for this method are still limited. In particular, successful examples using Schiff bases derived from aliphatic aldehydes are very rare (see below).

In a previous paper, we described that silver bis(trimethylsilyl)amide (AgHMDS; HMDS = hexamethyldisilazide) when combined with a chiral ligand works well in the enanitioselective [3+2] cycloaddition of α-aminophosphonate Schiff bases, which have less-acidic hydrogen atoms at the α position, with substituted olefins.[8] High yields and diastereoselectivities were attained without addition of external bases. We thought that the key was the use of a basic silver reagent, AgHMDS, which was indeed employed for the first time in organic synthesis. In contrast, for the [3+2] cycloaddition of α-amino ester Schiff bases, which have more-acidic hydrogen atoms at the α position, we thought that AgHMDS might be too basic and thereby lead to low yields and selectivities because of some undesired side reactions. However, unexpectedly, a AgHMDS/chiral ligand complex was found to be a very efficient catalyst for enanitioselective [3+2] cycloaddition of α-amino ester Schiff bases with substituted olefins.

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 enantioselectivity (Table 1, entry 1). In this catalyst system, the *endo* adduct was obtained as the major diastereomer (*endo*/*exo* = 72:18). In contrast, we investigated other ligand structures and found that the use of segphos-type ligands afforded the *exo* adduct preferentially (entries 3 and 4); in particular (*R*)-DTBM-segphos (**L4**) showed high *exo* selectivity (*endo*/*exo* = 4:96) and good enantioselectivity (84% *ee*, entry 4). Since typical chiral silver catalysts showed *endo* selectivity, it is remarkable that the *exo* product was

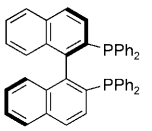
Table 1: Asymmetric [3+2] cycloaddition reaction of glycine Schiff base **1a** with methyl acrylate (**2a**).[a]



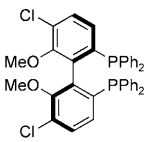
1a **2a** **3aa**

Entry	Ligand	Solvent	*t* [h]	Yield [%]	*endo*/*exo*	*ee* [%] *endo*	*ee* [%] *exo*
1[b,c]	**L1**	toluene	2	82	72:18	45	52
2[b,c]	**L2**	toluene	2	90	40:60	17	30
3[b,c]	**L3**	toluene	2	91	18:82	–	77
4[b,c]	**L4**	toluene	2	90	4:96	–	84
5[c]	**L4**	toluene	2	87	9:91	–	79
6	**L4**	toluene	24	37	1:99	–	94
7	**L4**	Et_2O	24	40	<1:>99	–	98
8[d]	**L4**	Et_2O	24	71	<1:>99	–	97
9[e]	**L4**	Et_2O	24	91	1:99	–	98
10[e,f]	**L4**	Et_2O	48	76	<1:>99	–	97
11[e,g]	–	Et_2O	72	6	>99:<1	–	–

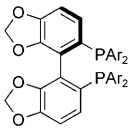
[a] Asymmetric [3+2] cycloaddition of **1a** with **2a** at 0.2 M at 0 °C in the presence of 5 mol% of the chiral AgHMDS catalyst prepared from AgOTf and KHMDS and the chiral phosphine ligand in situ unless otherwise noted. [b] 10 mol% of AgHMDS and the ligand were used. [c] 30 °C. [d] 0.4 M. [e] 0.6 M. [f] 1 mol% of the catalyst was used. [g] Used isolated AgHMDS.



(*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**)

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[**] This work was partially supported by a Grant-in-Aid for Science Research from the Japan Society for the Promotion of Science (JSPS), the Global COE Program (Chemistry Innovation through Cooperation of Science and Engineering), the University of Tokyo, and theMEXT (Japan). We thank Takasago Int. Co. for supply of (*R*)-DTBM-segphos.

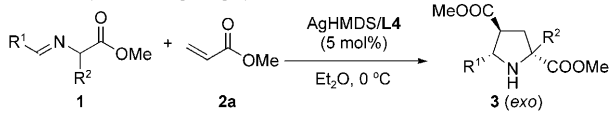
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201008272.

obtained selectively. With these promising results in hand, we optimized the reaction conditions so as to improve the selectivity and the efficiency of the reaction. Even when the reaction was conducted in the presence of 5 mol% of the silver catalyst, the reaction proceeded smoothly in good yield with a slight loss in the selectivity (entry 5). When the reaction was conducted at 0°C for 24 hours using 5 mol% of the Ag catalyst, the desired product was obtained in only 37% yield but with excellent *exo* selectivity and very high enantioselectivity (entry 6). Several solvents were then examined, and it was found that use of diethyl ether (Et_2O) was the best as excellent diastereo- and enantioselectivities [*endo*/*exo* = <1:>99, 98% *ee* (*exo*)] were obtained (entry 7). Finally, we found that the reactions run at higher concentrations were effective in improving the yield without significant loss in the selectivities (entries 8 and 9). Both a high yield and stereoselectivity were attained in the reaction run at 0.6 M (entry 9). Under these reaction conditions, 1 mol% of the catalyst worked well and afforded the desired product (entry 10). Interestingly, AgHMDS itself showed very low catalytic activity in the absence of the phosphine ligand (entry 11).

With the optimal reaction conditions in hand, we 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 Ag complex. The [3+2] reactions using the Schiff base with electron-donating groups on the aromatic ring gave almost identical results to the Schiff base derived from benzaldehyde, and the desired products were obtained in high yields with high stereoselectivities (entries 1 and 2). Not only the Schiff bases having electron-donating groups but also those having electron-withdrawing groups reacted with **2a** to afford the desired products in good yields with excellent *exo* selectivities and over 90% enantiomeric excesses (entries 3–5). The Schiff bases containing heteroatoms in their aromatic rings also worked well without significant loss in selectivity (entries 6 and 7). Bulky aromatics, such as 1-naphthyl, did not affect the asymmetric environment, and good to high *exo* selectivity and high enantiomeric excess were observed (entry 8). The Schiff base having an alkenyl substituent also reacted in high yield with high diastereo- and enantioselectivities (entry 9). Notably, the Schiff bases prepared from other amino acid esters worked well and the cycloadducts with quaternary carbon centers were obtained with high stereoselectivities (entries 10–12). Next, we tried to expand our methodology to reactions of Schiff bases prepared from aliphatic aldehydes. Usually, [3+2] cycloaddition reactions using aliphatic aldehyde Schiff bases are recognized to be very difficult. 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. In fact, successful examples of asymmetric [3+2] cycloadditions of aliphatic aldehyde Schiff bases of glycine esters are quite limited, and high enantioselectivities were obtained only in the cases of secondary alkyl aldehyde Schiff bases.[9] We tested the reaction of the cyclohexanecarboxyaldehyde Schiff base **1n** 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 for the Schiff base prepared from benzaldehyde (entry 13). We then tried to use the most challenging primary alkyl aldehyde Schiff bases (entries 14–16) and found that the desired reactions also proceeded well to give the desired adducts in good yields with high enantioselectivities. It is noted that, to the best of our knowledge, this is the first successful example of asymmetric [3+2] cycloaddition of primary alkyl aldehyde Schiff bases (see also Table 4).

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 (**2b** and **2c**) reacted with **1a** in high yields with high diastereo- and enantioselectivities (entries 1 and 2). The reaction of methyl vinyl ketone (**2d**) also gave the desired product with high selectivity (entry 3). These results indicated that the coordination ability of the carbonyl oxygen atom of the olefins did not affect asymmetric environment in the transition state. Other olefins having electron-withdrawing groups were also examined, and the olefins bearing sulfonyl (**2e**), phosphoryl (**2f**), and cyano (**2g**) groups reacted with **1a** to afford the corresponding pyrrolidine derivatives in high yields with high selectivities (entries 4–6). Whereas a *cis*-disubstitued olefin, dimethyl maleate (**2h**), was found to work well without any significant decrease of selectivity (entry 7), a *trans*-disubstituted olefin, dimethyl fumarate (**2i**), reacted to afford the desired product as a 1:1 diastereomer mixture with high enantioselectivity (entry 8). Thus, the wide scope of both the substrates, Schiff bases and olefins, using this chiral silver amide system is remarkable. In addition, it is noteworthy that the reactions proceeded smoothly without addition of any external bases.

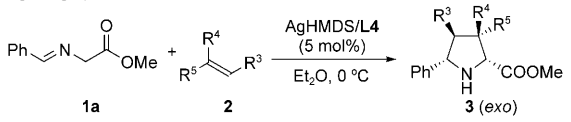
Table 2: Asymmetric [3+2] cycloaddition of **1** with olefin **2a**.[a]



Entry	R^1	R^2	**1**	**3**	Yield [%]	*exo*/*endo*	*ee* [%][b]
1	4-MeC_6H_4	H	**1b**	**3ba**	90	>99:<1	99
2	4-$MeOC_6H_4$	H	**1c**	**3ca**	93	>99:<1	98
3	4-FC_6H_4	H	**1d**	**3da**	82	>99:<1	95
4	4-BrC_6H_4	H	**1e**	**3ea**	88	97:3	92
5	4-NCC_6H_4	H	**1f**	**3fa**	98	>99:<1	96
6	3-pyridyl	H	**1g**	**3ga**	92	>99:<1	90
7	2-furyl	H	**1h**	**3ha**	90	>99:<1	94
8	1-naphthyl	H	**1i**	**3ia**	97	94:6	99
9	(*E*)-PhCH=CH	H	**1j**	**3ja**	90	>99:<1	98
10	Ph	Me[c]	**1k**	**3ka**	78	>99:<1	97
11	Ph	*i*Bu[c]	**1l**	**3la**	87	97:3	94
12	Ph	Bn[c]	**1m**	**3ma**	81	94:6	90
13	*c*-C_6H_{11}	H	**1n**	**3na**	71	>99:<1	97
14	$(CH_3)_2CHCH_2$	H	**1o**	**3oa**	64	>99:<1	88
15	$PhCH_2CH_2$	H	**1p**	**3pa**	70	>99:<1	92
16	$CH_3(CH_2)_5$	H	**1q**	**3qa**	62	>99:<1	82

[a] The reaction of **1** with **2a** was conducted at 0°C for 24 h at 0.6 M in the presence of the Ag catalyst (5 mol%) prepared from AgOTf and KHMDS and **L4** in situ. [b] Values are for the *exo* product. [c] An L-amino acid ester was used.

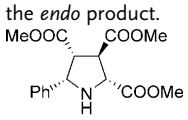
Table 3: Asymmetric [3+2] cycloaddition of **1a** with olefins **2**.[a]



1a 2 3 (*exo*)

Entry	2	R^3	R^4	R^5	3	Yield [%]	*exo*/*endo*	*ee* [%][b]
1	**2b**	$CO(NCH_2CH_2OCH_2CH_2$-)	H	H	**3ab**	92	>99:<1	96
2	**2c**	$CONMe_2$	H	H	**3ac**	97	>99:<1	95
3	**2d**	COMe	H	H	**3ad**	82	>99:<1	97
4	**2e**	SO_2Ph	H	H	**3ae**	83	>99:<1	97
5	**2f**	$P(O)(OEt)_2$	H	H	**3af**	80	>99:<1	98
6	**2g**	CN	H	H	**3ag**	96	>99:<1	99
7[c]	**2h**[d]	COOMe	COOMe	H	**3ah**	90	>99:<1	96
8	**2i**[e]	COOMe	H	COOMe	**3ai**	98	50:50	93 (90)[f]

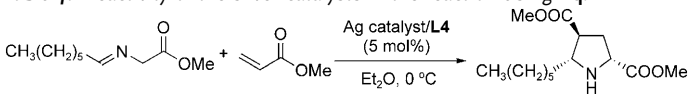
[a] The reaction of **1a** with **2** was conducted in the presence of the Ag catalyst (5 mol%) prepared from AgOTf and KHMDS and **L4** in situ at 0°C for 24 h in 0.6 M. [b] Values are for the *exo* product. [c] The Ag catalyst was used at a 10 mol% loading. [d] Dimethyl maleate. [e] Dimethyl fumarate. [f] The *ee* value of the *endo* product.



3ai (*endo*)

Finally, the present catalyst system was compared with other previously reported efficient catalyst systems (Table 4). While the [3+2] cycloaddition of **1q** with **2a** proceeded smoothly in the presence of the present AgHMDS system to afford the desired product **3qa** in good yield with good enantioselectivity, other Ag catalyst systems (AgOTf + Et_3N or DBU, AgOAc with (*R*)-DTBM-segphos) did not work at all under the same reaction conditions.

Table 4: Reactivity of the silver catalysts in the reaction using **1q**.[a]



1q 2a 3qa

Entry	Ag catalyst	Yield [%]	*exo*/*endo*	*ee* [%][b]
1	AgHMDS	62	>99:<1	82
2	AgOTf + Et_3N	n.r.	–	–
3	AgOTf + DBU	n.r.	–	–
4	AgOAc	n.r.	–	–

[a] The reaction of **1q** with **2a** was conducted in the presence of the Ag catalyst (5 mol%) at 0°C for 24 h at 0.6 M. [b] Values are for the *exo* product. n.r. = no reaction. DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene.

In summary, we have demonstrated the successful asymmetric [3+2] cycloaddition of α-aminoester Schiff bases with several activated olefins. A silver complex prepared from AgHMDS and a chiral phosphine ligand worked as an efficient base catalyst without an additional tertiary amine. Examination of the ligand structure has revealed that a large and bulky bidentate phosphine ligand, (*R*)-DTBM-segphos, was also effective for providing an asymmetric environment, and α-amino ester 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*- and enantioselectivities. Additional investigations into the substrate scope and mechanistic aspects are in progress.

Received: December 30, 2010

Keywords: asymmetric synthesis · cycloadditions · heterocycles · homogeneous catalysis · silver

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