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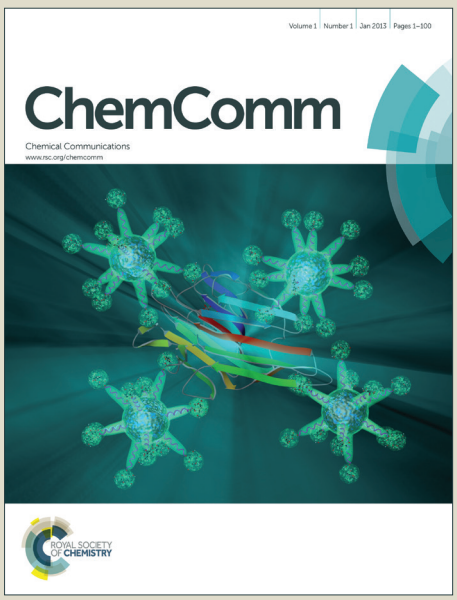

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Catalytic Asymmetric *endo*-Selective [3+2] Cycloaddition Reactions of Schiff Bases of α-Aminophosphonates with Olefins Using Chiral Metal Amides

Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

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A Catalytic asymmetric *endo*-selective [3+2] cycloaddition reactions of Schiff bases of α-aminophosphonates with olefins are described. While efficient asymmetric synthesis of several phosphonate analogues of proline derivatives is important in bioorganic chemistry, a direct catalytic method to prepare optically active *endo* [3+2] cycloadducts of α-aminophosphonates with olefins has never been developed. We found for the first time that catalyst systems prepared from group 11 metal amides with (*R*)-FeSulphos ligand were effective for the asymmetric *endo*-selective [3+2] cycloaddition to afford the desired proline phosphonate analogues in high yields with high *endo*- and high enantioselectivities.

α-Substituted-α-aminophosphonates, phosphonate analogues of α-amino acids, are potentially interesting synthetic units to prepare biologically active compounds.[1] Catalytic asymmetric synthesis provides one of the most efficient ways to their optically pure forms.[2] A [3+2] cycloaddition reaction of a Schiff base of α-amino ester with an olefin is a useful and reliable methodology to provide a highly substituted proline derivative stereoselectively.[3] However, efficient synthesis of a phosphonate analogue of a proline derivative, especially in an optically active form via a [3+2] cycloaddition reaction has not been established.[4] Proline and its derivatives are useful amino acids and are often employed in total synthesis of natural products as well as in several asymmetric reactions as chiral catalysts.[5] Grigg, *et al.* first reported [3+2] cycloadditions of Schiff bases of α-aminophosphonates with methyl acrylate using stoichiometric amounts of AgOAc-LiBr and DBU. The desired proline phosphonate analogues were obtained in high yields with excellent *endo* selectivity.[6] However, a catalytic asymmetric variant of the [3+2] cycloaddition using Schiff bases of α-aminophosphonates and olefins has not been explored yet. The challenging aspect of effecting a catalytic reaction of these substrates is the less acidic nature of α-hydrogen atom of a Schiff base of an α-aminophosphonate compared to the corresponding Schiff base of an α-amino ester.[7] Therefore, a stronger Brønsted base system is needed for efficient deprotonation to promote the desired reaction.

Our group has been interested in development of chiral metal amide catalysts for enantioselective carbon–carbon (C–C) bond forming reactions.[8] While metal amides (alkaline and alkaline earth metal amides) are known to be stoichiometric strong Brønsted bases to deprotonate less acidic hydrogens to form anion species for a long time, catalytic use of metal amides in C–C bond forming reactions has not been thoroughly investigated. The metal amide catalysis has some

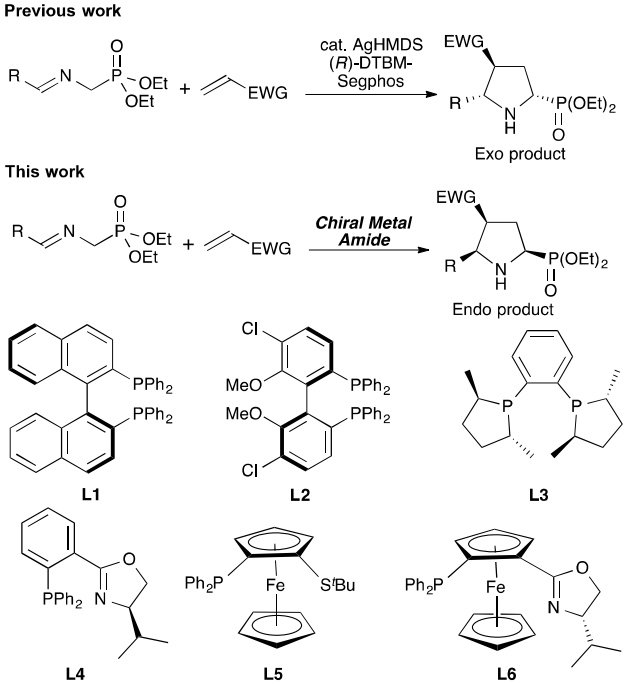

Figure 1 Catalytic asymmetric *endo*-selective [3+2] cycloaddition reaction of Schiff base of α-aminophosphonate

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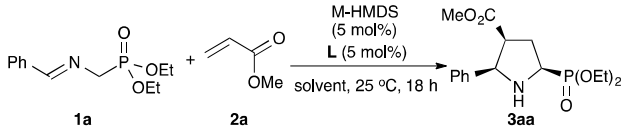
Electronic Supplementary Information (ESI) available: Physical data of obtained products and spectra charts. See DOI: 10.1039/x0xx00000x

advantages, it could show higher basicity compared to other acid/base catalyst systems. Efficient deprotonation could be expected because the acid/base species can deprotonate substrates in a pseudo-intramolecular fashion. Recently, we have developed catalytic, highly *exo*- and enantioselective [3+2] cycloaddition reactions of Schiff bases of α-aminophosphonates with olefins using a bulky chiral Ag amide consisting of $AgN(SiMe_3)_2$ (AgHMDS) and DTBM-SEGPHOS.[9,10] While the *exo*-adducts were obtained efficiently, the catalytic *endo*- and enantioselective [3+2] cycloaddition reaction of a Schiff base of α-aminophosphonate, has never been reported to our knowledge. Supply of both *exo* and *endo* adducts is very important in this field, therefore we decided to develop highly *endo*- and enantioselective [3+2] cycloaddition reactions of Schiff bases of α-aminophosphonates (Figure 1) .

We investigated the *endo*-selective [3+2] cycloaddition reaction of benzaldehyde Schiff base of α-aminophosphonate **1a** with methyl acrylate **2a** in the presence of a chiral metal amide catalyst (5 mol%) (Table 1). When a chiral Ag amide catalyst prepared from AgHMDS and bidentate bisphosphine ligands (**L1**-**3**) in toluene at 25 °C, the desired *endo* [3+2] cycloadduct was obtained in high yields; however, enantioselectivities observed were disappointing (entries 1-3). While the *P*,*N*-type chiral ligand **L4** was also unsuccessful with regard to enantioselectivity (entry 4); bidentate ligands **L5** and **L6** prepared based on a ferrocene backbone were found to be

Table 1 Development of chiral metal amide catalyst systems[a]



1a 2a 3aa

Entry	M	L	Solvent	Yield (%)[b]	*Endo*/*exo*[c]	ee (%)
1	Ag	**L1**	toluene	44	77/23	48
2	Ag	**L2**	toluene	73	70/30	-56
3	Ag	**L3**	toluene	76	97/3	13
4	Ag	**L4**	toluene	83	98/2	-15
5	Ag	**L5**	toluene	84	93/7	84
6	Ag	**L6**	toluene	45	96/4	64
7	Ag	**L5**	THF	84	91/9	83
8	Ag	**L5**	Et_2O	60	97/3	57
9	Ag	**L5**	mesitylene	67	97/3	92
10[d]	Ag	**L5**	mesitylene	71	97/3	95
11[d,e]	Ag	**L5**	mesitylene	82	98/2	95
12[d,f]	Ag	**L5**	mesitylene	90	97/3	95
13	Cu	**L5**	mesitylene	67	89/11	99
14[g]	Cu	**L5**	mesitylene	88	89/11	99
15[g,f,h]	Cu	**L5**	mesitylene	78	91/9	99

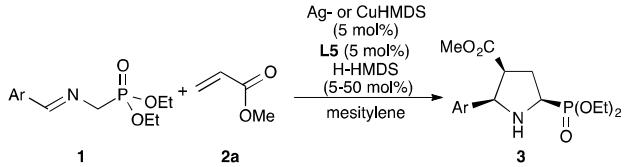
[a] The reaction was conducted by using **1a** (0.40 mmol) and **2a** (0.50 mmol) at 0.2 M at 25 °C for 18 h in the presence of a chiral metal amide catalyst prepared from Ag- or CuOTf (0.020 mmol) and KHMDS (0.020 mmol), and ligand **L** (0.020 mmol) unless otherwise noted. Relative and absolute configurations of **3aa** were confirmed by X-ray crystallographic analysis of a single crystal (CCDC number: 1409067). All other compounds were assigned by comparison with **3aa**. [b] Isolated yield. [c] Determined by ^1H NMR analysis of a crude reaction mixture. [d] At –40 °C, [e] $HN(SiMe_3)_2$ (H-HMDS) was used as an additive (20 mol%). [f] H-HMDS was used as an additive (50 mol%). [g] H-HMDS was used as an additive (5 mol%). [h] At 0 °C for 48 h.

promising to control the asymmetric environment (entries 5,6). The desired *endo*- product was obtained in good enantioselectivity by using **L5** and further screening showed aromatic solvents gave better selectivities (entries 5, 7-9)[11] The effects of solvents was then examinedwith high *endo*- and enantioselectivities obtained when the reaction was conducted in mesitylene at –40 °C (entry 10). However, the yield was still moderate due to formation of a significant amount of by-product. To suppress the by-product formation, use of an additive was examined. It was found that addition of $HN(SiMe_3)_2$ (H-HMDS) was effective, which could enhance the protonation step and release the catalyst from the catalyst-product complex and the desired product was obtained in high yields with high *endo*- and enantioselectivities (entries 11 and 12). We also investigated the reaction using CuHMDS instead of AgHMDS. In this case, the desired reaction proceeded in moderate yield (67%) with good *endo*- and excellent enantioselectivities (entry 13). Further improvement of the yield was achieved using H-HMDS as an additive, and the desired product was obtained in 88% yield (entry 14). The reaction at lower temperature gave slight improvement of the *endo* selectivity, but the yield decreased (entry 15). It was revealed that the chiral Ag or Cu amide catalyst successfully promoted the *endo*-selective asymmetric [3+2] cycloaddition reactions of Schiff bases of α-aminophosphonates in high *endo*- and enantioselectivities. To our knowledge, this is the first example of catalytic highly *endo*- and enantioselective [3+2] cycloaddition reaction of a Schiff base of α-aminophosphonate.

Substrate scope was then surveyed using the chiral Ag or Cu catalyst system (Table 2). In all cases, *endo*-products were obtained in high yields with high diastereo- and enantioselectivities. There was a tendency between the catalysts and selectivities observed; the chiral Ag amide catalyst gave higher *endo*-selectivities (condition A), while excellent enantioselectivities were obtained using the chiral Cu amide catalyst (condition B). It was found that several aromatic substituents of the Schiff bases **1** were acceptable for this [3+2] cycloaddition reaction. Steric effects from the substituted-phenyl derivatives was not significant, and *o*-, *m*- and *p*-tolyl substrates reacted with **2a** to afford the desired adducts **3** in good to high yields with good to high *endo*-selectivities and excellent enantioselectivities (entries 3-8). While lower reactivity was observed using the Schiff base bearing an electron-donating substituent, *p*-methoxy group (entries 9, 10). High yields and high selectivities were obtained when the Schiff bases bearing electron-withdrawing substituents were used (entries 11-15). The Schiff bases with larger aromatic substituents, 2-naphthyl and 1-naphthyl groups, were also good substrates, with high yields and selectivities obtained (entries 16-19). Schiff bases **1** with heteroaromatic and alkenyl groups were also applicable (entries 20-21).

Our attention then turned to the screening of the olefins (Table 3). Not only methyl acrylate but other acrylate derivatives were tolerated under the reaction conditions. Acrylamides, morpholine amide **2b** and *N*,*N*-dimethylamide **2c**

Table 2 Scope of phosphonate Schiff base 1 [a]

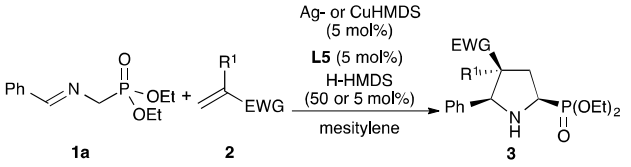


1 2a 3

Entry	Ar	Condition	3	Yield (%)[b]	*Endo/exo*	ee (%)
1	Ph (**1a**)	A	**3aa**	96	97/3	96
2	Ph (**1a**)	B	**3aa**	90	89/11	99
3	4-MeC_6H_4 (**1b**)	A	**3ba**	48	95/5	95
4	4-MeC_6H_4 (**1b**)	B	**3ba**	70	84/16	97
5	3-MeC_6H_4 (**1c**)	A	**3ca**	83	96/4	90
6	3-MeC_6H_4 (**1c**)	B	**3ca**	92	88/12	95
7	2-MeC_6H_4 (**1d**)	A	**3da**	89	98/2	93
8	2-MeC_6H_4 (**1d**)	B	**3da**	92	90/10	98
9	4-MeOC_6H_4 (**1e**)	A	**3ea**	46	99/1	96
10	4-MeOC_6H_4 (**1e**)	B	**3ea**	61	87/13	99
11	4-FC_6H_4 (**1f**)	A	**3fa**	65	95/5	94
12	4-FC_6H_4 (**1f**)	B	**3fa**	81	90/10	99
13	4-BrC_6H_4 (**1g**)	A	**3ga**	86	>99/1	91
14	4-BrC_6H_4 (**1g**)	B	**3ga**	85	91/9	99
15	4-$CF_3C_6H_4$ (**1h**)	B	**3ha**	90	90/10	98
16	2-naphthyl (**1i**)	A	**3ia**	87	97/3	88
17	2-naphthyl (**1i**)	B	**3ia**	79	89/11	99
18	1-naphthyl (**1j**)	A	**3ja**	85	96/4	91
19	1-naphthyl (**1j**)	B	**3ja**	87	85/15	99
20	Furyl (**1k**)	B	**3ka**	89	80/20	97
21	Cinnamyl (**1l**)	B	**3la**	84	79/21	98

[a] Condition A: The reaction was conducted by using **1** (R^1 = H, 0.40 mmol) and **2** (0.50 mmol) at 0.2 M at –40 °C for 18 h in the presence of a chiral Ag amide catalyst prepared from AgOTf and KHMDS, and ligand **L5** unless otherwise noted. H-HMDS (50 mol%) was also used as an additive. Condition B: The reaction was conducted by using **1** (0.40 mmol) and **2** (0.50 mmol) at 0.2 M at 25 °C for 48 h in the presence of a chiral Cu amide catalyst prepared from CuOTf•1/2 toluene complex and KHMDS, and ligand **L5** unless otherwise noted. H-HMDS (5 mol%) was also used as an additive. [b] Determined by ^{1}H NMR analysis of the crude product.

Table 3 Scope of olefins **2** [a]



1a 2 3

Entry	EWG	R^1	2	3	Cond.	Yield (%)	*Endo/exo*	Ee (%) [*endo*]
1		H	**2b**	**3ab**	A	81	>99/1	99
2		H	**2b**	**3ab**	B	98	83/17	88
3	$CONMe_2$	H	**2c**	**3ac**	A	90	99/1	83
4	$CONMe_2$	H	**2c**	**3ac**	B	94	81/19	89
5	CO_2Me	Me	**2d**	**3ad**	A	93	>99/1	92
6	CO_2Me	Me	**2d**	**3ad**	B	78	89/11	98
7	CO_2Me	CH_2CO_2Me	**2e**	**3ae**	A	67	>99/1	93

[a] Condition A: The reaction was conducted by using **1** (R^1 = H, 0.40 mmol) and **2** (0.50 mmol) at 0.2 M at –40 °C for 18 h in the presence of a chiral Ag amide catalyst prepared from AgOTf and KHMDS, and ligand **L5** unless otherwise noted. H-HMDS (50 mol%) was also used as an additive. Condition B: The reaction was conducted by using **1** (0.40 mmol) and **2** (0.50 mmol) at 0.2 M at 25 °C for 48 h in the presence of a chiral Cu amide catalyst prepared from CuOTf•1/2 toluene complex and KHMDS, and ligand **L5** unless otherwise noted. H-HMDS (5 mol%) was also used as an additive.

were successfully employed giving high yields and good to high diastereo- and enantioselectivities (entries 1-4). It was noted that the substitution at the α-position of acrylate did not affect the selectivities, and methyl methacrylate (**2d**) gave high yields and high selectivities (entries 5 and 6). Moreover, acrylate **2e,** bearing a functionalized substituent, also showed high diastereo- and enantioselectivity (entry 7).

While remarkable *endo*-selectivities were observed for a wide variety of substrates, it was considered that the origin of the *endo*-selectivity could be explained by steric effect of the ligands. We have previously reported the chiral Ag amide-catalyzed asymmetric *exo*-selective [3+2] cycloaddition reactions of Schiff bases of α-aminophosphonate **1** with α,β-unsaturated carbonyl compounds **2** by using a very bulky chiral ligand, DTBM-SEGPHOS.[9] The desired reaction proceeded in a concerted pathway to avoid steric repulsion between **2** and substituents on the ligand. These results indicated that steric bulkiness around the metal centre was a key for the diastereoselectivity (Figure 2). The current system, Cu- or Ag–FeSulphos (**L5**), had relatively less bulky nature around the metal compared with Ag–DTBM-SEGPHOS, therefore, acrylate could approach to the sterically less hindered face of the catalyst-Schiff base complex with an interaction to metal centre giving rise to the *endo*-selectivity, which was difficult in the reaction using the bulky DTBM-SEGPHOS as a ligand. In our assumption, the difference of diasteroselectivities between Ag and Cu amide catalysts might be caused by different tightness of the metal-ligand complexes.[11b] In the Cu amide case, Cu is smaller than Ag, therefore the Cu atom may ligate to the ligand more tightly. The reaction environment may be very crowded with enhanced steric bulkiness of the ligand, which leads to high enantioselectivity but slightly lower reactivity and diastereoselecitvity because of the affected chelation control. In the Ag amide case, a relatively loose complexation between Ag and the ligand compared with the Cu case may realize higher reactivity and diastereoselectivity via enhanced chelation control, but enantioselectivity decreases possibly due to the flexibleness around the metal center. [12]

In summary, we have developed the first catalytic highly *endo*- and enantioselective [3+2] cycloaddition reactions of Schiff bases of α-aminophosphonates **1** with α,β-unsaturated

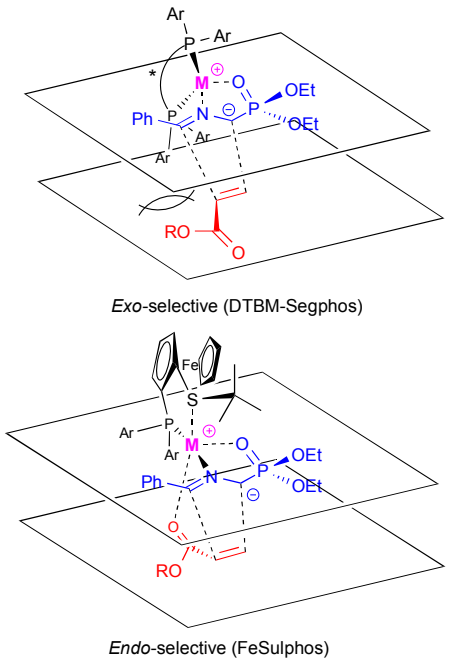


Figure 2 Origin of the *endo*-selectivity

carbonyl compounds **2** in the presence of a chiral metal amide catalyst, which was prepared from AgHMDS or CuHMDS and FeSulphos (**L5**). The desired *endo*-selective reactions proceeded in high yields with high diastereo- and enantioselectivities. Addition of H-HMDS was found to play a positive role in the catalytic reactions to enhance the catalytic turnover. Transition states of both *exo*- and *endo*-selective reactions were discussed, and the origin of the selectivity based on steric bulkiness of chiral ligands was suggested.

Acknowledgements

This work was partially supported by a Grant-in-Aid for Science Research from the Japan Society for the Promotion of Science (JSPS), Global COE Program, The University of Tokyo, MEXT, Japan, and the Japan Science and Technology Agency (JST). S. Y. thanks to MERIT program, The University of Tokyo for financial support.

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12 We propose a concerted [3+2] cycloaddition mechanism for these reactions based on our previous results (ref. 9) and Carretero's report (ref. 11b), but the possibility of stepwise process, 1,4-addition and cyclization process, cannot be excluded.

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