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Chiral Silver Amide-Catalyzed Enantioselective [3 + 2] Cycloaddition of α-Aminophosphonates with Olefins

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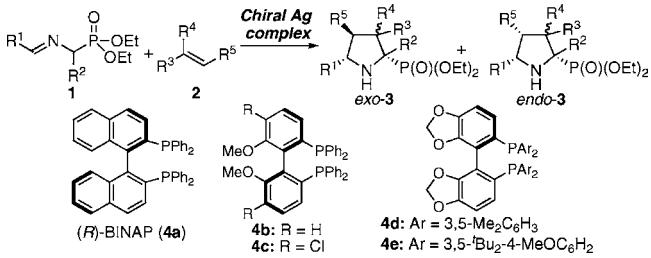
Silver−chiral phosphine complexes have relatively mild Lewis acidity, which allows efficient catalytic turnover in asymmetric catalysis.[1] Since the first report by Ito and co-workers,[2] highly enantioselective silver complexes have been developed in several acid-catalyzed carbon−carbon bond-forming reactions.[3] In particular, bidentate chiral phosphine ligands such as BINAP have been shown to form excellent asymmetric environments around silver.[1] On the other hand, chiral silver complexes are also employed in base-promoted reactions by combination with tertiary amines such as triethylamine[4] or using silver acetate itself.[5] However, chiral silver complexes with stronger conjugate bases based on silver alkoxides or silver amides have not been explored in asymmetric catalysis.[6]

The asymmetric [3 + 2] cycloaddition reaction of Schiff bases of α-aminoesters with olefins is one of the most efficient methods of preparing optically active proline derivatives.[7] α-Aminophosphonates, the phosphonic analogues of α-aminoesters, are also interesting as chiral building blocks for constructing peptide-mimic structures; however, application of the [3 + 2] cycloaddition methodology to α-aminophosphonate Schiff bases is extremely difficult because their active hydrogens are less acidic.[8a,b,e] Therefore, to the best of our knowledge, all previous examples use more than stoichiometric amounts of bases to achieve efficient [3 + 2] cycloaddition of α-aminophosphonate derivatives.[9] Here we report the first example of *catalytic* asymmetric [3 + 2] cycloaddition reactions of α-aminophosphonate Schiff bases with olefins (Scheme 1). The use of chiral silver amide complexes as chiral Brønsted base catalysts is a key, and silver amides have never been employed as catalysts previously.

Scheme 1. Catalytic Asymmetric [3 + 2] Cycloaddition of α-Aminophosphonates with Olefins Using a Chiral Silver Complex



First we investigated the reaction of phosphonate **1a** (R^1 = Ph, R^2 = H) with *tert*-butyl acrylate (**2a**) using silver triflate (AgOTf) and BINAP[3] (10 mol %) in the presence of barium bis[bis(trimethylsilyl)amide] [$Ba(HMDS)_2$] (10 mol %). While the desired reaction proceeded in high yield, the diastereo- and enantioselectivities were not sufficient (Table 1, entry 1). Interestingly, the major diastereomer obtained was an exo product, whereas most of these types of reactions show endo selectivity,[10] and cycloadducts as well as a small amount of 1,4-addition product were obtained. Other silver sources showed similar results (entries 2 and 3). The catalyst prepared from copper(I) triflate gave low conversion, and both the 1,4-adduct and the endo cycloadduct were obtained (entry 4). We then examined the effect of chiral bisphosphine ligands. While ligands with biphenyl skeletons improved the selectivities (entries 5 and 6), SEGPHOS-type ligands **4d** and **4e** were found to be much more effective for enantioselectivity, and high yield and high diastereo- and enantioselectivities were achieved using DTBM-SEGPHOS (**4e**) (entry 8). For bases, metal alkoxides or amides showed high yields, whereas no reaction occurred using tertiary amines such as Et_3N and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) (entries 9−12). Potassium hexamethyldisilazide (KHMDS) was found to be the most effective (entry 12), and an excess amount of KHMDS gave a lower diastereoselectivity with high ee (entry 12). These results indicate that the true active silver species in these reactions was silver hexamethyldisilazide (AgHMDS), which was produced from AgOTf and KHMDS.[11] It is noted that only 1 mol % Ag catalyst worked sufficiently well to give the product in excellent yield and selectivity (entry 16).[12]

Table 1. Asymmetric [3 + 2] Cycloaddition Reactions of **1a** with **2a**[a]

entry	ligand	base	yield (%)	exo/endo/1,4-addition	ee (%)[b]
1	**4a**	$Ba(HMDS)_2$	quant.[c]	74/20/6	29
2[d]	**4a**	$Ba(HMDS)_2$	quant.[c]	74/21/5	28
3[e]	**4a**	$Ba(HMDS)_2$	quant.[c]	72/23/5	29
4[f]	**4a**	$Ba(HMDS)_2$	44[c]	10/32/58	n.d.
5	**4b**	$Ba(HMDS)_2$	60[c]	70/22/8	42
6	**4c**	$Ba(HMDS)_2$	quant.[c]	82/17/1	46
7	**4d**	$Ba(HMDS)_2$	76[c]	7/37/56	87
8	**4e**	$Ba(HMDS)_2$	86	96/2/2	97
9	**4e**	Et_3N	trace	−	−
10	**4e**	DBU	trace	−	−
11	**4e**	KO^{t}Bu	89	>99/<1/<1	97
12	**4e**	KHMDS	92	>99/<1/<1	97
13[g]	**4e**	KHMDS	92	>99/<1/<1	97
14[h]	**4e**	KHMDS	quant.[c]	33/49/18	96
15[i]	**4e**	KHMDS	94	>99/<1	96
16[j]	**4e**	KHMDS	94	>99/<1	96

[a] The reaction was performed in toluene at 25 °C using **1a** (0.30 mmol) and **2a** (0.36 mmol) in the presence of a Ag catalyst prepared from AgOTf (10 mol %), ligand (10 mol %), and base (10 mol %), unless otherwise noted. [b] Enantiomeric excess of the exo product. [c] Conversion (%) determined by ^{31}P NMR analysis. [d] AgOAc was used instead of AgOTf. [e] $AgClO_4$ was used instead of AgOTf. [f] CuOTf·$0.5C_6H_6$ was used instead of AgOTf. [g] KHMDS (5 mol %) was used. [h] KHMDS (15 mol %) was used. [i] Ag complex (3 mol %) was used. [j] Ag complex (1 mol %) was used.

Several examples of catalytic asymmetric [3 + 2] cycloaddition reactions using the chiral silver complex (3 mol %) are shown in Table 2. α-Aminophosphonate Schiff bases derived from benzal-

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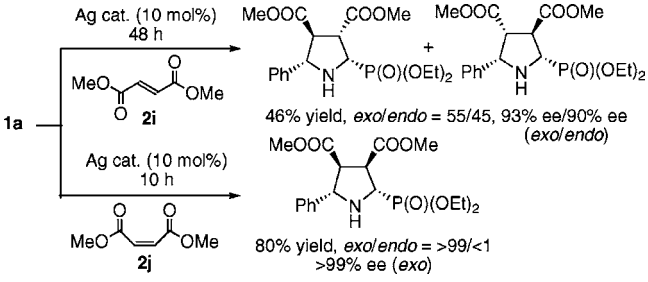
Table 2. Catalytic Asymmetric [3 + 2] Cycloaddition Reactions[a]

entry	**1** (R^1)[b]	**2** (R^5)	yield (%)[c]	dr[d]	ee (%)[e]
1	**1b** (4-MeC_6H_4)	**2a** ($CO_2{}^tBu$)	99	>99/<1	94
2[f,h]	**1c** (4-$MeOC_6H_4$)	**2a**	91	>99/<1	96
3	**1d** (4-FC_6H_4)	**2a**	94	>99/<1	97
4	**1e** (4-BrC_6H_4)	**2a**	93	>99/<1	95
5	**1f** (4-$CF_3C_6H_4$)	**2a**	91	>99/<1	95
6[f,i]	**1g** (1-naphthyl)	**2a**	80	94/6	>99
7	**1h** (2-naphthyl)	**2a**	85	>99/<1	97
8	**1i** (3-pyridyl)	**2a**	74	>99/<1	90
9[f,i]	**1j** (cinnamyl)	**2a**	77	>99/<1	97
10[g,j]	**1k** (^{i}Pr)	**2a**	56	>99/<1	82
11[f,k]	**1l** (Ph)[b]	**2a**	81	>99/<1	98
12	**1a** (Ph)	**2b** (CO_2Et)	95	>99/<1	97
13	**1a** (Ph)	**2c**[l]	93	>99/<1	99
14	**1a** (Ph)	**2d** ($CONMe_2$)	97	>99/<1	98
15	**1a** (Ph)	**2e** (COMe)	81	>99/<1	99
16	**1a** (Ph)	**2f** (SO_2Ph)	98	>99/<1	99
17	**1a** (Ph)	**2g**($PO(OEt)_2$)	85	>99/<1	98
18	**1a** (Ph)	**2h** (CN)	91	>99/<1	97

[a] The reaction was performed in toluene at 25 °C for 2 h at 0.2 M in the presence of a chiral Ag amide complex (3 mol %) prepared from AgOTf, (*R*)-DTBM-SEGPHOS, and KHMDS (1:1:1), unless otherwise noted. [b] R^2 = H, except for entry 11, where R^2 = Me. [c] Isolated yield. [d] Exo/endo. [e] Enantiomeric excess of the exo product. [f] The Ag complex (5 mol %) was used. [g] The Ag complex (10 mol %) was used. [h] Reaction time 20 h. [i] Reaction time 4 h. [j] At 0 °C for 4 days. [k] Reaction time 15 h. [l] R^5 = morpholin-4-ylcarbonyl.

dehyde derivatives bearing both electron-donating and -withdrawing groups reacted with **2a** to afford the desired compounds in high yields with excellent diastereo- and enantioselectivities (entries 1−5). Schiff bases derived from 1- and 2-naphthyl-, pyridine-, and cinnamylaldehyde also worked well (entries 6−9). Schiff base **1k** prepared from an aliphatic aldehyde showed a slight decrease in yield and enantioselectivity (entry 10). Moreover, alanine Schiff base **1l** reacted smoothly under the same reaction conditions to afford the desired product with a quaternary carbon center with excellent diastereo- and enantioselectivity (entry 11). In regard to olefins, α,β-unsaturated esters, amide and ketone derivatives, and olefins with electron-withdrawing groups [SO_2Ph, $P(O)(OEt)_2$, CN] reacted smoothly with **1a** to afford the desired pyrrolidine derivatives in high yields with excellent selectivities (entries 12−18).

Scheme 2. Asymmetric [3 + 2] Cycloaddition of **1a** with **2i** or **2j**



Reactions of **1a** with dimethyl fumarate (**2i**) and dimethyl malate (**2j**) were also conducted (Scheme 2). Although the exo and endo cycloadducts were obtained in almost equal amounts in the reaction with **2i**, the reaction with **2j** exclusively gave the exo cycloadduct with high enantioselectivity. It was also confirmed that no epimerization of the products occurred under the reaction conditions. These results indicate that the current reaction proceeded via a concerted pathway.[13]

In conclusion, we have developed the first *catalytic* asymmetric [3 + 2] cycloadditions of Schiff bases of α-aminophosphonates with olefins. Chiral silver amide complexes worked well as catalysts for the first time, and proline phosphonic analogues were obtained in high yields with excellent diastereo- and enantioselectivities. Further investigations using chiral silver amides and related complexes in asymmetric catalysis are ongoing in our laboratory.

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Supporting Information Available: Experimental procedures, product characterization, and crystallographic data for **3da** (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(13) The assumed transition state models are shown in the Supporting Information.

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