CHIRAL (S)-(+) 1-SUBSTITUTED ARYL-4- (1-PHENYL) ETHYLFORMAMIDO-5-AMINO-1, 2, 3-TRIAZOLE: A NEW CLASS OF CHIRAL LIGANDS FOR THE SILVER(I)-PROMOTED ENANTIOSELECTIVE ALLYLATION OF ALDEHYDES

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Abstract : Some novel chiral ligands (S)-(+) 1-substituted aryl-4- (1-phenyl) ethylformamido -5-amino -1, 2, 3-triazole were prepared starting from 1-substituted aryl-4- ethoxycarbonyl -5-amino-1, 2, 3- triazoles and other reagents. They were used as catalytic chiral ligands in the silver (I)-promoted enantioselective allylation reaction of aldehydes with allyltributyltin.

Catalytic asymmetric synthesis is a valuable method for the preparation of optically active substances(1). In this context, the stereoselective addition of organometallics to a carbonyl group has been extensively studied. In particular, the enantioselective allylation of carbonyl compounds is a challenging problem in organic synthesis. Although numerous important examples of the reaction using a stoichiomeric amount of chiral diamine have been reported(2), there is no method available for a catalytic process including chiral diamine having v-triazole. Recently Yamamoto reported a new catalytic enantioselective allylation reaction of aldehydes with allyltributyltin using a BINAP-silver (I) complex as a catalyst (3). To the best of our knowledge, this is the few case using a chiral silver (I) complex in a catalytic asymmetric reaction. This interesting result prompted us to design and synthesize other chiral ligands which are suitable for making chiral silver(I) complexes for catalytic asymmetric reactions. We wanted to try some chiral ligands containing a nitrogen atom because it is well known that nitrogen can easily coordinate to various metals such as Co, Cu, Zn and other metal giving stable chiral metal complexes(4) .Based on this concept, using (S)-(+)-1-phenylethylamine as a chiral scaffold, we started to prepare a series of the chiral (S)-(+) 1-substituted aryl-4- (1-phenyl) ethylformamido-5-amino-1, 2, 3-triazole from 1-substituted aryl-4-ethoxycarbonyl -5-amino-1, 2, 3-triazoles and other reagents. In this paper, we wish to report the results using them as catalytic chiral ligands for silver (I)-promoted enantioselective allylation reaction of various aldehydes with allyltributyltin.

Results and Discussion

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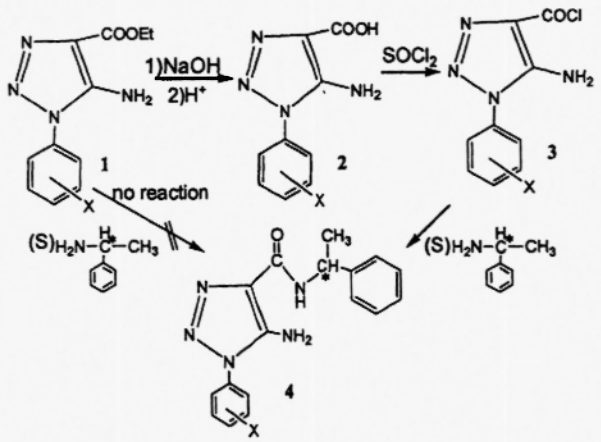
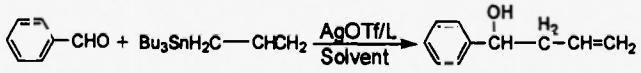
1-substituted aryl-4-ethoxycarbonyl-5-amino-1, 2, 3 –triazoles **1** react with sodium hydrate to give 1-substituted aryl-4-carboxyl-5-amino-1, 2, 3-triazole **2** in excellent yields. And then compounds **2** treatment using thionyl chloride to give 1-substituted aryl-4-carboxyl chloride-5-amino-1, 2, 3–triazole **3**. Compounds **3** reaction with (S)-(+)-1-phenylethylamine leads to (S)-(+) 1-substituted aryl-4- (1-phenyl) ethylformamido -5-amino-1, 2, 3-triazole. After usual workup and purification by silica gel column chromatography, compounds **4** were obtained as colorless solids in moderate to good yield. In addition, using (S)-(+)-1-phenylethylamine as a chiral scaffold reacts with 1-substituted aryl-4- ethoxycarbonyl-5-amino-1, 2, 3-triazole, we tried to synthesize the novel chiral ligand 4. No reaction took place between (S)-(+)-1-phenylethylamine and 1-substituted aryl-4- ethoxycarbonyl-5-amino-1, 2, 3-triazoles. Structures of compounds 4 were confirmed by spectral data and microanalysis. These chiral ligands were used for the silver(I)-promoted enantioselective allylation reaction of aldehydes with allyltributyltin. The ee value of the products were determined by HPLC analysis using a chiral stationary phase column (Chiralcel OD and OJ) and the absolute configuration of the major enantiomer was assigned according to the sign of the specific rotation. Silver(I) triflate is a good catalyst for allylation of aldehydes, By means of the novel chiral ligand 4, the ee value can reach 42% in THF at -20°C. In addition, if the reaction was carried out below -30°C, the reaction proceeded very slowly. By means of these optimized reaction conditions, various aldehydes were used as substrates for this addition reaction and the corresponding *sec*-alcohol could be obtained in 39–65% yield and 13.5–42% ee with *S*-configuration. These results are summarized in Table 1. The chiral compounds 4 are quite stable chiral ligands. For chiral ligands **4**, as expected the nitrogen atoms can coordinate to the silver(I) metal center to some extent giving a chiral environment, although the achieved ee value is low. This result strongly suggests that the coordination between the nitrogen atom and silver(I) metal plays an important role in this reaction. Thus, we believe that chiral ligand 4 is a diamine chiral ligand, namely, the nitrogen atoms can coordinate to the silver(I) metal affording a chiral silver(I) Lewis acid. In order to verify this speculation, we attempted to obtain a single crystal of the catalyst to confirm its structure. But despite extensive efforts, we could not obtain a single crystal of chiral silver(I) complex which could be subjected to X-ray crystal analysis.



X= 4'-CH_3; 4'-OCH_3; 4'-OC_2H_5; 3'-CF_3; 3'-Br;

Scheme -1 : Synthesis of compounds 4

In conclusion, the chiral diamine 4 was found to be a new class of relatively effective chiral ligands for the silver(I)-promoted enantioselective allylation reaction of aldehydes with allyltributyltin, although they are not as effective as BINAP_silver(I) complex(5). This paper, for the first time, discloses that chiral diamine obtaining v-triazole can catalyze the enantioselective allylation reaction using silver(I) salt. These results open a new way to design and synthesize new chiral ligands for asymmetric reactions. Efforts are underway to elucidate the mechanistic details of this addition reaction and to disclose the exact structure of the active species. Moreover, we are planning to synthesize similar diamine obtaining v-triazole in order to find more effective and stereoselective chiral ligands and to utilize these novel chiral ligands with regard to other catalytic asymmetric reactions.



Entry	Ligand	Solvent	Temp. [°C]	Time (h)	Yield (%)	Ee%	Config.
1	4a	THF	-20	48	65	42	S
2	4b	THF	-20	48	56	34	S
3	4c	THF	-20	48	43	15	S
4	4d	THF	-20	48	60	29	S
5	4e	THF	-20	48	39	13.5	

Experimental

Melting points were determined on X4 micromelting point apparatus (China) and uncorrected. ^1H NMR spectra were recorded on a Bruker 400A instrument ($CDCl_3$, DMSO-d_6)

with TMS as internal reference. IR spectra were recorded (KBr) using Bruker IFS 120 HP spectrophotometer. Mass spectra were recorded on HP6890/5973GC/MS. Optical rotations were determined in a solution of $CHCl_3$ at 25°C using a Perkin–Elmer 241 MC polarimeter; [α]D values are given in units of 10^{-1} deg cm^2 g^{-1}. The organic solvents used were dried by standard methods when necessary. All solid compounds reported in this paper gave satisfactory CHN microanalyses with an Vario EL Elemental Analyzer. Commercially obtained reagents were used without further purification. All reactions were monitored by TLC. Flash column chromatography was carried out using flash-chromatography on silica gel. All allylation experiments were performed under nitrogen using standard Schlenk techniques. The enantiomeric excesses of *sec*-alcohols were determined by HPLC analysis using a chiral stationary phase column (column, Daicel Co. Chiralcel OD and OJ; eluent, 99:1 hexane:2-propanol mixture).

Preparation of chiral (S)-(+) 1-substituted aryl-4- (1-phenyl) ethylformamido-5-amino-1, 2, 3-triazole **4**.

1-Substituted aryl-4-ethoxycarbonyl-5-amino-1, 2, 3-triazoles **1** was prepared according to the literature procedure(6).

1-substituted aryl-4-ethoxycarbonyl-5-amino-1, 2, 3 –triazole **1** (2mmol) in ethanol (95%) (25mL) was added sodium hydrate at room temperature, after the mixture was refluxed for 2h and then cooled to room temperature. Watery solution of acetic acid was added slowly, after adjustment to PH<6 with watery solution of acetic acid, a solid material slowly precipitated. It was collected by filtration and washed with water and to give 1-substituted aryl-4-carboxyl -5-amino-1, 2, 3-triazole **2**. To a stirred solution of compounds **2** (1mmol) in anhydrous acetonitrile (10mL) was added excess thionyl chloride at room temperature. After the mixture was stirred for 4h at room temperature, the solvent and excess thionyl chloride were removed under reduced pressure to give 1-substituted aryl-4-carboxyl chloride-5-amino-1, 2, 3 –triazole **3**, anhydrous acetonitrile solution (10mL) of (S)-(+)-1-phenylethylamine (1mmol) was added to the residue at room temperature, the mixture was stirred for 24 hours, solvent was evaporated under reduced pressure, the residue was purified by flash-chromatography on silica gel (hexane/EtOAc) and to give (S)-(+)-1-substituted aryl-4- (1-phenyl) ethylformamido-5-amino-1, 2, 3-triazole.

4a: (S)-(+)-1-(4'-CH_3)phenyl-4- (1-phenyl)ethylformamido-5-amino-1, 2, 3-triazole: m.p. 112-113°C, ^1H NMR ($CDCl_3$) δ: 1.56(d, *J*=4 Hz, 3H, CH_3), 2.44(s, 3H, Ph-CH_3), 2.56(m, 1H, CH-N), 5.26(s, 2H, NH_2); 7.26-7.37(9H, m), IR (KBr) ν: 3459, 3423, 3355, 1653 (C=O), 1624(C=N), 1026 (-N-N=N) cm^{-1}; MS-EI *m/z* (%):321(81.3), 250(16.3), 217(39.4), 146 (61.2), 105(100), 91(62.3) 77(31). 65(20.5). Anal. Calcd. for $C_{18}H_{19}N_5O$: C, 67.27, H, 5.96, N, 21.80; found C, 67.16, H, 5.90, N, 21.7.

4b: (S)-(+)-1-(4'-OCH_3)phenyl-4- (1-phenyl)ethylformamido-5-amino-1, 2, 3-triazole: m.p. 112-113°C, ^{1}H NMR ($CDCl_3$) δ: 1.56(d, *J*=4 Hz, 3H, CH_3), 3.71(m, 1H, CH-N), 3.98(s, 3H, Ph-OCH_3), 5.22(s, 2H, NH_2); 7.10-7.48(9H, m), IR (KBr) ν: 3449, 3412, 3353, 1661 (C=O), 1626(C=N), 1023 (-N-N=N) cm^{-1}; MS-EI *m/z* (%):337 δ75.3δ 266(16.3), 233 (9.4), 162 (71.2), 134(55.3), 105 (100), 92(32.3), 77(51). 65(15.3). Anal. Calcd. for $C_{18}H_{19}N_5O_2$: C, 64.09, H, 5.68, N, 20.77; Found C, 63.97, H, 5.60, N, 20.69.

4c: (S)-(+)-1-(4'-OC_2H_5)phenyl-4- (1-phenyl)ethylformamido-5-amino-1, 2, 3-triazole: m.p. 116-118°C, ^{1}H NMR ($CDCl_3$) δ: 1.31(t, *J*=6.0, 3H, OC_2H_5), 1.59(d, *J*=4 Hz, 3H, CH_3), 3.71(m, 1H, CH-N), 4.07(q, 2H, OCH_2CH_3), 5.22(s, 2H, NH_2); 7. 01-7.54 (9H, m). IR (KBr) ν: 3444, 3413, 3351, 1660 (C=O), 1625(C=N), 1020 (-N-N=N) cm^{-1}; MS-EI *m/z* (%):351 (83.3), 280(16.3), 247(15.4), 176 (51.2), 148 (58.5), 105 (100), 91 (12.3), 77(24.4), 29(10.5). Anal. Calcd. for $C_{19}H_{21}N_5O_2$: C, 64.94, H, 6.02, N, 19.93; Found C, 64.83, H, 5.96, N, 19.85.

4d: (S)-(+)-1-(3'-CF_3)phenyl-4- (1-phenyl)ethylformamido-5-amino-1, 2, 3-triazole: m.p. 126-128°C, ^{1}H NMR ($CDCl_3$) δ: 1.65(d, *J*=4 Hz, 3H, CH_3), 3.68(m, 1H, CH-N), 5.20(2H, s, NH_2); 7.23-7.53(9H, m), IR (KBr) ν: 3448, 3411, 3335, 1660 (C=O), 1627(C=N), 1018 (-N-N=N) cm^{-1}; MS-EI *m/z* (%):375 (38.3), 271 (40.3), 145 (21.4), 120(19.2) (10.2), 105 (100), 91(1.9), 77(76.4). Anal. Calcd. for $C_{18}H_{16}F_3N_5O$: C,57.6, H, 4.30, N, 18.67; Found C, 57.49, H, 4.23, N, 18.59.

4e: (S)-(+)-1-(3'-Br) phenyl-4- (1-phenyl) ethylformamido-5-amino-1, 2, 3-triazole: m.p. 116-117°C, ^{1}H NMR ($CDCl_3$) δ: 1.56(d, *J*=4 Hz, 3H, CH_3), 3.70(m, 1H, CH-N), 5.19(2H, s, NH_2); 7.34-7.76(9H, m), IR (KBr) ν: 3441, 3409, 3329, 1655 (C=O), 1627(C=N), 1019 (-N-N=N) cm^{-1}; MS-EI *m/z* (%): 385 (24.3), 280 (22.3), 185 (11.4), 157 (10.2), 105 (100), 91(2.3), 77(19.4). Anal. Calcd. for $C_{17}H_{16}BrN_5O$: C, 52.86, H, 4.18, N, 18.13; Found C, 52.74, H, 4.12, N, 18.05.

Typical reaction procedure

To a solution of (S)-(+) 1-substituted aryl-4- (1-phenyl) ethylformamido-5-amino-1, 2, 3-triazole **4**. (0.1 mmol) and AgOTf (25.7 mg, 0.1 mmol) in THF (4ml) was added benzaldehyde (53 mg, 0.5 mmol, 50μl) at room temperature. After stirring the reaction mixture for 2 h, allyltributyltin (199 mg, 0.6 mmol, 186 μl) was added into the reaction solution at-20°C and the reaction mixture was stirred at-20°C for 24 h. The reaction was quenched by a mixture of 10% aq. HCl (8 ml) and solid KF (1 g) at room temperature for 1 h. The resulting precipitate was filtered off, and the filtrate was dried over $MgSO_4$ and then concentrated under reduced pressure. The residue was purified by silica gel column chromatography to give the homoallylic alcohol as a colorless oil.

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