Catalytic, Enantioselective Propargyl- and Allenylation Reactions of α-Imino Ester

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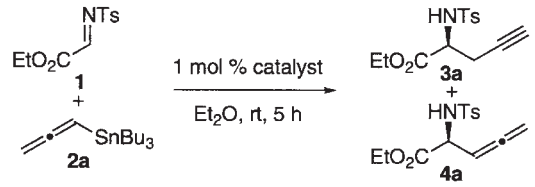
Catalytic, enantioselective propargyl- and allenylation reactions of α-imino ester have been achieved by means of the $[Cu(MeCN)_4]ClO_4$/(*R*)-tol-BINAP catalyst to afford the corresponding propargyl- and allenyl-substituted α-amino acid derivatives, respectively, in good yields with good enantiomeric excesses.

Chiral Lewis acid-catalyzed, enantioselective addition reactions of imines with carbon nucleophiles provide a powerful method for the synthesis of a variety of optically active nitrogen compounds.[1] When the reaction was carried out with α-imino esters as imine substrates, optically active α-amino acid derivatives could be obtained. Catalytic, enantioselective addition reactions of α-imino esters with carbon nucleophiles have been recently reported.[2–6] In addition to the above reactions, we anticipated that the catalytic, enantioselective addition reactions of α-imino esters with allenyl- and propargyl organometallics would provide a useful route for the synthesis of optically active propargyl- and allenyl-substituted α-amino acid derivatives, respectively. These compounds have been prepared by using a stoichiometric amount of chiral sources[7] or by enzymatic resolution[8] so far, and the catalytic, enantioselective propargyl- and allenylation reactions of imines have not been achieved yet irrespective of potential utility of the resultant products: They are (1) known to exhibit interesting biological activities[9] and (2) expected to be important synthetic intermediates for the synthesis of a number of unnatural α-amino acid derivatives because the carbon-carbon multiple bonds can be readily functionalized.[7d,9b,10] In this paper, we report the first catalytic, enantioselective propargyl- and allenylation reactions of α-imino ester with allenyl- and propargyltins, which afford optically active propargyl- and allenyl-substituted α-amino acid derivatives, respectively.[11]

We have initially investigated the reaction of α-imino ester **1** with allenyltributyltin (**2a**) under the various conditions to examine the effect of catalysts on yields and enantiomeric excesses (Table 1). We have chosen the copper/chiral diphosphine catalysts since they have shown to be the most promising for the enantioselective reactions using α-imino esters.[2b,c,3–6] In the presence of the chiral Lewis acid catalyst (1 mol%) prepared from $[Cu(MeCN)_4]ClO_4$ and (*R*)-tol-BINAP[12] in ether at room temperature, **1** (1.0 equiv) smoothly reacted with **2a** (1.1 equiv) to give a mixture of the two regioisomers, **3a** and **4a**, in 78% yield (entry 1). The reaction proceeded with S_E2' manner, and the regioselectivity was quite high (**3a** : **4a** = >97 : <3). The enantiomeric excess of the major product **3a** was 80%. Choice of the Lewis acid and chiral diphosphine ligand combination is crucial in order to obtain both good yields and enantiomeric excesses. For example, use of the chiral Lewis acid catalysts prepared from $[Cu(MeCN)_4]ClO_4$ and either (*R*)-BINAP[12] or (*R*,*R*)-DIOP[12] resulted in inferior enantiomeric excesses (entries 2 and 3). In addition, the reaction using a $Cu(OTf)_2$/(*R*)-tol-BINAP combination proceeded with a comparable enantiomeric excess though the yield of the product became lower (entry 4). In the presence of $[Cu(MeCN)_4]ClO_4$/(*R*)-tol-BINAP catalyst, better yield was obtained when a slightly excess amount of **1** was employed (entry 5). Lowering the reaction temperature to −30 °C further improved the enantiomeric excess to 86% (entry 6).

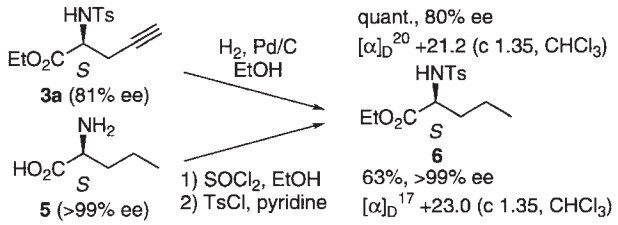
Table 1. Effect of catalysts in the reaction of **1** with **2a**[a]



Entry	Catalyst[b]	Yield/%	3a:4a[c]	ee/% of 3a[d]
1	$[Cu(MeCN)_4]ClO_4$/(*R*)-tol-BINAP	78	>97:<3	80
2	$[Cu(MeCN)_4]ClO_4$/(*R*)-BINAP	76	97:3	68
3	$[Cu(MeCN)_4]ClO_4$/(*R*,*R*)-DIOP	45	92:8	0
4	$Cu(OTf)_2$/(*R*)-tol-BINAP	62	93:7	80
5[e]	$[Cu(MeCN)_4]ClO_4$/(*R*)-tol-BINAP	84	>97:<3	81
6[f]	$[Cu(MeCN)_4]ClO_4$/(*R*)-tol-BINAP	96	97:3	86

[a]Molar ratio; **1**:**2a** = 1.0:1.1. [b][Cu]:ligand = 1.0:1.1. [c]Determined by 400 MHz ^{1}H NMR. [d]Determined by HPLC (Chiralpak AD). [e]Molar ratio; **1**:**2a** = 1.2:1.0. [f]Molar ratio; **1**:**2a** = 2.0:1.0. Reaction temperature; –30 °C.

The absolute configuration of **3a** was unambiguously determined to be *S* by conversion of both **3a** and commercially available (*S*)-2-aminopentanoic acid (**5**) into a common intermediate **6** as shown in Scheme 1.

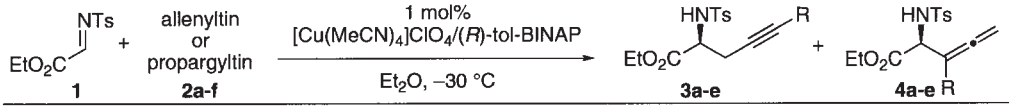


Scheme 1. Determination of the absolute configuration of **3a**.

Under the optimized conditions, catalytic, enantioselective propargylation reactions using allenyltin reagents were carried out (Table 2).[13] It was found that the nature of the substituents on the tin atom slightly affected both yields and enantiomeric excesses. When allenyltriphenyltin (**2b**) was subjected to the reaction, a mixture of **3a** and **4a** was produced in 38% yield, and the enantiomeric excess of **3a** was 77% (entry 2). Electron-withdrawing group significantly decreased the nucleophilicity of allenyltin **2**, thus the reaction using **2c** did not proceed completely (entry 3).

We have anticipated that in place of allenyltins, propargyltins would react with **1** to produce corresponding allenyl-substituted amino ester in a fashion of S_E2'. Then, we have focused on

Table 2. Catalytic, enantioselective propargyl- and allenylation reactions[a]



Entry	Tin reagent[b]		Time/h	Product	Yield/%	3:4[c]	ee/%[d]
1	$SnBu_3$	**2a** (>97:<3)	5	**3a, 4a** (R = H)	96	97:3	86
2	$SnPh_3$	**2b** (95:5)	24	**3a, 4a** (R = H)	38	89:11	77
3[e]	CO_2Me, $SnBu_3$	**2c**(>97:<3)	5	**3b, 4b** (R = CO_2Me)	34	>97:<3	11
4	$SnBu_3$	**2d** (8:92)	24	**3c, 4c** (R = Me)	95	5:95	61
5	Ph, $SnBu_3$	**2e** (11:89)	24	**3d, 4d** (R = Ph)	25	9:91	97
6	Me_3Si, $SnBu_3$	**2f** (<3:>97)	24	**3e, 4e** (R = $SiMe_3$)	72	<3:>97	93

[a]Molar ratio; **1**:**2** = 2.0:1.0. [Cu]:ligand = 1.0:1.1. [b]The values in parentheses represent ratio of allenyltin/propargyltin. [c]Determined by 400 MHz ^{1}H NMR. [d]Ee of the major isomers determined by HPLC (Chiralpak AD). The absolute configuration was tentatively assigned to be *S* except for **3a**. [e]Molar ratio; **1**:**2** = 1.2:1.0. Reaction temperature; rt.

development of allenylation of **1** with propargyltins. The reaction of methyl-substituted propargyltin **2d** afforded a mixture of **3c** and **4c** in 95% yield with a high regioselectivity (**3c** : **4c** = 5 : 95, entry 4). Unfortunately, the enantiomeric excess of the major product **4c** was moderate (61% ee). When the reaction of phenyl-substituted propargyltin **2e** was carried out, **4d** was obtained in a moderate yield with high enantiomeric excess (25%, 97% ee, entry 5). Gratifyingly, both yield and enantiomeric excess were greatly improved when trimethylsilyl-substituted propargyltin **2f** was used. The corresponding allenyl-substituted amine **4e** was obtained in 93% ee (entry 6).

In summary, we have developed catalytic, enantioselective propargyl- and allenylation reactions of α-imino ester in the presence of $[Cu(MeCN)_4]ClO_4$/(*R*)-tol-BINAP catalyst. The present reaction provides a new methodology for the synthesis of optically active α-amino acid derivatives.

Dedicated to Professor Teruaki Mukaiyama on the occasion of his 75th birthday.

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12 (*R*)-tol-BINAP = (*R*)-2,2′-bis(di-*p*-tolylphosphino)-1,1′-binaphthyl; (*R*)-BINAP = (*R*)-2,2′-bis(diphenylphosphino)-1,1′-binaphthyl;(*R*, *R*)-DIOP = (*R*, *R*)-2,3-*O*-isopropylidene-2,3-dihydroxy-1,4-bis(diphenylphosphino)-butane.

13 A typical experimental procedure for entry 1 of Table 2: The catalyst was prepared by treating $[Cu(MeCN)_4]ClO_4$ (0.65 mg, 2.0 μmol) and (*R*)-tol-BINAP (1.49 mg, 2.2 μmol) in ether (1 mL) and stirring at room temperature for 0.5 h. To this mixture was added **1** (102 mg, 0.40 mmol) in ether (0.5 mL), and the resultant mixture was cooled to $-30\,^{\circ}C$. To this mixture was added **2a** (66 mg, 0.20 mmol). After being stirred for 5 h at this temperature, the reaction was quenched with 10% aqueous KF. The aqueous layer was extracted with ether, and the combined organic layers were washed with brine and dried over Na_2SO_4. After filtration and concentration, the residue was purified by column chromatography (SiO_2, eluent: hexane to hexane/EtOAc = 5/1) to give the mixture of **3a** and **4a** (57 mg, 96%, **3a** : **4a** = 97 : 3). The enantiomeric excess of **3a** was determined to be 86% by HPLC analysis using Chiralpak AD column (hexane/*i*PrOH = 5/1).