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Cu(I)-Catalyzed Enantioselective [3 + 2] Cycloaddition Reaction of 1-Alkylallenylsilane with α-Imino Ester: Asymmetric Synthesis of Dehydroproline Derivatives

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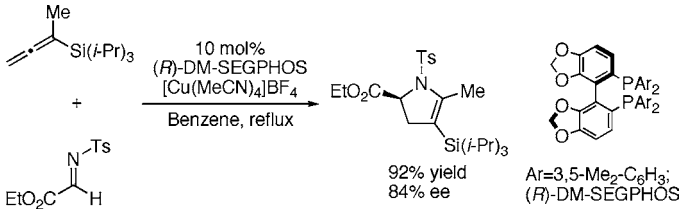
ABSTRACT



The catalytic, enantioselective [3 + 2] cycloaddition reaction of 1-alkyl-substituted allenylsilanes with α-imino ester has been achieved by means of [Cu(MeCN)$_4$]BF$_4$/(*R*)-DM-SEGPHOS catalyst to afford silyl-substituted dehydroproline derivatives in high yields and enantioselectivities.

The chiral Lewis acid-catalyzed cycloaddition reaction is a useful method for enantioselective formation of carbocyclic and heterocyclic compounds[1] which are important building blocks for natural product synthesis and thus attracts attention of synthetic organic chemists. α-Substituted allenylsilanes[2] are reported to work as counterparts of a cycloaddition reaction.[3] Their application to enantioselective reaction is limited. For example, 1-methylallenylsilane undergoes [3 + 2] cycloaddition reaction with electron deficient olefins, aldehydes, and *N*,*O*-hemiacetal to give five-membered carbocycles and heterocycles, respectively.[4] Chiral Lewis acid-catalyzed [3 + 2] cycloaddition reaction with aldehydes leading to dihydrofuran derivatives has been reported.[5] Catalytic enantioselective [3 + 2] cycloaddition reaction of allenylsilane with imine has not been reported as far as we know. Recently, we have reported Cu(I)-catalyzed enantioselective [2 + 2] cycloaddition reaction of 1-methoxyallenylsilane with α-imino ester.[6] We wish to report herein enantioselective [3 + 2] cycloaddition reaction of α-alkylallenylsilane with α-imino ester by means of chiral Cu(I) catalyst.

At the outset, 1-methylallenylsilane **1a**[7] and α-imino ester **2** were treated with [Cu(MeCN)$_4$]BF$_4$ (10 mol %) in THF.[6] Although no reaction proceeded at room temperature, [3 + 2] cycloaddition reaction took place under reflux conditions

(1) Evans, D. A.; Johnson, J. S. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer, Berlin, 1999; p 1177. Oi, T.; Maruoka, K. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer, Berlin, 1999; p 1237. *Cycloaddition Reactions in Organic Synthesis*; Kobayashi, S., Jørgensen, K. A., Eds.; Wiley-VCH: Weinheim, 2002.

(2) Allenylsilane has been used as a propargyl anion equivalent; see: Yamamoto, H. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, 1991; Vol 2, p 81. Danheiser, R. L.; Carini, D. J. *J. Org. Chem.* **1980**, *45*, 3925. Danheiser, R. L.; Carini, D. J.; Kwasigroch, C. A. *J. Org. Chem.* **1986**, *51*, 3870.

(3) Panek, J. S. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, 1991; Vol 1, p 579. Masse, C. E.; Panek, J. S. *Chem. Rev.* **1995**, *95*, 1293.

(4) Danheiser, R. L.; Carini, D. J.; Basak, A. *J. Am. Chem. Soc.* **1981**, *103*, 1604. Danheiser, R. L.; Fink, D. M. *Tetrahedron Lett.* **1985**, *26*, 2513. Danheiser, R. L.; Kwasigroch, C. A.; Tsai, Y.-M. *J. Am. Chem. Soc.* **1985**, *107*, 7233.

(5) Evans, D. A.; Sweeney, Z. K.; Rovis, T.; Tedrow, J. S. *J. Am. Chem. Soc.* **2001**, *123*, 12095.

(6) Akiyama, T.; Daidouji, K.; Fuchibe, K. *Org. Lett.* **2003**, *5*, 3691.

(7) For the preparation, see ref 5.

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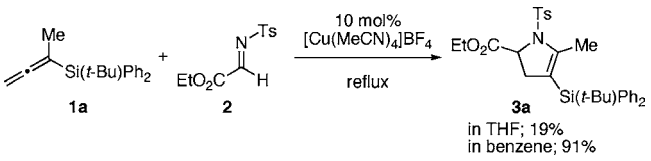
Scheme 1. Catalytic [3 + 2] Cycloaddition Reaction with α-Imino Ester

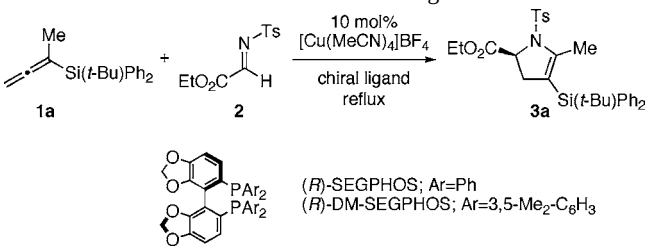


to give silyl-substituted dehydroproline derivative **3a** in 19% yield. Use of benzene as a solvent improved the chemical yield to 91% (Scheme 1).

We attempted the cycloaddition reaction of **1a** with other imine derivatives such as PhCH═NPh, PhCH═NTs, and EtOCOCH═NC_6H_4(*p*-OMe) using $[Cu(MeCN)_4]BF_4$ as the catalyst; no cycloadducts were obtained. It was found that use of highly reactive aldimine **2** is essential for the present cycloaddition reaction to proceed.

The asymmetric synthesis of silyl-substituted dehydroproline derivative **3a**[8] was investigated and the results are shown in Table 1. Treatment of **1a** (1.0 equiv) and **2** (1.2 equiv) with $[Cu(MeCN)_4]BF_4$/(*R*)-BINAP catalyst (10 mol %)[9] in refluxing benzene for 7 h afforded **3a** in 48% yield with 58% ee (entry 1). Enantiomeric excess was determined by HPLC with a chiral stationary phase column (Chiralpak AD-H). (*R*)-SEGPHOS[10] (entry 3) was more effective than (*R*)-Tol-BINAP (entry 2). When (*R*)-DM-SEGPHOS was used as a chiral ligand, the highest enantioselectivity (85% ee) was observed (entry 4). Use of 2.0 equiv of **2** significantly improved the chemical yield to 74% (entry 5). Other solvents gave inferior results (entries 6−8).

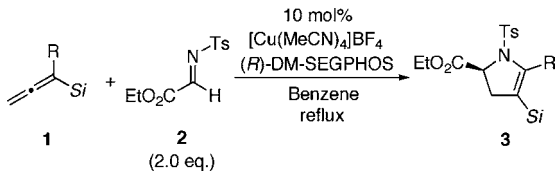
Table 1. Effect of Solvents and Chiral Ligands[a]



entry	solvent	chiral ligand	yield of **3a** (%)	ee of **3a** (%)
1	benzene	(*R*)-BINAP	48	58
2	benzene	(*R*)-Tol-BINAP	67	57
3	benzene	(*R*)-SEGPHOS	65	67
4	benzene	(*R*)-DM-SEGPHOS	53	85
5[b]	benzene	(*R*)-DM-SEGPHOS	74	78
6	1,4-dioxane	(*R*)-DM-SEGPHOS	32	78
7	1,2-dichloromethane	(*R*)-DM-SEGPHOS	55	73
8	toluene	(*R*)-DM-SEGPHOS	60	75

[a] 1.2 equiv of **2** was employed. [b] 2.0 equiv of **2** was employed.

Table 2. Reaction with Other Allenyl Derivatives



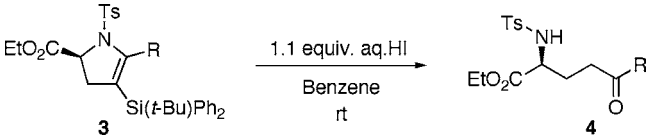
entry	Si	R	time (h)	yield of **3** (%)	ee of **3** (%)
1	Si(*t*-Bu)Ph_2	Me	7	74	85
2	Si(*t*-Bu)Ph_2	*n*-Pr	9	52	77
3	Si(*t*-Bu)Ph_2	*i*-Pr	24	50	78
4	Si(*t*-Bu)Ph_2	cyclohexyl	20	46	71
5[a]	Si(*t*-Bu)Me_2	Me	3	90	75
6	$SiPh_3$	Me	5	71	84
7[a]	Si(*i*-Pr)$_3$	Me	1	92	84
8	Si(*t*-Bu)Ph_2	H	3	0	

[a] $[Cu(MeCN)_4]PF_6$ was employed.

Other allenylsilanes were examined, and the results are shown in Table 2. Allenyl(*tert*-butyl)diphenylsilanes bearing bulky silyl group afforded cycloadducts in good enantioselective manner (entries 2−4). *tert*-Butyldimethylsilyl-, triphenylsilyl-, and triisopropylsilyl-subsituted allenylsilanes also gave [3 + 2] cycloadducts (entries 5−7). It is noted that parent allenylsilane gave no cycloadduct (entry 8). The presence of α-alkyl group is essential for the present cycloaddition reaction to proceed.

Treatment of 2-alkyl-substituted pyrroline esters **3** with aqueous HI solution at room temperature for 2−3 h furnished desilylated γ-amino ketones **4** in high yields and without decreasing enantioselectivities (Table 3).

Table 3. Ring-Opening Reaction



entry	R	time (h)	yield of **4** (%)	ee of **4** (%)
1	Me (85% ee)	3	98	85
2	*n*-Pr (77% ee)	2	97	77
3	cyclohexyl (71% ee)	3	89	71

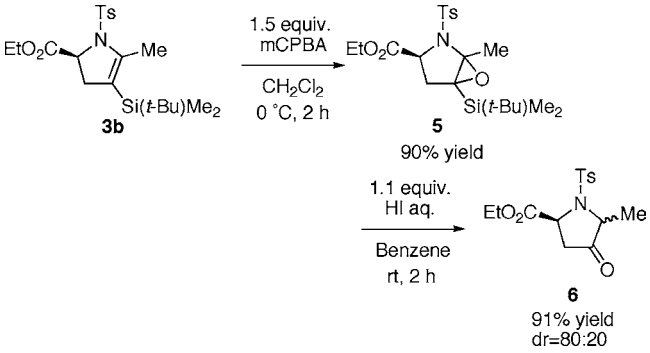
The 2-pyrroline esters described in this study afforded useful synthons. The vinylsilane functionality in pyrroline **3**

(8) For the chiral synthesis of 3-pyrroline, see: Kagoshima, H.; Okamura, T.; Akiyama, T. *J. Am. Chem. Soc.* **2001**, *123*, 7182.

(9) For enantioselective Cu(I)-catalyzed nucleophilic addition reaction with α-imino ester, see: Ferraris, D.; Young, B.; Dudding, T.; Lectka, T. *J. Am. Chem. Soc.* **1998**, *120*, 4548. Drury, W. J., III; Ferraris, D.; Cox, C.; Young, B.; Lectka, T. *J. Am. Chem. Soc.* **1998**, *120*, 11006. Yao, S.; Fang, X.; Jørgensen, K. A. *Chem. Commun.* **1998**, 2547. Yao, S.; Saaby, S.; Hazell, R. G.; Jørgensen, K. A. *Chem. Eur. J.* **2000**, *6*, 2435. Ferrars, D.; Young, B.; Cox, C.; Dudding, T.; Ryzhkov, L.; Taggi, A. E.; Lectka, T. *J. Am. Chem. Soc.* **2002**, *124*, 67. Taggi, A. E.; Hafez, A. M.; Lectka, T. *Acc. Chem. Res.* **2003**, *36*, 10.

(10) Saito, T.; Yokozawa, T.; Ishizaki, T.; Moroi, T.; Sayo, N.; Miura, T.; Kumobayashi, H. *Adv. Synth. Catal.* **2001**, *343*, 264.

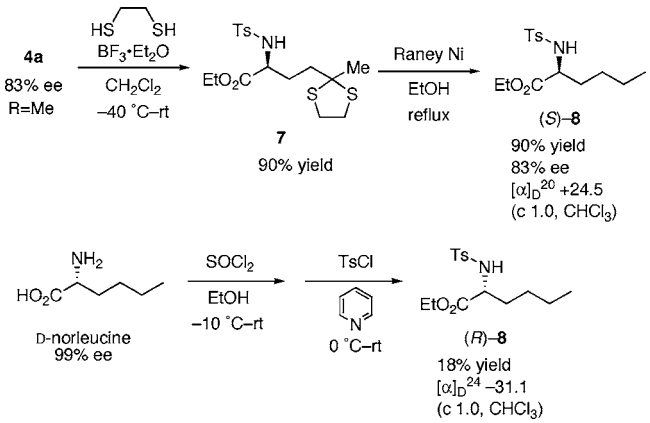
Scheme 2. Synthesis of Pyrrolidinone



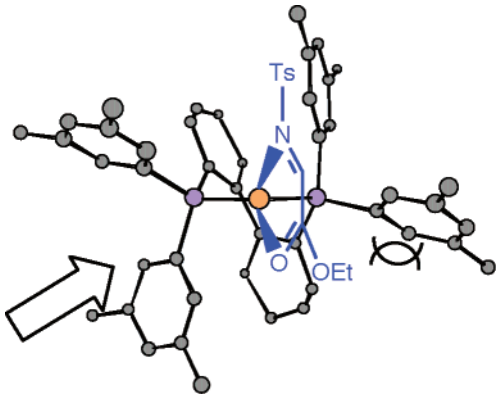
is nucleophilic, and can be epoxidized with *m*-CPBA to produce epoxypyrrolidine **5**. Subsequent treatment with aqueous HI solution at room temperature furnished desilylated 3-pyrrolidinone **6** in a high yield (Scheme 2). The relative stereochemistry of **6** has not been determined.[11]

Next, the absolute stereochemistry of γ-amino ketone **4a** (R = Me) was determined to be *S* by comparison of the optical rotation of **8**, which was prepared from **3a** via **4a**, with that of the authentic sample prepared from D-norleucine (Scheme 3). The absolute stereochemistry of pyrroline ester **3a** was thus found to be *S*. We surmised that the absolute

Scheme 3. Determination of the Absolute Configuration



Scheme 4. Plausible Transition State[a]



[a] Methylenedioxy moieties of (*R*)-DM-SEGPHOS are omitted for clarity.

stereochemistries of other γ-amino ketones and pyrrolines to be *S* by analogy.

The stereochemical outcome can be rationalized by the plausible transition state model as shown in Scheme 4.[12] Because the *Re*-face is blocked by the pseudoequatorial dimethyphenyl moiety, allenylsilane attacks the *Si*-face preferentially to give *S*-isomer selectively.

In summary, we have developed the first enantioselective [3 + 2] cycloaddition reaction of 1-alkyl-substituted allenylsilanes with α-imino ester by chiral Cu(I) catalyst. Use of (*R*)-DM-SEGPHOS as a chiral ligand resulted in high enantioselective cycloaddition reaction.

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Supporting Information Available: Experimental procedures, spectra data, and characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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(11) We could not obtain **6** as crystals. All our attempts to determine the relative stereochemistry of **6** by NOE experiments failed.

(12) Ferraris, D.; Young, B.; Cox, C.; Drury, W. J., III; Dudding, T.; Lectka, T. *J. Org. Chem.* **1998**, *63*, 6090. Yao, S.; Saaby, S.; Hazell, R. G.; Jørgensen, K. A. *Chem. Eur. J.* **2000**, *6*, 2435.