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Cu(I)-Catalyzed Enantioselective [2 + 2] Cycloaddition of 1-Methoxyallenylsilane with α-Imino Ester: Chiral Synthesis of α,*β*-Unsaturated Acylsilanes

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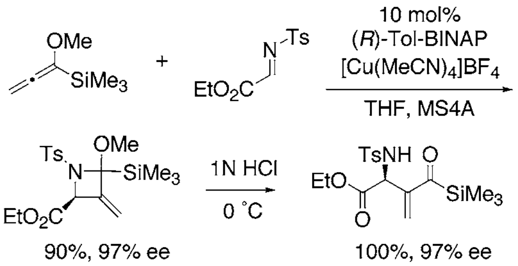
ABSTRACT



The catalytic, enantioselective [2 + 2] cycloaddition reaction of 1-methoxyallenylsilanes with α-imino ester has been achieved by means of the $[Cu(MeCN)_4]BF_4$/(*R*)-Tol-BINAP catalyst to afford 3-methylene-azetidine 2-carboxylates in good yields and with excellent enantiomeric excesses. The acid-catalyzed ring opening of the azetidines afforded chiral acylsilanes quantitatively.

The chiral Lewis acid-catalyzed cycloaddition reaction is a useful method for the stereoselective synthesis of carbo- and heterocycles.[1] The development of novel cycloaddition reactions has attracted the attention of synthetic organic chemists. We wish to report herein a novel chiral Cu(I)-catalyzed enantioselective [2 + 2] cycloaddition reaction.

While α-substituted-allenylsilane[2] has been recognized as a useful component of the cycloaddition reactions,[3] its application to chiral Lewis acid-catalyzed enantioselective cycloaddition reaction is quite limited at present. For example, Danheiser extensively studied [3 + 2] cycloaddition reaction of 1-methylallenyltrimethylsilane leading to five-membered carbo- and heterocycles.[4] Its application to chiral Lewis acid-catalyzed enantioselective cycloaddition reaction with aldehyde has been realized quite recently, giving chiral dihydrofuran derivatives.[5] Chiral Lewis acid-catalyzed [2 + 2] cycloaddition of 1-methylthio-substituted allenylsilane with α,*β*-unsaturated carbonyl compounds gave cyclobutane derivatives enantioselectively.[6−9] [2 + 2] cycloaddition reaction of allenylsilane with a carbon−heteroatom double

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[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.

[2] Allenylsilane without an α-substituent 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.

[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] Hayashi, Y.; Nihata, S.; Narasaka, K. *Chem. Lett.* **1990**, 209. Narasaka, K.; Hayashi, Y.; Shimadzu, H.; Niihata, S. *J. Am. Chem. Soc.* **1992**, *114*, 8869. Hayashi, Y.; Narasaka, K. In *Comprehensive Asymmetric Catalysis* Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer, Berlin, 1999; p 1255.

[7] For enantioselective [2 + 2] cycloaddition of vinyl sulfide, see: Hayashi, Y.; Narasaka, K. *Chem. Lett.* **1989**, 793.

[8] For enantioselective [2 + 2] cycloaddition of styrenes, see: Engler, T. A.; Letavic, M. A.; Reddy, J. P. *J. Am. Chem. Soc.* **1991**, *113*, 5068.

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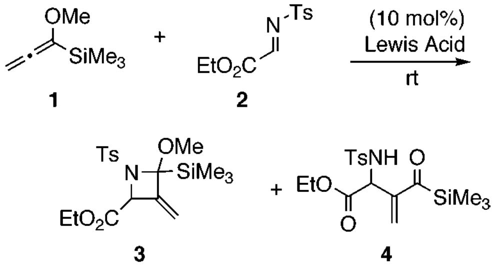
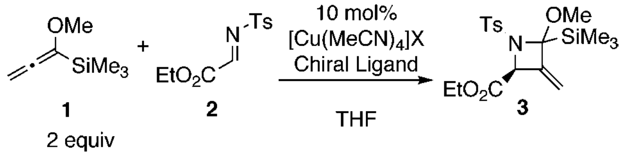
Table 1. Effect of Solvent and Lewis Acid



entry	Lewis acid	solvent	yield of **3**/%[a]	yield of **4**/%
1	$[Cu(MeCN)_4]ClO_4$	THF	74 (100:0)	0
2	$[Cu(MeCN)_4]ClO_4$	CH_2Cl_2	39 (74:26)	3
3	$[Cu(MeCN)_4]ClO_4$	Et_2O	19 (82:18)	3
4	$Cu(OTf)_2$	THF	10 (50:50)	10
5	$TiCl_4$	THF	15 (50:50)	15
6	$Sc(OTf)_3$	THF	8 (67:33)	2

[a] Figures in parentheses correspond to the ratio of the diastereomer.

Table 2. Effect of Lewis Acid and Chiral Ligand



entry	X	chiral ligand	temp/°C	yield/%	ee/%
1[a]	ClO_4	(*R*)-BINAP	rt	42	30
2[a]	PF_6	(*R*)-BINAP	rt	45	58
3[a]	BF_4	(*R*)-BINAP	rt	50	59
4[a]	BF_4	(*R*,*R*)-DIOP	rt	10	5
5[a]	BF_4	(*R*)-Tol-BINAP	rt	58	68
6	BF_4	(*R*)-Tol-BINAP	rt	69	68
7[b]	BF_4	(*R*)-Tol-BINAP	rt	98	68
8[b]	BF_4	(*R*)-Tol-BINAP	−40	97	74
9[b]	BF_4	(*R*)-Tol-BINAP	−78	90	97

[a] Performed with 1.0 equiv of **1** and 1.2 equiv of **2**. [b] In the presence of 4 Å molecular sieves.

bond, however, has not been reported.[10] Because four-membered heterocycles are potently useful synthetic intermediates for the biologically active compounds, we started our program to develop a novel enantioselective [2 + 2] cycloaddition reaction of allenylsilane with imines.[11] We already reported that the $[Cu(MeCN)_4]ClO_4$/(*R*)-Tol-BINAP-catalyzed[12] addition of allenylstannanes to α-imino ester furnished homopropargylic amines highly enantioselectively[13] and have selected α-imino ester **2** as a substrate.

At the outset, treatment of 1-methoxyallenyltrimethylsilane **1**[14,15] and α-imino ester **2** with $[Cu(MeCN)_4]ClO_4$ (10 mol %) in THF at room temperature for 2 h gave a mixture of azetidine **3** and acylsilane **4** after the usual workup. Because azetidine **3** is labile under acidic conditions, basic workup and subsequent purification by SiO_2 column chromatography by use of an eluent containing 10% Et_3N afforded **3** in 74% yield as a single stereoisomer, which was determined by 400 MHz ^1H NMR (Table 1, entry 1). Other solvents gave inferior results both in chemical yield and stereoselectivity. The relative stereochemistry of **3** has not been determined.[16] Use of other Lewis acids such as $TiCl_4$, $SnCl_4$, and $BF_3 \cdot OEt_2$ resulted in the formation of both **3** and **4** in modest yields (entries 2−6). The ring opening of **3** proceeded under acidic conditions. Treatment of **3** with 1 N HCl in THF at 0 °C for 12 h furnished **4** quantitatively. This is the first example of the [2 + 2] cycloaddition reaction of an allenylsilane with a carbon−nitrogen double bond.

Next, we attempted the cycloaddition reaction of **1** with other imine derivatives such as PhCH═NPh, PhCH═NTs, and EtOCOCH═NPh using $[Cu(MeCN)_4]ClO_4$ 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 **3** was next investigated by use of chiral phosphine ligand, and the results are shown in Table 2. Treatment of **1** (1.0 equiv) and **2** (1.2 equiv) with 10 mol % $[Cu(MeCN)_4]ClO_4$/(*R*)-BINAP catalyst at room temperature in THF afforded **3** in 42% yield with 30% ee (entry 1). Enantiomeric excess was determined by HPLC with a chiral stationary phase column (Chiralpak AD-H). The counteranion of the Lewis acid affected the enantioselectivity; $[Cu(MeCN)_4]BF_4$ was found to be the most effective in improving the enantioselectivity (entry 3). (*R*,*R*)-DIOP was not effective (entry 4). Use of (*R*)-Tol-BINAP significantly improved the enantioselectivity (entry 5). Use of 2.0 equiv of **1** and 1.0 equiv of **2** improved the chemical yield to 69% (entry 6). The addition of 4 Å molecular sieves further improved the yield to 98% (entry 7). The highest enantioselectivity (97% ee) was observed at −78 °C (entry 9).

Other allenyl compounds were examined, and the results are shown in Table 3. Allenylsilanes bearing dimethylphenylsilyl and *tert*-butyldimethylsilyl moieties afforded cy-

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(9) For [2 + 2] cycloaddition of allenylmethylsilane, see; Hojo, M.; Murakami, C.; Nakamura, S.; Hosomi, A. *Chem. Lett.* **1998**, 331.

(10) For the reaction of methythioallenylsilane to aldehyde and aldimine, see: Narasaka, K.; Shibata, T.; Hayashi, Y. *Bull. Chem. Soc. Jpn.* **1992**, *65*, 2825. Narasaka, K.; Shibata, T.; Hayashi, Y. *Bull. Chem. Soc. Jpn.* **1992**, *65*, 1392.

(11) For recent diastereoselective metal-catalyzed [2 + 2] cycloaddition, see: Baik, T.-G.; Luis, A. L.; Wang, L.-C.; Krische, M. J. *J. Am. Chem. Soc.* **2001**, *123*, 6716.

(12) 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. Ferraris, D.; Young, B.; Cox, C.; Dudding, T.; W. J. Drury, I.; 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.

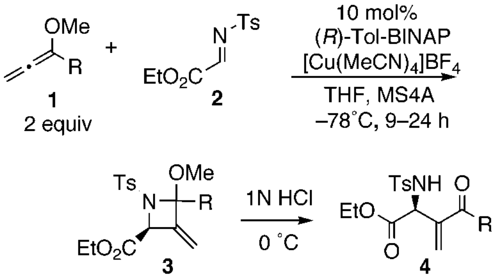
(13) Kagoshima, H.; Uzawa, T.; Akiyama, T. *Chem. Lett.* **2002**, 298.

(14) For preparation, see: Pappalardo, P.; Ehlinger, E.; Magnus, P. *Tetrahedron Lett.* **1982**, *23*, 309.

(15) For the reactions, see: Tanino, K.; Yoshitani, N.; Moriyama, F.; Kuwajima, I. *J. Org. Chem.* **1997**, *62*, 4206. Hayakawa, R.; Makino, H.; Shimizu, M. *Chem. Lett.* **2001**, 756. Conrads, M.; Mattay, J. *Chem. Ber.* **1991**, *124*, 1425.

(16) We could not obtain **3** as crystals. All our attempts to determine the relative stereochemistry of **3** by NOE experiments failed.

Table 3. Reaction with Other Allenyl Derivatives



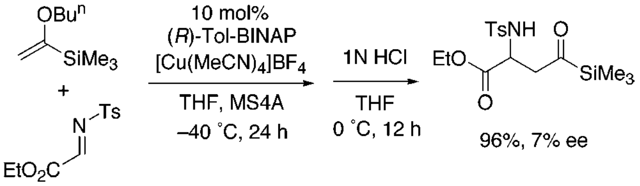
entry	R	yield of **3** /%	ee/%	yield of **4**/%	ee/%
1	$SiMe_3$	90	97	100	97
2[a]	$SiMe_2Ph$	89	89	100	89
3	Si(*t*-Bu)Me_2	60	95	100	92
4	Si(*i*-Pr)$_3$	60[b]	58	100	58
5[a]	$GeEt_3$	92	75	100	75

[a] $[Cu(MeCN)_4]PF_6$ was used. [b] Reaction was run at 0 °C.

cloadducts highly enantioselectively (entries 2 and 3). Allenyltriisopropylsilane gave a cycloadduct with moderate enantioselectivity (entry 4). Interestingly, allenyltriethylgermane also furnished the corresponding cycloadduct with good enantioselectivity (entry 5). All the cycloadducts **3** were obtained as a single diastereomer, as determined by 400 MHz ^{1}H NMR analysis, though the relative stereochemistries could not be established.[16] Acid treatment of the cycloadducts furnished α,β-unsaturated-β'-amino-acylsilane and acylgermane derivatives quantitatively with good to excellent enantioselectivity.

The absolute stereochemistries of acyl *tert*-butyldimethylsilane **4** (R = Si(*t*-Bu)Me_2) was determined to be *S* by X-ray analysis.[17] The absolute stereochemistry of the corresponding azetidinecarboxylate **3** (R = Si(*t*-Bu)Me_2) was thus found to be *S*. We surmised the absolute stereochemistries of other azetidines and acylsilanes to be *S* by analogy.

Scheme 1. Reaction with Butoxyvinylsilane



It is noted that use of 1-butoxyvinylsilane gave an acylsilane derivative in an excellent yield, but the enantioselectivity was as little as 7% (Scheme 1)[18] The result clearly demonstrates that the use of an allenylsilane moiety is essential for attaining high enantioselectivity. Furthermore, the fact that methoxyallene did not show reactivity under the identical reaction conditions[19] clearly indicates that the presence of the silyl group is essential for the present cycloaddition reaction to proceed.

In summary, we have developed a novel [2 + 2] cycloaddition reaction of 1-methoxyallenylsilane with α-imino ester catalyzed by a Cu(I) complex. Use of a chiral Lewis acid resulted in the highly enantioselective cycloaddition reaction. Ring opening of the azetidines furnished chiral α-amino esters bearing an acylsilane moiety with excellent enantioselectivities.

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Supporting Information Available: Experimental procedures and analytical and spectral data for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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[17] CCDC 207580 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via the Internet at http://www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK; fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).

[18] When the reaction was quenched under neutral conditions, both azetidine and acylsilane were obtained as a 1:1 mixture.

[19] Treatment of methoxyallene (2.0 equiv) and α-imino ester (1.0 equiv) with 10 mol % (*R*)-Tol-BINAP-$[Cu(CH_3CN)_4]BF_4$ in THF at −40 °C for 24 h in the presence of 4 Å molecular sieves gave $TsNH_2$ in 70% yield. $TsNH_2$ was the sole identifiable product.