Allylic Substitution Reactions with Grignard Reagents Catalyzed by Imidazolium and 4,5-Dihydroimidazolium Carbene-CuCl Complexes

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Abstract

Imidazolium and 4,5-dihydroimidazolium carbene-CuCl complexes effectively catalyzed the substitution reaction of allylic compounds with Grignard reagents in an S_N2'-selective fashion. It was noteworthy that the amount of the imidazolium carbene-CuCl complex could be reduced to 0.001 mol% and the catalysis recorded a high TON (10^5). Based on the experimental results, the ate-type complex(es) such as [(imidazolium carbene)-CuR_2]$^-$(MgX)$^+$ was postulated as an active species.

1. Introduction

Copper-catalyzed allylic substitution reactions with Grignard reagents have received widespread acceptance as valuable methods for preparation of α-substituted alkenes [1,2]. The regioselectivity, stereoselectivity and stereospecificity of the substitution are dependent upon the structure of the substrates and the Grignard reagents and are also influenced by the reaction conditions including copper salt, solvent(s), temperature and the addition order of reagents [1,2]. Investigation has also been focused on enantioselective reactions using copper catalysts with chiral ligands [3]. Recently, we have developed a novel procedure for S_N2'-selective reaction with a Grignard reagent which was catalyzed by copper *N*-heterocyclic carbene (NHC)[4] complexes and it has been applied to enantioselective substitution by using chiral modified NHC ligands [5,6]. Herein we discuss more detailed features of this catalysis based on experimental results regarding catalytic activities, stoichiometric reactions, stereospecificity and enantioselectivity.

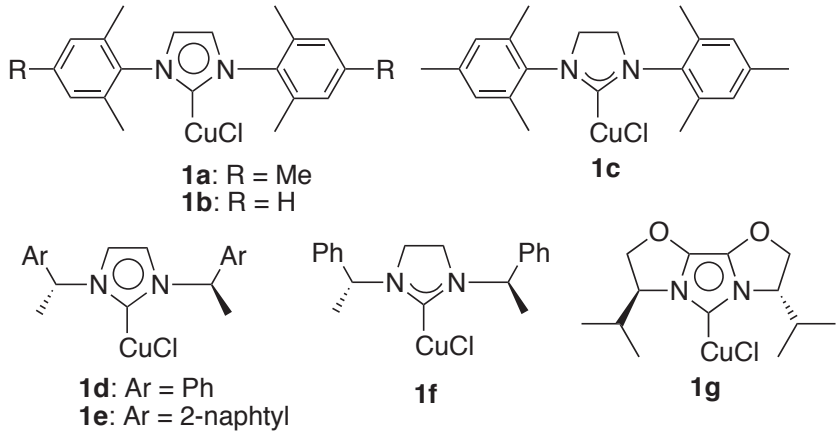
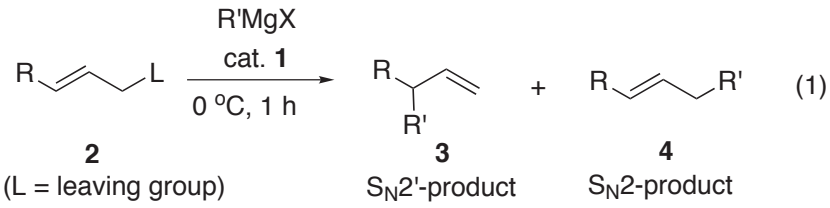


Figure 1

2. Results and Discussion

2.1. Catalytic Activity of Imidazolium and 4,5-Dihydroimidazolium Carbene-CuCl complexes

In a previous paper [7] we described the characteristic features, regarding the structure of allylic substrates and Grignard reagents, and solvent effects, of the NHC-CuCl-catalyzed allylic substitution reaction and found that the reaction was reasonably general: (i) The reaction in ethyl ether proceeded in a highly S_N2'-selective fashion (>94:6). (ii) The reaction in THF was relatively slow and an allylic substrate having an ester as a leaving group gave an S_N2 product mainly but reaction of allylic chloride proceeded S_N2'-selectively. (ii) A variety of allylic substrates and Grignard reagents except for aryl magnesium halides could be used and afforded S_N2'-product predominantly.



As revealed from the additional results shown in Table 1, which were obtained by the reactions of cinnamyl carbonate **2a** or chloride **2b** with *i*-PrMgCl catalyzed by imidazolium carbene complex **1a** and 4,5-dihydroimidazolium carbene complex **1c**, **1a** as well as **1c** could efficiently catalyze the reaction in a highly S_N2'-selective way (entries 1 and 2). It was observed again that the reaction of allyl chloride in THF proceeded S_N2'-selectively as well as that in ether but allyl carbonate gave mainly S_N2-product in THF (entries 1 and 3-5). It was noteworthy that the amount of the NHC-CuCl complex could be reduced to 0.001 mol% and the catalysis recorded a high TON (10^5) (entry 7).

Table 1[a] **1**-Catalyzed Substitution of **2** (R = Ph) with *i*-PrMgCl

entry	**2** (R = Ph)	**1** (mol%)	solvent	**3** : **4**[b]	total yield
1	**2a**: L = OCO_2Et	**1a** (1)	Et_2O	98:2	quant.
2	**2a**	**1c** (1)	Et_2O	98:2	quant.
3	**2a**	**1a** (1)	THF	8:92	21%[c]
4	**2b**: L = Cl	**1a** (1)	Et_2O	96:4	quant.
5	**2b**	**1a** (1)	THF	89:11	quant.
6	**2b**	**1a** (0.1)	Et_2O	96:4	quant.
7[d]	**2b**	**1a** (0.001)	Et_2O	92:8	quant. (98%)[e]

[a]A mixture of **1** (0.001~ 1 mol%), *i*-PrMgCl (1.5 equiv., 0.7~1.3 M in ether) and **2a** (1.0 equiv.) was stirred for 1 h at 0 °C, unless otherwise indicated. [b]Determined by 500 or 600 MHz ^{1}H NMR analysis of the crude mixture. [c]78% of **2a** was recovered. [d]The reaction was performed for 10 h at 0 °C. [e]Isolated by column chromatography.

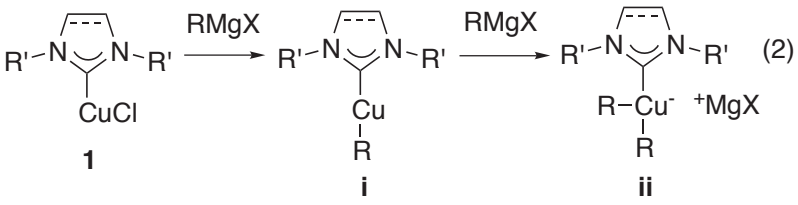
2.2. Comparison with Stoichiometric Reactions

To discuss the active species in the catalysis, we carried out the corresponding stoichiometric reactions and compared the results with those in the catalytic reactions (Table 2). Thus, the reaction of allylic carbonate **2a** and *i*-PrMgCl with a stoichiometric amount of **1** (entry 2) was found to be much slower than that with a catalytic amount of **2** (entry 1) or resulted in no reaction (entry 5). On the other hand, a mixture of one equiv of **1** and two equiv of *i*-PrMgCl could convert **2** to **3** and **4** very quickly with a high regioselectivity (entries 3 and 6).

Table 2 Reaction of **2a** with *i*-PrMgCl under various conditions

entry	**1** (equiv.)	*i*-PrMgCl (equiv.)	conditions	product, %		recovered **2a**
				3	**4**	
1	**1a** (0.01)	(1.5)	0 °C, 30 min	98	2	0
2	**1a** (1.5)	(1.3)	0 °C, 12 h	13	<1	86
3	**1a** (1.3)	(2.6)	0 °C, 5 min	93	5	2
4	**1c** (0.01)	(1.3)	0 °C, 15 min	98	2	0
5	**1c** (1.5)	(1.3)	0 °C, 24 h	0	0	~100
6	**1c** (1.3)	(2.6)	0 °C, 5 min	86	4	0

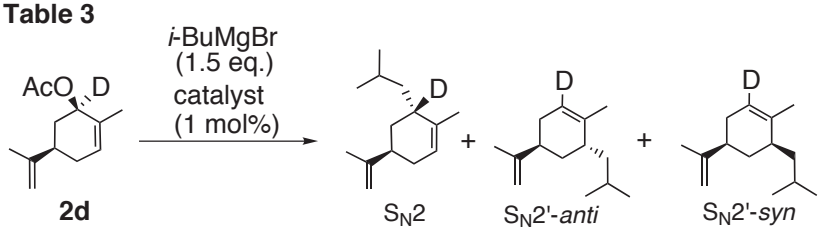
Based on these results, the major active catalyst in the present reaction can be postulated to be an ate-complex such as the type $[(NHC)CuR_2]^-(MgX)^+$ (**ii**) but not a complex of the type (NHC)CuR (**i**) [8].



2.3. Stereospecificity

The results showed in Table 3, which were obtained by copper-catalyzed substitution reactions of cyclic allyl acetate **2d**, indicate their reaction course and stereospecificity. Thus, deuterated allylic acetate **2d** [9], which was prepared from carvone by reduction with $LiAlD_4$ and the following acetylation, was treated with 1.5 equiv of *i*-BuMgBr in the presence of 1 mol% of copper salt. The reaction catalyzed by CuCl or CuCN afforded mainly an S_N2-product and it was found that minor S_N2' reaction proceeded in an *anti* fashion (entries 3 and 4). The **1b**-catalyzed reaction "in THF" gave similar results and the reaction was found to be relatively slow (entry 2). Meanwhile, it was noteworthy that the **1b**-catalyzed reaction "in ether" gave S_N2'-products predominantly and the reaction proceeded in a *syn* pathway mainly (entry 1). These results suggest that coordination between the acetoxy group and a metal atom present in an active species might affect the **1b**-catalyzed reaction in ether (Figure 2) [10].

Table 3



entry	catalyst	conditions	S_N2	S_N2'-*anti*	S_N2'-*syn*	total Yield %
1	**1b**	Et_2O, 0 °C, 2 h	35	7	58	97
2	**1b**	THF, 0 °C, 12 h	90	10	0	71
3	CuCl	Et_2O, 0 °C, 3 h	93	7	0	76
4	CuCN	Et_2O, 0 °C, 3 h	92	8	0	74

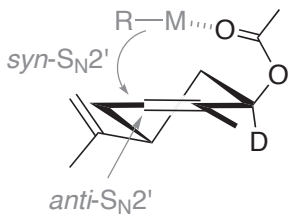
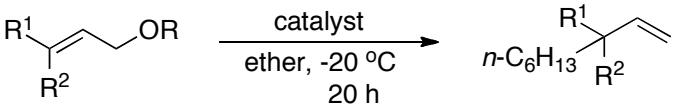


Figure 2

2.4. Enantioselectivity of the Reactions Catalyzed by Chiral NHC-CuCl Complexes [11]

Table 4 shows the results of the substitution reaction of 4-(silyloxy)-but-2-en-1-ol derivatives with *n*-$C_6H_{13}MgBr$ using C_2-chiral NHC-CuCl **1d**, **1e**, **1f** and **1g** as a catalyst precursor. Because the complexes **1d**, **1e**, **1f** and **1g** in their solid state were somewhat unstable toward moisture and/or air, the THF solution containing **1d**-**f** was respectively prepared from the corresponding imidazolium salt, *t*-BuONa and CuCl [6a] and the resulting solution was stored under Ar. The solution was charged into the reaction vessel and THF was removed under reduced pressure prior to use. As revealed from the results shown in entries 1-5, enantiomeric excess (e.e.) of the S_N2' product was highly dependent on the nature of the leaving group and the coordinative moiety such as acetoxy and 2-pyridyloxy groups gave better e.e. The complex with sterically demanding *N*-substituents (**1e**) or 4,5-dihydroimidazolium carbene-CuCl (**1f**) gave better e.e. than that obtained with **1d** (entry 1 vs. entries 6 and 7). Inversion of the product configuration was observed when (*E*)-allylic substrates were used instead of (*Z*)-isomers (entries 11 and 12). The highest enantiomeric ratio of 85:15 was attained by the reaction of (*Z*)-2-pyridyl ether with catalyst **1e** (entry 9). The fact that the reaction with conformationally rigid NHC-CuCl **1g** with (*S*,*S*)-configuration gave the S_N2' product with (*R*)-configuration (entry 10) suggests the conformation of *N*-substituents in the active catalysts derived from **1d**, **1e** and **1f**, the (*R*,*R*)-isomers of which produced (*R*)-product predominantly (*vide infra*).

Table 4[a]



entry	R^1	R^2	OR	catalyst (mol%)	% e.e.[b] (Config.)[b]	S_N2':S_N2
1	H	$TBSOCH_2$	OAc	**1d** (5)	40 (*R*)	87:13
2	H	$TBSOCH_2$	OCO_2Et	**1d** (5)	5 (*R*)	96:4
3	H	$TBSOCH_2$	$OP(O)(OEt)_2$	**1d** (5)	8 (*R*)	99:1
4	H	$TBSOCH_2$	Cl	**1d** (5)	8 (*S*)	77:23
5	H	$TBSOCH_2$	O-(2-pyridyl)	**1d** (5)	36 (*R*)	91:9
6	H	$TBSOCH_2$	OAc	**1f** (1)	52 (*R*)	49:51
7	H	$TBSOCH_2$	OAc	**1e** (5)	60 (*R*)	95:5
8	H	$TBSOCH_2$	$OC(O)NMe_2$	**1e** (5)	55 (*R*)	99:1
9	H	$TBSOCH_2$	O-(2-pyridyl)	**1e** (5)	70 (*R*)	98:2
10	H	$TBSOCH_2$	O-(2-pyridyl)	**1g** (1)	50 (*R*)	98:2
11	$TBSOCH_2$	H	OAc	**1e** (5)	38 (*S*)	97:3
12	$TBSOCH_2$	H	O-(2-pyridyl)	**1e** (5)	60 (*S*)	86:14

[a]All reactions proceeded quantitatively.
[b]For determination, see ref. 7.

2.5. Proposing Transition Structure

Although elucidation of the origin of the regioselectivity of the reaction remains difficult at this time, the results of the reactions with a stoichiometric amount of **1**, the solvent effect and the effect of

the coordinative nature of the leaving groups on regioselectivity, stereospecificity and enantioselectivity observed here suggest reaction mechanism as follows: The reaction might involve an ate-complex such as the type $[(NHC)CuR_2]^-(MgX)^+$ as an active species which could be generated *via* the (NHC)CuR complex (eq 2). The generated ate complex would react with the allylic substrate through the seven-membered cyclic structure (**a**) shown in Figure 3 which consists of π-complexation between the Cu atom and the carbon-carbon double bond of the substrate and the coordination between the leaving group and $^+$MgX counter cation [10]. Use of THF instead of diethyl ether as a solvent may inhibit the coordination to retard the reaction and cause change of the regioselectivity.

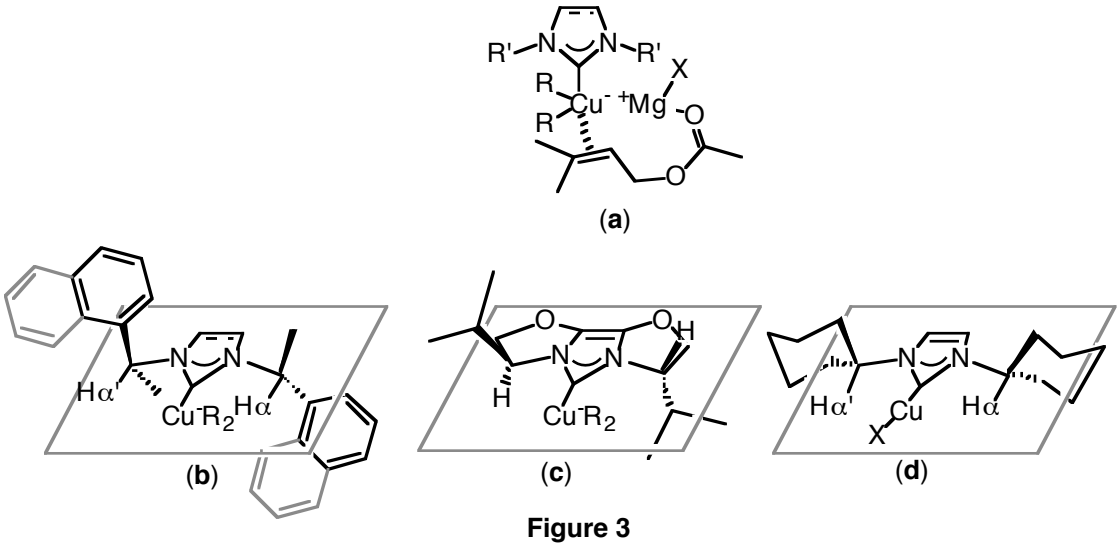


Figure 3

To discuss the enantioselection with **1d**-**f**, conformation of their 1-arylethyl side-chain in the active species is important and comparison of the results of the **1d**-**f** catalyzed reactions with those with **1g** suggest that their active structure would be as (**b**) shown in Figure 3. Thus, the aryl moieties present in complexes (**b**) derived from **1d**-**f** with the *R*,*R*-configuration should occupy the same quadrants around an imidazolium carbene-Cu axis as those which two *i*-Pr groups do in the rigid complex (**c**) derived from **1g** with *S*,*S*-configuration. In such conformation shown as (**b**) two hydrogen atoms Hα and Hα' locate around sterically hindered Cu atom similarly to the conformation of the side chain in the solid state structure reported for 1,3-bis(cyclohexyl)imidazolin-2-ylidene copper chloride (**d**) [6d].

These findings and the discussion described here will support further study for development of NHC-CuCl complexes giving better enantioselectivity of the present allylic substitution reaction and development of other reactions catalyzed by NHC-CuCl. Investigation along this line is under way in our laboratories.

3. Experimental

3.1. General

NMR spectra were recorded in $CDCl_3$ at 600, 500 and 270 MHz for ^1H and 150, 125 and 67.5 MHz for ^{13}C, respectively, on JEOL JNM-ECA600, 500 and –EX270 spectrometers. Chemical shifts are reported in parts per million (ppm, δ) relative to Me_4Si (δ 0.00) or residual $CHCl_3$ (δ 7.26 for ^1H and δ 77.0 for ^{13}C). IR spectra were recorded on an FT-IR spectrometer (HITACHI 270-30) and are reported in wave numbers (cm^{-1}). All reactions sensitive to oxygen and/or moisture were performed under an argon atmosphere. Dry solvents (THF and ethyl ether) were purchased from Kanto Chemicals. Grignard reagents were prepared from magnesium turnings and the corresponding organic halide in ethyl ether or THF, titrated by an acid-base titration using aqueous 1.0 M HCl and 0.5 M NaOH, and stored under argon. Imidazolium salts, i.e., 1,3-bis(2,4,6-trimethylphenyl)-3*H*-imidazol-1-ium chloride [4c,12], 1,3-bis(2,4,6-trimethylphenyl)-4,5-dihydro-3*H*-imidazol-1-ium chloride [13], (*R*,*R*)-1,3-bis(1-phenylethyl)-3*H*-imidazol-1-ium chloride [5c,14], (*R*,*R*)-1,3-bis[1-(1-naphtyl)ethyl]-3*H*-imidazol-1-ium chloride [5c,14], and (*S*,*S*)-1,6-diisopropyl-1,2,5,6-tetrahydro-3,4-dioxa-7a-aza-6a-azonia-cyclopenta[*a*]pentalene triflate [15] were prepared from the corresponding amines according to the reported procedures. Other chemicals are commercially available, unless otherwise indicated, and were used as received.

*3.2. Preparation of NHC-CuCl Complexes **1a-c***

1,3-Bis(2,6-dimethyl-phenyl)imidazolin-2-ylidene copper chloride (**1b**): To a mixture of 1,3-bis(2,6-dimethylphenyl)-3*H*-imidazol-1-ium chloride (313 mg, 1.0 mmol), CuCl (89 mg, 0.90 mmol) and *t*-BuONa (96 mg, 1.0 mmol) was added THF (7 mL). The resulting suspension was stirred for 6 h at room temperature and filtered through a pad of Celite. The filtrate was concentrated *in vacuo* to give **1b** (264 mg, 78% yield) as a red-brown powder. Mp. 268 °C; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.31 (t, J = 7.5, 2H), 7.21 (d, J = 8.0, 4H), 7.10 (s, 2H), 2.17 (s, 12H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 178.5, 137.4, 134.9, 129.6, 128.8, 122.1, 17.8; IR (neat) 3166, 1695, 1599, 1557, 1479, 1443, 1404, 1335, 1290, 1230, 1161, 1110, 1038, 948, 786, 735, 693, 609. Anal. Calcd. for $C_{19}H_2N_2OClCu$: C, 60.79; H, 5.37; N, 7.46. Found: C, 60.95; H, 5.54; N, 7.47.

1,3-Bis(2,4,6-trimethyl-phenyl)imidazolin-2-ylidene copper chloride (**1a**): ^1H NMR (500 MHz, $CDCl_3$) δ 7.06 (s, 2H), 7.00 (s, 4H), 2.34 (s, 6H), 2.10 (2, 12H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 178.7, 139.2, 134.9, 134.4, 129.3, 122.2, 21.1, 17.6; IR (KBr) 2914, 1485, 1400, 1234, 1076, 932, 862, 702 cm^{-1}. Anal. Calcd. for $C_{21}H_{24}ClCuN_2$: C, 62.52; H, 6.00; N, 6.94. Found: C, 62.33; H, 6.16; N, 6.86.

1,3-Bis(2,4,6-trimethyl-phenyl)imidazolidin-2-ylidene copper chloride (**1c**): The spectral data (^{1}H and ^{13}C NMR) were in good agreement with those reported [6d]. Anal. Calcd. for $C_{21}H_{26}ClCuN_2$: C, 62.21; H, 6.46; N, 6.91. Found: C, 62.34; H, 6.16; N, 6.98.

3.3. Allylic Substitution Reactions with Grignard Reagents Catalyzed by Imidazolium Carbene-CuX Complexes

*Reaction with 1 mol% of NHC-CuCl complexes **1***: To a suspension of an imidazolium or 4,5-dihydroimidazolium carbene-CuCl complex **1** (0.01 mmol, 1 mol%) in ether (1 mL) was added dropwise a solution of Grignard reagent (1.5 mmol) at 0 ^{o}C and the resulting mixture was stirred for 15 min. To this was added dropwise a solution of allylic substrate **2** (1.0 mmol) and the mixture was stirred for 1~2 h. After confirming the completion of the reaction by TLC analysis, saturated aqueous NH_4Cl was added. The mixture was extracted with hexanes (2 x 10 mL) and the combined organic layers were washed with brine, dried over $MgSO_4$, concentrated. The 500 or 600 MHz ^{1}H NMR analysis of the crude residue determined the regioselectivity. Chromatography on silica gel gave the substitution products. The following spectral data were recorded using a mixture of **3** and **4**.

*Reaction with 0.001 mol% of NHC-CuCl complex **1a***: In a flask a THF solution of **1a** (100 μL, 0.001 M, 10^{-4} mmol) was charged and THF was removed *in vacuo*. Under Ar atmosphere to this were added ether (1.5 mL), *i*-PrMgCl (11.5 mL, 1.3 M in ether, 15 mmol) and cinnamyl chloride (1.39 mL, 10 mmol) at 0 ^{o}C. The mixture was stirred for 10 h at 0 ^{o}C. The resulting white suspension was poured into aqueous 1M HCl (30 mL) and the mixture was extracted with ether (2 x 20 mL), washed with saturated aqueous $NaHCO_3$ (10mL), dried over $MgSO_4$, and concentrated. The residue was passed through a short silica gel column with hexanes and concentrated to give a mixture of **3** and **4** (R = Ph, R' = *i*-Pr, total 1.57 g, 98% yield) in a ratio of 92:8.

Spectral data of 4-methyl-3-phenyl-1-pentene obtained as the S_N2' product by the reaction shown in Table 1 and 2 were identical with those reported [3e].

3.4. Chiral Modified NHC-CuCl Complexes-Catalyzed Reactions

THF solutions of compounds **1d**-**f** were prepared from the corresponding imidazolium salts, *t*-BuONa and CuCl in THF [6a]. The resulting mixture was filtered through a pad of Celite and the filtrate was stored under Ar because the corresponding complexes in their solid state were unstable toward moisture and/or air. The THF-solution containing **1d**-**1f**, respectively, thus obtained was charged into the reaction vessel and THF was removed under reduced pressure prior to use.

In a flask a THF solution (0.05 mmol) thus prepared was charged and THF was removed *in vacuo*. Under Ar atmosphere to this were added ether (1.0 mL), *i*-PrMgCl (1.15 mL, 1.3 M in ether, 1.5 mmol) and 4-(silyloxy)-but-2-en-1-ol derivative (1.0 mmol) at -20 ^{o}C. The mixture was stirred for 20 h at -20 ^{o}C. To this was added saturated aqueous NH_4Cl (10 mL) and the mixture was extracted with ether (2 x 20 mL), washed with saturated aqueous $NaHCO_3$ (10mL), dried over $MgSO_4$, and concentrated. The residue was passed through a short silica gel column with hexanes and concentrated to give *tert*-butyldimethyl(2-hexylbut-3-enyloxy)silane. Enantiomeric excess of the product was determined by conversion to the corresponding MTPA-esters [16] after protodesilylation and their ^{1}H NMR analysis. The absolute configuration was confirmed by conversion to the known 2-(*tert*-butyldimethyl-silyloxymethyl)octan-1-ol [17] by ozonolysis and the following reduction with $NaBH_4$ and comparison of the optical rotation with that reported.

tert-Butyldimethyl(2-hexylbut-3-enyloxy)silane: ^{1}H NMR ($CDCl_3$, 270 MHz) δ 5.62 (ddd, J = 8.4, 9.7, 17.8 Hz, 1H), 4.97-5.07 (m, 2H), 3.52 (dd, J = 6.3, 11.2 Hz, 1H), 3.49 (dd, J = 6.3, 11.2 Hz, 1H), 2.07-2.23 (m, 1H), 1.10-1.60 (m, 10H), 0.89 (s, 9H), 0.88 (t, J = 7.1 Hz, 3H), 0.07 and 0.04 (2s, each 3H); ^{13}C NMR ($CDCl_3$, 67.5 MHz) δ 140.6, 115.2, 66.7, 31.8, 30.8, 29.4, 27.0, 26.0, 22.7, 18.4, 14.1, -5.3, -5.4; IR (neat) 3076, 2926, 2854, 1644, 1470, 1383, 1365, 1254, 1101, 1008, 942, 915, 837, 777 cm^{-1}. Anal. Calcd. for $C_{16}H_{34}0Si$; C, 71.04; H, 12.67. Found; C, 70.64; H, 13.00.

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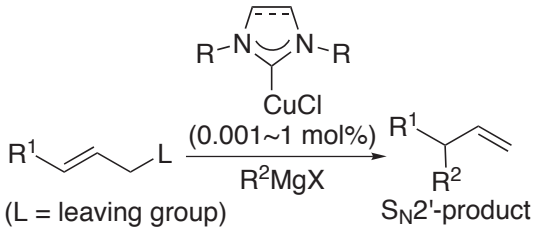
Graphical Abstract



The ate-type complex(es) such as [(imidazolium carbene)-CuR_2]$^-$$(MgX)^+$ was postulated as an active species.