

Copper(I) Chloride-Catalyzed Three-Component Coupling Reaction of Primary Amines with Electrophiles and α -Halogen-Substituted Allylsilanes to Form Unsymmetrical Tertiary Amines

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Abstract: Tertiary amines with three different substituents, in one of which a vinylsilane functionality was included, were straightforwardly formed by the copper(I) chloride-catalyzed tandem reaction of primary amines, α -halogen-substituted allylsilanes, and electrophiles such as electron-deficient olefins, alkyl halides, alkyl tosylates, or epoxides. In the case using electron-deficient olefins as the electrophile, the addition of chloroacetone to the reaction system afforded

the three-component coupling reaction more effectively. The addition of trimethyl borate as a co-catalyst improved the yields of the three-component coupling products in the reaction using alkyl halides, alkyl tosylates, or epoxides as the electrophiles, although the reaction times were lengthened.

Keywords: amines; C–N coupling; copper catalysis; silicon; three-component coupling

Introduction

The preparation of higher amines starting from primary amines has been widely accomplished by the reactions of the latter with a range of electrophiles, including alkyl halides. However, alkylated amines tend to undergo further alkylation more readily because of their enhanced nucleophilicity compared with that of the parent amines. Thus, primary amines usually incline to the formation of a complex mixture *via* polyalkylation by the reaction of electrophiles. Therefore, tertiary amines bearing three different substituents have commonly been prepared by step-wise alkylation on the nitrogen atom with some manipulations to effect the selective formation of secondary amines in the first steps.^[1] The production of tertiary amines from primary amines by the simultaneous formation of different nitrogen-carbon bonds in a single step has not yet been reported, to the best of our knowledge, although three-component joining reactions for the simultaneous formation of two different carbon-carbon bonds^[2] or the nitrogen-carbon bond together with the carbon-carbon bond^[3] in one step have been actively investigated, along with four-component joining reactions of amines, aldehydes, isocyanates,

and acids to afford amide derivatives which is known as the Ugi reaction.^[4]

We have recently found that tertiary amines with three different substituents are obtained in a single step by the CuCl-catalyzed three-component coupling reaction of primary amines, α -halogen-substituted allylsilanes **1**, and electrophiles such as electron-deficient olefins^[5] or halides.^[6] We herein present this type of reaction, including other electrophiles (i.e., tosylates and epoxides) in detail. The vinylsilane functionality, which is seemingly derived from the S_N2' bond formation from **1** and the amine, is included in one of three different substituents on the nitrogen atom of the tertiary amine obtained in this reaction. While the S_N2'-type of reaction of **1** with a nucleophile such as lithium amide to give vinylsilane derivatives has been known,^[7] **1** has been also reported to undergo an attack of electrophiles under activation by a Lewis acid to form vinyl halides *via* elimination of the silyl group accompanied by migration of the carbon-carbon double bond,^[8] similarly to the allylation reaction of electrophiles by allylsilanes.^[9]

Vinylsilanes are useful synthetic intermediates for effecting versatile transformations *via* reactions with a range of electrophiles,^[10] e.g., acyl halides to form conju-

gated enones.^[11] Although the preparation of vinylsilanes has been accomplished by various methods such as the hydrosilylation of alkynes,^[12] the reaction of carbonyl compounds with silylated metal species,^[13] the silylation of alkenylmetals,^[14] or the hydrometalation or hydrogenation of alkynylsilanes,^[15] it has been rather difficult to synthesize vinylsilane derivatives containing functional groups. The reaction developed in this investigation is able to provide vinylsilane derivatives bearing some functional groups along with an amino group. Thus, our method presented here is also intriguing from the viewpoint of usefully complementing previous techniques for the preparation of vinylsilanes.

Results and Discussion

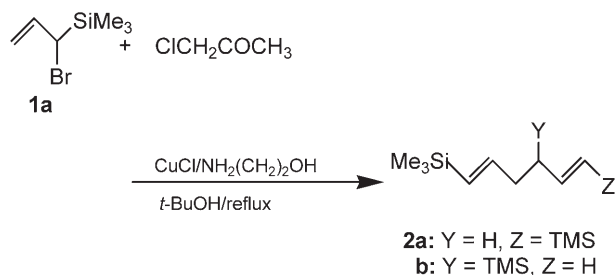
Three-Component Coupling Reaction using Electron-Deficient Olefins

We have recently explored the copper(I) halide-catalyzed reaction of polyhalides with **1**, and found that the α -halogen atom of **1** is eliminated in conjunction with the migration of the carbon-carbon double bond to form vinylsilane derivatives,^[16] in contrast to the elimination of the silyl group in the Lewis acid-promoted reaction of **1** with electrophiles.^[8] Furthermore, the reaction of **1** with α -halo esters also proceeded similarly under the same reaction conditions. However, when **1** was subjected to the reaction with chloroacetone, the dehalogenated dimerization products (**2a**, **b**) of **1** were formed (Scheme 1).

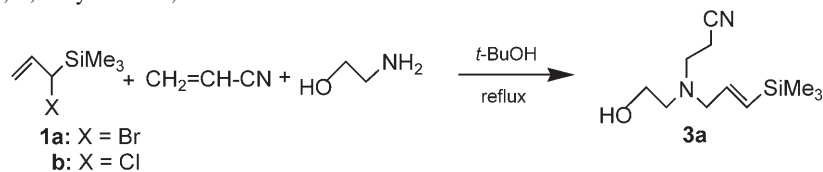
Supposing that **2** might be formed *via* the generation of a radical species by the dehalogenation of **1**, the reaction was examined in the presence of an olefin expected to trap the putative radical intermediate; a solution composed of (1-bromo-2-propenyl)trimethylsilane **1a** (2 mmol), acrylonitrile (3 mmol), chloroacetone (4 mmol), CuCl (0.2 mmol), ethanolamine (10 mmol), and *t*-BuOH (5 mL) was subjected to a thermal reaction at 80 °C for 3 h. Contrary to the initial expectation, the result was the formation of a three-component joining product, *N*-(2-hydroxyethyl)-*N*-(2-cyanoethyl)-(*E*)-3-

trimethylsilyl-2-propenylamine **3a** (23% yield) along with **2a** and **b** (33% yield) (Table 1, run 1). The substitution of electron-rich olefins such as 1-pentene or styrene instead of acrylonitrile did not afford the type **3** product, but formed **2** as well as the 1:2 S_N2'-type product, **4**, of **1a** with ethanolamine (**2a** and **b**: 40–42% and **4**: 39–41%) without consuming these olefins. The reaction using (1-chloro-2-propenyl)trimethylsilane **1b** instead of **1a** was also examined under the same conditions to afford **3a** in a 78% yield with no formation of **2** (Table 1, run 2). Diminishing the amount of ethanolamine decreased the yield of **3a** (Table 1, runs 2–5). Although reducing the amount of chloroacetone to 0.2 mmol gave **3a** in almost the same yield (74%) as 4 mmol had (Table 1, run 6), omitting chloroacetone from the reaction system altogether reduced the yield of **3a** to 27% (Table 1, run 7). The omission of copper(I) chloride under otherwise identical conditions afforded **3a** in only a trace amount (4% yield) (Table 1, run 8). Furthermore, the reaction in a system containing neither chloroacetone nor copper(I) chloride resulted in no formation of **3a** (Table 1, run 9). Thus, chloroacetone and copper(I) chloride seem to be essential promoters for the effective formation of **3a**. The use of phenacyl bromide as a halo ketone in place of chloroacetone diminished the yield of **3a** (10%) (Table 1, run 10). Based on the hypothesis that copper(II) chloride would be generated from chloroacetone and copper(I) chloride to work as the actual promoter, the reaction was performed in the presence of copper(II) chloride without copper(I) chloride and chloroacetone. The result, however, was no formation of **3a** (Table 1, run 11). Next, the catalytic abilities of copper(I) halides other than CuCl, i.e., CuBr and CuI, were examined to reveal that the yields of **3a** descended in the order of CuCl, CuBr, and CuI (Table 1, runs 2, 12 and 13). The reactions in Table 1 were not accompanied by concomitant formation of the mono- or symmetrically dialkylated derivative of ethanolamine, and thus the consumed starting materials may be transferred to non-volatile products, such as quaternary ammonium salts or polymerized products, besides **3a**.

Reactions of electron-deficient olefins other than acrylonitrile with ethanolamine and **1b** were carried out. Methyl acrylate gave a similar type of product, **3b**, in a slightly better yield (96%) than for the formation of **3a** from acrylonitrile (Table 2, run 2), while diethyl maleate necessitated more time for the consumption of **1b** and produced only a moderate yield of **3c** (Table 2, run 3). The reaction in the presence of a conjugated enone such as methyl vinyl ketone or acrolein afforded a complex mixture of unidentified products, although **1b** was consumed in 3 h. α -Chlorine-substituted allylsilanes other than **1b** were also used for this type of reaction. (1-Chloro-2-butenyl)trimethylsilane **1c** was reacted with acrylonitrile, methyl acrylate, and diethyl maleate to afford the three-component joining products **3d–f** in excellent or good yields (92, 84, 76%, respectively, Ta-



Scheme 1. Reaction of α -haloallylsilane in the presence of chloroacetone.

Table 1. Reaction of **1a**, **b**, acrylonitrile, and ethanolamine.^[a]

Run	1	Ethanolamine [mmol]	Additive [mmol]		Time [h]	Consumption of 1 [%] ^[d]	Yield of 3a [%] ^[d, e]
			Metal species ^[b]	Halo ketone ^[c]			
1	a	10	A (0.2)	E (4)	2	100	23
2	b	10	A (0.2)	E (4)	2	96	82
3	b	6	A (0.2)	E (4)	2	97	49
4	b	4	A (0.2)	E (4)	2	70	12
5	b	2	A (0.2)	E (4)	2	57	2
6	b	10	A (0.2)	E (0.2)	3	96	74
7	b	10	A (0.2)	–	3	99	27
8	b	10	–	E (4)	3	23	4
9	b	10	–	–	2	9	0
10	b	10	A (0.2)	F (4)	3	99	10
11	b	10	B (0.2)	–	3	91	0
12	b	10	C (0.2)	E (4)	3	93	49
13	b	10	D (0.2)	E (4)	3	94	33

^[a] Reaction conditions: **1** (2 mmol), CH₂=CH–CN (3 mmol).^[b] A = CuCl, B = CuCl₂, C = CuBr, D = CuI.^[c] E = ClCH₂COCH₃, F = BrCH₂COPh.^[d] Determined by GC analysis.^[e] Based on the starting **1**.

ble 2, runs 4–6). The reaction of (1-chloro-2-methyl-2-propenyl)trimethylsilane **1d** with acrylonitrile gave **3g** in a 96% yield (Table 2, run 7), while that with methyl acrylate afforded **3h** in a lower yield (Table 2, run 8). GC analysis of the reactions in Table 2 revealed no concomitant formation of the mono- or symmetrically dialkylated derivatives of ethanolamine.

The reactions of a range of amines with α -chloroallylsilanes (**1b–d**) and acrylonitrile are summarized in Table 3. The amines substituted with primary alkyl groups, i.e., benzylamine and heptylamine, produced the three-component joining products in excellent to good yields, similarly to the reactions using ethanolamine (Table 3, runs 1–3 and 10–15). GC analysis of these reaction mixtures revealed no concomitant formation of the secondary or symmetrical tertiary amines. In contrast, the stereo-congested amines bearing branched alkyl groups gave similar products in low yields under the standard reaction conditions, while the same products were obtained in good to moderate yields in the reaction system by reducing chloroacetone to a catalytic amount (0.1 equiv.), as exemplified by the reactions of **1b** with *tert*-butylamine to form **3k** and with cyclohexylamine to form **3l** (Table 3, runs 4–7). Aniline afforded no three-component joining products by the reaction with **1b** (Table 3, run 8), but formed the S_N2'-type product, (*E*)-3-phenylamino-1-trimethylsilyl-1-propene **5**, as the

main product (70% yield). Because cyclohexylamine formed a three-component joining product, albeit in low yield, the failure of aniline to form a product of type **3** might in a large part be due to the electronic effect, i.e., the weak basicity of aniline compared with an aliphatic amine, as well as to the steric effect. In fact, 4-ethylaniline gave a coupling product with **1b** and acrylonitrile, albeit in a trace amount (7% yield) (Table 3, run 9).

Three-Component Coupling Reaction using Alkyl Halides as Electrophiles

The binary promoter consisting of CuCl and chloroacetone, which proved to be the best conditions for the three-component coupling reaction including the elec-

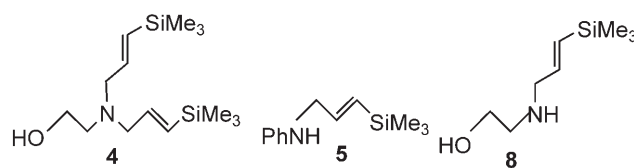
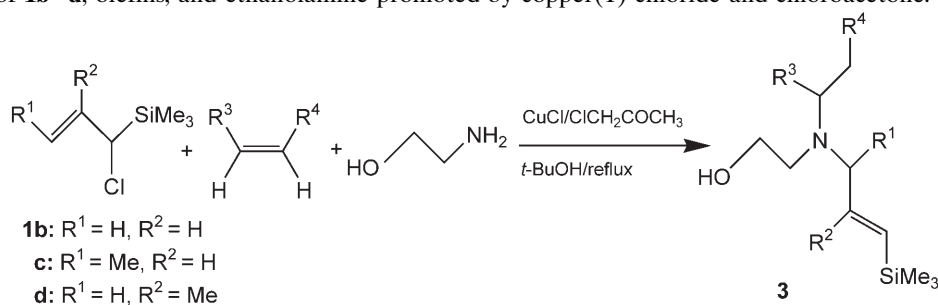
**Scheme 2.** S_N2'-type products of amines with α -haloallylsilanes.

Table 2. Reaction of **1b–d**, olefins, and ethanolamine promoted by copper(I) chloride and chloroacetone.^[a]

Run	1	Olefin		Time [h] ^[b]	Product	
		R ³	R ⁴		3	Yield [%] ^[c]
1	b	H	CN	2	a	82
2	b	H	COOMe	2	b	96
3	b	COOEt	COOEt	6	c	45 (37) ^[d]
4	c	H	CN	1	d	92
5	c	H	COOMe	1	e	84
6	c	COOEt	COOEt	2.5	f	76 (68) ^[d]
7	d	H	CN	3.5	g ^[e]	96
8	d	H	COOMe	1	h ^[e]	34

^[a] Reaction conditions: **1** (2 mmol), olefin (3 mmol), NH₂(CH₂)₂OH (10 mmol), CuCl (0.2 mmol), ClCH₂COCH₃ (4 mmol).

^[b] Time at which **1** was almost consumed.

^[c] Determined by GC analysis.

^[d] Determined by TLC isolation.

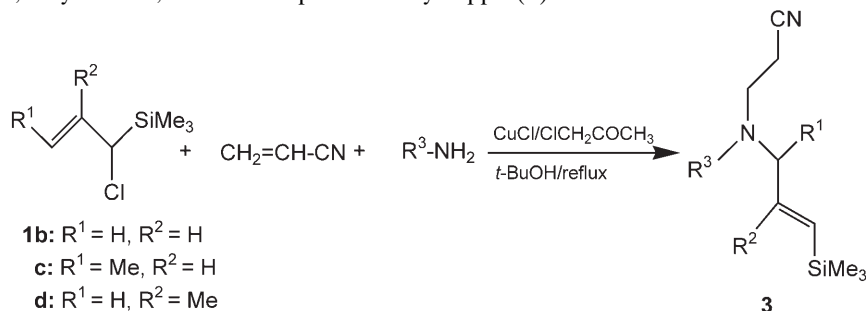
^[e] A 50/50 mixture of (*E*)- and (*Z*)-stereoisomers.

tron-deficient olefin, was applied to the reaction of 1-bromopropane (3 mmol), **1d** (2 mmol), and ethanolamine (10 mmol) in *t*-BuOH (5 mL), resulting in the formation of a trace amount of the expected three-component coupling product **6a** (Table 4, run 1). Next, the reaction using CuCl alone as a promoter was examined. As a result, the initial **1a** was entirely consumed after 4 h under reflux, and **6a** was formed in 69% yield (Table 1, run 2). The use of Al(*O*-*i*-Pr)₄ or B(OMe)₃ as a Lewis acid afforded **6a** in excellent yields, although a long period of time was necessary to complete the consumption of **1d** (96 and 72 h in runs 3 and 4, respectively). Increasing the amount of B(OMe)₃ did not shorten the time for consumption of **1d** (Table 4, run 5). Thus, the reaction using CuCl in combination with B(OMe)₃ as the promoter was explored with the expectation that it would produce **6a** in an excellent yield under the accelerated consumption of **1d**. Under these conditions, **6a** was produced in a 93% yield and **1d** was consumed in 18 h (Table 4, run 6). However, the use of CuCl together with Al(*O*-*i*-Pr)₃ gave **6a** in a 49% yield under the same time for consumption of **1a** (Table 4, run 7). The reaction without a promoter furnished only 23% yield of **6a** after consuming **1a** in 36 h (Table 4, run 8). The effect of the amount of ethanolamine upon the formation of **6a** was explored to reveal that the yield of **6a** was diminished as this was reduced (Table 4, runs 6, 9–11). GC analysis of the reactions in Table 4 revealed

no concomitant formation of the ethanolamine derivative *via* single or double alkylation with 1-bromopropane.

Although solvents other than *t*-BuOH (i.e., MeOH, THF, CH₂Cl₂ and cyclohexane) were examined, *t*-BuOH proved to be best.

Next, halides other than 1-bromopropane were subjected to the reaction with ethanolamine and **1d**. Allyl bromide, benzyl bromide, and 2,3-dibromopropene formed the three-component joining products, **6b–d**, in excellent to good yields (Table 5, runs 1–5). A stereo bulky halide, i.e., *tert*-butyl bromide, produced the three-component coupling product, **6e**, in a low yield (Table 5, run 6), and, in this case, the major products were the 1:1 and 1:2 S_N2' products of ethanolamine with **1d**. Furthermore, reactions using **1b** and **1c** instead of **1d** were explored. The B(OMe)₃-promoted reaction of **1b** with 1-bromopropane, allyl bromide, or benzyl bromide produced the three-component coupling products, **6f–h**, in an excellent yield (Table 5, runs 7, 9 and 11), while the binary promoter of CuCl/B(OMe)₃ formed **6f** in 70% yield (Table 5, run 8). The B(OMe)₃-promoted reaction of **1c** with allyl bromide, benzyl bromide, or 2,3-dibromopropene produced the corresponding three-component coupling products, **6i–k** in excellent yields (Table 5, runs 12–14). GC analysis of the reactions in Table 5 revealed no concomitant formation of the ethanolamine derivative *via* single or double alkyla-

Table 3. Reaction of **1**, acrylonitrile, and amines promoted by copper(I) chloride and chloroacetone.^[a]

Run	1	Amine R ³	Time [h] ^[b]	Product	
				3	Yield [%] ^[c]
1	b	HO(CH ₂) ₂	2	a	82
2	b	PhCH ₂	3	i	72(55) ^[d]
3	b	CH ₃ (CH ₂) ₆	3	j	89
4	b	(CH ₃) ₃ C	24	k	20
5 ^[e]	b	(CH ₃) ₃ C	24	k	70
6	b	cyclohexyl	5	l	15
7 ^[e]	b	cyclohexyl	5	l	42
8	b	Ph	7	m	0
9	b	4-EtC ₆ H ₄	7	n	7
10	c	HO(CH ₂) ₂	1	d	92
11	c	PhCH ₂	2	o	85(82) ^[d]
12	c	CH ₃ (CH ₂) ₆	3	p	76
13	d	HO(CH ₂) ₂	3.5	g ^[f]	96
14	d	PhCH ₂	2	q ^[f]	81(73) ^[d]
15	d	CH ₃ (CH ₂) ₆	4	r ^[f]	83(74) ^[d]

^[a] Reaction conditions: **1** (2 mmol), CH₂=CH-CN (3 mmol), amine (10 mmol), CuCl (0.2 mmol), ClCH₂COCH₃ (4 mmol).

^[b] Time at which the initial **1** was almost consumed.

^[c] Determined by GC analysis.

^[d] Determined by TLC isolation.

^[e] Amount of chloroacetone = 0.2 mmol.

^[f] A 50/50 mixture of (*E*)- and (*Z*)-stereoisomers.

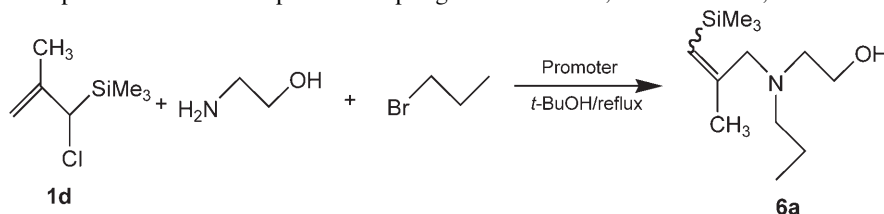
tion with the halide or, if any, in only trace amount except for the case using benzyl bromide where *N,N*-dibenzylethanolamine was obtained in 17–23% yields (Table 5, runs 3, 4, 11, and 13).

Amines other than ethanolamine, such as benzylamine, heptylamine, cyclohexylamine and *tert*-butylamine, were also subjected to reaction with **1d** and alkyl halides. In contrast to the results using ethanolamine shown in Table 4, the yield of the three component coupling product was almost same in the cases using 5 equivalents and 2 equivalents of the amine (Table 6, runs 1, 2 and 7, 8). Thus, the reactions were performed in the system containing 2 equivalents of the amine. The primary alkyl amines, such as benzylamine and heptylamine, gave the corresponding three-component coupling products **6l–n** in good yields (Table 6, runs 2, 4–6, 8, 10). On the other hand, secondary or tertiary alkyl amines, such as cyclohexylamine and *tert*-butylamine, formed the corresponding three-component coupling products **6o** and **p** in low yields (Table 6, runs 11–14),

giving the 1:1 and 1:2 S_N2'-products of the amine with **1d** as the primary by-products. GC analysis of the reactions in Table 6 revealed no concomitant formation of the amine derivative *via* single or double alkylation with the halide.

Three-Component Coupling Reaction using Alkyl Tosylates as Electrophiles

Propyl tosylate (3 mmol) was subjected to the reaction with **1d** (2 mmol) and ethanolamine (10 mmol) under reflux for 3 h in a *t*-BuOH solution containing the binary promoter of CuCl/B(OMe)₃. As a result, the three-component coupling product **6a** was formed in 78% yield (Table 7, run 1). On the other hand, the use of B(OMe)₃ alone diminished the yield of **6a** to 42% (Table 7, run 2), in contrast to the reaction using 1-bromopropane as an electrophile (*cf.* Table 4, runs 4 and 6). Some combinations of **1** and alkyl tosylates were similar-

Table 4. Effects of metal species on three-component coupling reaction of **1d**, ethanolamine, and 1-bromopropane.^[a]

Run	Promoter	Ethanolamine [mmol]	Time [h] ^[b]	Yield 6a ^[c] [%] ^[d]
1	CuCl/ClCH ₂ COCH ₃	10	3	Trace
2	CuCl	10	4	69
3	Al(O- <i>i</i> -Pr) ₃	10	96	92
4	B(OMe) ₃	10	72	93
5	B(OMe) ₃ ^[e]	10	72	93
6	CuCl/B(OMe) ₃	10	18	93 (87) ^[f]
7	CuCl/Al(O- <i>i</i> -Pr) ₃	10	18	49
8	None	10	36	23
9	CuCl/B(OMe) ₃	6	10	78
10	CuCl/B(OMe) ₃	4	2	58
11	CuCl/B(OMe) ₃	2	3	18

^[a] Reaction conditions: **1d** (2 mmol), 1-bromopropane (3 mmol), metal species (0.2 mmol).

^[b] Time at which the initial **1d** was almost consumed.

^[c] A 50/50 mixture of (*E*)- and (*Z*)-stereoisomers.

^[d] Determined by GC analysis.

^[e] B(OMe)₃ = 1 mmol.

^[f] Determined by column chromatographic isolation.

ly subjected to the reaction with ethanolamine and, furthermore, the reactions with amines (4 mmol) other than ethanolamine were also performed. These results are collected in Table 7. Compared with the cases using alkyl bromides, the three-component coupling reactions proceeded quickly, although in comparable or slightly lower yields. In these reactions using alkyl tosylates, the 1:1 or 1:2 products of amines with tosylates were not concomitantly formed.

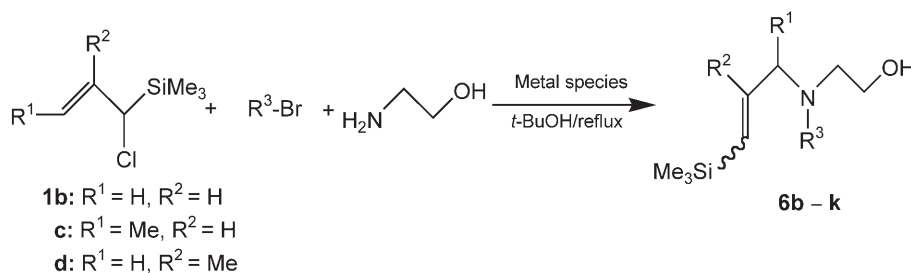
Three-Component Coupling Reaction using Epoxides as Electrophiles

The reaction of glycidyl methyl ether (3 mmol), **1d** (2 mmol), and butylamine (10 mmol) was performed for 3 h under reflux in a *t*-BuOH solution containing the binary promoter of CuCl and chloroacetone which was the best system for the three-component coupling reaction using the electron-deficient olefin. As a result, the expected three-component coupling product **7a** was afforded in a modest yield (55%, Table 8, run 1). The use of CuCl alone improved the yield of **7a** to 67% (Table 8, run 2). Using CuCl in combination with B(OMe)₃ still promoted the formation of **7a** (Table 8, run 3), although B(OMe)₃ alone gave **7a** in only a low yield (Table 8, run 4). The reaction without any promoter furnished only a 30% yield of **7a** along with lengthened time for the con-

sumption of **1d** (Table 8, run 5). Next, it was revealed that increasing the amount of butylamine did not promote the formation of **7a** (Table 8, runs 3, 6–10), in contrast to a proportional relationship of the yields of the three-component coupling products to the amounts of ethanolamine in the cases using electron-deficient olefins or alkyl halides. Thus, **7a** was obtained in a good yield even in the reaction using the same equivalents of glycidyl methyl ether, **1d**, and butylamine (Table 8, run 6). These results are collected in Table 8, and GC analysis of the reaction mixture revealed no concomitant formation of the 1:1 or 1:2 adduct of butylamine with glycidyl methyl ether, except for the reaction in run 1 where the 1:1 adduct (60% yield) was formed as a by-product.

The reactions in the solvents other than *t*-BuOH were performed, and it was revealed that *t*-BuOH was the best of the alcoholic and aprotic dipolar solvents examined, as shown in Table 9.

Various combinations of **1** (1 equiv.), an epoxide (1.5 equivs.), and an amine (2 equivs.) were subjected to a thermal reaction under reflux in a *t*-BuOH solution containing the binary promoter of CuCl and B(OMe)₃, and the results are shown in Table 10. The reaction of ethanolamine with **1d** and glycidyl methyl ether afforded the three-component coupling product **7d** in only a trace amount (Table 10, run 3), which is in contrast to the reaction of **1** with ethanolamine and an electrophile

Table 5. Reaction of **1b–d**, alkyl bromides, and ethanolamine promoted by CuCl/B(OMe)₃ or B(OMe)₃.^[a]

Run	1	Alkyl bromide R ³	Metal species	Time [h] ^[b]	Product	
					6	Yield [%] ^[c]
1	d	CH ₂ =CHCH ₂	CuCl/B(OMe) ₃	18	b ^[d]	98
2	d	CH ₂ =CHCH ₂	B(OMe) ₃	48	b ^[d]	98
3	d	PhCH ₂	B(OMe) ₃	60	c ^[d]	95
4	d	PhCH ₂	CuCl/B(OMe) ₃	14	c ^[d]	72
5	d	CH ₂ =CBrCH ₂	B(OMe) ₃	72	d ^[d]	94 (80) ^[e]
6	d	<i>t</i> -Bu	CuCl/B(OMe) ₃	18	e ^[d]	26 (18) ^[e]
7	b	Pr	B(OMe) ₃	72	f	99
8	b	Pr	CuCl/B(OMe) ₃	18	f	70
9	b	CH ₂ =CHCH ₂	B(OMe) ₃	55	g	96
10	b	CH ₂ =CHCH ₂	CuCl/B(OMe) ₃	18	g	95 (85) ^[e]
11	b	PhCH ₂	B(OMe) ₃	55	h	94
12	c	CH ₂ =CHCH ₂	B(OMe) ₃	36	i	90
13	c	PhCH ₂	B(OMe) ₃	36	j	93 (83) ^[e]
14	c	CH ₂ =CBrCH ₂	B(OMe) ₃	36	k	97

^[a] Reaction conditions: **1** (2 mmol), alkyl bromide (3 mmol), ethanolamine (10 mmol), metal species (0.2 mmol).

^[b] Time at which the initial **1** was almost consumed.

^[c] Determined by GC analysis.

^[d] A 50/50 mixture of (*E*)- and (*Z*)-stereoisomers.

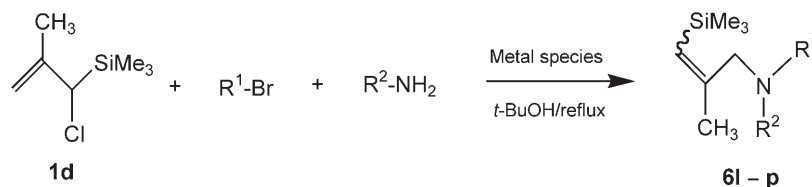
^[e] Determined by column chromatographic isolation.

other (e.g., halide) than an epoxide to afford the three-component coupling products in good yields. This may likely result from the low nucleophilicity of ethanolamine compared with an alkylamine such as butylamine, as exemplified by the findings that allyl glycidyl ether (3 mmol) was entirely consumed after 35 min by reaction with butylamine (4 mmol), while only after 110 min by reaction with ethanolamine (4 mmol). Furthermore, it may also be related to the rather low susceptibility of an epoxide to an amine compared with that of other electrophiles used in the present investigation; e.g., the consumption time of benzyl bromide (3 mmol) or propyl tosylate (3 mmol) in the reaction with ethanolamine (4 mmol) was shorter (30 min or 50 min, respectively) compared with that of the epoxide (*vide supra*). The primary, secondary, and tertiary alkylamines, except for ethanolamine, gave the three-component coupling products with **1b–d** and monosubstituted epoxides. In the reaction with **1b** and butylamine, a 1,1-disubstituted epoxide (i.e., 1,2-epoxy-2-methylpropane) formed the three-component coupling product **7k** in a good yield (Table 10, run 10), while the 1,2-disubstituted epoxide (i.e., cyclohexene oxide) gave the three-compo-

nent coupling product **7m** in a low yield (Table 10, run 12). GC analysis of the reactions in Table 10 revealed no concomitant formation of the amine derivatives *via* single or double alkylation with epoxides, except for run 3 in which the major product was the 1:1 adduct of ethanolamine with glycidyl methylamine (85% yield).

Three-Component Coupling Reaction using Analogues of **1**

The three-component coupling reaction using chlorotrimethylsilane, 1-chlorobutane, allyl chloride, and methallyl chloride as analogues of **1** was examined. The CuCl/chloroacetone-promoted reaction of acrylonitrile and ethanolamine with chlorotrimethylsilane or allyl chloride did not afford the corresponding three-component coupling product. In the CuCl/B(OMe)₃-promoted reaction of 1-bromopropane or propyl tosylate with ethanolamine or that of glycidyl methyl ether with butylamine, while chlorotrimethylsilane or 1-chlorobutane did not afford the three-component coupling product, methallyl chloride gave the corresponding three-com-

Table 6. Reaction of **1d**, alkyl bromides, and amines promoted by CuCl/B(OMe)₃ or B(OMe)₃.^[a]

Run	Alkyl bromide	Amine		Time [h] ^[b]	Metal species	Product ^[c]	
	R ¹	R ²	Amount [mmol]			6	Yield [%] ^[d]
1	CH ₂ =CHCH ₂	PhCH ₂	10	2	CuCl/B(OMe) ₃	l	62
2	CH ₂ =CHCH ₂	PhCH ₂	4	2	CuCl/B(OMe) ₃	l	62
3	CH ₂ =CHCH ₂ ^[e]	PhCH ₂	2	2	CuCl/B(OMe) ₃	l	18
4	CH ₂ =CHCH ₂	PhCH ₂	4	36	CuCl/B(OMe) ₃	l	72 (55) ^[f]
5	Pr	PhCH ₂	4	2	CuCl/B(OMe) ₃	m	67
6	Pr	PhCH ₂	4	24	B(OMe) ₃	m	85
7	Pr	CH ₃ (CH ₂) ₆	10	2	CuCl/B(OMe) ₃	n	61
8	Pr	CH ₃ (CH ₂) ₆	4	2	CuCl/B(OMe) ₃	n	61
9	Pr ^[e]	CH ₃ (CH ₂) ₆	2	2	CuCl/B(OMe) ₃	n	36
10	Pr	CH ₃ (CH ₂) ₆	4	32	B(OMe) ₃	n	50
11	Pr	cyclohexyl	4	10	CuCl/B(OMe) ₃	o	37
12	Pr	cyclohexyl	4	36	B(OMe) ₃	o	30
13	Pr	<i>t</i> -Bu	4	24	CuCl/B(OMe) ₃	p	24
14	Pr	<i>t</i> -Bu	4	96	B(OMe) ₃	p	26

^[a] Reaction conditions: **1d** (2 mmol), alkyl bromide (3 mmol), metal species (0.2 mmol).

^[b] Time at which the initial **1d** was almost consumed.

^[c] A 50/50 mixture of (*E*)- and (*Z*)-stereoisomers.

^[d] Determined by GC analysis.

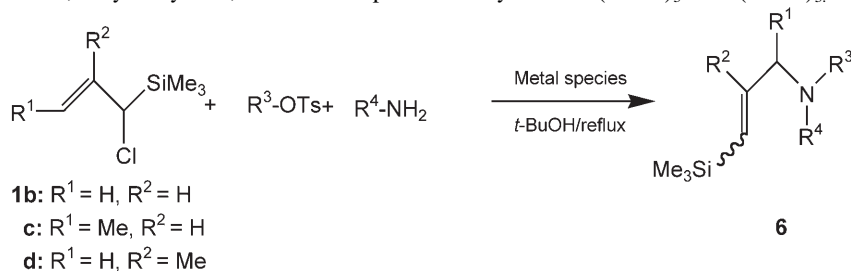
^[e] 2 mmol.

^[f] Determined by column chromatographic isolation.

ponent coupling product, albeit in a lower yield (60%, 14%, or 37%, respectively) compared with the reaction using **1d**. In the CuCl/B(Me)₃-promoted reaction of methallyl chloride and 1-bromopropane with ethanolamine, GC analysis along the time course revealed that the yield of the three-component coupling product attained the maximum value (60%), although methallyl chloride still remained, after 3 h and then gradually diminished (30% after 5 h) with the disappearance of methallyl chloride, probably owing to conversion to a quaternary ammonium salt. This reaction course is in contrast to that of **1d** and 1-bromopropane with ethanolamine catalyzed by CuCl/B(OMe)₃ in which the three-component coupling product, **6a**, was accumulated proportionally to the disappearance of **1d** (Table 4, run 6). Thus, it may be likely that the trimethylsilyl substituent at the allyl position is operative to impede transformation of a three-component coupling product to a quaternary ammonium salt *via* the further reaction with the α -chloroallylsilane.

Insights into the Mechanistic Aspects of the Reaction

Concerning the reaction mechanism, a step-wise pathway by way of the intermediate formation of a secondary amine was envisaged for the production of tertiary amines with three different substituents from the primary amines in our reaction system. Actually, the otherwise similar reaction of ethanolamine with **1b**, except without the electrophile, gave the 1:1 S_N2'-type product **8**. Furthermore, when the secondary amine, i.e., **8** or diethylamine, was reacted in a *t*-BuOH solution with acrylonitrile in the presence of CuCl or with **1d** in the presence of CuCl/B(OMe)₃, respectively, the expected tertiary amine, i.e., **3a** or diethyl(2-methyl-3-trimethylsilyl-2-propenyl)amine, was formed. GC analysis of our reaction using any electrophile along the time course, however, did not reveal an intermediate production of a secondary amine, such as **8** or the 1:1 adduct of an amine with an electrophile, but resulted in the direct appearance of the three-component coupling product, along with the 1:2 S_N2 product of an electrophile with an amine in some cases. On the other hand, the time course for the consumption of **1** and the electrophile varied depending on the type of electrophile; i.e., while an electron-deficient olefin was consumed according to al-

Table 7. Reaction of **1b–d**, alkyl tosylates, and amines promoted by CuCl/B(OMe)₃ or B(OMe)₃.^[a]

Run	1	Alkyl tosylate R ³	Amine R ⁴	Metal species	Time [h] ^[b]	Product	
						6	Yield [%] ^[c]
1	d	Pr	HO(CH ₂) ₂	CuCl/B(OMe) ₃	3	a ^[d]	78
2	d	Pr	HO(CH ₂) ₂	B(OMe) ₃	72	a ^[d]	42
3	d	CH ₂ =CHCH ₂	HO(CH ₂) ₂	CuCl/B(OMe) ₃	2	b ^[d]	82
4	d	PhCH ₂	HO(CH ₂) ₂	CuCl/B(OMe) ₃	2	c ^[d]	72
5	b	Pr	HO(CH ₂) ₂	CuCl/B(OMe) ₃	1	f	75
6	b	CH ₂ =CHCH ₂	HO(CH ₂) ₂	CuCl/B(OMe) ₃	2	g	92
7	c	CH ₂ =CHCH ₂	HO(CH ₂) ₂	CuCl/B(OMe) ₃	0.5	i	50
8	d	Pr	PhCH ₂	CuCl/B(OMe) ₃	2	l ^[d]	44
9	d	CH ₂ =CHCH ₂	PhCH ₂	CuCl/B(OMe) ₃	2	m ^[d]	46
10	d	Pr	CH ₃ (CH ₂) ₆	CuCl/B(OMe) ₃	3	n ^[d]	73
11	d	Pr	cyclohexyl	CuCl/B(OMe) ₃	3	o ^[d]	37

^[a] Reaction conditions: **1** (2 mmol), alkyl tosylate (3 mmol), amine (10 mmol), metal species (0.2 mmol).

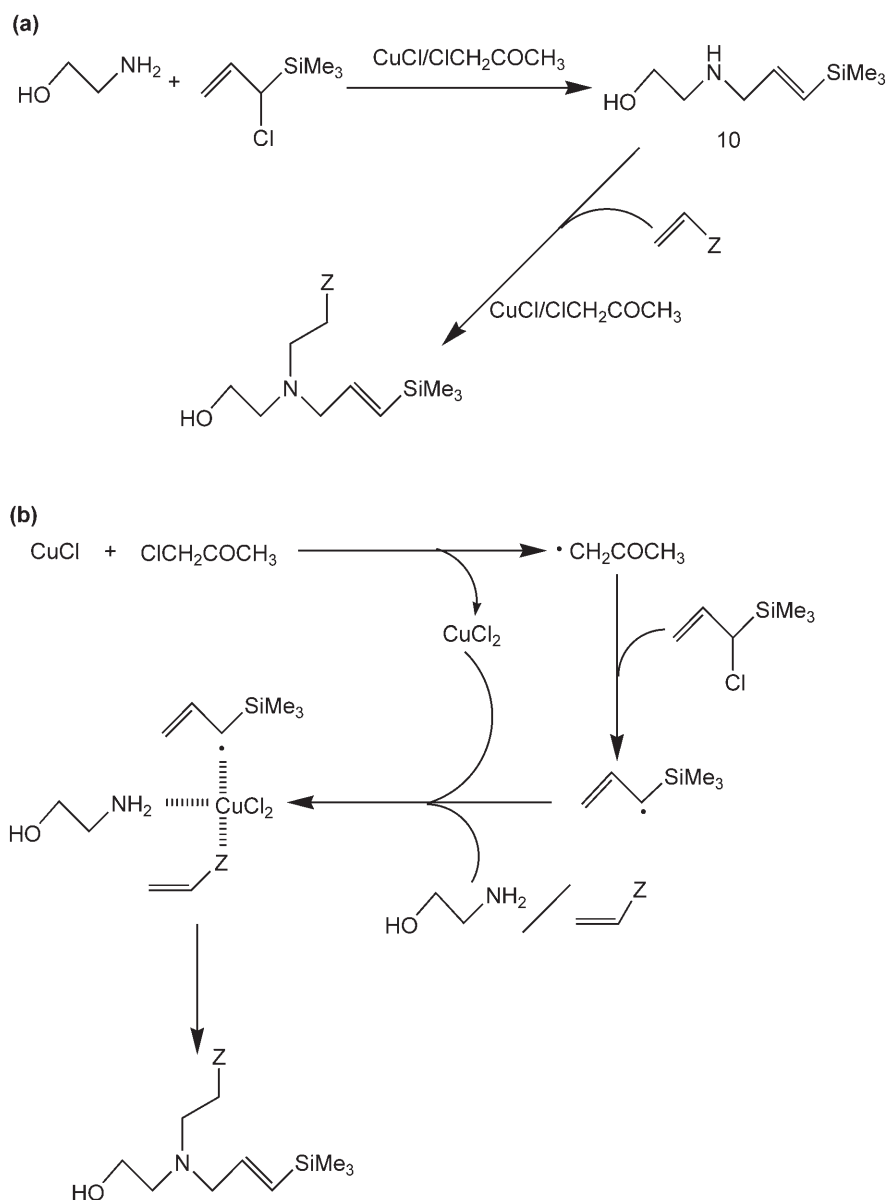
^[b] Time at which the initial **1** was almost consumed.

^[c] Determined by GC analysis.

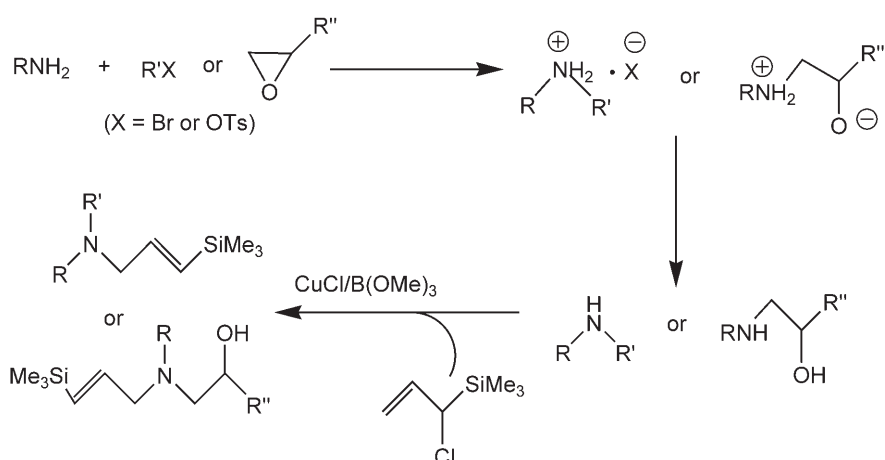
^[d] A 50/50 mixture of (*E*)- and (*Z*)-stereoisomers.

most the same time course with **1**, other electrophiles such as halides, tosylates, or epoxides were consumed prior to **1**. The addition of chloroacetone as a co-promoter in addition to CuCl substantially increased the yield of the three-component coupling product in the reaction using an electron-deficient olefin (Table 1, runs 2 and 7), but rather inhibited the three-component coupling reaction using other electrophiles such as halides or epoxides (Table 4, runs 1 and 2; Table 7, runs 1 and 2). From these findings, it could be speculated that some different mechanisms would operate between the three-component coupling reactions using electron-deficient olefins and other electrophiles. The reaction of **1a** and chloroacetone in the presence of CuCl and ethanolamine without an electrophile furnished the dimerization product of **1a**, i.e., **2**, in which the pathway *via* the radical intermediate based on the dehalogenation of **1a** by CuCl under the intervention of chloroacetone might be assumed (*vide supra*). Thus, the chloroacetone-promoted reaction including an electron-deficient olefin to furnish **3** might also proceed *via* the radical pathway. Therefore, the addition of a radical quencher (i.e., galvinoxyl, 0.1 equiv.) to the standard reaction system for **1b**, acrylonitrile, and ethanolamine was examined to result in a diminution of the yield of **3a** from 82% to 46%. Thus, some radical species generated *via* the reaction of CuCl and chloroacetone might play a critical role in

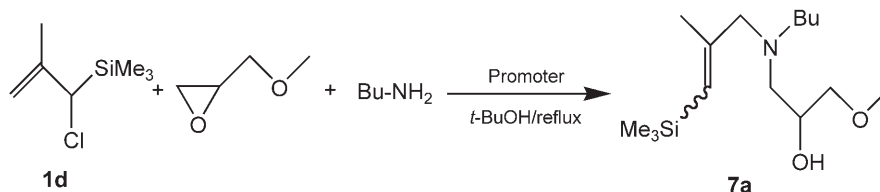
the efficient formation of **3**. Furthermore, in order to get some mechanistic information about the reaction using the electron-deficient olefins, the reaction of run 2 of Table 2 were compared with that between each component, i.e., ethanolamine with **1b** or methyl acrylate, the ethanolamine-methyl acrylate 1:1 adduct with **1b**, or the ethanolamine-**1b** S_N2' product with methyl acrylate, in the presence or absence of CuCl/ClCH₂COCH₃. The results are revealed in Table 11. GC analysis of the reaction along the time course revealed that methyl acrylate and **1b** were consumed almost at the same time in the three-component mixing reaction in the presence of the binary promoter of CuCl and chloroacetone to result in the direct appearance of **3b** without the detection of the secondary amine *via* the reaction of ethanolamine with **1b** or methyl acrylate (Table 11, runs 1 and 2). Subjecting the 1:1 adduct **9** of ethanolamine and methyl acrylate to the reaction with **1b** in the presence of the binary promoter brought about the disappearance of **9** along with **1b** remaining intact after 1 h (Table 11, run 11). Thus, the pathway *via* the intermediate formation of **9** may be less possible. When the 1:1 S_N2' product **10** of ethanolamine and **1b** was subjected to the reaction with methyl acrylate in the presence of the binary promoter, **3b** was formed along with a slightly faster consumption of methyl acrylate compared with that of **1b** in the reaction of **1b** and ethanolamine (Table 11, runs



Scheme 3. Postulated pathways for the reactions using electron-deficient olefins as electrophiles.



Scheme 4. Postulated pathway for the reactions using halides, tosylates, or epoxides as electrophiles.

Table 8. Effect of promoters and amounts of reagents on the three-component coupling reaction of **1d**, butylamine, and glycidyl methyl ether.^[a]

Run	Amount [mmol]		Promoter	Yield 7a ^[b] [%] ^[c]
	Epoxide	Amine		
1	3	10	CuCl/ $\text{ClCH}_2\text{COCH}_3$	55
2	3	10	CuCl	67
3	3	10	CuCl/ $\text{B}(\text{OMe})_3$	78
4 ^[d]	3	10	$\text{B}(\text{OMe})_3$	30
5 ^[d]	3	10	none	12
6	2	2	CuCl/ $\text{B}(\text{OMe})_3$	80
7	3	3	CuCl/ $\text{B}(\text{OMe})_3$	78
8	3	4	CuCl/ $\text{B}(\text{OMe})_3$	83
9	3	6	CuCl/ $\text{B}(\text{OMe})_3$	78
10	3	8	CuCl/ $\text{B}(\text{OMe})_3$	78

^[a] Reaction conditions: **1d** (2 mmol), promoter (0.2 mmol), reaction time = 3 h except for runs 4 and 5.

^[b] A 50/50 mixture of (*E*)- and (*Z*)-stereoisomers.

^[c] Determined by GC analysis.

^[d] Reaction time = 72 h.

8, 9 and 13, 14). Both steps of formation of **10** and its conversion to **3b** were accelerated by the binary promoter (Table 11, runs 9, 10 and 14, 15). The results of these control experiments may suggest that the step-wise pathway in which **10** was temporarily formed to be converted to **3b** immediately after its formation without detection by GC analysis may likely be operative [Scheme 3 (a)], although the pathway *via* the simultaneous formation of two different C–N bonds cannot be entirely excluded [Scheme 3 (b)], considering the somewhat faster consumption of **1b** in the three-component mixing system compared with that in the two-component system consisting of **1b** and ethanolamine (Table 11, runs 1 and 8).

In the cases using electrophiles (i.e., halides, tosylates, and epoxides) other than electron-deficient olefins, those electrophiles were perfectly consumed prior to **1**, and the three-component coupling products were then formed progressively along with the disappearance of **1**. Therefore, a step-wise pathway *via* the intermediary formation of the 1 : 1 product of the primary amine and electrophile could be considered a possible candidate. GC analysis of the reaction mixture along the time course, however, did not disclose the generation of such an intermediate. Thus, although the precise mechanism for the selective formation of the three-component coupling product has not been unambiguously ascertained, it might be reasonable to assume the pathway where the secondary amine, which is at first generated in a protonated form *via* the reaction of the primary amine

with the electrophile to hinder detection by GC analysis, in turn reacts with **1** immediately after gradual deprotonation (Scheme 4). The reason why the three-component coupling reaction using the tosylate proceeded faster than that using the halide (e.g., Table 5, run 1 and Table 6, run 3) might be due to the fact that HBr is a stronger acid than TsOH,^[17] and thus the ammonium salt of the latter undergoes deprotonation more readily compared to that of the former. A promoter such as CuCl alone or in combination with $\text{B}(\text{OMe})_3$ might function to accelerate, not the step to form the secondary amine intermediate, but rather the reaction step of **1** with this putative intermediates in the above-mentioned hypothetical pathway, since the absence of the promoter resulted in the sluggish consumption of **1** and the low yield of the three-component coupling product (e.g., Table 4, runs 2, 6, and 8) while the consumption time of the electrophile was almost not influenced by the presence of the promoter.

Conclusion

We have demonstrated the preparation of a tertiary amine bearing three different substituents by way of the tandem assembly reaction of a primary amine, an electrophile, and an α -halogenated allylsilane. While the binary promoter of CuCl/ $\text{ClCH}_2\text{COCH}_3$ was advantageous for the reaction using an electron-deficient ole-

Table 9. Effect of solvent on the three-component coupling reaction of **1d**, butylamine, and glycidyl methyl ether promoted by CuCl/B(OMe)₃.^[a]

Run	Solvent	Yield 7a [%] ^[b]
1	<i>t</i> -BuOH	83
2	EtOH	79
3	<i>n</i> -BuOH	79
4	<i>sec</i> -BuOH	81
5	THF	34
6	CH ₃ CN	59
7	CH ₃ COCH ₃	49
8	DMF	19

^[a] Reaction conditions: **1d** (2 mmol), glycidyl methyl ether (3 mmol), butylamine (4 mmol), CuCl (0.2 mmol), B(OMe)₃ (0.2 mmol), reaction time = 3 h.

^[b] Determined by GC analysis.

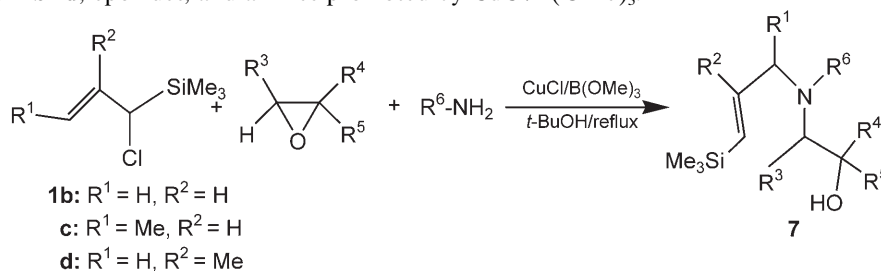
fin as an electrophile, the reaction using an alkyl halide, alkyl tosylate, or an epoxide as an electrophile was effectively accomplished by the binary promoter of CuCl/B(OMe)₃. From a comparison with the reactions of analogues of **1**, the use of α -chlorinated allylsilanes proved

to be essential for the effective progression of the three-component coupling reaction presented herein.

Experimental Section

General Remarks

Infrared spectra were recorded on a Horiba FT-210 spectrometer. NMR spectra were recorded on a JNM GX400 spectrometer (¹H: 400 MHz, ¹³C: 100 MHz) for CDCl₃ solutions using TMS as internal standard (δ = 0) unless otherwise noted. MS and HR-MS were obtained at 70 eV using a Hitachi M-80b GC-MS instrument equipped with a 10 m megabore DB-1 column. GC analysis was performed in 10% silicon SE-30 on Chromosorb using a Shimadzu GC-14B. Preparative GC was carried out using a Shimadzu GC-12A. Preparative TLC was performed on Merck silica gel 60F₂₅₄ (0.5 mm, 20 cm $\times$ 20 cm). Column chromatography was performed on Merck silica gel 60F₂₅₄ (45–75 μ m). α -Halogenated allylsilanes **1a–d** were prepared according to methods of Hosomi^[8] and Julia.^[18] Tosylates were synthesized according to literature procedures.^[19] Characterization data of the products are reported in the Supporting Information.

Table 10. Reaction of **1b–d**, epoxides, and amines promoted by CuCl/B(OMe)₃.^[a]

Run	1	Epoxide			Amine R ⁶	Time [h] ^[b]	Product	
		R ³	R ⁴	R ⁵			7	Yield [%] ^[c]
1	d	H	CH ₂ OCH ₃	H	PhCH ₂	3	b ^[d]	65
2	d	H	CH ₂ OCH ₃	H	<i>t</i> -Bu	24	c ^[d]	70
3	d	H	CH ₂ OCH ₃	H	HO(CH ₂) ₂	3	d ^[d]	trace
4	d	H	CH ₂ OCH ₃	H	cyclohexyl	5	e ^[d]	70 (67) ^[e]
5	d	H	CH ₂ CH ₃	H	CH ₃ (CH ₂) ₃	3	f ^[d]	72
6	d	H	CH ₂ OCH ₂ CH=CH ₂	H	CH ₃ (CH ₂) ₃	3	g ^[d]	74
7	b	H	CH ₂ CH ₃	H	CH ₃ (CH ₂) ₃	2.5	h	65
8	b	H	CH ₂ OCH ₃	H	CH ₂ (CH ₂) ₃	3	i	78
9	b	H	CH ₂ OCH ₂ CH=CH ₂	H	CH ₂ (CH ₂) ₃	3	j	78 (72) ^[e]
10	b	H	CH ₃	CH ₃	CH ₂ (CH ₂) ₃	3	k	73
11	b	H	Ph	H	CH ₂ (CH ₂) ₃	3	l	65 (58) ^[e]
12	b	-(CH ₂) ₄ -	H	H	CH ₂ (CH ₂) ₃	8	m	7 (7) ^[e]
13	c	H	CH ₂ OCH ₃	H	CH ₂ (CH ₂) ₃	2	n	74
14	c	H	CH ₂ CH ₃	H	CH ₂ (CH ₂) ₃	1.5	o	70

^[a] Reaction conditions: **1** (2 mmol), epoxide (3 mmol), amine (4 mmol), CuCl (0.2 mmol), B(OMe)₃ (0.2 mmol).

^[b] Time at which the initial compound **1** was almost consumed.

^[c] Determined by GC analysis.

^[d] A 50:50 mixture of (*E*)- and (*Z*)-stereoisomers.

^[e] Determined by column chromatographic isolation.

Table 11. Comparison of the reaction in the system consisting of **1b**, methyl acrylate, and ethanolamine with that in the two-component system.^[a]

Run	System	Catalyst ^[b]	Time [min]	Consumption [%]		Yield 3b [%]
				1b	Methyl acrylate	
1	1b /methyl acrylate/ethanolamine ^[c]	presence	60	90	92	81
2			120	100	100	96
3	1b /methyl acrylate/ethanolamine ^[c]	absence	120	9	100	4
4	methyl acrylate/ethanolamine ^[d]	presence	60		32	
5			240		100	
6	methyl acrylate/ethanolamine ^[d]	absence	10		39	
7			30		100	
8	1b /ethanolamine ^[e]	presence	60	65		
9			120	100		
10	1b /ethanolamine ^[e]	absence	90	0		
11	1b / 9 ^[f]	presence	60 ^[g]	0		0
12	1b / 9 ^[f]	absence	60	0		0
13	methyl acrylate/ 10 ^[h]	presence	30		48	45
14			60		100	82
15	methyl acrylate/ 10 ^[h]	absence	60		29	27
16			180		100	82

^[a] Reaction conditions: reflux in a *t*-BuOH solution.^[b] CuCl/B(OMe)₃.^[c] **1b** (2 mmol), methyl acrylate (3 mmol), ethanolamine (10 mmol).^[d] Methyl acrylate (3 mmol), ethanolamine (10 mmol).^[e] **1b** (2 mmol), ethanolamine (10 mmol).^[f] **9** = HO(CH₂)₂NH(CH₂)₂COOMe; **1b** (2 mmol), **9** (3 mmol).^[g] **9** was completely consumed at this time.^[h] **10** = HO(CH₂)₂NHCH₂CH=CHSiMe₃; methyl acrylate (3 mmol), **10** (2 mmol).

General Procedure for the Three-Component Coupling Reaction of Electron-Deficient Olefins with **1** and Amines

After an amine (10 mmol), CuCl (0.02 g, 0.2 mmol), and *t*-BuOH (3 mL) had been added to a flask and then rendered a transparent solution by ultrasonic wave irradiation, a *t*-BuOH (2 mL) solution containing **1** (2 mmol), an electron-deficient olefin (3 mmol), and chloroacetone (0.37 g, 4 mmol) was further added. The resulting solution was stirred under reflux. The reaction mixture was then poured into H₂O and extracted with Et₂O. After the solvent was mostly removed under reduced pressure, some parts of the residue were subjected to preparative GC or TLC (eluent: hexane/ethyl acetate = 1:2) for the identification of the structure of the product.

General Procedure for the Three-Component Coupling Reaction of Halides, Tosylates, or Epoxides with **1** and Amines

After an amine (4–10 mmol), CuCl (0.1–0.2 mmol), B(OMe)₃ (0.1–0.2 mmol), and *t*-BuOH (3 mL) were added to a flask and then rendered a transparent solution by ultrasonic wave irradiation, a *t*-BuOH (2 mL) solution containing **1** (2 mmol) and an electrophile (3 mmol) was further added. The reaction mixture was worked up similarly to the above procedure, and then some parts of the residue were subjected to column chromatography or TLC isolation using hexane/ethyl acetate (1:2) as an eluent for the identification of the structure of the product.

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