

The direct synthesis of tertiary amines with three different substituents via the reaction of primary amines, alkyl halides, and α -chlorine substituted allylsilanes catalyzed by Lewis acids

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Abstract—Tertiary amines with three different substituents were obtained in a single step by the $\text{CuCl}/\text{B}(\text{OMe})_3$ or $\text{B}(\text{OMe})_3$ -catalyzed reaction of α -chlorine substituted allylsilanes, alkyl halides, and primary amines.

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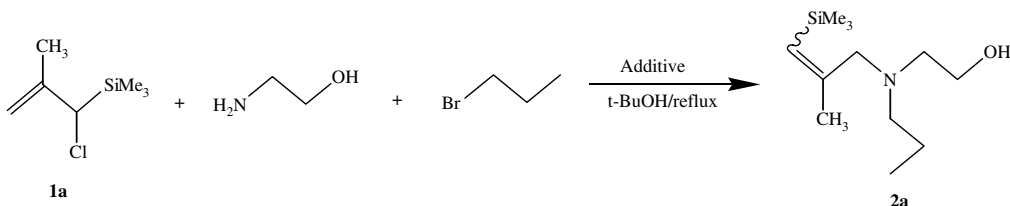
The reactions of halides with amines have been most commonly put to use in various methods of nitrogen–carbon bond formation. However, alkylated amines tend to undergo further alkylation more readily due to their enhanced nucleophilicity compared with that of the parent amines. Thus, primary amines usually result in the formation of a complex mixture based on poly-alkylation by the reaction of alkyl halides. The preparation of tertiary amines with three different substituents has commonly been performed by step-wise alkylation on the nitrogen atom with some manipulation to yield the selective formation of secondary amines in the first step.¹ To the best of our knowledge, no method of preparing tertiary amines by the simultaneous formation of different nitrogen–carbon bonds in a single step has yet been reported, although three-component joining reactions for the simultaneous formation of two different carbon–carbon bonds² or the nitrogen–carbon bond together with the carbon–carbon bond³ in one step have been actively investigated. In the present communication, we wish to report a novel three-component joining reaction to form tertiary amines having three different substituents in a single step, which consists of a Lewis acid-catalyzed reaction of the primary amines, alkyl halides, and α -chlorine substituted allylsilanes. The reactions of α -halogen substituted allylsilanes with

electrophiles promoted by the Lewis acid such as TiCl_4 or BF_3 have been known to form vinyl halide derivatives via the elimination of the silyl group accompanied by the migration of the carbon–carbon double bond,⁴ similarly to the allylation reaction of electrophiles by allylsilanes.⁵ We have recently found that the copper(I)-catalyzed reactions of polyhalides with α -halogen substituted allylsilanes bring about the formation of vinylsilane derivatives by the elimination of the α -halogen atom in conjunction with migration of the carbon–carbon double bond.⁶ Furthermore, a mono-halogen compound having an electron-withdrawing group such as ethyl bromoacetate also afforded the same type of product.⁶ The use of an alkyl mono-halide, however, has proved to give the three-component joining product containing the amine used as the ligand for the dissolution of the copper(I) catalyst, as disclosed by this investigation.

At first, a *t*-BuOH solution containing (1-chloro-2-methyl-2-propenyl)trimethylsilane **1a**, 1-bromopropane, ethanolamine, and copper(I) chloride was subjected to a thermal reaction under reflux for 4 h. As a result, the initial **1a** was entirely consumed and the three-component joining product **2a** was formed in a 69% yield (Table 1, Run 1). The use of $\text{Al}(\text{O}-i\text{-Pr})_4$ or $\text{B}(\text{OMe})_3$ as a Lewis acid afforded **2a** in excellent yields, although a long period of time was necessary to complete the consumption of **1a** (96 and 72 h in Runs 2 and 3, respectively). Increasing the amount of $\text{B}(\text{OMe})_3$ did not shorten the consumption time of **1a** (Run 4). Thus, the reaction using CuCl in combination with $\text{B}(\text{OMe})_3$ as the

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Table 1. Effects of metal species on three-component joining reaction of **1a**, ethanolamine, and 1-bromopropane^a

Run	Additive	Time/h ^b	2a ^c Yield/% ^d
1	CuCl	4	69
2	Al(O- <i>i</i> -Pr) ₃	96	92
3	B(OMe) ₃	72	93
4	B(OMe) ₃ ^e	72	93
5	CuCl/B(OMe) ₃	18	93
6	CuCl/Al(O- <i>i</i> -Pr) ₃	18	49
7	None	36	23

^a Conditions: *t*-BuOH = 5 ml, **1a** = 2 mmol, 1-bromopropane = 3 mmol, NH₂(CH₂)₂OH = 10 mmol, metal species = 0.2 mmol.

^b Time at which the initial **1a** was perfectly consumed.

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

^d Determined by GC analysis.

^e B(OMe)₃ = 1 mmol.

promoter was explored with the expectation that it would produce **2a** in an excellent yield under accelerated consumption of **1a**. Under these conditions, **2a** was produced in a 93% yield and **1a** was consumed in 18 h (Run 5). However, the use of CuCl together with Al(O-*i*-Pr)₃ gave **2a** in a 49% yield under the same consumption time of **1a** (Run 6). The reaction without a promoter furnished only a 23% yield of **2a** after consuming **1a** in 36 h (Run 7).

Next, halides other than 1-bromopropane were subjected to reaction with ethanolamine and **1a**. Allyl bromide, benzyl bromide, and 2,3-dibromopropene formed the three-component joining product, **2b–d**, in excellent to good yields (Table 2, Runs 1–5). A sterobulky halide, *tert*-butyl bromide, produced the three-component joining product, **2e**, in a low yield (Run 6), and, in this case, the major products were the 1:1 and 1:2 S_N2' products of ethanolamine with **1a**. Furthermore, reactions using unsubstituted α -chloroallylsilane **1b** and 1-chloro-1-trimethylsilyl-2-butene **1c** instead of **1a** were explored. The B(OMe)₃-promoted reaction of **1b** with 1-bromopropane, allyl bromide, or benzyl bromide produced the three-component joining product, **2f–h**, in an excellent yield (Runs 7, 9, and 10), while the binary promoter of CuCl/B(OMe)₃ formed **2f** in a 70% yield (Run 8). The B(OMe)₃-promoted reaction of **1c** with allyl bromide, benzyl bromide, or 2,3-dibromopropene produced the corresponding three-component joining product, **2i–k** in excellent yields (Runs 11–13).

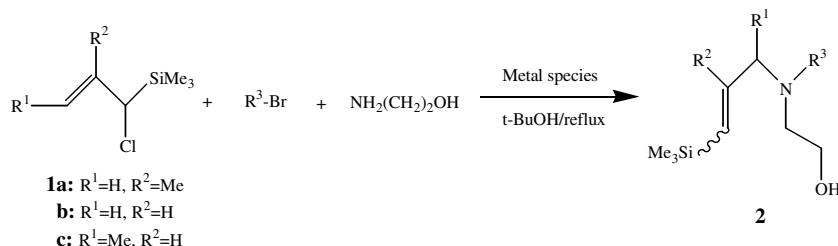
Next, amines other than ethanolamine, such as benzylamine, heptylamine, cyclohexylamine, and *tert*-butylamine, were subjected to reaction with **1a** and alkyl halides. The CuCl/B(OMe)₃-promoted reactions of benzylamine with 1-bromopropane or allyl bromide produced the corresponding three-component joining product, **3a–b**, in yields of 67% and 62%, respectively, after 2 h, while the B(OMe)₃-promoted reaction gave

3a in a 72% yield after 36 h. The reaction of heptylamine with 1-bromopropane afforded the three-component joining product in a 61% yield after 2 h. Additionally, secondary or tertiary alkyl amines, such as cyclohexylamine or *tert*-butylamine, formed the corresponding three-component joining product with 1-bromopropane in a yield of 37% or 24% after 10 or 24 h, respectively, giving the 1:1 and 1:2 S_N2' products of the amine with **1a** as the primary by-products.

The analogues of **1** were subjected to reaction with ethanolamine and 1-bromopropane in the presence of CuCl/B(OMe)₃. While chloromethyltrimethylsilane and 1-chlorobutane gave no corresponding three-component joining product, 3-chloro-2-methylpropene was found to form the three-component joining product, *N*-(2-methyl-2-propenyl)-*N*-propylethanolamine, in a 60% yield.

GC analysis of the reaction shown in Run 5 of Table 1 along the time course revealed the formation of the 1:2 S_N2 product of 1-bromopropane with ethanolamine, *N,N*-dipropylethanolamine **4**, in addition to **2a**. During the entire course of the reaction, however, the 1:1 product of these components, *N*-propylethanolamine, which may reasonably be assumed to be a precursor of the formation of **2a**, was not detected. The use of independently prepared **4** in a reaction with **1a** in the presence of CuCl/B(OMe)₃ did not afford **2a**. In order to examine if the secondary amine performs the reaction with **1** under our reaction conditions, diethylamine was subjected to reaction with **1a** in the presence of CuCl/B(OMe)₃, producing diethyl(2-methyl-3-trimethylsilyl-2-propenyl)amine **5** in a 46% yield after 5 h, while a similar reaction without a catalyst did not form **5** after 5 h.

GC analysis of the reaction shown in Run 4 of Table 2 along with the time course revealed that benzyl bromide was completely consumed after 1 h, while **1a** remained intact, and that **2c** was then formed progressively along

Table 2. Reaction of α -chloroallylsilanes, alkyl bromides, and ethanolamine promoted by CuCl/B(OMe)₃ or B(OMe)₃⁷

Run	1	Alkyl bromide R ³	Metal species	Time/h ^a	Product	
					2	Yield/% ^b
1	a	CH ₂ =CHCH ₂	CuCl/B(OMe) ₃	18	b^c	98
2	a	CH ₂ =CHCH ₂	B(OMe) ₃	48	b^c	98
3	a	PhCH ₂	B(OMe) ₃	60	c^c	95
4	a	PhCH ₂	CuCl/B(OMe) ₃	14	c^c	72
5	a	CH ₂ =CBrCH ₂	B(OMe) ₃	72	d^c	94
6	a	<i>t</i> -Bu	CuCl/B(OMe) ₃	18	e^c	26
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	PhCH ₂	B(OMe) ₃	55	h	94
11	c	CH ₂ =CHCH ₂	B(OMe) ₃	36	i	90
12	c	PhCH ₂	B(OMe) ₃	36	j	93
13	c	CH ₂ =CBrCH ₂	B(OMe) ₃	36	k	97

^a Time at which the initial **1a** was perfectly consumed.^b Determined by GC analysis.^c A 50/50 mixture of (*E*) and (*Z*) stereoisomers.

with the disappearance of **1a**. In this case, no intermediary species other than the 1:2 S_N2 product of benzyl bromide with ethanolamine, *N,N*-dibenzylethanolamine, was detected. The GC analysis after the consumption of **1a** and the TLC analysis following the work-up of the reaction mixture also revealed no notable product other than **2c** and *N,N*-dibenzylethanolamine. The starting amount of benzyl bromide balanced with the combined amount of these two products. Concerning the mechanism for the formation of **2c**, the pathway that the HBr salt of *N,N*-dibenzylethanolamine, **6**, generated in situ might effect the benzylation of the 1:1 S_N2' product of **1a** with ethanolamine, **7**, which would be later formed may be less likely, since **6** prepared from benzyl bromide (2 equiv) and ethanolamine (1 equiv) was subjected to the reaction with **7** in the presence of CuCl/B(OMe)₃ to result in no formation of **2c**. Quaternary ammonium salt might be assumed to be a potential intermediate for the formation of the three-component joining product. However, this possibility must be discarded since tetrabutylammonium bromide did not react with **1a** in the presence of CuCl/B(OMe)₃. Thus, the precise mechanism for the selective formation of the three-component joining product and the role of the promoter have not yet been unambiguously ascertained, although it may be speculated from the above control experiments that the secondary amine derived from the amine and the alkyl bromide, which may appear primarily as a protonated ammonium salt, hindering detection by GC analysis, functions as a working-intermediate.

In summary, reactions to produce three-component joining products of primary amines with alkyl bromide

and **1** were developed by catalysis with B(OMe)₃ or CuCl/B(OMe)₃; the latter was found to shorten the conversion time of **1** compared with the former. Allyl chloride without the silyl group was also found to afford a similar product in a moderate yield.

References and notes

- Buehler, C. A.; Pearson, D. E. *Survey of Organic Syntheses*; Wiley-Interscience: New York, 1970, p 444.
- (a) Husang, T.-H.; Change, H.-M.; Cheng, C.-H. *J. Org. Chem.* **2002**, *67*, 99; (b) Chandrasekhar, S.; Narsihmulu, C.; Reddy, N. R.; Reddy, M. S. *Tetrahedron Lett.* **2003**, *44*, 2583; (c) Yamamoto, Y.; Nakano, S.; Maekawa, H.; Nishiguchi, I. *Org. Lett.* **2004**, *6*, 799; (d) Chetia, A.; Saikia, C. J.; Lekhok, K. C.; Boruah, R. C. *Tetrahedron Lett.* **2004**, *45*, 2649.
- (a) Ollevier, T.; Ba, T. *Tetrahedron Lett.* **2003**, *44*, 9003; (b) Kamijo, S.; Jin, T.; Huo, Z.; Yamamoto, Y. *J. Org. Chem.* **2004**, *69*, 2386; (c) Li, Z.; Wei, C.; Chen, L.; Varma, R. S.; Li, C.-J. *Tetrahedron Lett.* **2004**, *45*, 2443; (d) Shi, L.; Tu, Y.-Q.; Wang, M.; Zhang, F.-M.; Fan, C.-A. *Org. Lett.* **2004**, *6*, 1001.
- Hosomi, A.; Ando, M.; Sakurai, H. *Chem. Lett.* **1984**, 1385.
- (a) Pilot, J. P.; Dunogues, J.; Calas, R. *Tetrahedron Lett.* **1976**, 1871; (b) Hosomi, A.; Endo, M.; Sakurai, H. *Chem. Lett.* **1976**, 941; (c) Hosomi, A.; Sakurai, H. *Tetrahedron Lett.* **1976**, 1295; (d) Hosomi, A.; Sakurai, H. *J. Am. Chem. Soc.* **1977**, *99*, 1673; (e) Hosomi, A. *Acc. Chem. Res.* **1988**, *21*, 200; (f) Schinzer, D. *Synthesis* **1988**, 263.
- Mitani, M.; Masuda, M.; Inoue, A. *Synlett* **2004**, 1227.
- General procedure: After an amine (10 mmol), CuCl (0.01 g, 0.1 mmol), B(OMe)₃ (0.01 g, 0.1 mmol), and *t*-BuOH (3 ml) were added to a flask and then made transparent by ultrasonic wave irradiation, a *t*-BuOH (2 ml)

solution containing an α -chlorine substituted allylsilane **1** (2 mmol) and an alkyl halide (3 mmol) was added to the flask. The resulting solution was stirred under reflux. The reaction mixture was then poured into water and extracted

with diethyl ether. After the solvent was mostly removed under reduced pressure, some parts of the residue were subjected to the TLC-isolation for the identification of the structure of the product.