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Copper-Catalyzed Allylation of Carbonyl Derivatives Using Allyl(2-pyridyl)silanes

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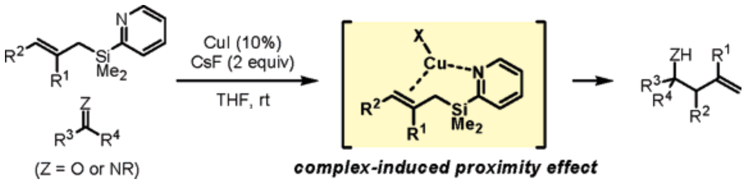
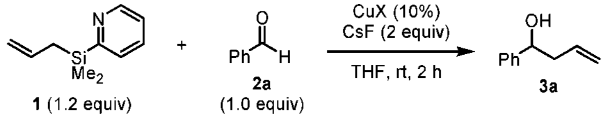
ABSTRACT



We have developed an efficient copper-catalyzed allylation of carbonyl derivatives using allyl(2-pyridyl)silanes, in which the strong directing effect of the 2-pyridyl group was observed. A useful synthesis and allylation of substituted allyl(2-pyridyl)silanes is also described.

Over the last three decades of extensive worldwide research, the addition reaction of allylmetals to C═Z bonds (Z = O or NR) has emerged as one of the most useful carbon−carbon bond-forming reactions.[1] Although it has now become a textbook reaction in organic synthesis, there still exists considerable room for further development and improvement. As a part of our studies using a 2-pyridylsilyl group as a "removable directing group" in metal catalysis,[2] we previously reported the AgOAc-catalyzed allylation of aldehydes using allyldimethyl(2-pyridyl)silane (**1**).[3] Though interesting from a mechanistic point of view (most likely via Lewis base activation mechanism), the reaction suffered severely from limited scope. We herein report a unique copper catalysis in the allylation using **1**, where a wide range of carbonyl derivatives, including ketones and imines, can be applied. A useful synthesis and allylation of substituted allyl(2-pyridyl)silanes is also described.

Table 1. Effect of Copper Salts in the Allylation of **2a** Using **1**



entry	CuX	yield (%)
1	CuI	86
2	CuI (without CsF)	0
3	none	0
4	CuI (5%)	87
5	CuI (1 equiv CsF)	91
6	CuBr	62
7	CuCl	79
8	CuCN	53
9	$[Cu(CH_3CN)_4]PF_6$	86
10	Cu_2O	0
11	$CuCl_2$	5
12	CuF_2	0

During our study aimed at developing reliable allylation using **1**, we found that the allylation of benzaldehyde (**2a**, 1.0 equiv) using **1** (1.2 equiv) proceeded smoothly even at room temperature under the influence of CuI (10 mol %) and CsF (2.0 equiv) in THF, giving homoallylic alcohol **3a** in 86% yield after acidic workup (Table 1, entry 1). The results using various copper salts are depicted in Table 1. The omission of either promoter (CuI or CsF) completely failed to promote the reaction (entries 2 and 3). Other copper(I) salts, such as CuBr, CuCl, and CuCN, also promoted this allylation, but the efficacy was somewhat lower than that of CuI (entries 6−8). Interestingly, the cationic copper(I)

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(1) Reviews: (a) Yamamoto, Y.; Asao, N. *Chem. Rev.* **1993**, *93*, 2207. (b) Denmark, S. E.; Fu, J. *Chem. Rev.* **2003**, *103*, 2763. (b) Kennedy, J. W. J.; Hall, D. G. *Angew. Chem., Int. Ed.* **2003**, *42*, 4732.

(2) Selected examples: (a) Itami, K.; Mitsudo, K.; Kamei, T.; Koike, T.; Nokami, T.; Yoshida, J. *J. Am. Chem. Soc.* **2000**, *122*, 12013. (b) Itami, K.; Nokami, T.; Yoshida, J. *J. Am. Chem. Soc.* **2001**, *123*, 5600. (c) Itami, K.; Koike, T.; Yoshida, J. *J. Am. Chem. Soc.* **2001**, *123*, 6957. (d) Itami, K.; Kamei, T.; Yoshida, J. *J. Am. Chem. Soc.* **2001**, *123*, 8773. (e) Itami, K.; Nokami, T.; Ishimura, Y.; Mitsudo, K.; Kamei, T.; Yoshida, J. *J. Am. Chem. Soc.* **2001**, *123*, 11577. (f) Itami, K.; Kamei, T.; Yoshida, J. *J. Am. Chem. Soc.* **2003**, *125*, 14670. (g) Itami, K.; Mitsudo, K.; Fujita, K.; Ohashi, Y.; Yoshida, J. *J. Am. Chem. Soc.* **2004**, *126*, 11058.

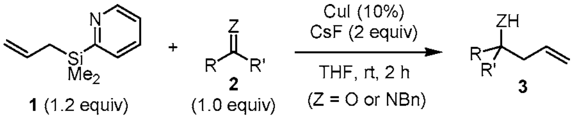
(3) Itami, K.; Kamei, T.; Mineno, M.; Yoshida, J. *Chem. Lett.* **2002**, 1084.

10.1021/ol051925s CCC: $30.25

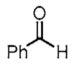
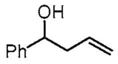
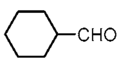
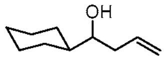
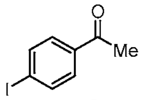
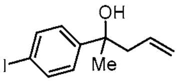
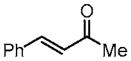
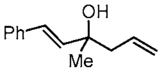
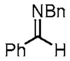
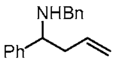
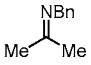
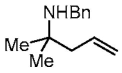
complex $[Cu(CH_3CN)_4]PF_6$ also catalyzed this allylation (86%, entry 9). On the other hand, Cu_2O and copper(II) salts, such as $CuCl_2$ and CuF_2, were found not to promote this allylation (entries 10−12). Although reducing the amount of either promoter also promoted the reaction (entries 4 and 5), 10% CuI was employed for further reaction because of the lower efficacy in the allylation using substituted allyl-(2-pyridyl)silanes.

With an efficient protocol for allylation using **1** in hand, we subsequently surveyed various carbonyl derivatives to roughly grasp the scope of the present allylation (Table 2).

Table 2. CuI/CsF-Promoted Allylation of Various Carbonyl Derivatives **2** Using **1**



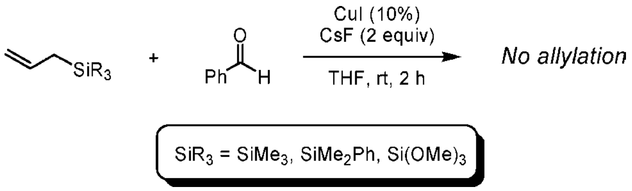
1 (1.2 equiv) **2** (1.0 equiv) **3**

entry	2		3 (yield, %)	
1		**2a**		**3a** (86)
2		**2b**		**3b** (71)
3		**2c**		**3c** (95)
4		**2d**		**3d** (77)
5		**2e**		**3e** (76)
6		**2f**		**3f** (77)

It was found that not only aldehydes and ketones but also aldimines and ketimines can be applied in this allylation, furnishing various substituted homoallylic alcohols and amines in good to excellent yields. The aryl−I functionality is tolerated under the reaction conditions (entry 3). When α,β-unsaturated carbonyl compounds (such as **2d**) were employed, the reaction exhibited excellent 1,2-addition selectivity (entry 4).

Currently, we assume allylcopper[4] to be the actual nucleophile in this reaction. Considering the similarity of conditions and reaction scope, the reaction might proceed in a manner similar to the Cu-catalyzed allylation using allyltrimethoxysilane developed recently by Shibasaki and Kanai.[5,6] Interestingly, however, we found that the present CuI/CsF system cannot be applied to allyltrimethoxysilane or other allyltrialkylsilanes under otherwise identical conditions (Scheme 1). Therefore, a unique promoting effect of the 2-pyridyl group on silicon was obvious at this point.

Scheme 1



During further study aimed at revealing the role of the 2-pyridyl group, we found the production of Cu complex **4** by the stoichiometric reaction of **1** and CuI (Figure 1). Such a complex was not obtained when allyltrimethylsilane or allyltrimethoxysilane was used. The ^1H NMR and X-ray crystal structure analysis revealed the bidentate coordination of pyridyl group and C═C moiety in **4**.[7] Moreover, it was also found that the allylation took place when CsF was added to the mixture of **4** and PhCHO. The allylation did not take place without CsF. Thus, we are currently assuming that the beneficial role of the pyridyl group is to help the reacting C═C bond to coordinate to copper through precoordination (complex-induced proximity effect), thereby facilitating the subsequent Si-to-Cu transmetalation to generate allylcopper species by the action of CsF.[8]

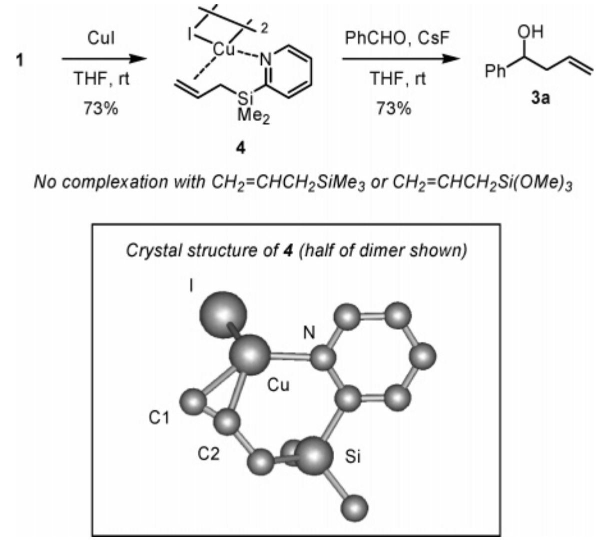


Figure 1. Synthesis, crystal structure, and reaction of Cu complex **4**.

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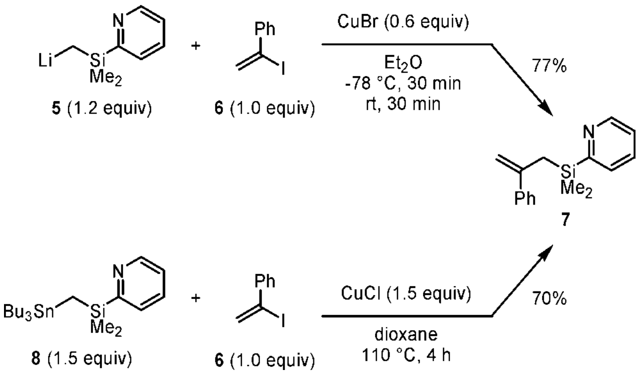
[4] (a) Stack, D. E.; Dawson, B. T.; Rieke, R. D. *J. Am. Chem. Soc.* **1992**, *114*, 5110. (b) Lipshutz, B. H.; Ellsworth, E. L.; Dimock, S. H.; Smith, R. A. J. *J. Am. Chem. Soc.* **1990**, *112*, 4404.

[5] (a) Yamasaki, S.; Fujii, K.; Wada, R.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2002**, *124*, 6536. Also see: (b) Wada, R.; Oisaki, K.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2004**, *126*, 8910. (c) Ding, H.; Friestad, G. K. *Synthesis* **2004**, 2216.

[6] The complete 1,2-addition selectivity in the reactions using enones (Table 2, entry 4) is similar to that observed by Shibasaki and Kanai (ref 5a) but is different from those observed by Rieke and Lipshutz (ref 4).

This reaction can be further extended to substituted allyl(2-pyridyl)silanes, but the accessibility of functionalized allylic silanes remained limited like other allylic metals. If an efficient synthesis of substituted allyl(2-pyridyl)silanes using a common platform could be devised, the utility of present allylation should be substantially enhanced. Gratifyingly, we found that 2-PyMe$_2$SiCH$_2$Li (**5**), which can be quantitatively generated by the directed deprotonation of commercially available 2-pyridyltrimethylsilane with *t*-BuLi or (*i*-Pr)$_2$NLi,[9] underwent the cross-coupling with α-iodostyrene (**6**) in the presence of CuBr (0.6 equiv), affording substituted allyl(2-pyridyl)silane **7** in 77% yield (Scheme 2).[10]

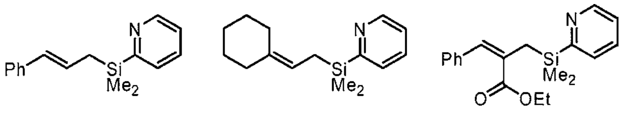
Scheme 2



The use of CuCl or CuI in place of CuBr resulted in low coupling efficiency. Interestingly, the use of Me$_3$SiCH$_2$Li in place of **5** resulted in extremely low cross-coupling efficiency (<5% yield) under otherwise identical conditions, implicating a strong promoting effect of 2-pyridyl group.

In addition to this Li-based method, we also found that 2-PyMe$_2$SiCH$_2$SnBu$_3$ (**8**), which can be easily prepared from **5**,[9] underwent the cross-coupling with **6** in the presence of CuCl (1.5 equiv), affording **7** in 70% yield (Scheme 2).[11] Interestingly, commonly used Pd complexes were totally ineffective for this cross-coupling. We also found that the use of PhMe$_2$SiCH$_2$SnBu$_3$ in place of **8** resulted in no cross-coupling, attesting to the unique reactivity of **8** in cross-coupling as in the case of **5**. Currently, we assume that this beneficial effect of the 2-pyridyl group on silicon is attributed to the directing (coordination) effect in the Si-to-Cu transmetalation step.[12]

Listed in Figure 2 are the substituted allyl(2-pyridyl)silanes that can be prepared using the cross-coupling described in Scheme 2. While the Li-based method was effective in the production of somewhat robust allylic silanes, the Sn-based method was useful in the cross-coupling using base-sensitive alkenyl iodides.



95% (Li method)
88% (Sn method)

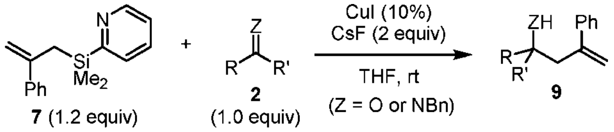
78% (Li method)
72% (Sn method)

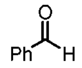
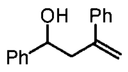
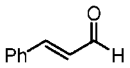
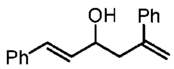
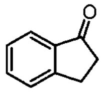
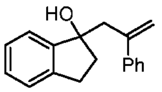
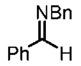
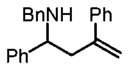
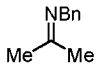
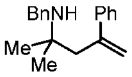
11% (Li method)
62% (Sn method)

Figure 2. Other substituted allyl(2-pyridyl)silanes prepared by cross-coupling reaction.

Finally, we examined the applicability of substituted allyl(2-pyridyl)silanes to the CuI/CsF-promoted allylation of carbonyl derivatives. Gratifyingly, it was found that all representative carbonyl derivatives (aldehydes, ketones, aldimines, and ketimines) can be applied in this allylation using **7**, producing substituted homoallylic alcohols and amines in excellent yields (Table 3).

Table 3. CuI/CsF-Promoted Allylation of Various Carbonyl Derivatives **2** Using **7**



entry	2		9 (yield, %)	
1		**2a**		**9a** (99)
2		**2g**		**9g** (99)
3		**2h**		**9h** (93)
4		**2e**		**9e** (93)
5		**2f**		**9f** (65)

It was found that γ-substituted allyl(2-pyridyl)silanes **10** reacted with carbonyl compounds in a regioselective manner at γ-position of allylsilane (Table 4). However, diastereo-

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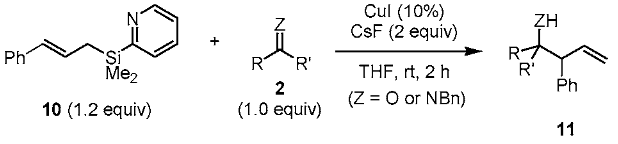
(7) The structure of one of the components of dimeric Cu complex **4** is shown in Figure 1. X-ray data for **4**: $C_{20}H_{30}N_2Si_2I_2Cu_2$, triclinic, space group $P\bar{1}$ (No. 2), $R = 0.066$, $R_w = 0.100$. Selected bond lengths (Å): Cu−I = 2.637(3), Cu−N = 2.02(1), Cu−C1 = 2.10(2), Cu−C2 = 2.07(2). Selected bond angles (deg): N−Cu−C1 = 135.7(8), N−Cu−C2 = 105.3(1), C1−Cu−C2 = 30.5(1), Cu−C1−C2 = 73.2(2), Cu−C2−C1 = 76.3(2).

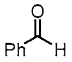
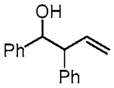
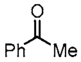
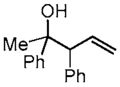
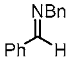
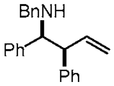
(8) Similar directed Si-to-Cu transmetalation in the generation of the allylcopper species may be involved in the Takeda's Cu-mediated allylation of allylic silanes bearing a potentially coordinating 2-pyridylthio group at the α-position. Takeda, T.; Uruga, T.; Gohroku, K.; Fujiwara, T. *Chem. Lett.* **1999**, 821.

(9) Itami, K.; Kamei, T.; Mitsudo, K.; Nokami, T.; Yoshida, J. *J. Org. Chem.* **2001**, *66*, 3970. 2-Pyridyltrimethylsilane is now commercially available from Tokyo Kasei Kogyo Co., Ltd (TCI).

(10) Cross-coupling of organocuprates with alkenyl halides: (a) Corey, E. J.; Postner, G. H. *J. Am. Chem. Soc.* **1967**, *89*, 3911. (b) Yoshikai, N.; Nakamura, E. *J. Am. Chem. Soc.* **2004**, *126*, 12264.

Table 4. CuI/CsF-Promoted Allylation of Various Carbonyl Derivatives **2** Using **10**

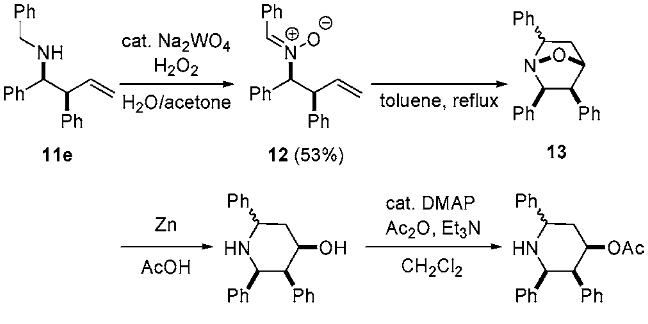


entry	**2**		**11** (yield, %)	
1		**2a**		**11a** (77) (syn/anti = 48/52)
2		**2i**		**11i** (46) (syn/anti = 34/66)
3		**2e**		**11e** (77) (syn/anti = >99/1)

selectivity was low in the reaction with aldehydes and ketones, generating **11a** (syn/anti = 48/52, entry 1) and **11i** (syn/anti = 34/66, entry 2). Amazingly, allylation using aldimine **2e** afforded homoallylic amine **11e** with virtually complete diastereoselectivity (syn/anti = >99/1, entry 3). The origin of this high selectivity is currently under investigation.

The configuration of **11e** could be determined by NOE analysis[13] of 4-acetoxypiperidine **15**, which was synthesized from **11e** through transformations shown in Scheme 3.[14,15]

Scheme 3



11e → **12** (53%) → **13** → **14** → **15** (49%, 3 steps)

In summary, we found that an efficient allylation of carbonyl derivatives using allyl(2-pyridyl)silanes took place under the influence of copper(I) salts and CsF, providing a range of substituted homoallylic alcohols and amines in good to excellent yields. We also observed a unique and strong directing effect of the 2-pyridyl group on silicon in this allylation. The control experiments as well as X-ray crystal structure analysis of the key Cu complex implicated that the beneficial role of the pyridyl group is to help the reacting C=C bond to coordinate to copper through precoordination, thereby facilitating the subsequent Si-to-Cu transmetalation to generate the allylcopper species. The reactions demonstrated herein not only expand the scope of existing metal-mediated allylation protocols but also provide some insights to mechanisms and the implication of alternative controlling factors in this chemistry. Ease of preparation of substrates, stability of allyl(2-pyridyl)silanes toward air and moisture, wide scope of carbonyl derivatives that can be applied, and various opportunities for directed reactions distinguish this chemistry and suggest multiple possibilities for further development. The investigations along this line are currently ongoing in our laboratory.

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

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(12) We previously observed similar promoting effect of the 2-pyridyl group on silicon in the Pd-catalyzed cross-coupling of **8** with aryl iodides. See ref 2d for detail.

(13) The NOE experimental details are given in the Supporting Information.

(14) Varlamov, A.; Kouznetsov, V.; Zubkov, F.; Chernyshev, A.; Shurupova, O.; Méndez, L. V.; Rodríguez, A. P.; Castro, J. R.; Rosas-Romero, A. J. *Synthesis* **2002**, 771.

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