

A General Catalytic Allylation Using Allyltrimethoxysilane

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The allylation of carbonyl derivatives such as aldehydes, ketones, and imines is one of the most important carbon–carbon bond-forming reactions because of the versatility of homoallylic alcohols and amines as synthetic intermediates.¹ Among various allylmetal reagents, allylsilanes and allylstannanes are very useful because of their moderate reactivity, which can be increased by catalyst activation and thus allows for application to catalytic enantioselective reactions. Allylsilanes are generally more desirable, particularly for environmental reasons, because they are less toxic and more stable than allylstannanes. The low reactivity of allylsilanes, however, has limited their synthetic utility.² The present contribution describes a new catalytic allylation methodology using allylsilanes that can be applied to a broad range of carbonyl derivatives including imines.

To overcome the low reactivity of allylsilanes, our initial idea was to use the dual activation concept: if a catalyst activates both an allylsilane and a carbonyl substrate simultaneously, high catalyst activity is obtained.³ A fluoride anion can activate the silylated nucleophiles.⁴ Therefore, we investigated the combination of a fluoride anion and a Lewis acid metal to activate an allylsilane and a substrate, respectively.⁵ Allyltrimethoxysilane should be more suitable for the present purpose than allyltrimethylsilane because it can form a pentacoordinate silicate⁶ more easily than allyltrimethylsilane. Thus, using tetrabutylammonium difluorotriphenylsilicate (TBAT; 10 mol %)⁷ and allyltrimethoxysilane⁸ (1.5 equiv), the combination was screened with various Lewis acids for the reaction of benzaldehyde as a substrate. Although combinations with hard Lewis acids such as Et₂AlCl, ZrCl₄·2THF, and HfCl₄·2THF did not promote the reaction at all, a facile and clean conversion was obtained using soft metals such as AgCl (60% yield) and CuCl (100% yield; 1.5 h). Completely optimized reaction conditions were determined (1 mol % of CuCl and TBAT in THF at room temperature) after surveying the copper salts, the fluoride anion sources, solvents, and the catalyst loading.⁹

As shown in Table 1, the reaction proved to be general and could be applied to a broad range of aldehydes, ketones, and imines. Specifically, the reaction proceeds smoothly under very mild conditions at ambient temperature and neutral pH with a synthetically acceptable catalyst loading (1–10 mol %). The applicability to the relatively complex substrate **1h** clearly demonstrates these advantages (entry 8).¹⁰ The reaction was completely chemoselective, and the lactone was tolerated. Enone **3h** gave the 1,2-adduct **4h** with complete regioselectivity (entry 16).¹¹ Imines, including aliphatic imines and a ketoimine, gave the allylated compounds in high yield with slow addition (5 h) of a proton source, ^tBuOH (entries 17–20).¹² The present reaction was also applicable to

Table 1. Catalytic Allylation Using Allylsilane^a

entry	substrate	cat. (Y mol %)	product	time/h	yield/% ^b
1		1	2a	2.5	94
2 ^c		1	2b	15	93
3 ^c		1	2c	15	92
4 ^c		10	2d	0.8	97
5		1	2e	4	91
6		1	2f	2.5	97
7		1	2g	4	79
8 ^d		10	2h	24	87
9		2	4a	4	90
10		2	4b	4	95
11 ^c		2	4c	10	95
12		2	4d	7	94
13		2	4e	5	94
14		2	4f	4	76
15		2	4g	5.5	95
16 ^c		2	4h	15	90
17 ^e		2	6a	8	96
18 ^e		10	6b	6	92
19 ^e		10	6c	6	90
20 ^e		5	6d	26	68

^a For experimental procedures, see Supporting Information. ^b Isolated yield. ^c Desilylation was conducted with TBAF. ^d A mixture of diastereomers was used. ^e 2 equiv of allylsilane was used. ^tBuOH (1 equiv) was slowly added for 5 h.

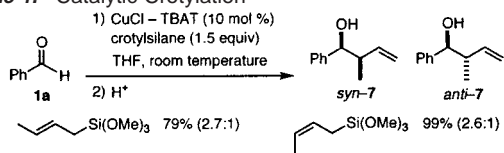
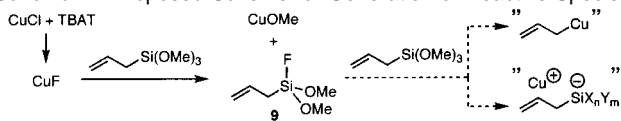
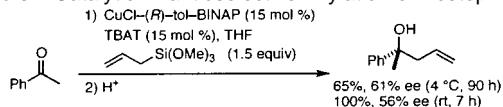
crotysilanes, and the reactions with **1a** proceeded with complete γ -selectivity, giving *syn*-**7** as the major isomer from both *E*- and *Z*-crotysilanes (Scheme 1). Therefore, this new allylation reaction is general and synthetically useful.

To gain insight into the reaction mechanism, we traced the reaction procedure observing ¹⁹F NMR in THF (Scheme 2).¹³ The reaction of CuCl with TBAF (1:1) afforded a new ¹⁹F NMR peak (–155.7 ppm, broad) that was assigned to be CuF on the basis of

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Scheme 1. Catalytic Crotylation**Scheme 2.** Proposed Scheme for Generation of Reactive Species**Scheme 3.** Catalytic Enantioselective Allylation of Acetophenone

the chemical shift of the reported $\text{CuF}\cdot 3\text{PPh}_3\cdot 2\text{EtOH}^{14}$ (**8**). Upon addition of allyltrimethoxysilane (1 equiv) to the mixture, the CuF peak disappeared, and a new peak (-129.0 ppm) appeared, which was assigned to be allylfluorodimethoxysilane **9** on the basis of the chemical shift and the presence of a doublet ($J = 112$ Hz) satellite peak derived from coupling with ^{29}Si . Therefore, CuOMe should be generated at this stage. On one hand, the addition of aldehyde **1a** to this reaction mixture (CuOMe and **9**) did not give any product, at least in 3 h. On the other hand, further addition of allyltrimethoxysilane (1 equiv) to the mixture produced **2a**. Thus, CuOMe and allyltrimethoxysilane are necessary to generate the reactive species.

At this point, we hypothesized that the fluoride ion might only work as an initiator to generate the copper alkoxide and that direct entry into the catalytic cycle might be possible with the copper alkoxide and allyltrimethoxysilane, deduced from the mechanism of the catalytic enantioselective aldol reaction reported by Carreira.^{15,16} In the present system, however, this was not the case; only a trace amount ($<1\%$) of **2a** was obtained from **1a** in the presence of $\text{CuO}^t\text{Bu}^{17}$ (10 mol %) and allyltrimethoxysilane (1.5 equiv). When $(\text{EtO})_3\text{SiF}$ (10 mol %) was added as an analogue of **9**, however, the reaction proceeded, and **2a** was obtained in 27% yield (4 h).¹⁸ Because addition of Ph_3SiF , instead of $(\text{EtO})_3\text{SiF}$, produced no product, alkoxysilyl fluoride appears to be the required structural element for promoting the reaction. Therefore, in the present reaction, the fluoride anion is not only an initiator to produce the actual catalytic species, but it also has an active role in the catalytic cycle, and CuOMe, allyltrimethoxysilane, and silyl fluoride **9** are all essential for the facile catalytic promotion of the reaction. Although elucidation of the precise reactive species is under investigation, these three components should generate the reactive species¹⁹ through dynamic ligand exchange.²⁰

Preliminary attempts to extend this reaction to a catalytic enantioselective allylation of ketones were promising (Scheme 3). Thus, **4a** was obtained from **3a** in 65% yield with 61% ee (4 °C) using *p*-tol-BINAP-CuCl-TBAT (15 mol %). Although the enantioselectivity was still moderate, this is the first example of catalytic enantioselective allylation of ketones using allylsilane.²¹

In summary, we developed a general catalytic allylation of carbonyl derivatives using allyltrimethoxysilane that can be applied to aldehydes, ketones, and imines. The reaction is promoted by a catalytic amount of CuCl and TBAT under very mild conditions. Elucidation of the exact reactive species and improvement of the enantioselectivity are in progress.

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Supporting Information Available: Experimental procedures and characterization of the products (PDF). This material is available free of charge via the Internet at <http://pubs.acs.org>.

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- See Supporting Information (SI) for details. Both a copper (I) salt and a fluoride source are essential for the facile reaction. No reaction occurred using allyltrimethylsilane as an allylating reagent.
- Due to the ability to form the linear triene compound through β -elimination at the lactone moiety, **1h** is not stable under acidic or basic conditions. No target allylated product **2h** was obtained through the Grignard reaction or the conventional Lewis acid (Ti)-catalyzed allylation using allyltributyltin.
- This complete selectivity is different from either the reaction of allylcopper (1,2-adduct:1,4-adduct = 1:3.6) generated through transmetalation (Lipshutz, B. H.; Ellsworth, E. L.; Dimock, S. H.; Smith, R. A. *J. Am. Chem. Soc.* **1990**, *112*, 4404) or the reaction of allyltrimethylsilane catalyzed by TBAF (1,2-adduct:1,4-adduct = 2:1; ref 2a).
- In the absence of the protic additive, the reaction was very sluggish. The presumed role of the additive is to facilitate catalyst turnover through the protonation of the allylated intermediate. For an example of a beneficial effect of a protic additive, see: Takamura, M.; Hamashima, Y.; Usuda, H.; Kanai, M.; Shibasaki, M. *Angew. Chem., Int. Ed.* **2000**, *39*, 1650.
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