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Iron(III) Chloride-catalyzed Nucleophilic Substitution of Propargylic Alcohols: A General and Efficient Approach for the Synthesis of 1,4-Diynes

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A wide variety of 1,4-diynes have been constructed via a novel $FeCl_3$-catalyzed coupling reaction of propargylic alcohols with alkynylsilanes. This synthetic approach provides a general, efficient, and economical route to 1,4-diynes.

1,4-Diynes represent valuable building blocks owing to their ability to serve as precursors for the synthesis of pharmaceuticals, functional materials, polyunsaturated fatty acids, and a wide variety of heterocyclic compounds.[1] Historically, this motif has been constructed via the substitution of propargyl(2-propynyl) halides with prepared alkynylide anions or in situ generated metal acetylides under rigorous conditions.[2] In these processes, a stoichiometric amount of strong base is usually required to convert terminal alkynes to the corresponding alkynylide anions, making base-sensitive substrates unsuitable for the traditional methods. Furthermore, the production of large amounts of halide salts makes these methods less desirable. Alternatively, halide by-products would be avoided if propargylic alcohols could be employed as the electrophiles, making the transformation more environmentally benign.

Compared with propargylic halides and esters, alcohols do not react easily with nucleophiles by virtue of the poor leaving ability of the hydroxy group. Very limited reports on the preparation of 1,4-diynes via alkynylation of propargylic alcohols have existed up to now. Kuninobu, Takai, et al. recently demonstrated a rhenium-catalyzed smooth alkynylation of propargylic alcohols with an alkynylsilane.[3] Yadav and coworkers described an efficient procedure for the substitution of aryl propargylic alcohols with alkynylsilanes using molecular iodine as the catalyst.[4] However, more extensive use of these methodologies is confined to some extent due to the high price of the catalysts. Thus, the development of general, efficient and economical methodologies for the synthesis of 1,4-diynes is still highly demanding.

Lately, our research group has developed an acid-treated K10 montmorillonite (H-K10 mont) catalyzed nucleophilic substitution of propargylic alcohols with alkynylsilanes under solvent-free condition.[5] This approach provides a green and rapid route to 1,4-diynes. Nevertheless, the scope of the alkynylsilane component of the reaction has been limited to terminal TMS-substituted aromatic alkynes. In our continued effort to find novel approach for the synthesis of 1,4-diynes, we sought to explore a more general synthetic strategy.

In recent years, iron catalysts have attracted significant attention in synthetic organic chemistry, since iron is highly abundant in nature and iron salts are inexpensive and environmentally friendly.[6,7] Our pioneering work has demonstrated the use of $FeCl_3$ for efficient activation of propargylic alcohols toward various nucleophiles.[8] We envisioned that the reaction between propargylic alcohols and alkynylsilanes catalyzed by $FeCl_3$ would be feasible.

Table 1. $FeCl_3$-catalyzed nucleophilic substitution of various propargylic alcohols with alkynylsilane **2a**[a]

1 2a 3

Entry	**1**: R^1; R^2	Product/Yield[b]
1	**1a**: Ph; Ph	**3aa**/93%
2	**1b**: Ph; *n*-Bu	**3ba**/90%
3	**1c**: Ph; cyclopropyl	**3ca**/85%
4	**1d**: Ph; 1-cyclohexenyl	**3da**/86%
5	**1e**: Ph; TMS	**3ea**/94%
6	**1f**: 1-naphthyl; TMS	**3fa**/92%
7	**1g**: (*trans*)PhCH=CH; TMS	**3ga**/92%
8	**1h**: Ph; H	**3ha**/86%
9	**1i**: 4-Cl-C_6H_4; *n*-Bu	**3ia**/90%
10	**1j**: 4-Br-C_6H_4; *n*-Bu	**3ja**/89%
11	**1k**: 4-COOMe-C_6H_4; *n*-Bu	**3ka**/n.r.[c]
12	**1l**: 2-MeO-C_6H_4; *n*-Bu	**3la**/89%
13	**1m**: *n*-pentyl; Ph	**3ma**/36%, 79%[d]

[a]Reaction conditions: **1** (0.5 mmol), **2a** (0.5 mmol), $FeCl_3$ (0.025 mmol), CH_3NO_2 (2 mL), 25 °C. [b]Isolated yield. [c]n.r.: No reaction. Reaction ran for 1 h at 25 °C, then for 24 h at 80 °C. [d]The propargylic acetate was used instead of propargylic alcohol as the substrate. Reaction ran at 80 °C for 2 h.

With this in mind, we initially investigated the $FeCl_3$-catalyzed substitution reaction of propargylic alcohol **1a** with alkynylsilane **2a**. Gratifyingly, 5 mol % of $FeCl_3$ in nitromethane (CH_3NO_2) at 25 °C cleanly produced the desired 1,4-diyne **3aa** in 93% yield (Table 1, Entry 1). It is noteworthy that the reaction finished within just 5 min, which is several-fold faster than previous strategies.[3–5] Our further study revealed that various aryl- and alkyl-substituted propargylic alcohols effectively underwent the $FeCl_3$-catalyzed substitution.[9] Typical results are shown in Table 1. Employment of propargylic alcohols bearing an alkyl chain at the terminal position of the acetylene moiety smoothly afforded the desired products under mild conditions (Table 1, Entries 2, 9, 10, and 12). Also, as expected, 1,4-diyne **3ca** was obtained from propargylic alcohol **1c** in 85% yield, and no ring-opening of the cyclopropyl groups was observed (Table 1, Entry 3). When R^2 was replaced with an unsaturated alkyl group, the reaction also led to the formation of desired product in good yield (Table 1, Entry 4). Interestingly,

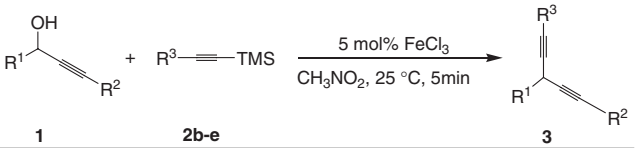
propargylic alcohols **1e**–**1g** containing an alkynylsilane moiety gave the corresponding 1,4-diynes with TMS groups maintained (Table 1, Entries 5–7). The nucleophilic attack of alkynylsilane moiety in substrate **1** toward another propargylic alcohol **1** was not observed. Fused aromatic propargylic alcohol **1f** readily underwent this nucleophilic substitution (Table 1, Entry 6). Additionally, propargylic alcohol **1g** containing a substituted olefin also underwent facile coupling with **2a** to produce 1,4-enediyne **3ga** in 92% yield (Table 1, Entry 7). The reaction was not limited to substrates bearing internal alkyne groups. For example, propargylic alcohol **1h** with a terminal alkyne group afforded the corresponding 1,4-diyne in a high yield under the same conditions (Table 1, Entry 8).

Electron-deficient substrates **1i**–**1j** and electron-rich substrate **1l** were well tolerated in the $FeCl_3$-catalyzed alkynylation (Table 1, Entries 9–10 and 12), nevertheless propargylic alcohol **1k** bearing a 4-methoxycarbonylphenyl group failed to give any desired product even with prolonged reaction time and at elevated reaction temperature (Table 1, Entry 11), perhaps due to the strong electron-withdrawing property of the methoxycarbonyl group. The experimental results suggested an S_N1 mechanism, in which a propargylic cation intermediate was formed, whose instability obviously hindered the nucleophilic substitution.

In accordance with the S_N1 mechanism, it was observed that treatment of aliphatic propargylic alcohol **1m** with alkynylsilane **2a** in the presence of $FeCl_3$ led to the formation of desired 1,4-diyne **3ma** in a low yield. In contrast, using propargylic acetate as the electrophile instead provided **3ma** in 79% yield under proper reaction conditions (Table 1, Entry 13). This result deserves special attention because efficient alkynylations of aliphatic propargylic alcohols are usually difficult to achieve.[3–5] Unfortunately, our attempt to insert **2a** into a primary propargylic alcohol/acetate failed, owing to the extreme instability of primary cation. However, to our surprise, the coupling reaction of several tertially propargylic alcohols and substrate **2a** led to undetermined mixtures. It is presumed that steric effects also play an important role in the reaction.[10]

We next turned our attention to expand the scope of alkynylsilane **2**. We were delighted to find that both electron-rich and electron-poor phenyl alkynylsilanes **2b** and **2c** reacted smoothly with propargylic alcohols affording the corresponding 1,4-diynes in high yields (Table 2, Entries 1–5). It is worth noting that the reaction of propargylic alcohols with **2c** at 25 °C unexpectedly led to a complex mixture, containing a small amount of desired 1,4-diynes. We supposed that electron-rich alkynylsilane **2c** was extremely active toward some undesired side reactions under our standard reaction conditions. We consequently attempted to run the reactions at lower temperature. As expected, treatment of propargylic alcohols and alkynylsilane **2c** with 5 mol % of $FeCl_3$ in CH_3NO_2 at 0 °C cleanly produced corresponding 1,4-diynes (Table 2, Entries 4 and 5). When phenyl ring in alkynylsilane was replaced with heterocycle such as a furyl group, the reaction also led to the formation of desired products (Table 2, Entries 6 and 7). The above reaction conditions were also applied to the coupling of propargylic alcohols with an aliphatic alkynylsilane. We were pleased to find that subjecting propargylic alcohol **1a** and alkynylsilane **2e** to our typical conditions afforded desired 1,4-diyne **3ae** in an acceptable yield (Table 2, Entry 8). Changing

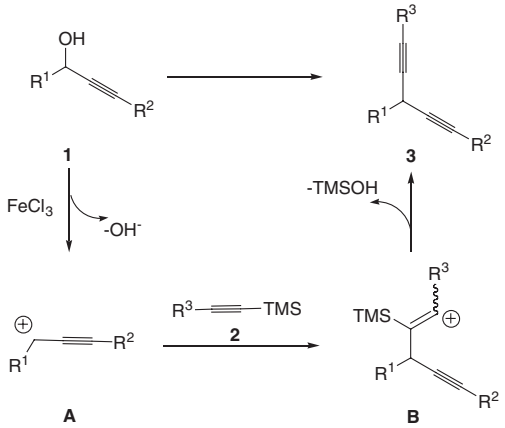
Table 2. $FeCl_3$-catalyzed nucleophilic substitution of propargylic alcohols with other alkynylsilanes[a]



1 2b-e 3

Entry	**1**: R^1; R^2	**2**: R^3	Product/Yield[b]
1	**1a**: Ph; Ph	**2b**: 4-Br-C_6H_4	**3ab**/88%
2	**1c**: Ph; cyclopropyl	**2b**: 4-Br-C_6H_4	**3cb**/84%
3	**1h**: Ph; H	**2b**: 4-Br-C_6H_4	**3hb**/85%
4[c]	**1a**: Ph; Ph	**2c**: 4-MeO-C_6H_4	**3ac**/87%
5[c]	**1b**: Ph; *n*-Bu	**2c**: 4-MeO-C_6H_4	**3bc**/84%
6	**1a**: Ph; Ph	**2d**: 5-Me-2-furyl	**3ad**/73%
7	**1n**: 4-MeO-C_6H_4; TMS	**2d**: 5-Me-2-furyl	**3nd**/78%
8[d]	**1a**: Ph; Ph	**2e**: *n*-Bu	**3ae**/34%
9[d]	**1e**: Ph; TMS	**2e**: *n*-Bu	**3ee**/53%

[a]Reaction conditions: **1** (0.5 mmol), **2** (0.5 mmol), $FeCl_3$ (0.025 mmol), CH_3NO_2 (2 mL), 25 °C, 5 min. [b]Isolated yields. [c]Carried out at 0 °C. [d]Reaction time was 20 min.



Scheme 1. Proposed mechanism.

R^2 from a phenyl ring to a TMS group provided an increase in yield, probably owing to the ability of silicon atom to stabilize positive charges in the γ-position (Table 2, Entry 9).

A tentative mechanism for this reaction is proposed in Scheme 1. Propargylic alcohols **1** are first activated by $FeCl_3$, generating the cationic intermediates **A**. Then, the nucleophilic attack of alkynylsilanes **2** would proceed to give alkenyl cationic intermediates **B**,[11] followed by the elimination of the trimethylsilyl group to give the desired products **3**.

In summary, we have developed a $FeCl_3$-catalyzed coupling reaction of propargylic alcohols with alkynylsilanes, providing a general and rather facile approach to 1,4-diynes.[12] The low loading of inexpensive iron salt as catalyst, broad substrate scope, operational simplicity, mild reaction conditions, and minimal waste generation of this process would be beneficial for its large-scale use.

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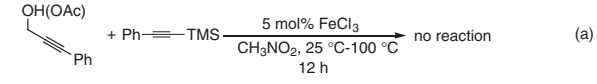
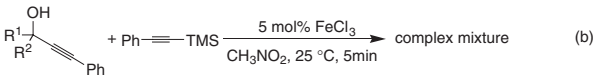
9 *General procedure for the synthesis of 1,4-diyne* **3**: To a solution of propargylic alcohol **1** (0.5 mmol) and alkynylsilane **2** (0.5 mmol) in CH_3NO_2 (2 mL), $FeCl_3$ (4 mg, 0.025 mmol) was added and it was stirred at room temperature. When the reaction was completed (monitored by TLC), the solvent was removed under vacuum and the residue was further purified by silica gel column chromatography (petroleum ether) to afford 1,4-diyne.

10 Several primary and tertially propargylic alcohols were employed in the coupling reaction.





1o: R^1 = Ph, R^2 = Ph
1p: R^1 = Ph, R^2 = Me

11 Aryl groups in the nucleophiles (R^3 = aryl) favor the reaction due to their well-known ability to stabilize alkenyl cations. The intermediates **B** provide a reasonable explanation for the relatively low activity of alkynylsilane **2e**. Several α-phenyl-β-silyl-substituted vinyl cations have been characterized, see: a) H.-U. Siehl, F.-P. Kaufmann, *J. Am. Chem. Soc.* **1992**, *114*, 4937. b) T. Müller, R. Meyer, D. Lennartz, H.-U. Siehl, *Angew. Chem., Int. Ed.* **2000**, *39*, 3074.

12 Supporting Information is available electronically on the CSJ-Journal Web site, http://www.csj.jp/journals/chem-lett/index.html.

