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A General and Efficient $FeCl_3$-Catalyzed Nucleophilic Substitution of Propargylic Alcohols

Zhuang-ping Zhan,* Jing-liang Yu, Hui-juan Liu, Yuan-yuan Cui, Rui-feng Yang, Wen-zhen Yang, and Jun-ping Li

Department of Chemistry and The Key Laboratory for Chemical Biology of Fujian Province, College of Chemistry and Chemical Engineering, Xiamen University, Xiamen 361005, P. R. China

zpzhan@xmu.edu.cn

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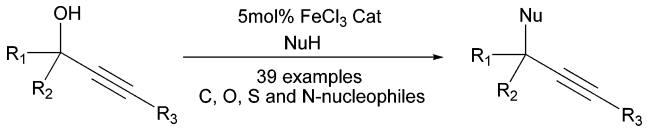

A general and efficient $FeCl_3$-catalyzed substitution reaction of propargylic alcohols with carbon- and heteroatom-centered nucleophiles such as allyl trimethylsilane, alcohols, aromatic compounds, thiols, and amides, leading to the construction of C−C, C−O, C−S and C−N bonds, has been developed.

Transition-metal-catalyzed allylic substitution reaction of allylic alcohol derivatives with nucleophiles has become an important chemical transformation, as it provides a direct and reliable approach to a wide variety of allylated products.[1] In contrast, related transition-metal-catalyzed propargylic substitution reactions of propargylic alcohol derivatives with nucleophiles are relatively rare. The flexibility of the alkyne functional group in organic synthesis makes the propargylic substitution reaction a desirable method for development. In addition to allowing access to saturated products by hydrogenation, the alkyne moiety offers a handle for transformation into various other functional groups.

The Nicholas reaction has been widely accepted as a powerful tool for propargylic substitution reaction[2] but has some drawbacks: a stoichiometric amount of $[Co_2(CO)_8]$ is required, and several steps are necessary to obtain propargylic product from propargylic alcohols via cationic propargylic complexes $[Co_2(CO)_6(propargyl)]^+$.[2,3] On the other hand, several transition-metal-catalyzed propargylic substitution reactions have been recently reported. Among them, a ruthenium-catalyzed process is a versatile and direct method.[4] A wide variety of nucleophiles such as alcohols, amines, amides, and thiols are available for this reaction. Nevertheless, with this method, the substrate is generally limited to the propargylic alcohols bearing terminal alkyne group.[5] More recently, Toste[6] and Campagne[7] have respectively described efficient nucleophilic substitution of propargylic alcohols in the presence of catalytic amounts of rhenium [(dppm) $ReOCl_3$] and/or gold [$NaAuCl_4 \cdot 2H_2O$] catalyst. However, the peculiarity and high cost of such catalysts make a barrier to their large-scale use. Therefore, development of a general, efficient, cheap, and readily available catalyst for propargylic substitution is highly desirable.

Herein, we wish to report an efficient $FeCl_3$-catalyzed nucleophilic substitution reaction of propargylic alcohols bearing not only terminal alkyne group but also internal alkyne group with various carbon- and heteroatom-centered nucleophiles to afford the corresponding products in high yields with complete regioselectivities under mild reaction conditions.

At first, we investigated the $FeCl_3$-catalyzed coupling reactions of various propargylic alcohols with allyl trimethylsilane. We were pleased to find that 5 mol % $FeCl_3$ in acetonitrile at room temperature cleanly produced the substituted 1,5-enynes in excellent yields and no α,β-unsaturated compounds via the Meyer−Schuster-type rearrangement were detected.[8] Various aryl- and alkyl-substituted propargylic alcohols (**1a**−**i**) effectively underwent the $FeCl_3$-catalyzed substitution. Typical results are shown in Table 1. The reaction proceeded smoothly without exclusion of moisture or air from the reaction mixture. Both electron-rich and electron-poor aromatic substrates (**1g**−**i**) reacted smoothly with allyltrimethylsilane affording the corresponding allylated products in high yields (Table 1, entries 7−9). Functional groups, such as methoxyl, bromo, and cyano

* To whom correspondence should be addressed. Tel: +86(592) 2180318. Fax: +86(592) 2185780.

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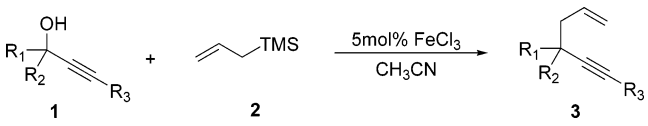
TABLE 1. $FeCl_3$-Catalyzed Substitution of Various Propargylic Alcohols 1 with Allyltrimethylsilane 2[a]



1 2 3

entry	R_1; R_2; R_3	product	isolated yield (%) of **3**
1	**1a**, Ph; H; *n*-Bu	**3aa**	90
2	**1b**, Ph; H; Ph	**3ba**	95
3	**1c**, Ph; H; TMS	**3ca**	86
4	**1d**, CH_3; CH_3; Ph	**3da**	61[b]
5	**1e**, Ph; H; H	**3ea**	70
6	**1f**, CH_3; H; Ph	**3fa**	15[c]
7	**1g**, *o*-$MeOC_6H_4$; H; *n*-Bu	**3ga**	83
8	**1h**, *p*-BrC_6H_4; H; *n*-Bu	**3ha**	90
9	**1i**, *p*-CNC_6H_4; H; *n*-Bu	**3ia**	85

[a] The reactions of **1** (1 mmol) with allyltrimethylsilane **2** (3 mmol) were carried out in the presence of $FeCl_3$ (0.05 mmol) in CH_3CN (2 mL) at room temperature for 2 h. [b] At 60 °C for 1 h. [c] At 60 °C for 24 h.

in propargylic alcohols did not affect the course of the construction of carbon−carbon bonds. Variation in the alkyne substituent from an alkyl to an aryl, trimethylsilyl (**1a**−**c**) is well tolerated. Gratifyingly, 1-phenylprop-2-yn-1-ol (**1e**) bearing a terminal alkyne group was successfully allylated in 70% isolated yield as well under the same reaction conditions, and no ploymerization was detected (Table 1, entry 5). Tertiary aliphatic alcohol **1d** allows for the construction of a quaternary carbon by increased the reaction temperature to 60 °C (Table 1, entry 4). However, compared with secondary benzylic alcohol **1b**, secondary aliphatic substrate **1f** reacted more sluggishly to give desired 1,5-enynes product in lower yield (Table 1, entry 6 vs entry 2). The primary aliphatic alcohol 3-phenylprop-2-yn-1-ol (R_1, R_2 = H) failed to get allylated product. The experimental results suggest a mechanism through the formation of propargylic cation intermediate. Unstability of the propargylic cation intermediate clearly made the substitution reaction less favorable. Other Lewis acid-catalyzed nucleophilic propargylic substitution have been existed,[9a−e] but the substrate were limited to propargylic ester. For example, the reaction of propargylic alcohols with allyltrimethylsilane catalyzed by $B(C_6F_5)_3$ did not afford desired 1,5-enynes but corresponding silyl ether; while propargylic ester instead of propargylic alcohols, substitution proceeded successfully to give the desired 1,5-enynes in good yields.[9c] The result exhibits the superiority of $FeCl_3$ as the catalyst in the reaction.

We next extended the propargylic substitution by employing heteroatom-centered and aromatic compound nucleophiles. All reactions proceeded in the presence of 5 mol % of $FeCl_3$ in acetonitrile. Typical results are shown in Table 2.

A series of alcohols as the nucleophiles were first treated with various propargylic alcohols (**1a**−**e**), and the corresponding propargylic ethers were obtained in good yields with complete regioselectivity (Table 2, entries 1−10). Functional groups such as alkenyl (Table 2, entries 2 and 4) and chloro (Table 2, entries 1, 3, and 5) in the alcohol were readily carried through the reaction, allowing for the subsequent elaboration of the products after the propargylic etherification event. The reaction is not limited to benzylic substrates. For example, tertiary alcohol (**1d**) readily undergoes propargylic etherification to afford tertiary ether in 64% and 82% isolated yields, respectively (Table 2, entries 5 and 10). Notably, the use of ethanol as the nucleophile did not lead to the formation of the rearranged enone, which was obtained as the main product in the process catalyzed by gold(III) (Table 2, entries 8−10).[7]

Similarly, reactions of propargylic alcohols bearing a terminal alkyne group or internal alkyne group with various aromatic compound nucleophiles were also carried out (Table 2, entries11−19). The corresponding Friedel−Crafts arylated products were obtained from heteroaromatic compounds furan and pyrrole in good yields with complete regioselectivity (Table 2, entries14−16). Propargylation occurred selectively at the α-position of the heterocyclic rings. Electron-rich aromatic compounds such as anisole, 1,3-dimethoxybenzene, phenol, *β*-naphthol, and 2-methoxynaphthalene reacted smoothly with propargylic alcohols affording the corresponding propargylated compounds in moderate to excellent yields (Table 2, entries 11−13 and 17−19). The high-yield formation of Friedel−Crafts arylated products were obtained in the reaction of phenol, *β*-naphthol, and 2-methoxynaphthalene with 1,3-diphenylprop-2-yn-1-ol (**1b**) (Table 2, entries13, 17, and 18). In the processes involving furan and *β*-naphthol, the substrate-bearing terminal alkyne group gave the propargylic adduct in lower yields (Table 2, entry 15 vs 14; entry 19 vs 17). In all cases, propargylation occurred selectively at the electron-rich position of aromatic compounds. The results indicated that the reactions proceed electrophilically. Lewis acid $BF_3{\cdot}Et_2O$ also efficiently catalyzed the substitution of propargylic alcohols with arenes, and the corresponding Friedel−Crafts arylated products were obtained in excellent yields. However, the catalyst loading is very high (100% equiv).[10]

Transition-metal-catalyzed substitution of propargylic alcohols with thiols has been considered difficult to achieve, probably due to that sulfur-containing compounds are catalyst-poison because of their strong coordinating properties.[11,5b] Gratifyingly, by employing 5 mol % of $FeCl_3$ as the catalyst, the construction of sp^3 C−S bonds was achieved by the nucleophilic substitution of propargylic alcohols with a series of thiols. Propargylic alcohols possessing an alkyl or aryl substituent on the alkyne part reacted rapidly with various thiols such as ethyl 2-mercaptoacetate, benzenethiol, and mercaptoethanol affording the corresponding sulfide products in excellent yields with complete regioselectivity (Table 2, entries 20, 21, 23, and 24). In contrast to the result obtained by using phenol as nucleophile, no Friedel−Crafts arylated product was detected while using benzenethiol as the nucleophile, and the propargylic sulfide was the only product (Table 2, entry 21 vs 13). Remarkably, the hydroxyl moiety is well tolerant in the reaction; 5 mol % of $FeCl_3$ efficiently catalyzed the propargylation of mercaptoethanol while avoiding competitive O-alkylation and the formation

(9) The significant characteristic feature of this reaction is the direct use of propargylic alcohols as the substrates. For nucleophilic substitution of propargylic esters, see: (a) Mahrwald, R.; Quint, S. *Tetrahedron Lett.* **2001**, *42*, 1655−1656. (b) Imada, Y.; Yuasa, M.; Nakamura, I.; Murahashi, S. I. *J. Org. Chem.* **1994**, *59*, 2282−2284. (c) Schwier, T.; Rubin, M.; Gevorgyan, V. *Org. Lett.* **2004**, *6*, 1999−2001. (d) Mahrwald, R.; Quint, S.; Scholtis, S. *Tetrahedron* **2002**, *58*, 9847−9851. (e) Bartels, A.; Mahrwald, R.; Quint, S. *Tetrahedron Lett.* **1999**, *40*, 5989−5990. (f) Kondo, T.; Kanda, Y.; Baba, A.; Fukuda, K.; Nakamura, A.; Wada, K.; Morisaki, Y.; Mitsudo, T. A. *J. Am. Chem. Soc.* **2002**, *124*, 12960−12961. For nucleophilic substitution of propargylic ethers, see: (g) Yoshimatsu, M.; Shimizu, H.; Kataoka, T. *Chem. Commun.* **1995**, 149−150.

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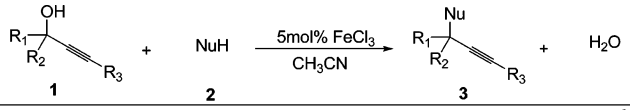
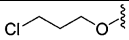
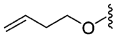
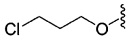
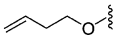
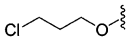
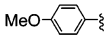
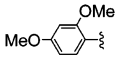
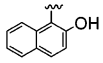
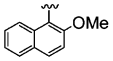
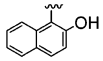
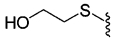
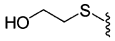
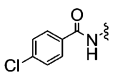
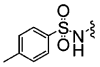
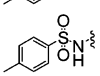
TABLE 2. $FeCl_3$-Catalyzed Substitution of Various Propargylic Alcohols 1 with Various Nucleophiles 2[a]



entry	R_1; R_2; R_3	Nu	time (h)	3 isolated yields (%)
1	**1a**, Ph; H; *n* -Bu		0.5	**3ab**, 84
2	**1b**, Ph; H; Ph		3.0	**3bb**, 92
3	**1c**, Ph; H; TMS		3.0	**3cb**, 83
4	**1c**, Ph; H; TMS		8.0	**3cc**, 82
5	**1d**, CH_3; CH_3; Ph		2.0	**3db**, 64
6	**1a**, Ph; H; *n* -Bu		2.0	**3ac**, 77
7	**1b**, Ph; H; Ph		1.0	**3bc**, 91
8	**1a**, Ph; H; *n* -Bu		2.0	**3ad**, 90
9	**1e,** Ph; H; H		4.5	**3eb**, 85
10	**1d**, CH_3; CH_3; Ph		12	**3dc**, 82
11	**1b**, Ph; H; Ph		2.5	**3bd**, 81
12	**1c**, Ph; H; TMS		5.0	**3cd**, 76
13	**1b**, Ph; H; Ph		0.5	**3be**, 91
14	**1b**, Ph; H; Ph		0.5	**3bf**, 82
15	**1e,** Ph; H; H		0.5	**3ec**, 55[b]
16	**1b**, Ph; H; Ph		4.5	**3bg**, 61[b]
17	**1b**, Ph; H; Ph		0.5	**3bh**, 95
18	**1b**, Ph; H; Ph		0.5	**3bi**, 90
19	**1e,** Ph; H; H		3.0	**3ed**, 56
20	**1b**, Ph; H; Ph		2.0	**3bj**, 92
21	**1b**, Ph; H; Ph		0.5	**3bk**, 94
22	**1e,** Ph; H; H		2.0	**3ee**, 38[b]
23	**1b**, Ph; H; Ph		1.0	**3bl**, 93
24	**1a**, Ph; H; *n* -Bu		1.0	**3ae**, 90
25	**1e,** Ph; H; H		4.0	**3ef**, 41
26	**1b**, Ph; H; Ph		5.0	**3bm**,73
27	**1a**, Ph; H; *n* -Bu		6.0	**3af**, 62[b]
28	**1e,** Ph; H; H		6.0	**3eg**, 56[b]
29	**1b,** Ph; H; Ph		6.0	**3bn**, 82
30	**1e**, Ph; H; H		6.5	**3eh**, 78

[a] The reactions of **1** (1 mmol) with **2** (3 mmol) were carried out in the presence of $FeCl_3$ (0.05 mmol) in CH_3CN (2 mL) at room temperature. [b] The reaction was carried out at 60 °C.

of the propargylic ethers. Hydroxyl, ethoxycarbonyl, and phenyl moieties contained in the propargylic sulfides provide a handle for transformation into a variety of other functional groups. However, the propargylic alcohol bearing terminal alkyne group participated in the substitution reaction to give propargylic adduct in lower yields (Table 2, entries 22 and 25).

Finally, selected amides also acted as efficient nucleophiles to give the corresponding propargylic amides in moderate to good yields. The employment of benzamide, *p*-chlorobenzamide, and *p*-toluenesulfonamide effectively led to the formation of C−N bonds. Unfortunately, no propargylation occurred under these conditions when acetamide, aniline, and piperidine were used as the nucleophiles, even using propargyl esters as the substrate. However, amination of propargyl esters can be achieved in the presence of CuCl as the catalyst.[12]

In summary, we have developed a general and efficient $FeCl_3$-catalyzed substitution reaction of propargylic alcohols with carbon- and heteroatom-centered nucleophiles such as allyltrimethylsilane, alcohols, aromatic compounds, thiols, and amides, leading to the construction of C−C, C−O, C−S, and C−N bonds. Propargylic alcohols bearing a terminal alkyne group or internal alkyne group are readily available.[9] The corresponding propargylic products were obtained in high yields with complete regioselectivity. In comparison with cobalt, rhenium, ruthenium, and gold complexes, which are usually used to catalyze the nucleophilic substitution of propargylic alcohols, $FeCl_3$ as the catalyst offers several relevant advantages including cheapness and commercial availability, broad scope, and mild reaction conditions of this transformation. Further development on this methodology is currently underway in our laboratory.

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Experimental Section

A typical experimental procedure for the reaction of 1-phenylhept-2-yn-1-ol (**1a**) with allyl trimethylsilane catalyzed by 5 mol % of $FeCl_3$ is described below: to a 5-mL flask were successively added 1-phenylhept-2-yn-1-ol (**1a**) (188 mg, 1 mmol), allyl trimethylsilane (343 mg, 3.0 mmol), CH_3CN (2 mL), and anhydrous $FeCl_3$ (8 mg, 0.05 mmol), and then the mixture was magnetically stirred at room temperature for 2 h. The solvent was concentrated under reduced pressure by an aspirator, and then the residue was purified by silica gel column chromatography (EtOAc/hexane) to afford 1-(dec-1-en-5-yn-4-yl)benzene (**3aa**) as a clear colorless oil (191 mg, 90% yield): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.91 (t, 3H, J = 7.2 Hz), 1.37−1.55 (m, 4H), 2.23 (td, 2H, J = 7.2 and 2.4 Hz), 2.45 (dd, apparent t, 2H, J = 7.2 and 7.2 Hz), 3.65 (tt, 1H, J = 7.2 and 2.4 Hz), 4.98−5.06 (m, 2H), 5.82 (ddt, 1H, J = 17.2, 10.4 and 7.2 Hz), 7.16−7.23 (m, 1H), 7.26−7.36 (m, 4H) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.1, 18.9, 22.3, 31.5, 38.3, 43.3, 81.0, 83.7, 116.3, 126.2, 127.1, 127.9, 135.4, 141.6 ppm; IR (film) 3062, 3029, 2204, 1644, 1599, 1581, 1494 cm^{-1}; MS (FAB) *m*/*z* 213 (M + H$^+$).

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

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