$BiCl_3$-Catalyzed propargylic substitution reaction of propargylic alcohols with C-, O-, S- and N-centered nucleophiles†

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

Received (in Cambridge, UK) 9th May 2006, Accepted 12th June 2006
First published as an Advance Article on the web 27th June 2006
DOI: 10.1039/b606470a

A general and efficient $BiCl_3$-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.

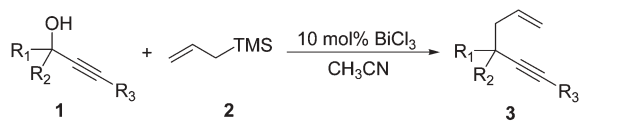
A direct and reliable approach to a wide variety of allylated products is the allylic substitution reaction of allylic alcohol derivatives with nucleophiles catalyzed by transition metals.[1] In contrast, related transition metal-catalyzed propargylic substitution reactions of propargylic alcohol derivatives with nucleophiles are relatively rare. The flexibility of the alkyne functional group makes propargylic substitution reaction assume a pivotal role in organic synthesis. 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 the propargylic product from propargylic alcohols *via* cationic propargylic complexes $[Co_2(CO)_6$-(propargyl)$]^+$.[2,3] On the other hand, several transition metal-catalysed propargylic substitution reactions have been recently reported. Among them, a ruthenium-catalysed 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 propargylic alcohols bearing a terminal alkyne group.[5] More recently, Toste and co-workers[6] and Campagne and co-workers[7] have described efficient rhenium [(dppm)$ReOCl_3$] and gold [$NaAuCl_4 \cdot 2H_2O$] catalysed nucleophilic substitution of propargylic alcohols, respectively. However, the specific and high cost of such catalysts makes a barrier to their large-scale use. Therefore, development of a general, efficient, cheap and readily available catalyst for propargylic substitution reaction is highly desirable.

Recently, bismuth(III) compounds have received attention in organic synthesis due to their low toxicity, low cost and relative insensitivity to air and to small amounts of moisture. Bismuth has an electron configuration of $[Xe]4f^{14}5d^{10}6s^26p^3$. Due to the weak shielding of the 4f electrons (lanthanide contraction), bismuth(III) compounds exhibit Lewis acidity and they have been used in many chemical transformations.[8] Bismuth trichloride is particularly attractive because it not only is commercially available and inexpensive, but also of high stability. Herein, we report an efficient $BiCl_3$-catalyzed nucleophilic substitution reaction of propargylic alcohols bearing not only terminal alkyne groups but also internal alkyne groups 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 $BiCl_3$-catalyzed coupling reactions of various propargylic alcohols with allyl trimethylsilane. We were pleased to find that 10 mol% $BiCl_3$ in acetonitrile at 35 or 60 °C, successfully produced the substituted 1,5-enynes. Various aryl- and alkyl-substituted propargylic alcohols (**1a–1i**) effectively underwent the $BiCl_3$-catalyzed substitution. Typical results are shown in Table 1. The reaction proceeded smoothly without exclusion of moisture or air from the reaction mixture. Electron-rich or moderately electron-poor aromatic substrates (**1g–1h**) reacted smoothly with allyl trimethylsilane affording the corresponding allylated products in high yields (Table 1, entries 7 and 8), the substrate with strongly electron-withdrawing CN^- group afforded the adduct in low yield (Table 1, entry 9). Functional groups, such as methoxy, bromo and cyano 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–1c**) is well tolerated. Gratifyingly, 1-phenylprop-2-yn-1-ol (**1e**) bearing a terminal alkyne group was successfully

Table 1 $BiCl_3$-Catalyzed substitution of various propargylic alcohols **1** with allyltrimethylsilane **2**[a]



1 **2** **3**

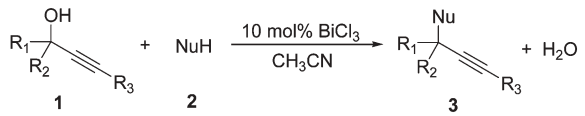
Entry	R_1; R_2; R_3	Product	Time/h	Isolated yield of **3** (%)
1	**1a**, Ph; H; *n*-Bu	**3aa**	0.5	91
2	**1b**, Ph; H; Ph	**3ba**	0.5	89
3	**1c**, Ph; H; TMS	**3ca**	3	78
4	**1d**, CH_3; CH_3; Ph	**3da**	2	70
5	**1e**, Ph; H; H	**3ea**	24	61[b]
6	**1f**, CH_3; H; Ph	**3fa**	48	10[c]
7	**1g**, *o*-$MeOC_6H_4$; H; *n*-Bu	**3ga**	0.5	86
8	**1h**, *p*-BrC_6H_4; H; *n*-Bu	**3ha**	4	87
9	**1i**, *p*-CNC_6H_4; H; *n*-Bu	**3ia**	24	17[b]

[a] The reactions of **1** (1 mmol) with allyltrimethylsilane 2 (3 mmol) were carried out in the presence of $BiCl_3$ (0.1 mmol) in CH_3CN (2 mL) at 35 °C. [b] At 60 °C for 24 h. [c] At 60 °C for 48 h.

Department of Chemistry and The Key Laboratory for Chemical Biology of Fujian Province, College of Chemistry and Chemical Engineering, Xiamen University, Xiamen, 361005, Fujian, P. R. China.
E-mail: zpzhan@xmu.edu.cn; Fax: +86-592-2185780;
Tel: +86-592-2180318

† Electronic supplementary information (ESI) available: Experimental section. See DOI: 10.1039/b606470a

Table 2 $BiCl_3$-catalyzed substitution of various propargylic alcohols **1** with various nucleophiles **2**[a]



1 **2** **3**

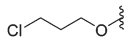
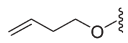
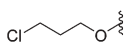
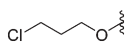
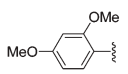
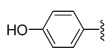
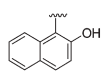
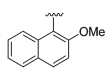
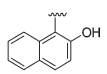
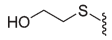
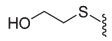
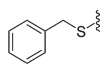
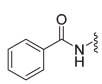
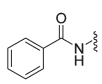
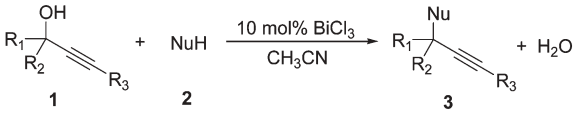
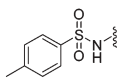
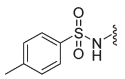
Entry	R_1; R_2; R_3	Nu	Time/h	Isolated yield of **3** (%)
1	**1a**, Ph; H; *n*-Bu		0.5	**3ab**, 89
2	**1b**, Ph; H; Ph		12	**3bb**, 83
3	**1c**, Ph; H; TMS		3	**3cb**, 85
4	**1d**, CH_3; CH_3; Ph		2	**3db**, 65
5	**1a**, Ph; H; *n*-Bu		1	**3ac**, 66
6	**1a**, Ph; H; *n*-Bu		2	**3ad**, 84
7	**1d**, CH_3; CH_3; Ph		15	**3dc**, 75
8	**1c**, Ph; H; TMS		3	**3cc**, 75
9	**1b**, Ph; H; Ph		0.5	**3bc**, 93
10	**1b**, Ph; H; Ph		0.5	**3bd**, 85
11	**1e**, Ph; H; H		1	**3eb**, 50
12	**1b**, Ph; H; Ph		4	**3be**, 60
13	**1b**, Ph; H; Ph		0.5	**3bf**, 94
14	**1b**, Ph; H; Ph		0.5	**3bg**, 90
15	**1e**, Ph; H; H		24	**3ec**, 62[b]
16	**1b**, Ph; H; Ph		0.5	**3bh**, 90
17	**1b**, Ph; H; Ph		1	**3bi**, 89
18	**1a**, Ph; H; *n*-Bu		0.5	**3ae**, 90
19	**1e**, Ph; H; H		6	**3ed**, 55[b]
20	**1b**, Ph; H; Ph		3	**3bj**, 75[b]
21	**1a**, Ph; H; *n*-Bu		7	**3af**, 60[b]

Table 2 $BiCl_3$-catalyzed substitution of various propargylic alcohols **1** with various nucleophiles **2**[a] (*Continued*)



1 **2** **3**

Entry	R_1; R_2; R_3	Nu	Time/h	Isolated yield of **3** (%)
22	**1b**, Ph; H; Ph		6	**3bk**, 80
23	**1e**, Ph; H; H		24	**3ee**, 46[b]

[a] The reactions of **1** (1 mmol) with **2** (3 mmol) were carried out in the presence of $BiCl_3$ (0.1 mmol) in CH_3CN (2 mL) at 35 °C. [b] The reaction were carried out at 60 °C.

allylated in 61% isolated yield at 60 °C, and no polymerization was detected (Table 1, entry 5). Compared with secondary benzylic alcohols **1b** and **1e**, secondary aliphatic substrate **1f** reacted more sluggishly to give the desired 1,5-enyne product in lower yield (Table 1, entry 6 *cf*. entries 2 and 5). The primary aliphatic alcohol 3-phenylprop-2-yn-1-ol (R_1, R_2 = H) failed to give allylated product. The experimental results suggest a mechanism through the formation of a propargylic cation intermediate. The instability of the propargylic cation intermediate clearly made the substitution reaction less favourable. Under the same conditions, the reaction of propargylic alcohols with allyltrimethylsilane, catalyzed by Lewis acid $B(C_6F_5)_3$, did not afford the desired 1,5-enynes but instead the corresponding silyl ether; while with propargylic esters substitution proceeded successfully to give the desired 1,5-enynes in good yields.[9c] Several Lewis acid-catalyzed nucleophilic substitution reactions of propargylic esters have been reported.[9a–e]

We next extended the propargylic substitution by employing heteroatom-centered and aromatic nucleophiles. All reactions proceeded in the presence of 10 mol% $BiCl_3$ in acetonitrile. Typical results are shown in Table 2.

A series of alcohols as the nucleophiles were firstly treated with various propargylic alcohols (**1a–1d**) and the corresponding propargylic ethers were obtained in good yields with complete regioselectivity (Table 2, entries 1–7). Functional groups such as alkenyl (Table 2, entry 2) and chloro (Table 2, entries 1, 3 and 4) 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 give the tertiary ether in 65 and 75% isolated yield, respectively (Table 2, entries 4 and 7). Notably, the use of ethanol as 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 6 and 7).[10]

Similarly, reactions of propargylic alcohols bearing a terminal alkyne group or an internal alkyne group with various aromatic compound nucleophiles were also carried out (Table 2, entries 8–15). The corresponding Friedel–Crafts arylated products were obtained from the heteroaromatic furan and pyrrole in 85, 50, 60% yields with complete regioselectivity (Table 2, entries 10–12).

Propargylation occurred selectively at the α-position of the heterocyclic rings. Electron-rich aromatic compounds such as 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 8, 9 and 13–15). 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, entries 9, 13 and 14). In the processes involving furan and β-naphthol, the substrate bearing a terminal alkyne group gave the propargylic adduct in lower yields (Table 2, entry 11 *cf*. 10; entry 15 *cf*. 13). In all cases, propargylation occurred selectively at the electron-rich position of aromatic compounds. The result indicated that the reaction proceeds electrophilically.

Transition metal-catalysed coupling of propargylic alcohols with thiols has seldom been reported, probably due to that sulfur-containing compounds are catalyst poisons because of their strong coordinating properties.[11,5b] Gratifyingly, by employing 10 mol% $BiCl_3$ 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 alkyl or aryl substituents on the alkyne part reacted rapidly with various thiols such as benzenethiol and mercaptoethanol affording the corresponding sulfide products in excellent yields with complete regioselectivity (Table 2, entries 16–18). In contrast to the result obtained when 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 16 *cf*. 9). Remarkably, the hydroxy moiety is well tolerant in the reaction; 10 mol% $BiCl_3$ efficiently catalysed the propargylation of mercaptoethanol while avoiding competitive O-alkylation and the formation of the propargylic ethers. Hydroxy 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, entry 19).

Finally, selected amides also acted as efficient nucleophiles to give corresponding propargylic amides in moderate to good yields. The employing of benzamide 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.

In summary, we have developed a general and efficient $BiCl_3$-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. 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 catalyse the nucleophilic substitution of propargylic alcohols, $BiCl_3$ 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 under way in our laboratory.

The research was financially supported by the National Natural Science Foundation of China (NO. 30572250).

Notes and references

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5 The ruthenium-catalyzed propargylic substitution was reported to run *via* allenylidene complex intermediates which can be produced only from propargylic alcohols bearing a terminal alkyne group, see ref. 4; on the other hand, ruthenium-catalyzed substitution of propargylic alcohols bearing an internal alkyne group were also investigated, see: (*a*) Y. Nishibayashi, Y. Inada, M. Yoshikawa, M. Hidai and S. Uemura, *Angew. Chem., Int. Ed.*, 2003, **42**, 1495; (*b*) Y. Inada, Y. Nishibayashi, M. Hidai and S. Uemura, *J. Am. Chem. Soc.*, 2002, **124**, 15172.

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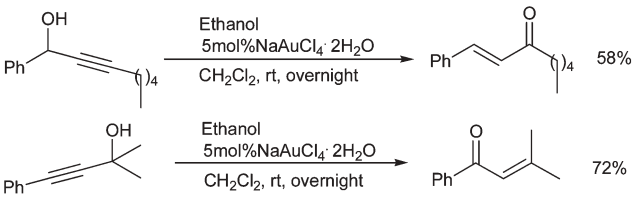
10 In gold(III)-catalyzed nucleophilic substitution of propargylic alcohol with ethanol, the rearranged unsaturated ketones are obtained in good yield. For details, see: M. Georgy, V. Boucard and J. M. Campagne, *J. Am. Chem. Soc.*, 2005, **127**, 14180.



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