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Direct substitution of propargylic alcohol with oxygen, nitrogen, and carbon nucleophiles catalyzed by molybdenum(VI)

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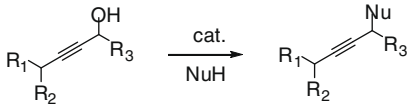
ABSTRACT

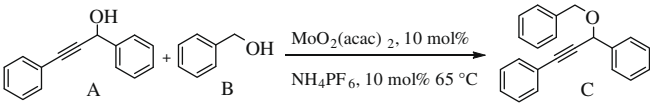
Efficient and direct substitution of propargylic alcohol with a variety of oxygen, nitrogen, and carbon nucleophiles catalyzed by $MoO_2(acac)_2/NH_4PF_6$ system was developed. The functional alkynes were obtained in modest to good yields with this versatile and practical protocol.

It is well known that propargylic alcohols represent an important group of chemical intermediates for the synthesis of many natural products and pharmaceuticals.[1] The direct substitution of propargyl alcohols would constitute a straightforward method for the synthesis of functional alkynes, which can readily convert to a variety of other functional groups.[2] Nucleophilic substitution of the hydroxy group in propargylic alcohol usually requires a multistep synthesis because of its poor leaving ability. Consequently, the hydroxyl group generally transforms into a more reactive substituent, such as halide, carboxylate, carbonate, phosphonate, sulfonate, or other related compounds with good leaving ability. However, in these processes, both preactivation process and subsequent substitution process of the halides and related compounds inevitably produce stoichiometric amounts of salt waste. Therefore, the direct catalytic substitution of propargylic alcohols is a desirable method for development. The Nicholas group reported the first example of the direct substitution of propargylic alcohol catalyzed by cobalt.[3] As it is considered an ideal and more efficient way, the direct substitution of propargylic alcohols (Scheme 1) has emerged as an attractive area of research.[4] So far, direct substitution of propargylic alcohols has been examined with some transition metals or brønsted acid catalysts, including ruthenium,[5] rhenium,[6] gold,[7] indium,[8] bismuth[2a,9] and *p*-toluenesulfonic acid,[10] under different conditions. Nevertheless, these catalysts often restrict to catalyze the substitution with limited nucleophiles.



Scheme 1. The direct substitution of propargylic alcohols.

Table 1
Nucleophilic substitution of 1,3-diphenylprop-2-yn-1-ol (**A**) with phenylmethanol (**B**) under different conditions[a]



Entry	Catalyst	Additive	Solvent	Yield[b] (%)
1	$MoO_2(acac)_2$	—	CH_3CN	18
2	$MoO_2(acac)_2$	NH_4PF_6	CH_3CN	67
3	—	NH_4PF_6	CH_3CN	—
4	$MoO_2(acac)_2$	NH_4PF_6	Toluene	56
5	$MoO_2(acac)_2$	NH_4PF_6	CH_3NO_2	61
6	$MoO_2(acac)_2$	NH_4PF_6	Dioxane	11
7	$MoO_2(acac)_2$	NH_4PF_6	DMF	24
8[c]	$MoO_2(acac)_2$	NH_4PF_6	CH_3CN	15

[a] Reaction conditions: **A** (0.5 mmol), **B** (1.5 mmol), catalyst (0.05 mmol), 65 °C, 6 h.
[b] Isolated yields.
[c] **A** (0.5 mmol), **B** (1.5 mmol), catalyst (0.025 mmol), 65 °C, 6 h.

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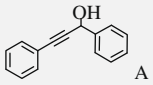
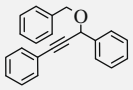
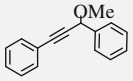
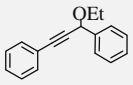
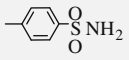
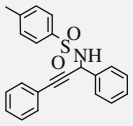
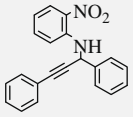
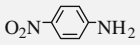
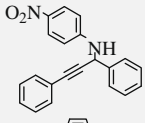
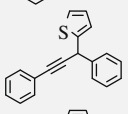
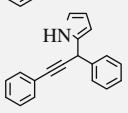
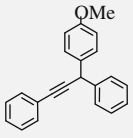
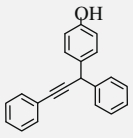
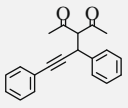
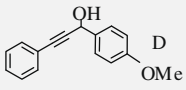
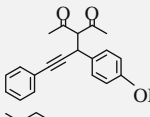
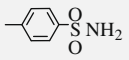
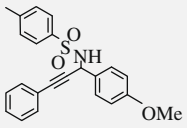
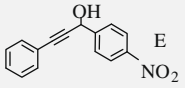
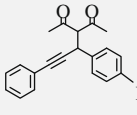
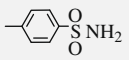
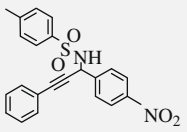
Table 2
$MoO_2(acac)_2$-catalyzed substitution of propargylic alcohol with various oxygen, nitrogen and carbon nucleophiles

Entry	Propargylicalcohol	NuH	Time (h)	Product	Yields[a] (%)
1			6		67
2[b]	A	MeOH	18		53
3[b]	A	EtOH	12		93
4	A		10		65
5	A		1		82
6	A		0.5		70
7	A		4		41
8	A		12		40
9	A		1		90
10	A		0.5		81
11	A		6		83
12			5		75
13	D		5		68
14			5		NR
15	A		5		NR

[a] Isolated yields .
[b] Thirty-three equivalents of nucleophiles were used.

Therefore, a versatile catalyst which can catalyze the substitution with a wide scope of nucleophiles is desirable.

Molybdenum(VI) compounds constitute a family of significant compounds in chemistry. Several industrial processes such as olefin epoxidation, olefin metathesis, and ammoxidation are carried out with molybdenum(VI) catalysts.[11] Furthermore, molybdenum(VI) has been found to have a role in the biological systems, many molybdenum(VI) complexes have been studied as models of molybdoenzymes.[12] However, most of the applications of molybdenum(VI) complexes in organic synthesis are focused on oxidation and polymerization.[13] Reddy reported the direct amidation of secondary benzyl alcohols with sulfonamides and carbamates in the presence of molybdenum(V) chloride in 2007.[14] We have recently reported the molybdenum-catalyzed asymmetric pinacol coupling reaction of aromatic aldehydes[15] and direct nucleophilic substitution of allylic alcohols with various nucleophiles.[16] In this context, the direct nucleophilic substitution of propargylic alcohols catalyzed by $MoO_2(acac)_2/NH_4PF_6$ system with oxygen, nitrogen, and carbon nucleophiles will be discussed.

As a preliminary study, we treated 1,3-diphenylprop-2-yn-1-ol (**A**) with phenylmethanol (**B**) (3 equiv) in the presence of $MoO_2(acac)_2$ (10 mol %) in acetonitrile, the reaction mixture was heated to 65 °C for 6 h, and the desired product (3-(benzyloxy)prop-1-yne-1,3-diyl)dibenzene (**C**) could be obtained in 18% (Table 1, entry 1). The higher yield was obtained by using NH_4PF_6 (10 mol %) as an additive (Table 1, entry 2), whereas NH_4PF_6 alone showed no catalytic activity (Table 1, entry 3). The reaction took place without exclusion of air or moisture from the reaction mixture. When the reaction was carried out in toluene or nitromethane, a decrease in reactivity was observed (Table 1, entries 4 and 5). When dioxane and DMF were used, only 11% and 24% yields were obtained, respectively (Table 1, entries 6 and 7). It should be noted that lower yield would be obtained when decreasing the catalyst loading (Table 1, entry 8).

We applied the optimized reaction procedure[17] to the reaction of 1,3-diphenylprop-2-yn-1-ol with methanol and ethanol. The results for alcohols are shown in Table 2 (entries 1–3). Methanol gave the desired propargylic ether in moderate yields, while ethanol provided the product in excellent yield. Campagne reported that the rearranged unsaturated ketones were obtained in high yields in gold-catalyzed the substitution reaction of propargylic alcohols in the presence of ethanol and 5% of $NaAuCl_4{\cdot}2H_2O$.[7a]

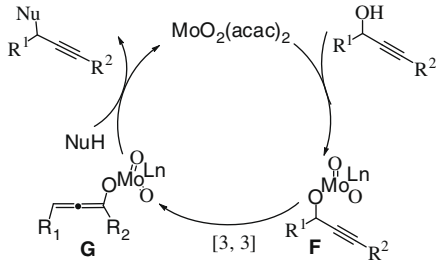
In order to check the scope of this process, we performed a set of experiments with several nitrogen nucleophiles. The results are summarized in Table 2 (entries 4–6). $TsNH_2$ provided the corresponding product in a long time with moderate yield (entry 4). On the other hand, the electron-withdrawing group-substituted aromatic amines, 2-nitroaniline and 4-nitroaniline, showed higher reactivity (entries 5 and 6).

To further demonstrate the utility of this catalytic system, thiophene (entry 7) and pyrrole (entry 8) were also investigated as nucleophiles. The α-carbon-substituted products were obtained in the yields of 41% and 40%, respectively. This implies that the C–C bond can be formed through this procedure, although the reactivity is lower. When anisole and phenol were used, the corresponding *para*-carbon-substituted products were obtained in 90% and 81% yields, respectively (entries 9 and 10). The desired product was also obtained in good isolated yield when **A** was treated with 1,3-diketone.

Other propargylic alcohols were also examined as substrates. The reaction of 1-(4-methoxyphenyl)-3-phenylprop-2-yn-1-ol (**D**) with acetylacetone and 4-methylbenzenesulfonamide at 65 °C for 5 h gave the corresponding propargylic products (entries 12, and 13) in moderate yields. Unfortunately, 1-(4-nitrophenyl)-3-phenylprop-2-yn-1-ol (**E**) failed to give the products under the same conditions. 3-Phenylprop-2-yn-1-ol and 1-phenylpent-1-yn-3-ol were also explored with this catalyst system, and no products were detected.

A possible mechanism for molybdenum-catalyzed direct substitution of propargylic alcohol with different nucleophiles is shown in Scheme 2. It is supposed that the transition state involves propargyl alcohol combined with molybdenum complex to form intermediate **F**, which was followed by [3,3] rearrangement to form allenolate **G**.[6a,18] Nucleophile attacks allenolate **G** to give the corresponding product. In the cases of 3-phenylprop-2-yn-1-ol and 1-phenylpent-1-yn-3-ol, it could not be easy for the transformation of intermediate **F** to **G** with less conjugated effect. So they showed no reactivity with this catalyst system.

In summary, we have developed direct substitution of propargylic alcohol using $MoO_2(acac)_2/NH_4PF_6$ as catalyst. The reaction is compatible with a wide range of nitrogen, oxygen, and carbon nucleophiles. The functional alkynes can be obtained in modest to good yields with this versatile and practical protocol.



Scheme 2. The plausible reaction mechanism.

Acknowledgments

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References and notes

1. (a) Trost, B. M.; Krische, M. J. *J. Am. Chem. Soc.* **1999**, *121*, 6131; (b) Fox, M. E.; Li, C.; Marino, J. P. J.; Overman, L. E. *J. Am. Chem. Soc.* **1999**, *121*, 5467; (c) Corey, E. J.; Cimprich, K. A. *J. Am. Chem. Soc.* **1994**, *116*, 3151; (d) Vourloumis, D.; Kim, K. D.; Petersen, J. L.; Magriotis, P. A. *J. Org. Chem.* **1996**, *61*, 4848.
2. (a) Zhan, Z. P.; Yang, W. Z.; Yang, R. F.; Yu, J. L.; Li, J. P.; Liu, H. J. *Chem. Commun.* **2006**, 3352; (b) Zhan, Z. P.; Yu, J. L.; Liu, H. J.; Cui, Y. Y.; Yang, R. F.; Yang, W. Z.; Li, J. P. *J. Org. Chem.* **2006**, *71*, 8298.
3. (a) Nicholas, K. M. *Acc. Chem. Res.* **1987**, *20*, 207; (b) Green, J. R. *Curr. Org. Chem.* **2001**, *5*, 809; (c) Teobald, B. J. *Tetrahedron* **2002**, *58*, 4133.
4. Reviews see: (a) Kabalka, G. W.; Yao, M. L. *Curr. Org. Synth.* **2008**, *5*, 28; (b) Ljungdahl, N.; Kann, N. *Angew. Chem., Int. Ed.* **2009**, *48*, 642.
5. (a) Nishibayashi, Y.; Inada, Y.; Yoshikawa, M.; Hidai, M.; Uemura, S. *Angew. Chem., Int. Ed.* **2003**, *42*, 1495; (b) Inada, Y.; Nishibayashi, Y.; Uemura, S. *Angew. Chem., Int. Ed.* **2005**, *44*, 7715; (c) Nishibayashi, Y.; Shinoda, A.; Miyake, Y.; Matsuzawa, H.; Sato, M. *Angew. Chem., Int. Ed.* **2006**, *45*, 4835; (d) Matsuzawa, H.; Miyake, Y.; Nishibayashi, Y. *Angew. Chem., Int. Ed.* **2007**, *46*, 6488.
6. (a) Sherry, B. D.; Radosevich, A. T.; Toste, F. D. *J. Am. Chem. Soc.* **2003**, *125*, 6076; (b) Luzung, M. R.; Toste, F. D. *J. Am. Chem. Soc.* **2003**, *125*, 15760; (c) Kennedy-Smith, J. J.; Yong, L. A.; Toste, F. D. *Org. Lett.* **2004**, *6*, 1325.
7. (a) Georgy, M.; Boucard, V.; Campagne, J. M. *J. Am. Chem. Soc.* **2005**, *127*, 14180; (b) Georgy, M.; Boucard, V.; Ddbleds, O.; Zotto, C. D.; Campagne, J.-M. *Tetrahedron* **2009**, *65*, 1758.
8. Yadav, J. S.; Reddy, B. V. S.; Rao, K. V. R.; Kumar, G. G. K. S. N. *Synthesis* **2007**, 3205.
9. Qin, H.; Yamagiwa, N.; Matsunaga, Y.; Matsunaga, S.; Sbibasaki, M. *Angew. Chem., Int. Ed.* **2007**, *46*, 409.
10. (a) Sanz, R.; Martinez, A.; Alvarez-Gutierrez, J. M.; Rodriguez, F. *Eur. J. Org. Chem.* **2006**, 1383; (b) Sanz, R.; Miguel, D.; Martinez, A.; Alvarez-Gutierrez, J. M.; Rodriguez, F. *Org. Lett.* **2007**, *9*, 727.
11. (a) Stiefel, E. L. Molybdenum, 4th ed.. In *Kirk-Othmer Encyclopedia of Chemical Technology*; Wiley: New York, 1995; Vol. 16, p 940; (b) Braithwaite, E. R.; Haber, J. *Molybdenum: An Outline of Its Chemistry and Uses*; Elsevier: Amsterdam, 1994.

12. Enemark, J. H.; Cooney, J. J. A.; Wang, J. J.; Holm, R. H. *Chem. Rev.* **2004**, *104*, 1175.
13. Kühn, F. E.; Santos, A. M.; Abrantes, M. *Chem. Rev.* **2006**, *106*, 2455.
14. Reddy, C. R.; Madhavi, P. P.; Reddy, A. S. *Tetrahedron Lett.* **2007**, *48*, 7169.
15. Yang, H. W.; Wang, H. S.; Zhu, C. J. *J. Org. Chem.* **2007**, *72*, 10029.
16. Yang, H. W.; Fang, L.; Zhang, M.; Zhu, C. J. *Eur. J. Org. Chem.* **2009**, 666.
17. *General procedure for $MoO_2(acac)_2$-catalyzed direct substitution of propargylic alcohol with versatile nucleophiles:* The corresponding nucleophile (1.5 mmol) was added to a solution of $MoO_2(acac)_2$ (16 mg, 0.05 mmol) and NH_4PF_6 (9 mg, 0.05 mmol) in acetonitrile (2 ml) at 65 °C, and the resulting mixture was stirred for 5 min before the addition of propargylic alcohol (0.5 mmol). The mixture was stirred at this temperature and the reaction was monitored by TLC analysis. After the reaction was complete, the mixture was then cooled to room temperature and directly purified by flash chromatography on silica gel to afford the corresponding product.
18. Trost, B. M.; Oi, S. *J. Am. Chem. Soc.* **2001**, *123*, 1230.