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B(C₆F₅)₃ catalyzed direct nucleophilic substitution of benzylic alcohols: an effective method of constructing C–O, C–S and C–C bonds from benzylic alcohols†

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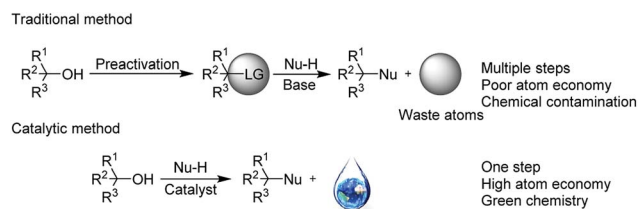
An efficient and general method of nucleophilic substitution of benzylic alcohols catalyzed by non-metallic Lewis acid B(C₆F₅)₃ was developed. The reaction could be carried out under mild conditions and more than 35 examples of ethers, thioethers and triarylmethanes were constructed in high yields. Some bioactive organic molecules were synthesized directly using the methods.

Alcohols are ideal building blocks for high-value chemicals because of their high stability, low toxicity and wide availability.¹ However, due to the poor leaving ability of the hydroxyl group, in most cases, alcohol substitution requires hydroxyl preactivation or the use of excess Brønsted acids or stoichiometric amounts of Lewis acids. In 2005, the OH-activation for nucleophilic substitution was considered a central issue by the ACS Green Chemistry Institute² because the direct catalytic nucleophilic substitutions of alcohols are highly desirable in constructing high-value organic compounds such as ethers, thioethers and a variety of bioactive molecules. Furthermore, the reaction produces only H₂O as a byproduct, which meets the requirements of green chemistry and atom-economy.³

In recent years, the direct catalytic nucleophilic substitution of alcohol has been explored, however, many urgent, difficult problems are still waiting to be solved. The catalytic nucleophilic substitutions of π -activated alcohols such as allylic/propargyl alcohols have been developed as well as the double bond or triple bond of the substrates being able to coordinate to the metal catalysts (Au, Bi, In, Al, Fe *etc.*), stabilizing the carbocations.⁴ In contrast, for benzylic alcohols, the catalytic substitution reactions are much less explored.⁵ Furthermore, harsh conditions and excess nucleophiles are two major defects in the existing reports, and for different nucleophiles, varied catalysts are always required. Therefore, a mild, green, efficient and general method of benzylic alcohol nucleophilic substitution is highly desirable (Scheme 1).

In recent years, B(C₆F₅)₃ as a non-metallic Lewis acid has drawn notable attention because of its strong Lewis acidity, high-stability and environmental friendliness.⁶ Furthermore, the borane hydrate is also a strong Brønsted acid.⁷ And these inspired us that the borane may offer another chance to realize the direct substitution reaction of benzylic alcohols such as etherification, thioetherification and arylation (Scheme 2).

For the etherification of alcohols, the difficulty is that how to realize the high selectivity between cross-etherification and homo-etherification. Initially we chose diphenylmethanol **1a** and BnOH as the model alcohol compounds. The reaction was carried out with 10 mol% B(C₆F₅)₃ in toluene at 60 °C (Table 1). To our delight, the cross-etherification product was obtained in high yield and the homo-etherification product could not be detected (85%, entry 1). In the examination of several common solvents for the cross-etherification of **1a**, 1,2-dichloroethane was found to be superior (95%, entry 2). The reaction could not give any products in the THF (entry 4) because a “Frustrated Lewis Pair”⁸ was formed between B(C₆F₅)₃ and THF. When the catalyst loading was decreased to 5 mol%, the yield had no erosion (entry 6), and a further decrease led to a longer reaction time and a slight lower yield (entry 7). Longer time was needed when the reaction was carried out at room temperature.



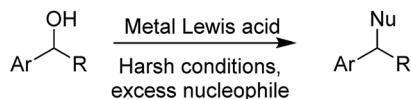
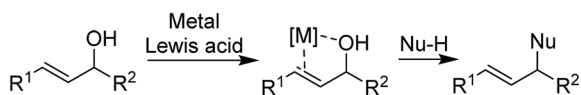
Scheme 1 The difference between traditional method and catalytic method.

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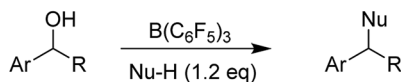
† Electronic supplementary information (ESI) available. See DOI: 10.1039/c8ra05811c



Previous works



This work



Nu-H = ROH, RSH, ArH. Non-metallic catalyst
Mild conditions 88-99% yields >35 examples

Scheme 2 Catalytic substitution of alcohols.

Table 1 Optimization conditions^a

Entry	X%	Solvent	Yield ^b %
1	10	Toluene	85
2	10	1,2-Dichloroethane	95
3	10	Ethyl acetate	30
4	10	THF	<5
5	10	DCM	88
6	5	1,2-Dichloroethane	95
7	1	1,2-Dichloroethane	93
8 ^c	10	1,2-Dichloroethane	89

^a Unless otherwise noted, all reactions were conducted using 1.2 equiv. BnOH with a substrate concentration 0.2 M in the indicated solvent at 60 °C on a 0.2 mmol scale, 12 h. ^b Isolated yield. ^c Room temperature, 48 h.

After we optimized the reaction conditions, we decided to investigate the etherification substrates scope (Table 2). Diphenylmethanol with different substitutes coupled with BnOH always provided the desired ethers in excellent yields (2b–e), the electron-rich groups gave slightly higher yields compared to the electron-withdrawing groups such as F, Cl. But for the substrate with 2-CF₃, no products could be obtained. Even for a bulky substrate, the etherification also occurred smoothly (2f, 88%). A little longer reaction-time was required when less reactive substrates were tested, the yields were still satisfactory (2g–j, 93–96%). All the reaction did not give any product of homo-etherification products. When a secondary alcohol ⁱPrOH was used as coupling reagent, the reaction still gave good yields and excellent selectivities (2k–m, 91–96%). The homo-etherification of alcohol was also tested in the reaction conditions, e.g. diphenylmethanol, the product could be isolated in a high yield (2n, 95%).

Table 2 Substrates scope of alcohol etherification

<p>2a: R¹=H, R²=H, 95% 2b: R¹=4-CH₃, R²=4-CH₃, 99% 2c: R¹=4-F, R²=4-F, 95% 2d: R¹=H, R²=2-CH₃, 97% 2e: R¹=H, R²=4-Cl, 98%</p>			
2g: 96%	2h: 93%	2i: 94%	2j: 94%
2k: 96%	2l: 92%	2m: 91%	2n: 95%

As we had realized the cross-etherification of alcohols, we decided to look into the possibility of applying the system in the C–S bonds construction as the thioether-containing compounds have a unique significance in drugs.⁹ To our delight, the product of thioetherification between 1a and 4-methylbenzenethiols was isolated in 97% yield (Table 3) when the reaction was carried in the optimal conditions, and the different types of substitutes on the benzene ring had slight effect on the yields (3b–e). For the substrate containing heteroaromatic-ring, the thioetherification product could be

Table 3 Substrates scope of alcohol thioetherification

3a: 97%	3b: 94%	3c: 95%	3d: 96%
3e: 92%	3f: 99%	3g: 95%	
3h: 99%	3i: 94%	3j: 93%	3k: 95%



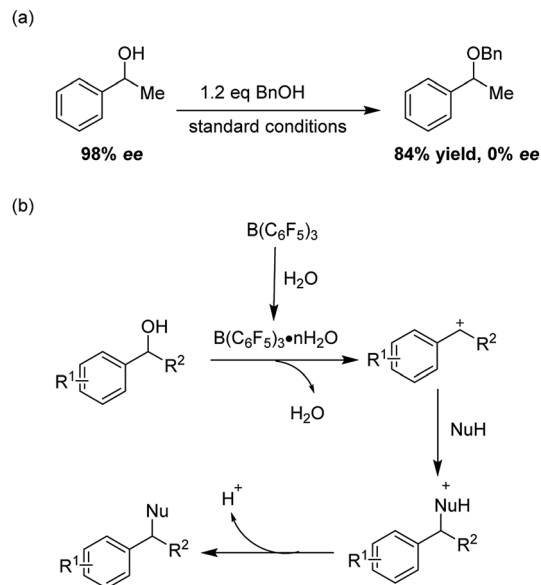
Table 4 Substrates scope of alcohol arylation

$\text{R}^1\text{CH(OH)R}^2 + \text{Aryl-H} \xrightarrow[\text{DCE, 60 } ^\circ\text{C, 4h}]{\text{B(C}_6\text{F}_5)_3 \text{ 5 mol\%}}$		$\text{R}^1\text{CH(Ar)R}^2$
5a: R ₁ = H, R ₂ = H, 95% 5b: R ₁ = 4-F, R ₂ = 4-F, 93% 5c: R ₁ = 4-CH ₃ , R ₂ = 4-CH ₃ , 98% 5d: R ₁ = 2-CH ₃ , R ₂ = H, 98% 5e: R ₁ = 4-Cl, R ₂ = H, 91% 5f: R ₁ = 4-OMe, R ₂ = 4-OMe, 99%		
5g: 92% 5h: 91% 5i: 94% 5j: 91% 5k: 89% 5l: 91% 5m-5n: 1:3, 92%		

isolated in a quantitative yield (3f). The reaction finished in high yields for phenethyl alcohols (3g–i) and the cyclic substrates also gave the similar results (3j, 3k).

Triarylmethanes are well-known structures in several areas, including photochromic agents, dye precursors and applications in materials,¹⁰ they also play an important role in medicinal chemistry.¹¹ Naturally we applied our catalytic system in the synthesis of triarylmethanes (Table 4). The substitution reaction between diphenylmethanols and 2,6-di-*tert*-butylphenol worked quite well and gave the desired triarylmethanes in 91–99% yields (5a–f). For the benzylic alcohols, the target products were isolated in high yields (5g–j) as well. A similarity of antitubercular compound 5k was also synthesized effectively. Different aromatic nucleophiles were tested in the reaction, the indole substitution product 5l was obtained in 91% yield. Isoerianin as an excellent anti-cancer small molecule and its isomerism (5m and 5n) were also synthesized in 92% yield totally.¹²

To give more insight of the reaction, a S_N1 mechanism was proposed (Scheme 3). When the B(C₆F₅)₃ was under moisture conditions, it could generate a strong Brønsted acid B(C₆F₅)₃·nH₂O, and the Brønsted acid could activated the alcohol substrates, the hydroxyl group leaved as one molecular H₂O giving a carbocation, then the nucleophile attacked the carbocation forming the product.



Scheme 3 Plausible mechanism.

Conclusions

In summary, *via* a rational design, a general, practical, green and efficient method of direct nucleophilic substitution of benzylic alcohols was developed by our group. The reaction only needs a mild temperature (60 °C), a low catalyst loading (as low as 1 mol%) and a slight excess of nucleophile (1.2 equivalent). A series of unsymmetrical ethers were synthesised by the method in high yields without any homo-etherification products. Furthermore, the catalytic system was also suitable for the thioetherification and arylation of benzylic alcohols, and a wide range of thioethers and triarylmethanes were obtained in high efficiency. Further application and extension of B(C₆F₅)₃-catalyzed substitution reactions is still being explored by our group.

Conflicts of interest

There are no conflicts to declare.

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