BMC Chemistry

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Adaptive alcohols-alcohols cross-coupling via TFA catalysis: access of unsymmetrical ethers

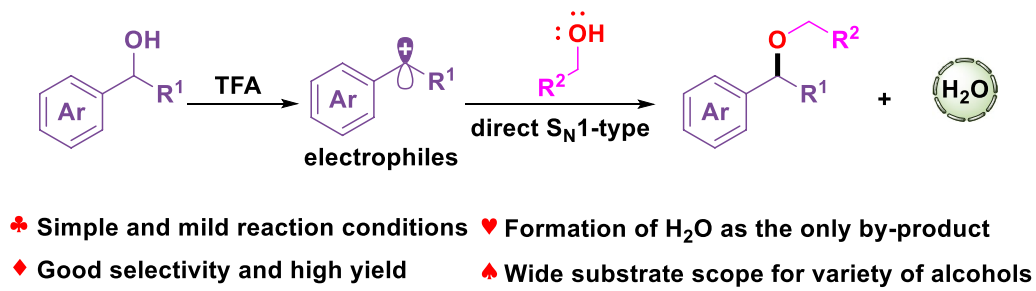
Chengxiu Liu[1], Jiaxin Liang[1], Yuqiu Liang[1], Lu Ouyang[1*] and Youchun Li[2*]

Abstract

Ethers are high value organic compounds widely applied in chemical industry, natural products, material, pharmaceuticals, argochemicals, as well as modern organic synthesis. Herein, we report an adaptive TFA-catalyzed cross-coupling of alcohols with various oxygen nucleophiles (nitro-, halogen-, sulfur-, nitrogen-, aryl-, and alkynyl-substituted aliphatic alcohols), delivering diverse unsymmetrical ethers under mild conditions and simple operation. This protocol features a broad range of substrate scope and high catalytic efficiency (54 examples, up to 99% yield). The decagram scale performance and one-step synthesis of drug molecules evidenced the potential industrial production and practicability of this protocol.

Keywords Unsymmetrical etherification, Alcohol-alcohol cross-coupling, Catalytic nucleophilic substitution

Graphical Abstract



Introduction

Ethers are high value organic compounds, which are widely used in chemical industry, natural products, material, pharmaceuticals, argochemicals, as well as modern organic synthesis (Scheme 1) [1–5]. In this content, the antihistamine compounds of (*S*)-Neobenodine and Bepotastine are representatives of this class of molecules [6]. Traditional strategies for ether synthesis include Williamson etherification [7, 8], Ullman reaction [9, 10], as well as Buchwald-Harting C-O coupling [11, 12]. However, the requirement of strong base, metal catalysts,

*Correspondence:
Lu Ouyang
oyl3074@163.com
Youchun Li
liyouchun2007@163.com
[1] Jiangxi Province Key Laboratory of Pharmacology of Traditional Chinese Medicine, School of Pharmacy, Gannan Medical University, Ganzhou 341000, Jiangxi, People's Republic of China
[2] The Affiliated Ganzhou Hospital, Jiangxi Medical College, Nanchang University, Ganzhou 341000, Jiangxi, People's Republic of China

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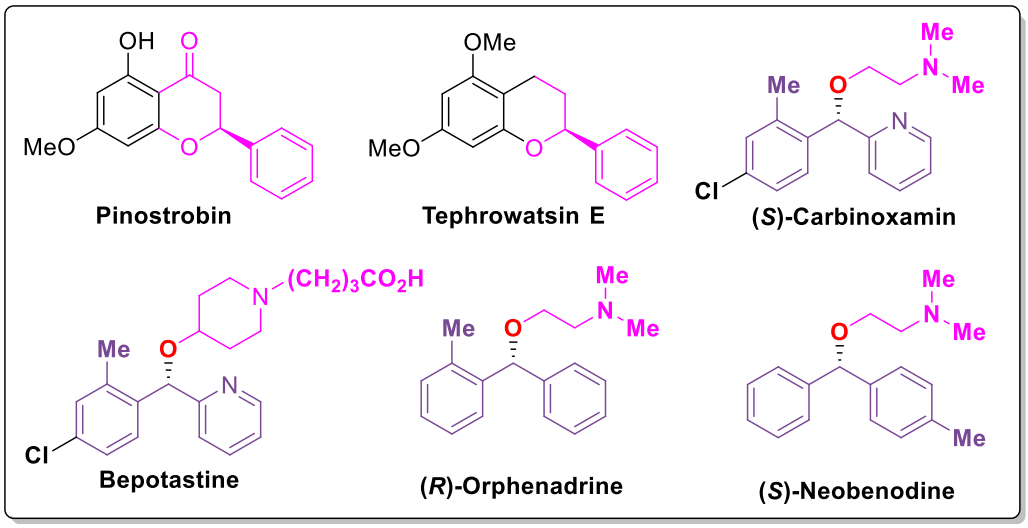


Scheme 1 Represented bioactive ether molecules

undesired waste salts, and competing β-H elimination of halides hindered the practical applications of these methods. In addition, the preparation of toxic halide precursors from corresponding alcohols also reduced the step and atom efficiencies.

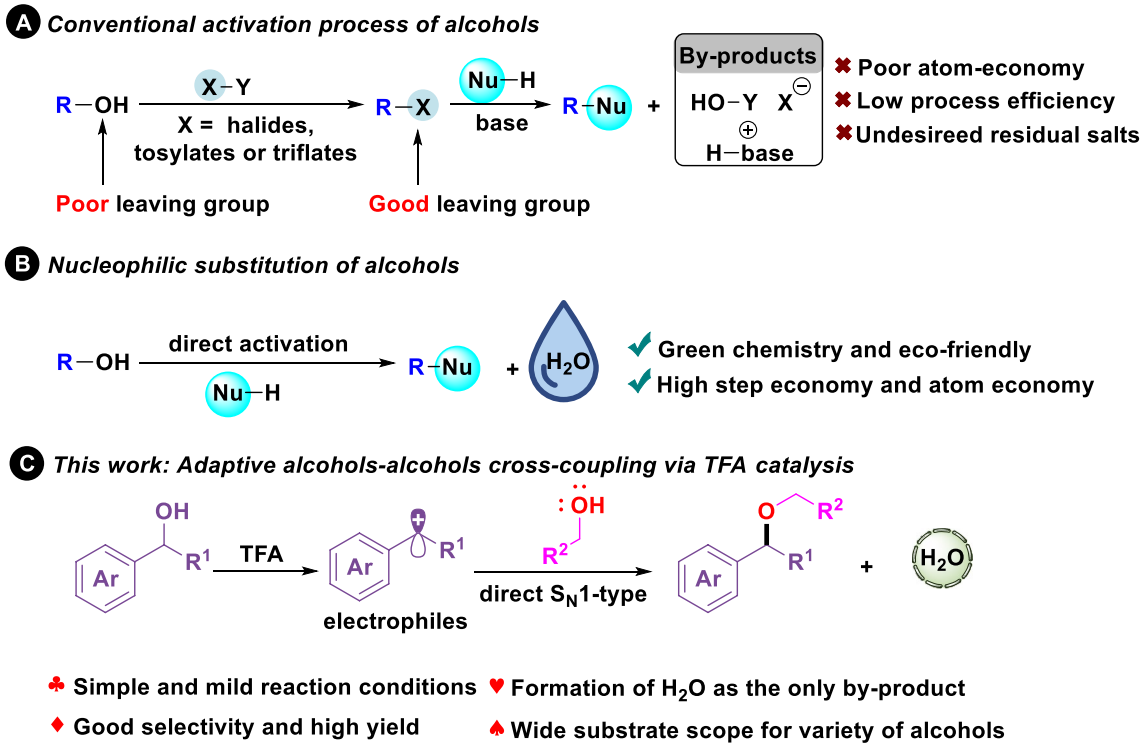
Avoiding the traditional drawbacks of etherification, direct etherification is an alternative solution to address the aforementioned issues, the by-product of which just loses an equivalent of H_2O. In this regard, the acid-mediated condensation of alcohols was recognized as the oldest method for symmetrical ether synthesis. Nevertheless, the harsh conditions and the indispensable of strong acid also limited the application of this protocol.

It is known that hydroxyl group (-OH) is a useful synthetic handle for diverse transformation due to the high stability, low toxicity and wide availability of alcohols [13, 14]. Recently, direct substitution of alcohols via OH-activation is not only identified as a critical issue by the ACS Green Chemistry Institute [15], but also emphasized as a key green chemistry research area by American Chemical Society Pharmaceutical Roundtable [16]. However, the poor leaving ability of -OH makes the direct substitution of -OH for final valuable products difficult, which needs pre-functionalization (Scheme 2A) [17]. Therefore, direct substitution of alcohols with H_2O as an only byproduct is consistent with the requirements of green chemistry [18, 19]. Therefore, catalytic nucleophilic substitution of alcohols by transition metal catalysis via π-complexes [20] or hydrogen borrowing [21–25], and direct substitution using Lewis basic [21–28] or Lewis/Brønsted acidic catalysts [29–31] were developed for this purpose (Scheme 2B). In recent decades, significant progress has been achieved in this field with active allylic alcohols, and propargylic alcohols as the electrophilicity parameters and different atom centers (C, N, O, S) as nucleophiles. For instance, the direct nucleophilic substitution of two different alcohols was realized by the catalytic system of organoboron $B(C_6H_5)_3$ [32], $F_5C_6B(OH)_2$) [33], Fe ($Fe(OTf)_2$ [34], $FeCl_2{\cdot}4H_2O$) [35], $ReBr(CO)_5$ [36], NIS [37], Ph_2CHBr [38], $Zr(Cp)_2(CF_3SO_3)_2$ [39], $[(C_6H_5)(PCy_3)(CO)RuH]^+ BF_4^-$ [40]. Despite great achievements have been made in direct nucleophilic substitution of allylic/propargyl alcohols, a general, mild, and green method for catalytic nucleophilic substitution of benzylic alcohols with protonic acid as catalyst is rare and in highly desirable.

Very recently, we reported coupling reactions via benzylic carbocation process under acid conditions [41–43]. Based on the previous work, we envisioned the benzylic carbocation can be trapped not only by electron-rich nucleophiles, but also by alcohols containing lone-electron pairs. Herein, we presented an adaptive TFA-catalyzed cross-coupling of alcohols with various oxygen nucleophiles (nitro-, halogen-, sulfur-, nitrogen-, aryl-, and alkynyl-substituted aliphatic alcohols), delivering diverse unsymmetrical ethers under mild conditions and simple operation (Scheme 2C). This protocol features a broad range of substrate scope and H_2O as only byproduct.

Results and discussion

The cross-coupling of diphenyl methanol (**1a**) and nitro ethanol (**2a**) was employed as model reaction to explore the optimal reaction conditions (Table 1). Firstly, the solvents were screened (Table 1, entries 1–7) using trifluoroacetic acid (TFA) as catalyst, which found that



Scheme 2 Strategies for activation of alcohols for the synthesis of ether

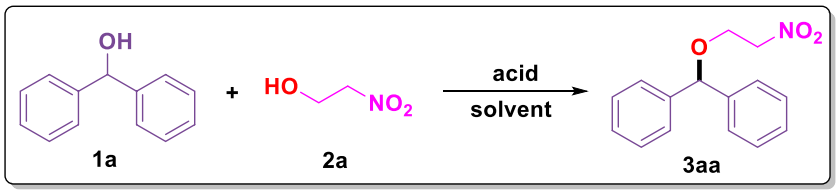
dichloroethane (DCE) and *p*-xylene showed the optimal reaction medias, delivering the desired ether product of **3aa** in full conversions (Table 1, entries 5 and 6). Similar excellent yields of the corresponding **3aa** were afforded even lowering the equivalent of nitro ethanol (**2a**) (Table 1, entries 8 and 9). In contrast, none of the target product **3aa** was given without TFA (Table 1, entry 10). The choice of acids was proven to have markedly influence on the yield of this cross-coupling transformation (Table 1, entries 11–14). The loading of TFA and reaction temperature also had influence on the yield of the reaction (Table 1, entries 15–19), with 0.4 equivalent of TFA at 80 °C being the optimal conditions (Table 1, entry 16).

With the optimized conditions in hand, the scope of this alcohol-alcohol cross- coupling was investigated. As shown in Scheme 3, using nitro ethanol (**2a**) as nucleophile, various diphenyl alcohols could be cross-coupled to unsymmetric aryl ethers, affording the corresponding products **3ba**-**3ja** in good to excellent yields. Diphenyl alcohols with electron-donating groups, such as methyl (**1b**, **1c** and **1 h**) and methoxy (**1f** and **1 g**), and electron-withdrawing groups, including fluorine (**1i**), bromine (**1e**), and chlorine (**1d** and **1j**), were component cross-coupling partners. Of note, the structure of **3 ha** (CCDC: 2,409,618) was characterized by single-crystal X-ray diffraction. Notably, a similar excellent yield of the product (**3 ka**) was observed when the more sterically hindered alcohol of 9-phenyl-9*H*-fluoren-9-ol (**1 k**) was loaded as substrate. Moreover, introducing the aryl allyl alcohol in this system gave the corresponding cross coupling product (**3la**) in 93% yield. Mono-aryl alcohols were also tolerated as well under these standard conditions, delivering the coupling products (**3ma-3xa**) in good to excellent yields. For instance, the 2-naphthalene ethanol (**1 m**) and phenyl ethanols (**1n-1q**) gave the desired products (**3ma**, **3na-3qa**) in good to excellent yields just extending the reaction time. However, only moderate yields of the ether products (**3ra-3wa**) were produced using longer chain of phenyl alkyl alcohols (**1r-1w**) as substrates even under conditions of prolonged reaction time. Similar results were showcased when aryl cyclic and aliphatic alcohols (**1 ×** and **1y**) were utilized as substrates. Noteworthily, triphenyl methanol could be coupled efficiently to afford the corresponding ether product (**3za**) in 80% yield.

Next, the scope of the nucleophiles of aliphatic alcohols in this TFA-catalyzed cross-coupling using diphenyl methanol (**1a**) as substrate was also investigated (Scheme 4).

As showcased in Scheme 4, various substituted halogenated ethanols (**2b**-**2e**, **2 l**) reacted smoothly with

Table 1 Optimization of reaction conditions [a]



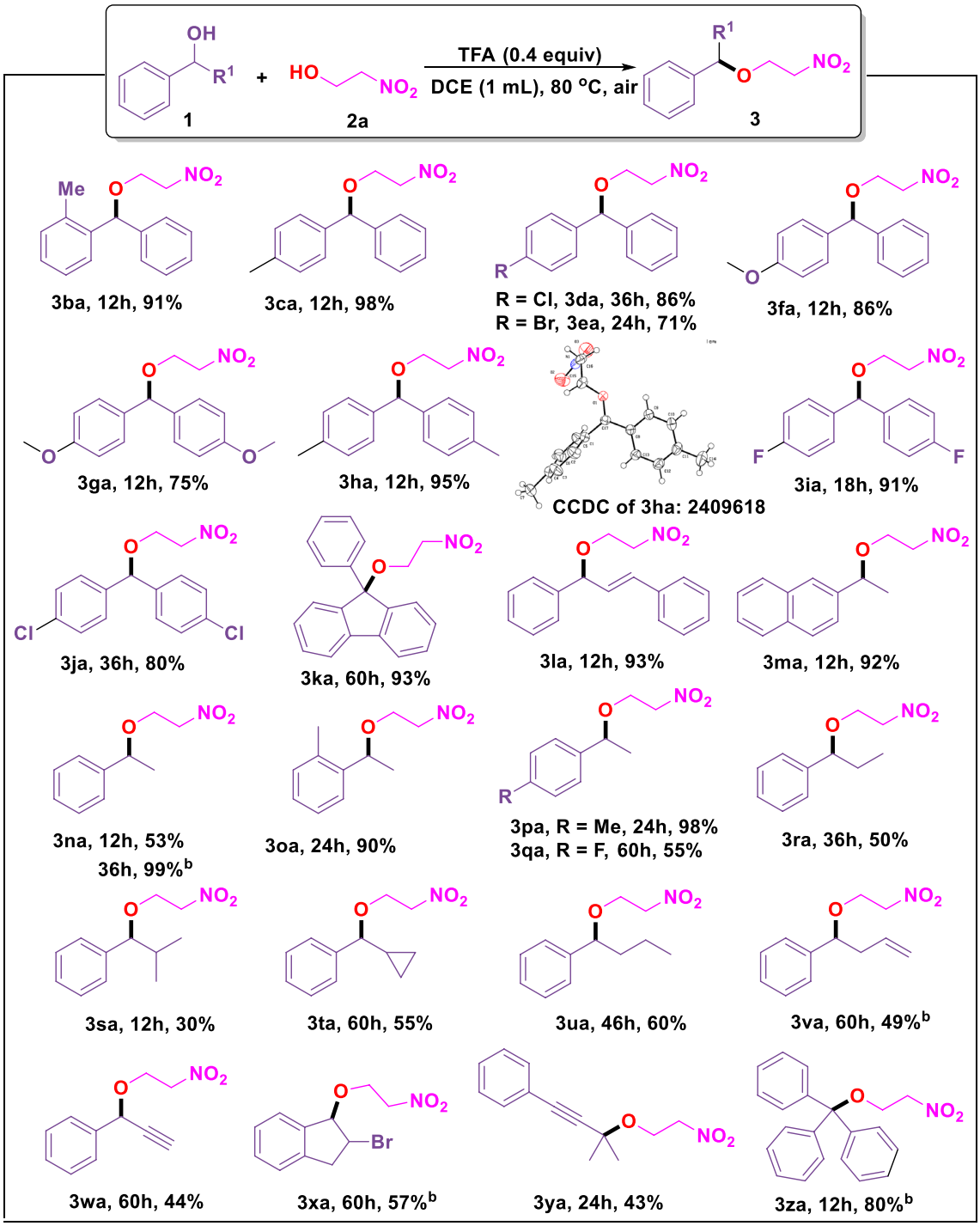
Entry	2a (equiv.)	Cat. (equiv.)	Solvent	Temp. (℃)	Yield of 3aa (%)[b]
1	3	TFA (1.0)	H_2O	80	33
2	3	TFA (1.0)	MeCN	80	68
3	3	TFA (1.0)	THF	80	99
4	3	TFA (1.0)	DMF	80	–
5	3	TFA (1.0)	DCE	80	> 99
6	3	TFA (1.0)	*p*-xylene	80	> 99
7	3	TFA (1.0)	dioxane	80	20
8	1	TFA (1.0)	DCE	80	93
9	2	TFA (1.0)	DCE	80	97
10	3	-	DCE	80	nr
11	3	TCA (1.0)	DCE	80	92
12	3	PFPA (1.0)	DCE	80	> 99
13	3	CAA (1.0)	DCE	80	54
14	3	TfOH (1.0)	DCE	80	31
15	3	TFA (0.2)	DCE	80	96
16	3	TFA (0.4)	DCE	80	> 99 (87)[c]
17	3	TFA (0.4)	DCE	40	48
18	3	TFA (0.4)	DCE	60	90
19	3	TFA (0.4)	DCE	100	79

[a] Reaction conditions: **1a** (0.5 mmol), with **2a** reacted under air for 12 h (TFA = CF_3CO_2H, TCA = CCl_3CO_2H, PFPA = $CF_3CF_2CO_2H$, CAA = $ClCH_2CO_2H$). [b] The yield was determined by NMR method using 1,3,5-trimethoxybenzene as the internal standard. [c] Isolated yield of **3aa**

diphenyl methanol (**1a**), offering the desired ether products (**3ab**-**3ae**, **3al**) in high yields. Notably, the substituted straight-chain halogenated propanols could produce the coupling products with similar high yields, while the branch-chain gave the desired product (**3ai**) in only moderate yield, comparable yield of product (**3aj**) was afforded by using trifluoromethyl substituted propanol (**1j**) as nucleophile. Notably, the cross-coupling of sulfur- and nitrogen-substituted aliphatic alcohols with diphenyl methanol (**1a**) was explored, but almost both reactions offered the corresponding products (**3ak** and **3am**) in low yields. It should also be noted that alcohols bearing the aryl group were suitable nucleophiles in this cross-coupling system, delivering the products (**3an**-**3ay**) in differential yields. Of note, the structure of **3ax** (CCDC: 2,409,617) was characterized by single-crystal X-ray diffraction. Moreover, alkynyl alcohols underwent this cross-coupling smoothly, providing the target products (**3az**, **3 cc**-**3 cd**) in moderate to excellent yields.

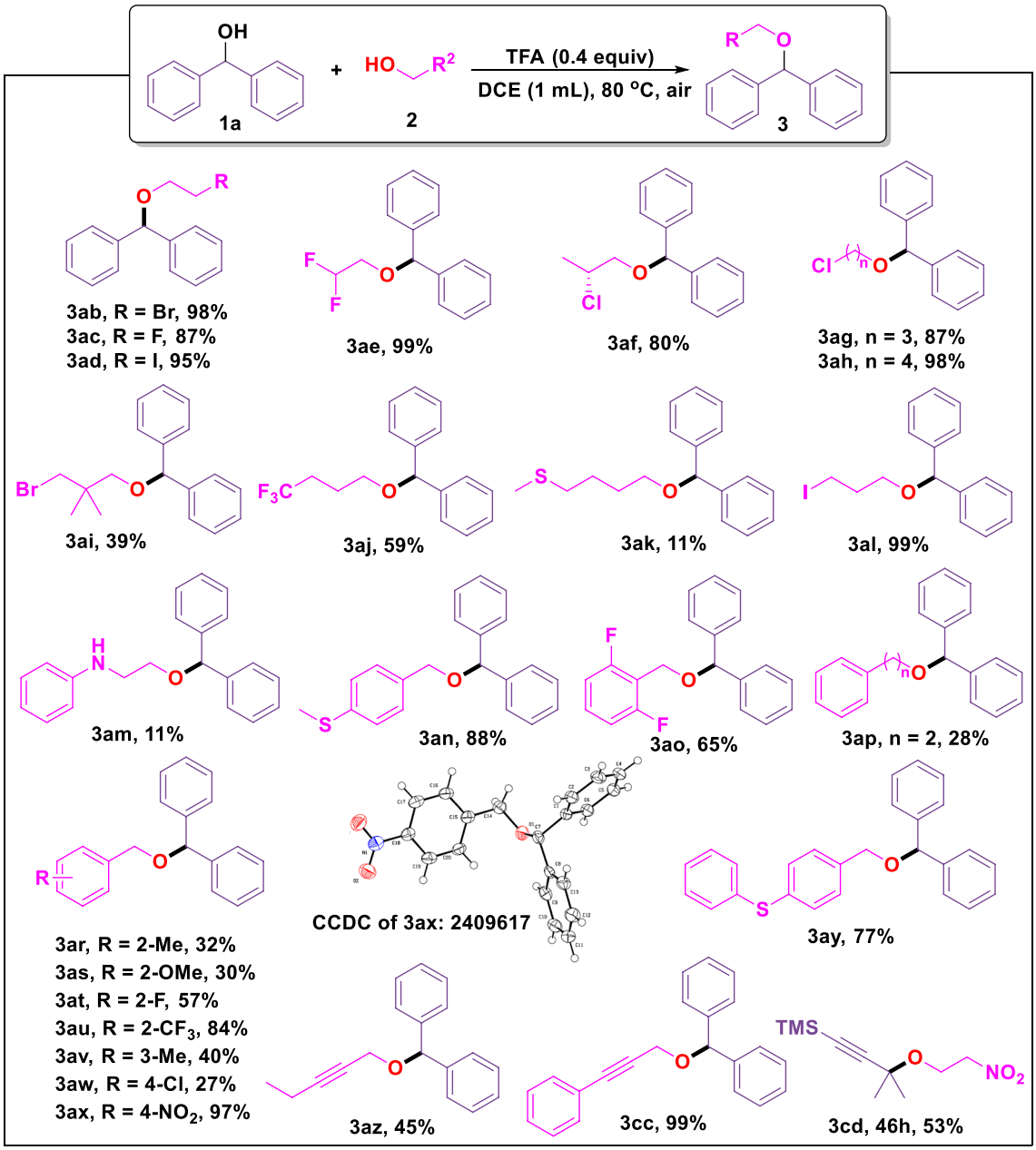
Isoxazolines are valuable molecules widely applied in the chemical and life science industries [44]. Firstly, a large scale at 50.0 mmol experiment of model reaction was performed under standard conditions, affording the 12.4 g cross-coupling product **3aa** in 96% yield (Scheme 5a).

With the **3aa** in hand, isoxazolines of **5aa**-**5ac** were synthesized under differential conditions (see the Supporting Information, Section D). Single-crystal X-ray diffraction has demonstrated the structure of **5ab** (CCDC: 2,409,627). The above results indicated that this cross-coupling showcased potential industrial production, and these compounds can be used as important precursors of bioactive molecules.



Scheme 3 Electrophilic substrate scope of aryl alcohols in TFA-catalyzed cross-coupling[a]. [a]Reaction conditions: **1** (0.5 mmol) and **2a** (3.0 equiv.) reacted in DCE (1.0 mL) at 80 °C under air. Isolated yield. [b] TFA (1.0 equiv.), 100 ℃

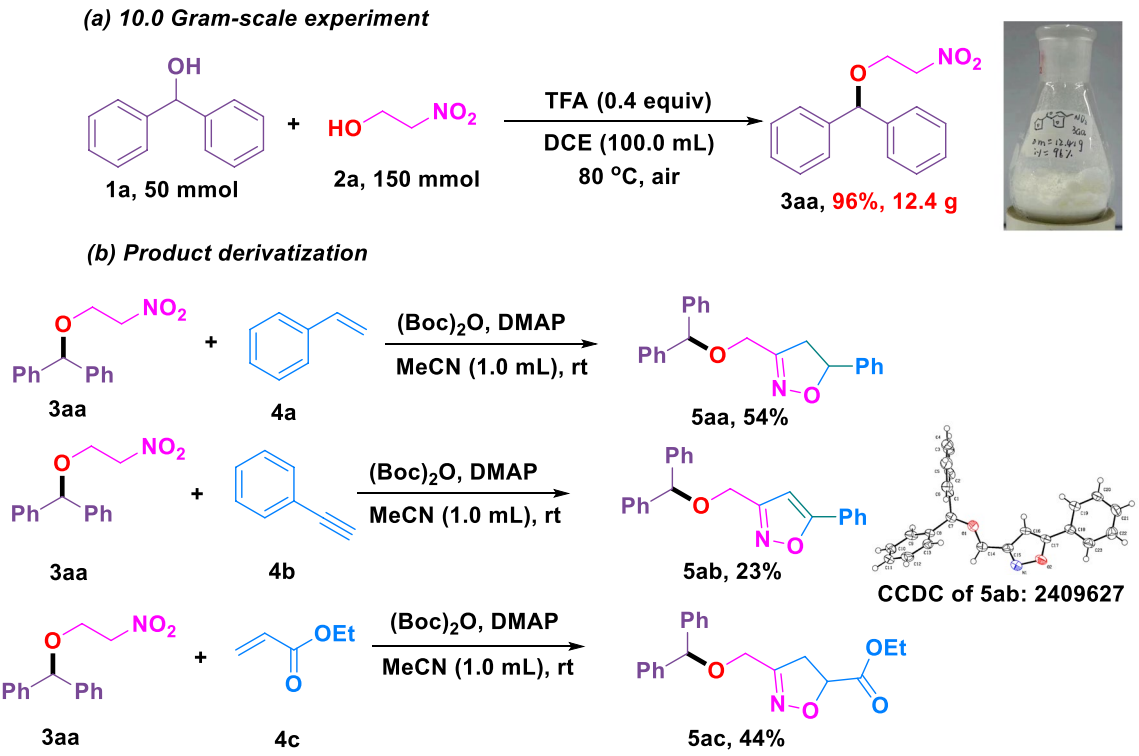
To investigate the applicability of this cross-coupling reaction in drug synthesis, the construction of Orphenadrine and Neobenodine was conducted (Scheme 6). As anticipated, the Orphenadrine and Neobenodine were obtained in 41% and 46% yield respectively via the cross-coupling of diphenyl methanols (**1b** and **1c**) with amino alcohol (**4d**) under this standard conditions.



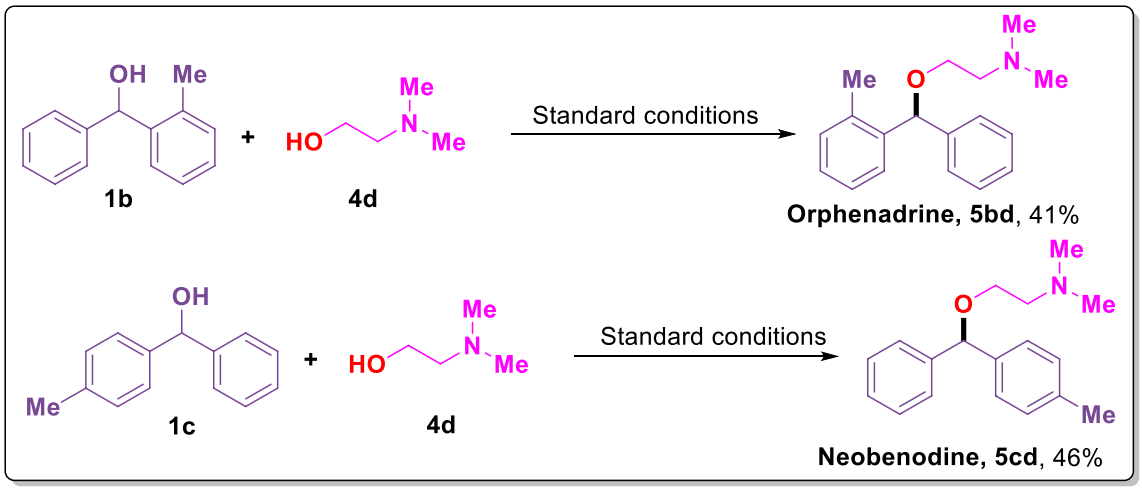
Scheme 4 Nucleophilic substrate scope of aliphatic alcohols in TFA-catalyzed cross-coupling[a]. [a]Reaction conditions: **1a** (0.5 mmol) and **2** (3.0 equiv.) reacted in DCE (1.0 mL) under air. Isolated yield. [b] TFA (1.0 equiv.), 100 ℃

Conclusion

In summary, we had established an adaptive TFA-catalyzed cross-coupling between two different alcohols (benzylic alcohols as carbocation precursors and alkyl alcohols as oxygen nucleophiles). This protocol produced diverse unsymmetrical aryl ethers in generally high yields with good functional group tolerance (54 examples, up to 99% yield). More importantly, the robustness of this TFA-catalyzed cross-coupling transformation was documented by decagram scale and one-step synthesis drug molecules.



Scheme 5 Gram-scale performance and product derivatization



Scheme 6 One-step synthesis of Orphenadrine and Neobenodine

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s13065-025-01379-4.

Supplementary Material 1

Acknowledgements
Not applicable.

Author contributions
CXL performed the chemical experiments and data processing; JXL and YQL fulfilled data processing; LO provided funding support, supervision, writing and editing; YCL provided funding support, supervision.

Funding
This work was funded by the Fundamental Research Funds for Gannan Medical University (QD202019, QD202106, TD202310), the Ganzhou Bureau of Science and Technology (2022-YB1402).

Availability of data and materials
Data is provided within the manuscript or supplementary information files.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

Received: 7 October 2024 Accepted: 2 January 2025
Published online: 12 January 2025

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