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Scalable deoxygenative alkynylation of alcohols via flow photochemistry

Pin Xu & Cong Ma

Internal alkynes are often contained in bioactive pharmaceuticals and crucial intermediates in material sciences, yet their production methods are often limited and challenging, necessitating the development of more efficient and versatile synthetic routes. Here we report a method of deoxygenative alkynylation of alcohols via flow photochemistry. Formation of *N*-heterocyclic carbene-alcohol adducts undergoes oxidation by a photocatalyst, generating alkyl radicals. These radicals are subsequently trapped by an alkynylation agent, yielding the desired alkyne. Compared to batch reactions, the strategy using flow photochemistry is practical and efficient to complete the reaction in relatively short time with good yields. A wide range of functional groups were tolerated. The broad application of this method for alkyne synthesis in industry settings is anticipated, supported by the potential in late-stage functionalization of biomolecules and gram-scale synthesis.

Internal alkynes exist in various natural products[1] and are also widely used in drug discovery and material sciences for the synthesis of antibiotics[2,3], antifungals[4], polymers and liquid crystal materials[5,6]. The unique reactivity of alkynes also makes them valuable as precious building blocks, including heterocycles, alkenes, and carbonyl compounds[7,8]. Transition metal-catalyzed Sonogashira coupling reaction is a common method for synthesizing internal alkynes[9–11]. Under the catalysis of metal catalysts like palladium and copper salts, (pseudo)halogenated aromatics or alkanes react with terminal alkynes, which showed good functional group compatibility[12–16]. However, this protocol often accompanies a few issues, such as the use of expensive metals and ligands, harsh reaction conditions and competitive β-H elimination side reactions[17]. Despite great progress made by researchers by avoiding the utilization of transition metals[18–25], there is still a practical need to develop a mild, efficient and versatile method for synthesizing internal alkynes.

Using the electron-deficient type of reagents, visible-light-mediated radical alkynylation demonstrated the characteristics of mild reaction conditions and adaptation to various precursors, such as carboxylic acids or esters[26–31], C(sp^3)-H substrates[32–37], alkyl trifluoroborates[38,39] and aldehydes[40–42], etc.[43,44], making it an ideal alternative to Sonogashira reaction (Scheme 1a). However, the deoxyalkynylation of alcohols, which are the most diverse and commercially available substrates[45–47], has seldom been reported. In 2016, Fu and co-workers described a visible-light photoredox synthesis of internal alkynes containing quaternary carbons (Scheme 1b)[48]; Waser group and Xie group reported a similar visible-light-mediated deoxyalkynylation of activated tertiary alcohols in 2021 (Scheme 1c)[49,50]. The limitation of substrates and the additional purification steps associated to the pre-activation step affected the practicality of the above two methods. The direct alkynylation of alcohols (1°, 2° and 3°) has become an urgent problem that remained to be solved.

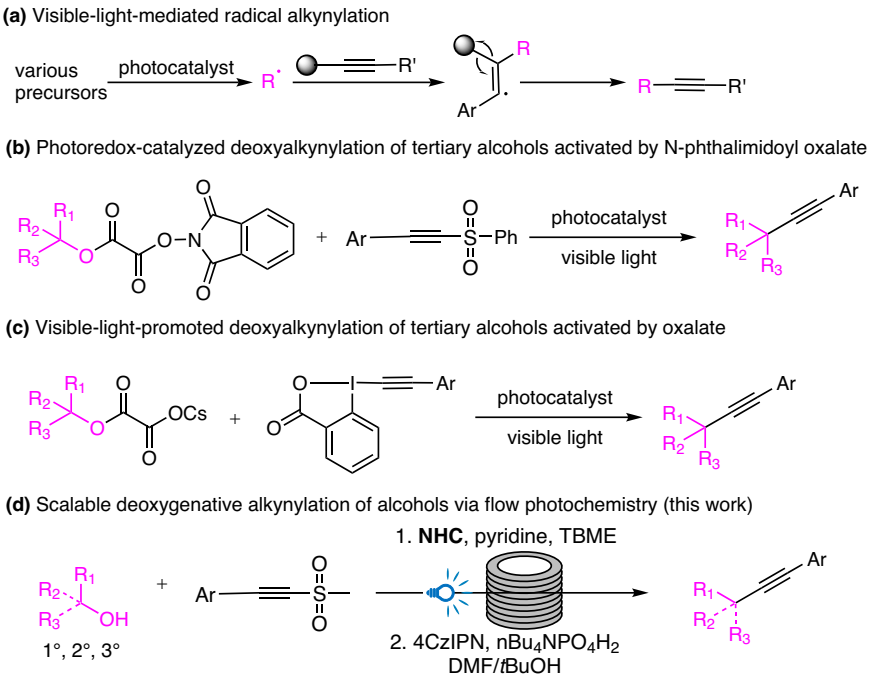
Since 2021, MacMillan has reported a series of photoredox-enabled deoxygenative arylation[51], alkylation[52–56], sulfination[57], fluoromethylation[58,59], phosphonylation[60], and amination[61] of alcohols, directly activated by *N,O*-heterocyclic carbenes (NHC) without purification. This strategy offers a novel approach to sp^3-sp^2 and sp^3-sp^3 cross-coupling reactions using widely available alcohol-containing reagents. However, the sp^3-sp coupling reaction has not yet been explored. Additionally, the scalability of product synthesis via photochemistry remains a challenge to be addressed.

According to the Bouguer-Lambert-Beer Law, the propagation of the photons in the reaction mixture decays rapidly, especially in a large photoreactor[62,63]. This effect significantly prolonged the reaction time and increased energy consumption. Additionally, it may lead to the formation of by-products, making purification difficult and costly. Nevertheless, flow photochemistry[64–68], which combines the advantages of flow chemistry and photochemistry, can effectively resolve these problems[69–73]. Herein, we report a practical, efficient, and scalable deoxygenative alkynylation of alcohols, which combines NHC activation with flow photochemistry (Scheme 1d).

Results and discussion

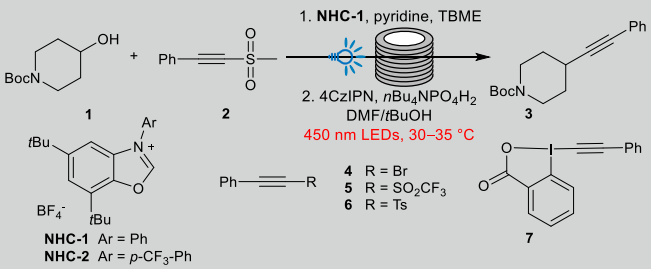
Following the extensive optimization as described in the Supplementary Information "Reaction Optimization" (Tables S1-S6), we provided the ideal reaction conditions as shown in Table 1. 2.0 equiv of *tert*-butyl 4-hydroxypiperidine-1-carboxylate (**1**) was condensed with NHC-1 affording the NHC-alcohol adduct in 15 min (see Supplementary Information "General Procedure"), and the adduct then subjected to react with a reaction

State Key Laboratory of Chemical Biology and Drug Discovery, Department of Applied Biology and Chemical Technology, The Hong Kong Polytechnic University, Hung Hom, Hong Kong SAR, China. e-mail: cong.ma@polyu.edu.hk



Scheme 1 | Visible-light-mediated radical alkynylation. **a** General reaction mechanism of visible-light-mediated radical alkynylation using electron-deficient reagents. **b** Photoredox synthesis of internal alkynes from tertiary alcohols activated by *N*-phthalimidoyl oxalate. **c** Visible-light-promoted deoxyalkynylation from secondary and tertiary alcohols activated by oxalate in the presence of ethynylbenziodoxolones. **d** This work presents a visible-light-mediated deoxyalkynylation from alcohols activated by *N*-heterocyclic carbenes (NHC).

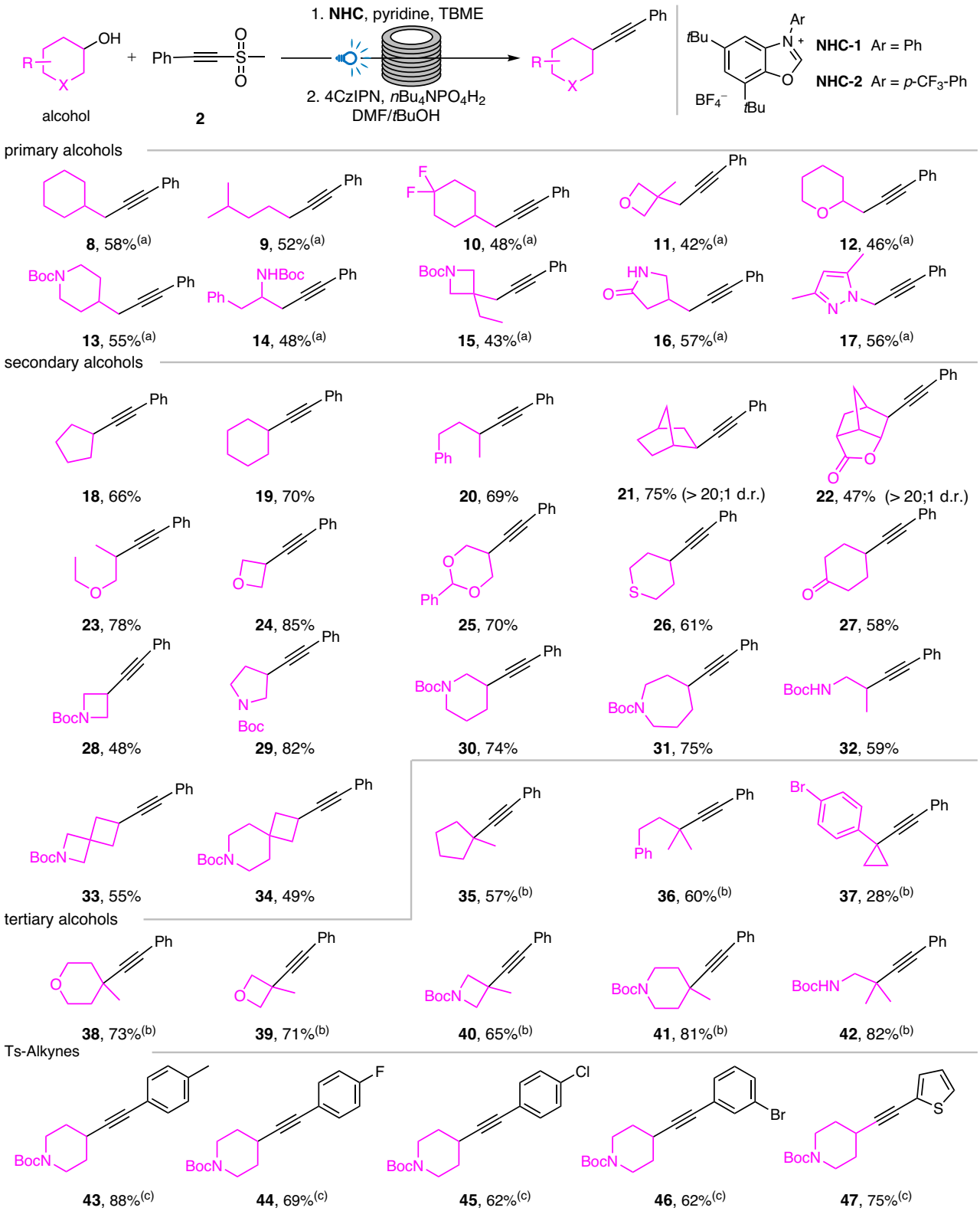
Table 1 | Optimization of reaction conditions[a]



Entry	Deviation of standard conditions	Yield[%][b]
1	none	77
2	NHC-2	46
3	**4** instead of **2**	N.D.
4	**5** instead of **2**	N.D.
5	**6** instead of **2**	46[c]
6	**7** instead of **2**	26
7	Pyridine as base for step 2	trace
8	Quinuclidine as base for step 2	15
9	TMG as base for step 2	18
10	No light or no 4CzIPN	N.D.
11	Reaction in a batch reactor	65[d]

[a]reaction conditions: **1** (2.0 equiv), NHC-1 (2.0 equiv), and pyridine (2.0 equiv) in MTBE (0.1 M), then **2** (0.3 mmol, 1.0 equiv), $nBu_4NPO_4H_2$ (4.0 equiv), and 4CzIPN (5 mol%) in MTBE/DMF/*t*BuOH (1:1:1, 0.017 M), 2*100 W 450 nm blue LEDs, the inner diameter of PTFE capillary is 0.75 mm, flow rate = 1.2 mL min^{-1}, 3.6 min residence time.
[b]Determined by ^1H NMR analysis using 1,3,5-trimethoxybenzene as the internal standard.
[c]28% of **6** remained.
[d]4 h reaction time.

mixture, including 5 mol% 1,2,3,5-Tetrakis(carbazol-9-yl)-4,6-dicyanobenzene (4CzIPN), 1.0 equiv of ((methylsulfonyl)ethynyl)benzene (**2**) and 4 equiv of $nBu_4NPO_4H_2$ in DMF/*t*BuOH, in a polytetrafluoroethylene (PTFE) capillary under the irradiation of 450 nm LEDs (for reaction setup see Supplementary Information "General information"). The alkynylation reaction completed to provide the product in 77% yield via flow photochemistry (entry 1). The NHC variant with *p*-CF_3 group resulted in a yield reduced to 46% (entry 2). The screening of the alkynylation reagents showed **2** with a simple methyl group attached to alkyne demonstrating superior atom economy and reactivity to other analogs (entries 3–6). Moreover,



Scheme 2 | Substrate scope for deoxygenative alkynylation of alcohols via flow photochemistry. Reaction conditions: alcohol (2.0 equiv), NHC-1 (2.0 equiv), and pyridine (2.0 equiv) in MTBE (0.1 M), then **2** (0.3 mmol, 1.0 equiv), nBu$_4$NPO$_4$H$_2$ (4.0 equiv), and 4CzIPN (5 mol%) in MTBE/DMF/tBuOH (1:1:1, 0.017 M), 2*100 W 450 nm blue LEDs, the inner diameter of PTFE capillary is 0.75 mm, flow rate = 1.2 mL min^{-1}, 3.6 min residence time. **a** flow rate = 0.75 mL min^{-1}. **b** NHC-2 instead of NHC-1, PhCF$_3$ instead of TBME. **c** Tosyl alkynes were used.

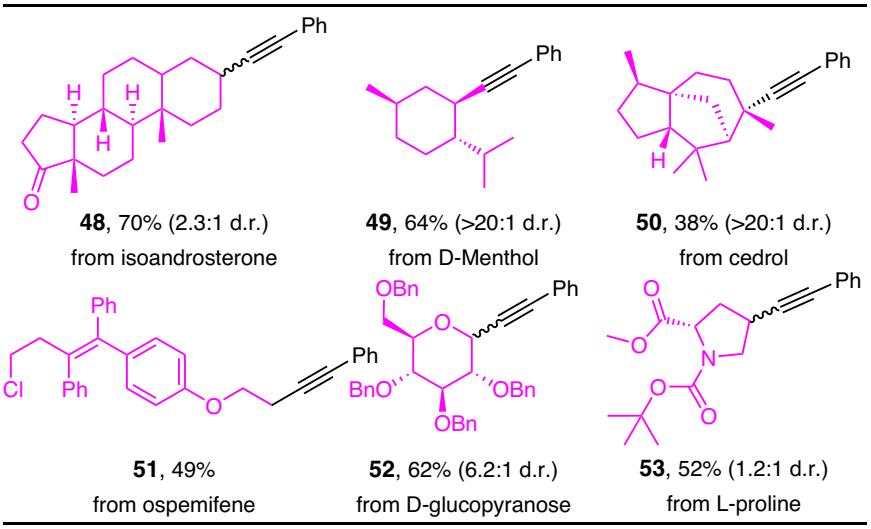
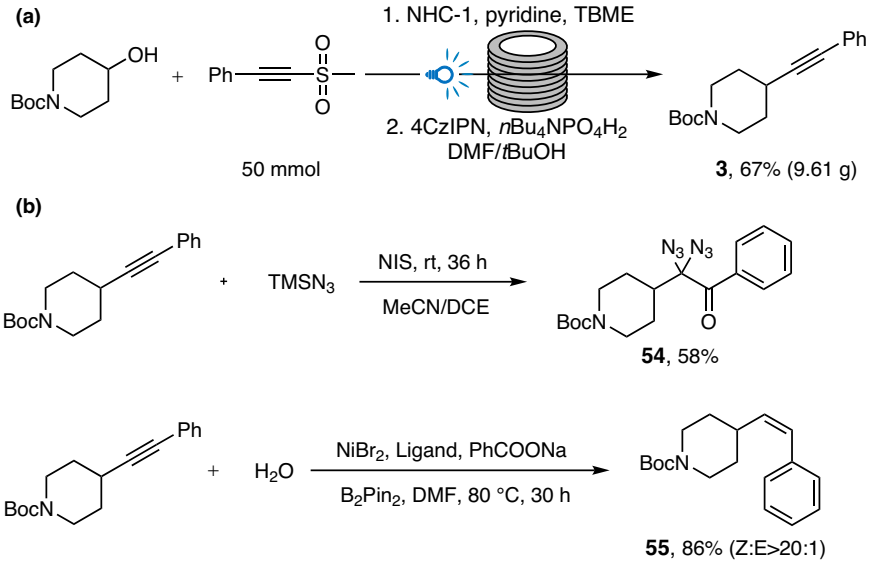


Fig. 1 | Late-stage functionalization of biomolecules. Ospemifene (Primary alcohol), isoandrosterone, D-Menthol, protected D-glucopyranose, protected L-proline (Secondary alcohols), and cedrol (Tertiary alcohol) can be converted to the corresponding alkyne derivatives **48**–**53**.



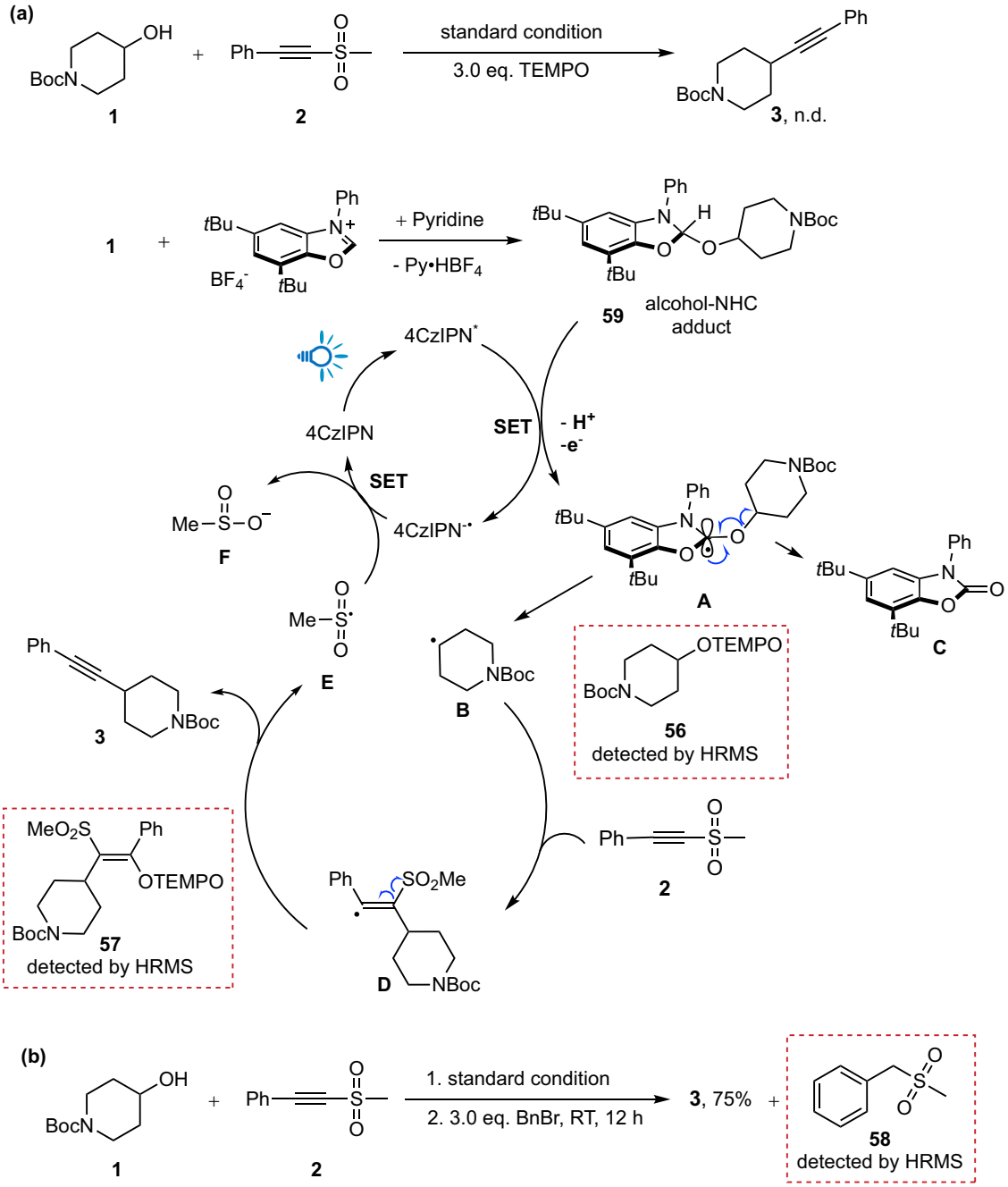
Scheme 3 | Gram-scale synthesis and synthetic applications of **3**. **a** Internal alkyne **3** synthesized in 10-gram scale. **b** Further functionalization potential towards azido and olefin derivatives.

other organic bases were also found to give inferior results (entries 7–9). The attempts in the absence of light or 4CzIPN (entry 10) led to no reaction occurring. Although this sp^3-sp coupling reaction can also be performed in a batch reactor, significantly longer reaction time and yield drop were observed (entry 11). While we were concluding this study, a batch reaction on the deoxyalkynylation of alcohols was reported[74]. Compared to the flow photochemistry method, the reported 36-hour reaction time and scalability present practical challenges. Furthermore, the use of their described reagent led to a slower conversion rate and lower yield (entry 5 vs. entry 1).

Under the optimized conditions, we explored the alcohol scope of the deoxygenative alkynylation with **2** (Scheme 2). Inactivated primary alcohols attached to cyclic alkyl, chain alkyl, and fluorinated alkyl groups formed viable substrates in this reaction, affording **8, 9**, and **10** in reasonable yields. Alcohols bearing cyclic ethers, cyclic and acyclic carbamates provided the corresponding products (**11**–**14**) with 42%–55% yields. Primary alcohols with sterically hindered substitution at β position, lactam, and pyrazole structures were well tolerated to give the desired products (**15, 16**, and **17**) with 43%, 57%, and 56% yields, respectively.

Secondary alcohols acted as better substrates for this alkynylation reaction. Products (**18, 19**, and **20**) were obtained from the corresponding cyclopentyl, cyclohexyl, and 4-phenyl-2-butyl alcohols with good yields (66–70%). Notably, *exo*-norborneol and the lactone derivative reacted stereoselectively to give the corresponding products **21** (69% yield) and **22** (47% yield) with >20:1 diastereoselective ratio. Other function groups in secondary alcohols, including ether (**23, 24**), acetal (**25**), thioether (**26**), and carbonyl (**27**) were compatible with the deoxygenative alkynylation conditions, giving moderate to good yields (58–85% yield). A variety of medicinally relevant cyclic and acyclic carbamates (**28**–**32**) could be obtained by the direct alkynylation from the corresponding alcohols, yielding the products in fair to good yields (48–82% yield). Additionally, the four-membered ring-containing spirocyclic system, attracting significant attention in drug discovery[75], was successfully alkynylated in 55% (**33**) and 49% (**34**) yields.

Next, a series of tertiary alcohols were investigated as precursors under the activation of NHC-2, a more electrophilic reagent that generated the NHC-*tert*-alcohol adduct effectively. To our gratification, except the product (**37**) derived from arylcyclopropanol, other tertiary alcohols afforded the desired products (**35, 36, 38**–**42**) with satisfactory yields (57–82%). Consequently, we turned our attention to the scope of the alkyne reagents. As expected, including thiophenyl alkyne, the substituent groups on the aromatic rings, such as *p*-CH_3, -F, -Cl, and *m*-Br, showed little effect on the yields of products **43**–**47** (62–88% yields).



Scheme 4 | Mechanistic study and plausible mechanism. **a** Reaction with TEMPO leading to the identification of **56** and **57**. **b** Addition of BnBr in the reaction resulting in sulfone **58**.

To further demonstrate the outstanding tolerance of functional groups and the capability of this deoxygenative alkynylation protocol in late-stage derivatizations, a variety of natural products and their derivatives, as well as a marketed drug containing the hydroxyl group were subjected to alkynylation under our conditions (Fig. 1). It was found that the secondary alcohols in isoandrosterone and D-Menthol provided the corresponding products **48** and **49** in good yields, but cedrol containing a tertiary alcohol showed relatively moderate yield (**50**), probably due to steric hindrance, whereas the diastereoselectivity was always excellent (>20:1 d.r.). Finally, ospemifene (**51**), as well as benzyl-protected D-glucopyranose (**52**) and protected L-proline (**53**) served as competent vectors for the deoxygenative alkynylnation of alcohols.

Reaction scale-up for photochemical reactions used to be hampered by the poor penetration of light through the reaction mixture in large batch reactors, which can be overcome by the narrow channel of flow photochemistry. As a result, the synthesis of **3** could be conducted in 10 g scale within 2.5 h by employing flow photochemistry (Scheme 3a). Moreover, with an additional step, product **3** can be converted to compounds **54**[48] and **55**[76], containing useful azido and olefin groups, respectively (Scheme 3b), which can undergo diverse reactions thereafter.

To further investigate reaction mechanism, we conducted the reaction in the presence of TEMPO to detect the generation of radicals, according to the previously reported sp^3-sp^3 and sp^3-sp^2 coupling reactions[51–61]. As a result, several key intermediates in the reaction were captured: Under standard conditions, the addition of TEMPO completely inhibited the formation of **3** (see Supplementary Information "Mechanistic experiments"). Meanwhile, compounds **56** and **57** were detected by HRMS (Scheme 4a), indicating the presence of the alkyl radical (**B**) and the alkenyl

radical (**D**). Additionally, compound **58** was also detected when the electrophilic reagent BnBr was introduced to the reaction mixture (Scheme 4b), suggesting the presence of methyl sulfinate (**F**), which can be converted from the methylsulfonyl radical (**E**).

In summary, we have developed a practical and efficient method for the visible-light-promoted deoxygenative alkynylation of alcohols via flow photochemistry, utilizing NHC to activate alcohols without purification. This protocol demonstrated broad compatibility with a wide range of alcohols and good late-stage derivatization possibilities of biomolecules. Gram-scale synthesis further showcased the potential of our method.

Methods

General procedure for deoxygenative alkynylation of alcohols

To an oven-dried 25 mL Schlenk tube was added NHC (0.6 mmol, 2.0 equiv), alcohol (0.60 mmol, 2.5 equiv), and anhydrous methyl *tert*-butyl ether (6 ml). Pyridine (0.6 mmol, 2.0 equiv) was added dropwise, and the suspension was stirred at room temperature under nitrogen atmosphere for 15 min. Another oven-dried 25 mL Schlenk tube was charged with 4CzIPN (0.015 mmol, 5 mol%), nBu$_4$NPO$_4$H$_2$ (1.2 mmol, 4.00 equiv) and the alkynylation reagent (0.30 mmol, 1.0 equiv). DMF (6 mL) and tBuOH (6 mL) were added to the mixture. The methyl *tert*-butyl ether suspension was transferred to a 10 mL syringe under air. Then a syringe filter and new needle were installed on the syringe. The methyl *tert*-butyl ether solution was injected through the syringe filter into the DMF/tBuOH solution. Then the reaction mixture was transferred to a 20 mL syringe. The LEDs were turned on and the reaction solution was slowly injected using an injection pump. For primary alcohols, the flow rate was 0.75 mL min^{-1}, 5.8 min residence time; For secondary and tertiary alcohols, the flow rate was 1.2 mL min^{-1}, 3.6 min residence time. The inner diameter of PTFE capillary is 0.75 mm. For tertiary alcohols, methyl *tert*-butyl ether was replaced by PhCF$_3$. The mixture in the receiving bottle was diluted with ethyl acetate, washed with H$_2$O and brine. The organic phase was dried with Na$_2$SO$_4$, then filtered, and concentrated *in vacuo*. The crude product was purified by flash column chromatography.

Data availability

All data generated during this study are included in this article and Supplementary Information. Experimental procedure, condition optimization, product characterization, and NMR spectra are provided in the Supplementary Information.

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Author contributions

P.X. and C.M. conceived the idea. C.M. supervised the project and acquired the funding. P.X. conducted the laboratory work. P.X. and C.M. analyzed the data. P.X. and C.M. wrote the manuscript.

Competing interests

The authors declare no competing interests.

Additional information

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Correspondence and requests for materials should be addressed to Cong Ma.