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Research Article

Keywords: alkynylation, deamination, N-anomeric amide, primary amine, radical

Posted Date: January 21st, 2026

DOI: https://doi.org/10.21203/rs.3.rs-8644719/v1

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Additional Declarations: The authors declare no competing interests.

Direct Deaminative Alkynylation of Aliphatic Primary Amines

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KEYWORDS: alkynylation; deamination; *N*-anomeric amide; primary amine; radical

ABSTRACT: Alkyl-substituted internal alkynes are useful motifs in organic synthesis and medicinal chemistry, but their preparation from common amine precursors remains challenging. Aliphatic primary amines are widespread functional groups, yet their direct use as alkylating reagents is limited by the strength of the C(sp^3)–N bond. Herein, we describe a direct deaminative alkynylation of aliphatic primary amines using alkynyl bromides as coupling partners. The transformation proceeds under metal-free conditions with an *N*-anomeric amide as a nitrogen-deletion reagent, enabling formation of C(sp^3)–C(sp) bonds without prior amine prefunctionalization. The reaction shows good functional-group tolerance and accommodates a range of aliphatic amines, including substrates derived from pharmaceuticals and natural products. This study demonstrates the feasibility of converting aliphatic primary amines into internal alkynes and expands the scope of deaminative C–C bond-forming reactions.

Introduction

Alkynes are widely used in chemical biology[1], medicinal chemistry[2-3], and materials science[4], and serve as versatile building blocks in organic synthesis due to the diverse reactivity of the C≡C bond[5-6]. Classical alkyne syntheses, such as the Corey–Fuchs and Seyferth–Gilbert reactions[7-8], rely on strong bases and are therefore poorly suited for late-stage functionalization. Consequently, strategies that construct C(sp^3)–C(sp) bonds—most notably the Sonogashira coupling—have been extensively developed, enabling alkynylation from organohalides[9-11], carboxylic acids[12-14], alcohols[15-16], or organoborons[17-18], and even C–H bonds[19-20].

Aliphatic amines are ubiquitous in functional molecules, yet are rarely exploited as retrons for direct functional group interconversion because of their poor leaving-group ability, high C(sp^3)–N bond dissociation energies, and intrinsic nucleophilicity and basicity[21-35]. As a result, deaminative alkynylation of aliphatic primary amines remains largely unexplored and is typically achieved through prefunctionalization to Katritzky-type pyridinium salts[36-41] (right, Fig. 1a). A rare exception was reported recently by Leonori[42], who disclosed a single example of tertiary-amine deaminative alkynylation via boryl-radical β-scission, albeit in low yield and with potential site-selectivity issues when three different alkyl groups sharing similar radical stability are present (left, Fig. 1a).

Recent advances have enabled the conversion of primary amines into isodiazene intermediates[43-46], which decompose to alkyl radicals and have been successfully applied to deamination and C–heteroatom bond formation[47-49](Fig. 1b). However, C–C bond formation via this strategy is substantially more challenging. We previously reported a direct deaminative trifluoromethylation of aliphatic primary amines using Levin's anomeric amide reagents and stoichiometric bpyCu(CF_3)$_3$[50], and

subsequently, in collaboration with Levin, achieved the first catalytic deaminative cyanation of aliphatic primary amines[51]. Very recently, Lu disclosed a deaminative Giese-type reaction using *O*-diphenylphosphinylhydroxylamine (DPPH) as a nitrogen-deletion reagent[52], enabling C(sp^3)–C(sp^3) bond formation.

Herein, we report a direct deaminative alkynylation of aliphatic primary amines using alkynyl bromides as efficient coupling partners (Fig. 1b). The electrophilic bromo radical plays a crucial role by rapidly undergoing hydrogen atom transfer (HAT) with the isodiazene intermediate, thereby suppressing the competing and challenging hydrodeamination pathway. This transformation proceeds under metal-free conditions and exhibits a broad substrate scope, including drug and natural-product derivatives, and enables versatile late-stage alkynylation and derivatization.

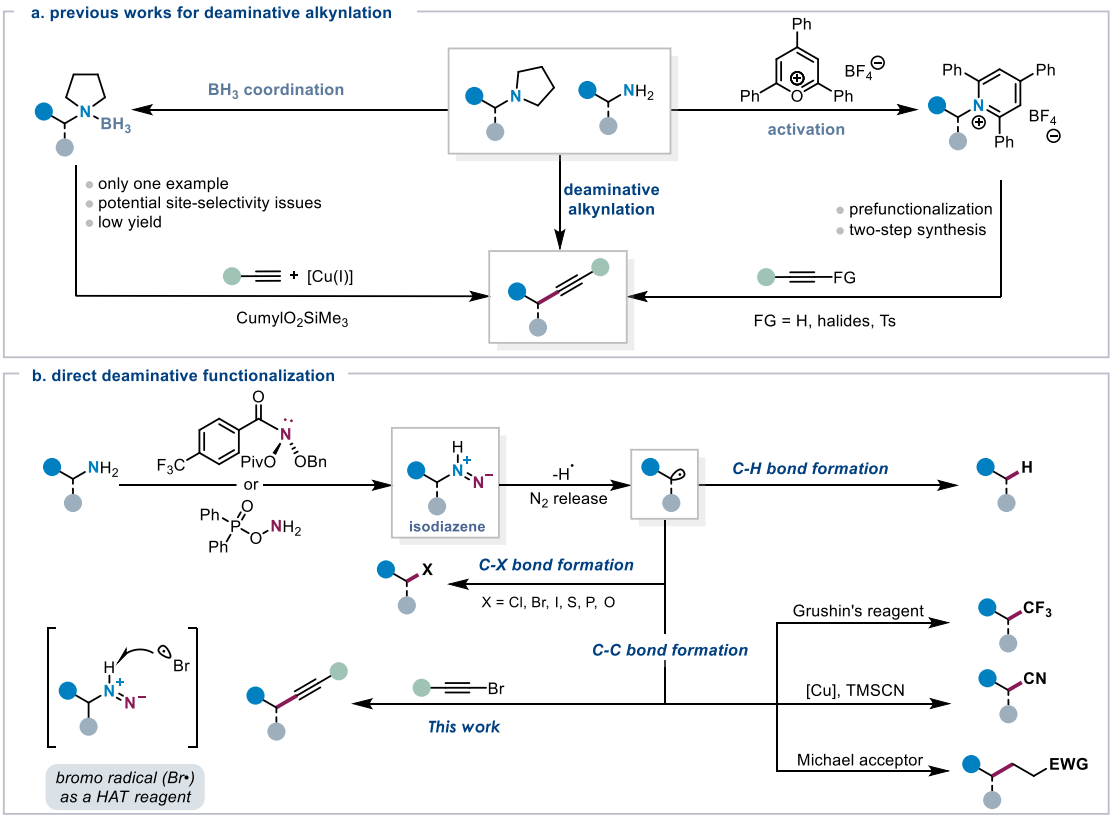


Fig. 1. Overview. a, Previous deaminative alkynylation via preactivation or BH_3 coordination. **b**, Previous direct deaminative functionalization via isodiazene and our work: direct deaminative alkynylation of aliphatic primary amines.

Results and discussion

Reaction discovery and optimization

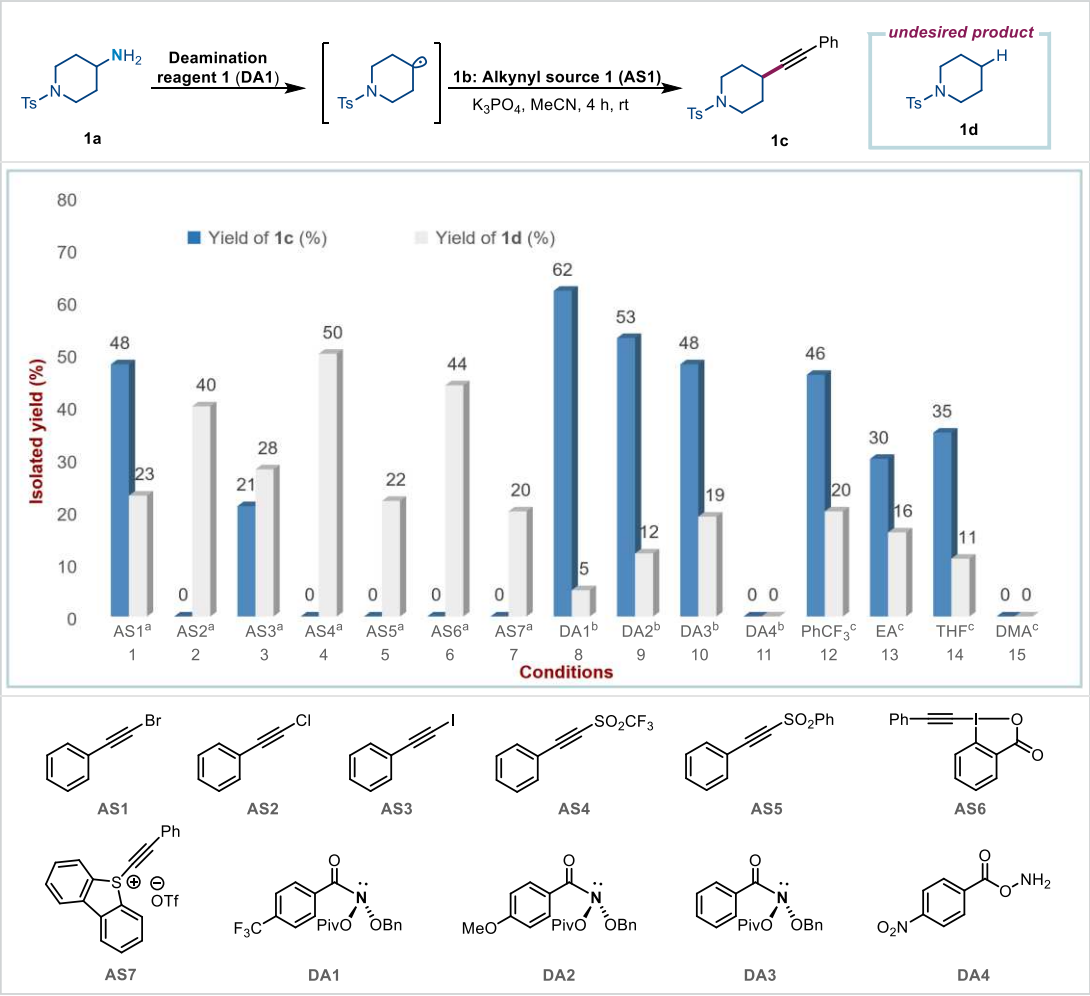


Fig. 2. Reaction optimization. [a]Using **DA1** (1.5 equiv), **AS** (2.0 equiv), w/o base, MeCN (0.05 M). [b]Using **AS1** (4.0 equiv), **DA** (1.5 equiv), K_3PO_4 (2.0 equiv), MeCN (0.05 M). [c]Using **AS1** (4.0 equiv.), **DA1** (1.5 equiv), K_3PO_4 (2.0 equiv), solvent (0.05 M). Yields are isolated.

We initiated our investigation using 1-tosylpiperidin-4-amine (**1a**) as the model substrate and **DA1** as deamination regent. When bromoethyne (**AS1**) was utilized as the alkynyl source in MeCN, the reaction furnished the target product **1c** in 48% yield alongside 23% of the hydrogenated byproduct **1d**, (column 1, Fig. 2). We then evaluated a series of alternative alkynyl sources, including chloroalkyne (**AS2**) and iodoalkyne (**AS3**) (columns 2–3). Among these two reagents, only iodoalkyne (**AS3**) afforded the target product, albeit with a moderate yield of 21%. Further exploration was conducted with alkynyl sulfones (**AS4** and **AS5**) (columns 4–5). Despite being previously reported as effective deaminative alkynylation reagents, almost only the deamination product was detected when these sulfones were employed. Similarly, neither Togni-type alkynyl reagent (**AS6**) nor Umemoto-type alkynyl reagent (**AS7**) led to the generation of the desired product (columns 6–7). To further improve the yield, we attempted adding a base to the reaction system to neutralize the hydrogen bromide produced in situ. Pleasingly, the addition of potassium phosphate significantly enhanced the reaction performance: the yield of **1c** was improved to 62%, and the formation of the hydrogenated byproduct **1d** was suppressed to less than 5% (column 8). We subsequently screened other deaminative reagents, and the results indicated that none of the three alternative reagents outperformed the anomeric amide **DA1** (columns 9–11). The reaction

efficiency declined noticeably when other solvents were used as substitutes (columns 12–15, for more details, see supporting information).

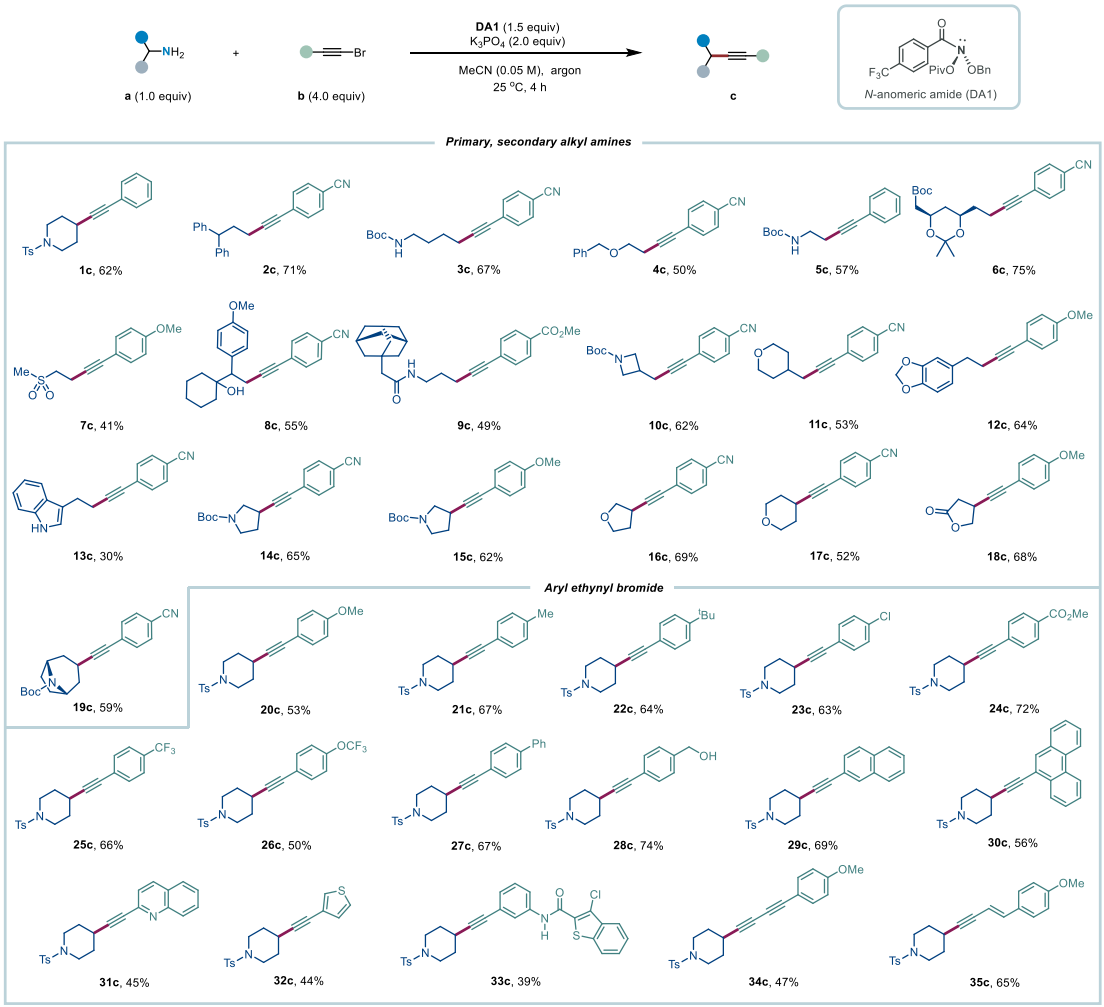


Figure 3. Substrate scope of deaminative alkynylation.

Substrate scope studies

Having optimized reaction conditions (column 8, Fig. 2), we began investigating the scope of deaminative alkynylation. As shown in the Fig. 3, a wide variety of α-primary and α-secondary amines bearing different substituents (e.g., carbamate, sulfonamide, cyano, amide, ether, acetal, sulfonyl, ester, and hydroxyl groups) were smoothly converted into the corresponding deaminative alkynylation products (**1c–19c)** in moderate to good yields. Aryl ethynyl bromide substituted with diverse substituents (e.g., methoxy, halogen, trifluoromethyl, and hydroxyl groups) also afforded the target products (**20c–33c)** in moderate to good yields. Notably, substrates featuring indole (**13c**), quinoline (**13c**), and thiophene (**32c, 33c**) motifs were also amenable to this reaction system. Furthermore, 1,3-butadiyne (**34c**) and conjugated enyne (**35c**) substrates were also compatible. These results highlight the generality of this transformation.

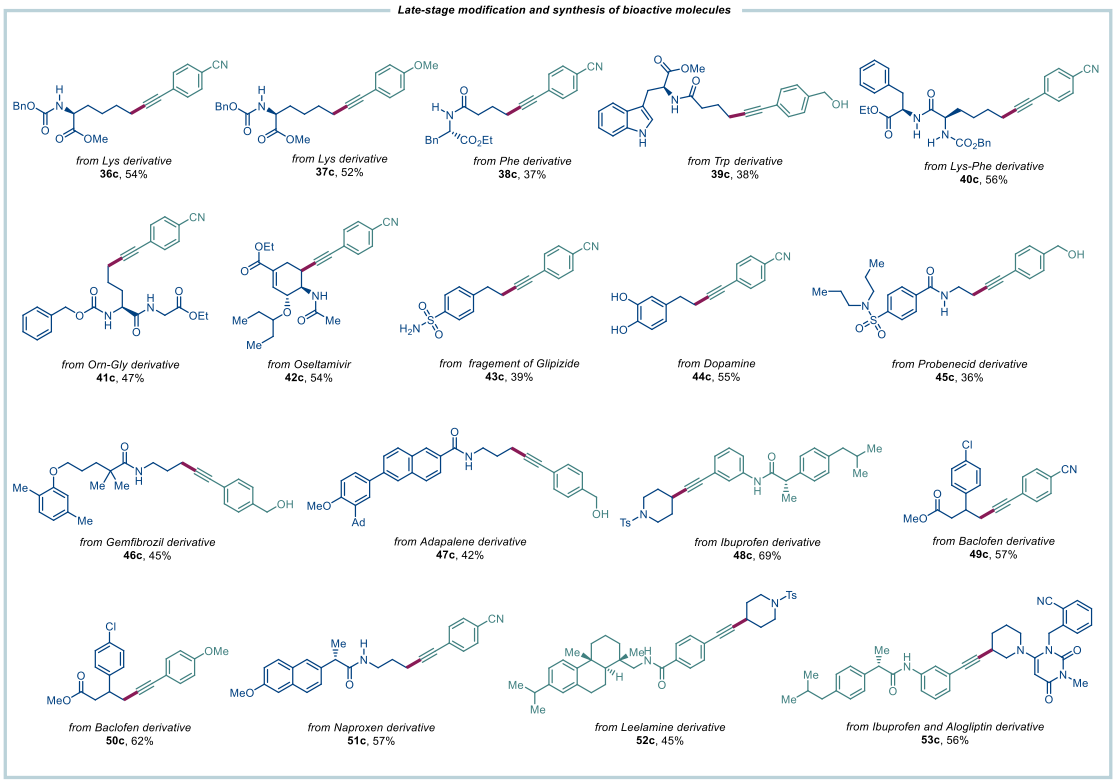


Figure 4. The direct deaminative alkynylation of amino acid derivatives and bioactive molecules.

To further challenge the robustness of the protocol, late-stage modifications of complex and bioactive molecules were performed (Fig. 4). Various amino acids and dipeptides were compatible with the reaction, providing the corresponding alkynylated products (**36c–41c**). A range of pharmaceuticals and their derivatives—including oseltamivir, the glipizide moiety, dopamine, probenecid, gemfibrozil, adapalene, ibuprofen, baclofen, and naproxen—were also successfully converted to the desired products in good yields (**42c–51c**). The natural product leelamine was similarly amenable to this transformation (**52c**). Notably, the alkynyl group can serve as a linker between two different drugs; for example, ibuprofen and alogliptin were coupled to afford the hybrid product **53c** in moderate yield. Collectively, these results demonstrate a practical method for converting aliphatic primary amines—ubiquitous in commercial reagents and bioactive molecules—into alkynyl groups, providing opportunities for the diversification of drug-like chemical libraries.

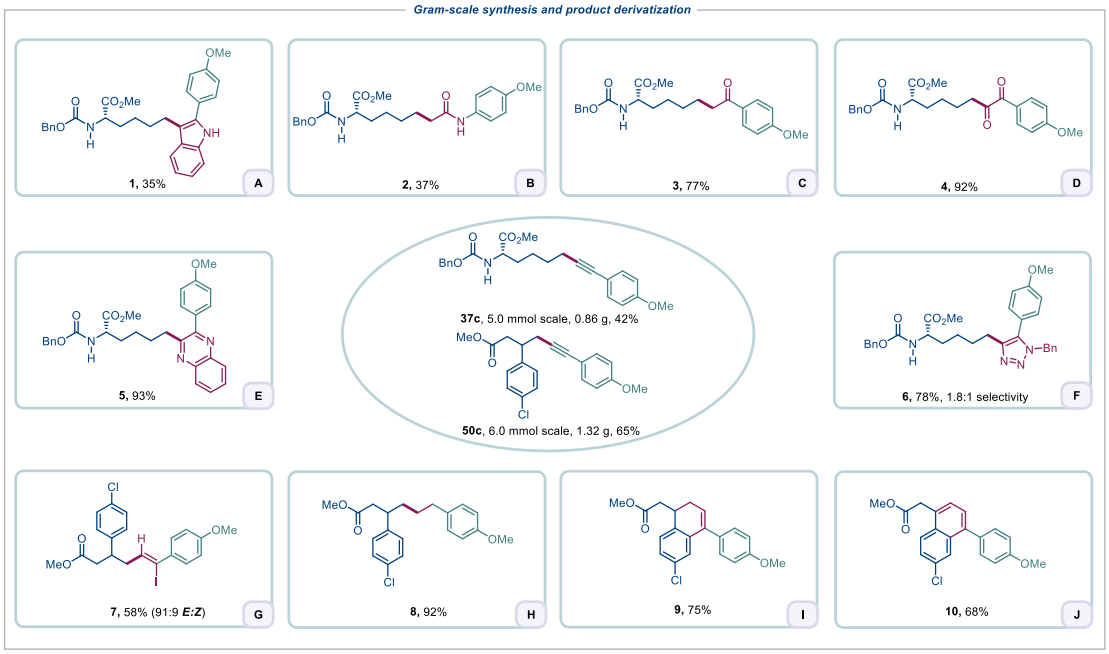


Figure 5. Gram-scale synthesis and product derivatization. All product derivatizations were performed on a 0.2 mmol scale. Conditions: A. 2-Iodoaniline (2.0 equiv), $Pd(OAc)_2$ (10 mol%), PPh_3 (20 mol%), TBAC (1.0 equiv), Na_2CO_3 (5.0 equiv), DMF (0.2 M), 95 °C, 24 h. B. $TMSN_3$ (1.0 equiv), PPh_3AuCl (10 mol%), Ag_2CO_3 (10 mol%), H_2O (2.0 equiv), TFA/DCE (0.2 M), 60 °C, 12 h. C. TfOH (1.2 equiv), DCM (0.05 M), 25 °C, 4 h. D. $RuCl_3$ (1 mol%), PIDA (3.0 equiv), DCM/H_2O, 25 °C, 1 h. E. **4** (1.0 equiv), *o*-phenylenediamine (1.0 equiv), NH_4Cl (0.5 equiv), MeOH (0.1 M), 25 °C, 2 h. F. BnN_3 (1.0 equiv), $CpRu(MeCN)_3PF_6$ (5 mol%), toluene (0.2 M), 110 °C, 48 h. G. $HSiEt_3$ (2.0 equiv), I_2 (2.0 equiv), toluene (1.0 M), 25 °C, 4 h. H. H_2 (1 atm), Pd/C (10 mol%), ^{i}PrOH (0.1 M), 25 °C, 48 h. I. Tf_2O (3.0 equiv), MeCN/toluene (0.1 M), 70 °C, 24 h. J. Tf_2O (3.0 equiv), MeCN/toluene (0.1 M), 70 °C, 24 h, then DDQ (1.1 equiv), THF (0.1 M), 25 °C, 30 min.

Synthetic utility

Given the broad diversity of alkyne conversion chemistry, we next explored the synthetic utility of this method (Fig. 5). Gram-scale synthesis of substrates **37c** and **50c** proceeded smoothly, providing the corresponding products in yields comparable to those obtained on small scale. We then investigated downstream derivatization of the products. Using **37c** as a representative substrate, the classic palladium-catalyzed Larock indole synthesis afforded product **1**[53]; following Jiao's method[54], the alkyne moiety was readily converted into amide **2**; and TfOH-mediated hydration of the alkyne delivered product **3**. Under reported highly selective oxidation conditions, the alkyne was converted into 1,2-diketone **4**[55], which subsequently underwent condensation with *o*-phenylenediamine to construct quinoxaline **5**. In addition, a ruthenium-catalyzed alkyne–azide cycloaddition (RuAAC) provided triazole **6**[56]. Using **50c** as the substrate, trans-hydroiodination via our previously reported method afforded *E*-α-iodostyrene **7**[57], whereas Pd/C-catalyzed hydrogenation cleanly reduced the alkyne to alkane **8**. Notably, treatment of **50c** with Tf_2O induced an intramolecular cyclization to give **9**, and subsequent DDQ oxidation delivered the naphthalene-containing compound **10**.

Mechanism

Based on previous reports[46-47, 50-51], a plausible reaction mechanism is proposed (Fig. 6). As previously established, the amine attacks the anomeric amide **DA1**, generating the isodiazene intermediate **I** in situ. This intermediate undergoes homolysis to produce the alkyl radical **A**, which initiates the radical chain. Radical **A** is then trapped by bromoethyne, forming the vinyl radical **C**. Subsequent β-scission restores the triple bond and releases a bromo radical, which efficiently abstracts a hydrogen atom from isodiazene **I**, thereby regenerating the alkyl radical **A**. The superior performance of bromoethyne compared to other alkynyl sources (**AS2–7**) is likely due to a well-matched hydrogen atom transfer (HAT) rate from the bromo radical; in contrast, direct HAT with radical **A** would lead predominantly to the unproductive hydrodeamination product.

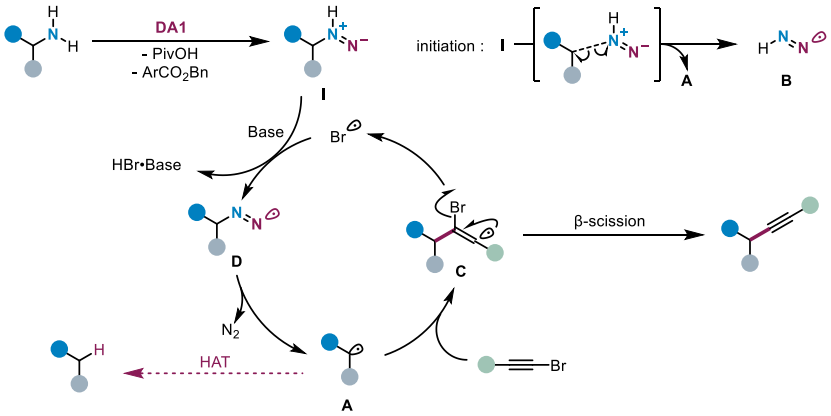


Fig. 6. Mechanistic proposal.

Conclusion

We report a metal-free deaminative alkynylation of aliphatic primary amines using alkynyl bromides, enabling direct C(sp^3)–C(sp) bond formation without prior amine prefunctionalization. This transformation converts abundant amine functionalities into alkyl sources for the synthesis of internal alkynes. The reaction shows broad substrate scope and is applicable to late-stage alkynylation of complex molecules, including drug and natural-product derivatives. This study expands the scope of deaminative C–C bond formation and highlights the synthetic potential of aliphatic amines in alkynylation chemistry.

Methods

General Procedure for direct deamination alkynylation. To a 10 mL vial equipped with a magnetic stir bar was added the **DA1** (0.3 mmol, 1.5 equiv), **b** (0.8 mmol, 4.0 equiv), K_3PO_4 (2.0 equiv) and degassed MeCN (2 mL) in glove box. Then, the primary amine **a** (0.2 mmol, 1.0 equiv) was dissolved in degassed MeCN (2.0 mL), and was added dropwise to the vial over 1 hour using a syringe pump (if the amine is insoluble in MeCN or exists as a hydrochloride salt, the amine is first charged into the vial, followed by the addition of the **DA1** dissolved in MeCN.). After the addition finished, stir for another 3 hours and monitor the reaction with TLC. After the amine a is completely consumed, the solvent was removed under reduced pressure. The residue was dilute with water (5 mL) and extracted with EtOAc (5 mL) for three times. The organic layer was dried over with Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel with a gradient eluent of PE and EtOAc to afford the desired products.

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Acknowledgements

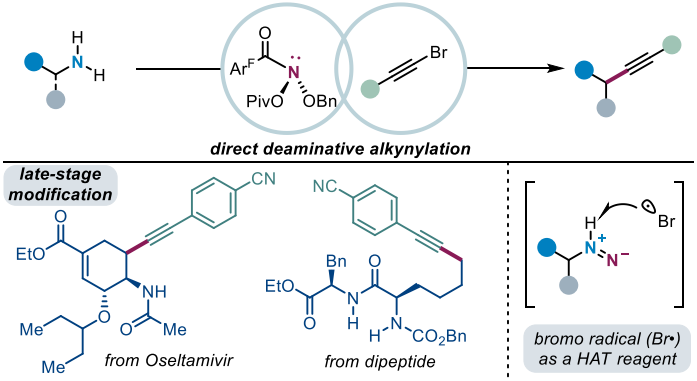
This work was supported by Noncommunicable Chronic Diseases-National Science and Technology Major Project (2023ZD0507600), the National Natural Science Foundation of China (22371311 and 22571328), Guangzhou Municipal Science and Technology Project (2025A04J7101), and the GBRCE for Functional Molecular Engineering.

Author contributions

H. W. conceived the project. J.-L. F. conducted reaction optimization and contributed to the substrate scope and analysis of the data. J.-Y. W., Q. F., J.-H. X. contributed to the substrate synthesis and product derivatizations. H. W., J.-L. F., and Q. L. wrote the paper. All authors contributed to discussions.

Competing interests

The authors declare no competing interests.



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