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Rapid access to azetidines *via* allylation of azabicyclo[1.1.0]butanes by dual copper/photoredox catalysis†

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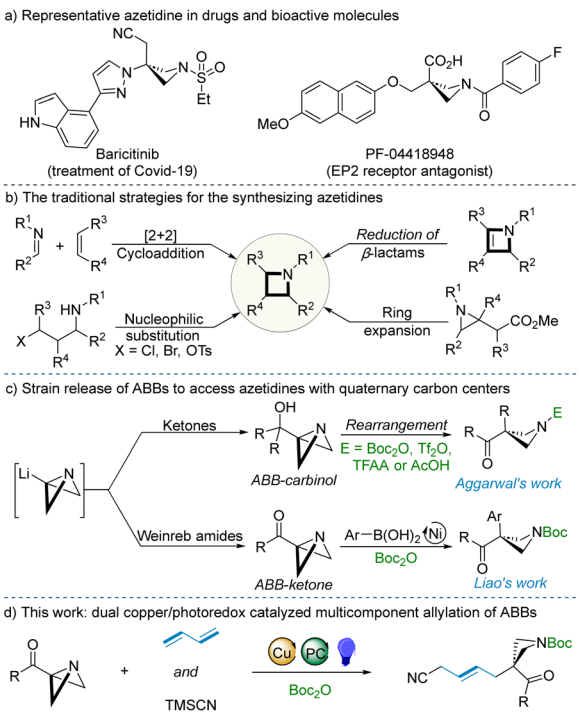
Recently, the strain-release-driven synthesis of N_1/C_3 functionalized azetidines from azabicyclo[1.1.0]butanes has generated significant interest in the fields of medicinal and synthetic chemistry. This paper presents a mild and efficient dual copper/photoredox-catalyzed multi-component allylation of azabicyclo[1.1.0]butanes using a radical-relay strategy. This strategy enables the synthesis of C3 quaternary center-containing azetidines *via* a radical relay mechanism with a high yield of 91%. The method's utility is highlighted by late-stage derivatization of bioactive molecules, demonstrating exceptional functional group compatibility.

Azetidines are a significant class of aza-heterocyclic compounds known for their intrinsic rigidity. This characteristic has attracted considerable attention in the synthesis of pharmaceutical molecules. The incorporation of azetidine moieties into active molecules and relevant scaffolds has the potential to enhance bioavailability and metabolic stability.[1] In particular, azetidines with a quaternary carbon center have been recognized as a critical structural element in many important therapeutic agents (Scheme 1a).[2–5] Additionally, the inherent structural rigidity of azetidines enhances their pharmacokinetic properties while avoiding chirality, thereby simplifying synthesis. However, the challenging synthetic accessibility of functionalized azetidines has restricted their broader application in medicinal chemistry. Consequently, the development of efficient, diversity-oriented strategies is urgently needed to expand the scope of azetidine compounds in drug discovery. In addition to the [2+2] cycloaddition between alkenes and imines or isocyanates, the nucleophilic substitution cyclization of linear alkylamines, reduction of β-lactams, and ring expansion of aziridines are important approaches for synthesizing azetidine scaffolds (Scheme 1b).[6,7] While most studies have concentrated on heteroatom substitution, the synthesis of azetidines with a C_3 all-carbon quaternary center remains underdeveloped.[8,9]

Azabicyclobutane (ABB), a versatile intermediate, has the potential to be a useful substrate for the preparation of azetidines (Scheme 1c).[10] Aggarwal and colleagues synthesized ABB-



Scheme 1 (a) Representative molecules containing azetidines with a quaternary carbon center; (b) previous synthesis of azetidines; (c) strain-release strategies of ABBs for synthesizing azetidines with quaternary carbon centers; (d) multi-component allylation of azabicyclo[1.1.0]butanes.

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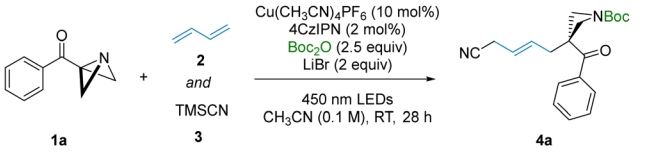
carbinol by adding 3-lithium ABBs (ABB-Li) to ketones, which then enabled the formation of azetidines with C_3 quaternary carbon centers.[11] Liao's group demonstrated a nickel-catalyzed Suzuki cross-coupling reaction of ABBs with arylboronic acids to synthesize 3,3-dicarbofunctionalized azetidines.[12] While significant progress has been made, further investigation is still required to explore the construction of diverse azetidines through the strain-release functionalization of ABBs.

In recent years, copper-catalyzed cyanidation has emerged as a compelling technique in cyanide synthesis and has evolved into an effective strategy.[13] One particularly appealing area involves the copper-catalyzed selective radical cyanidation of conjugated dienes.[13,14] Researchers such as Chen, Xiao, and Zhu have made significant contributions to this field.[15] Building upon these accomplishments, in this work, we introduce a mild and efficient dual copper/photoredox-catalyzed, multicomponent radical coupling of ABBs, 1,3-butadiene, and TMSCN. This method allows for the rapid synthesis of azetidine scaffolds with an allyl group and C_3 quaternary carbon centers (Scheme 1d).

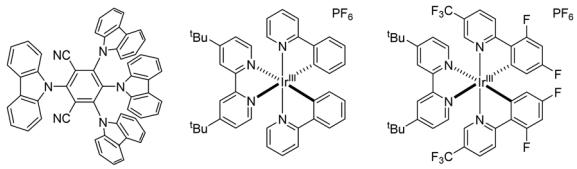
The benzoyl ABB **1a**, 1,3-butadiene **2** (0.2 M in tetrahydrofuran), and TMSCN **3** were selected as the starting materials. After a thorough exploration of various reaction conditions, we identified the optimal conditions: $Cu(CH_3CN)_4PF_6$ (10 mol%), 4CzIPN (2 mol%), Boc_2O (2.5 equiv.), and LiBr (2 equiv.) in acetonitrile (0.1 M) at room temperature. The resulting mixture was exposed to a 450 nm LED lamp for 28 hours, resulting in a product **4a** yield of 82% (Table 1, entry 1). Similar reaction performance was observed with other photocatalysts, such as $Ir(ppy)_2(dtbbpy)PF_6$ **Ir-1** and $Ir[dF(CF_3)ppy_2](dtbbpy)PF_6$ **Ir-2** (entries 2 and 3, 77% and 80% yields). The choice of copper salts did not appear to have a significant impact on the reaction outcomes (entries 4 and 5). Replacing acetonitrile with THF or DCM as the reaction solvent led to decreased yields (entries 6 and 7). Identifying the halide anion as a crucial component, subsequent screening of halides showed that LiCl produced **4a** in 71% yield (entry 8), while KI yielded only 38% (entry 9). Control experiments indicated that the reaction proceeded even in the absence of a copper salt, yielding the target product **4a** in 15% yield. This result may be attributed to the nucleophilic addition of the cyano anion to the allyl cation (entry 10).[16] Furthermore, a yield of 31% was observed in the absence of LiBr, indicating that ABB-Boc adducts could also directly undergo single-electron transfer with photocatalysts (entry 11). However, each of the photocatalysts and visible light were essential for optimal efficiency of azetidine formation (entries 12 and 13).

After establishing the optimal reaction conditions, the scope of the transformation was then evaluated. Aromatic and aliphatic substituted ABBs proved to be effective coupling substrates with 1,3-butadiene and TMSCN, yielding all-carbon quaternary center azetidines in good yields, as shown in Scheme 2. In the initial stage, a wide range of functionalized aromatic substituted ABBs were examined. Substrates with both electron-deficient groups (**4b**, **4f**, **4h**, **4i**) and electron-rich groups such as OMe-, *t*Bu-, Me- (**4c**, **4d**, **4e**, **4g**, and **4j**) at

Table 1 Optimization of the reaction conditions[abc]

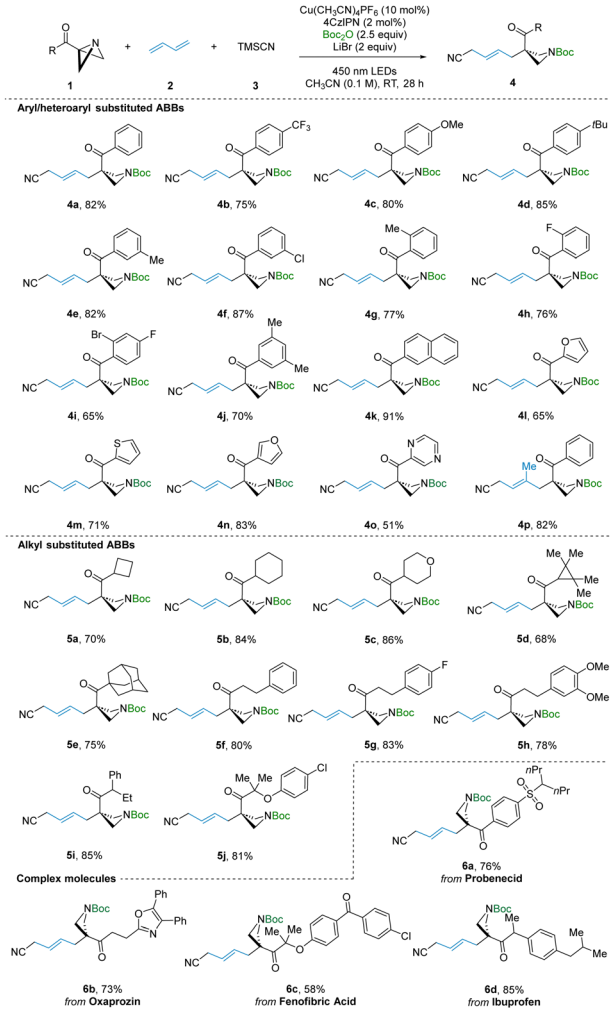


Entry	Variation from standard conditions	Yield/%
1	None	84 (82)[c]
2	**Ir-1** instead of 4CzIPN	77
3	**Ir-2** instead of 4CzIPN	80
4	CuCl instead of $Cu(CH_3CN)_4PF_6$	74
5	CuCN instead of $Cu(CH_3CN)_4PF_6$	79
6	THF instead of CH_3CN	57
7	DCM instead of CH_3CN	64
8	LiCl instead of LiBr	71
9	KI instead of LiBr	38
10	No $Cu(CH_3CN)_4PF_6$	15
11	No LiBr	31
12	No 4CzIPN	<5
13	No light	0



[a] Reaction scale: **1a** (0.2 mmol, 1 equiv.), **2** (0.4 mmol, 2 equiv.), **3** (0.3 mmol, 1.5 equiv.). [b] Yields were determined by ^1H NMR spectroscopy *vs.* an internal standard (1,2,3-trimethoxybenzene). [c] Isolated yield.

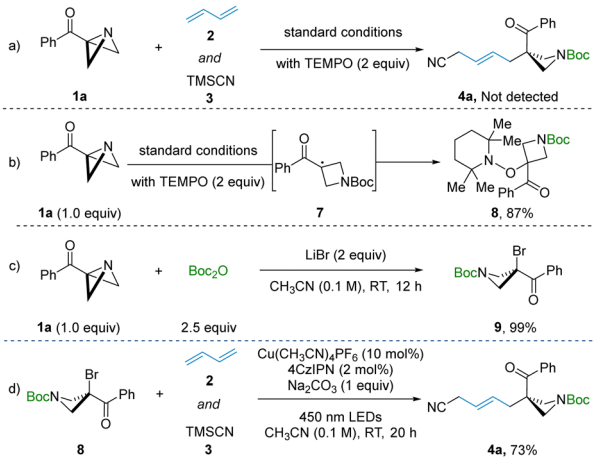
the *para*-, *meta*-, or *ortho*-positions were accommodated well, resulting in comparable yields of azetidines. The naphthyl-substituted ABB proved to be a suitable partner and yielded product **4k** in a 91% yield. Furthermore, a series of heteroaromatic-substituted ABBs were screened under the same conditions. To our delight, substrates of ABBs containing oxygen, sulfur, and nitrogen atoms were also well tolerated, resulting in the desired products with yields ranging from 51% to 83% (**4l–4o**). Moreover, isoprene was also compatible with this reaction system, affording the corresponding product in 54% yield (**4p**). Subsequently, various aliphatic ABBs were also investigated, demonstrating that cyclobutane **5a**, cyclohexane **5b**, and tetrahydropyran **5c** substituted ABBs were competent coupling partners, delivering azetidine products in excellent yields. Both ABBs with steric hindrance, such as 2,2,3,3-tetramethylcyclopropane and adamantane groups, were successfully synthesized, yielding **5d** and **5e** in 68% and 75% yields. Phenylpropyl substrates such as **5f–5h** proceeded smoothly, with the substituents on the benzene ring having no effect on the high yields. Moreover, the reaction also provided excellent yields when α-branched ketones **5i** and **5j** were used. To further demonstrate the potential applicability of the current methodology, late-stage functionalization of biologically active compounds and drug derivatives was conducted. Various structurally complex ABBs derived from natural products and pharmaceutical agents, including probenecid **6a**, oxaprozin **6b**, fenofibric acid **6c**, and ibuprofen **6d** were



Scheme 2 Scope of reaction.[a,b] [a] Reaction conditions: **1** (0.2 mmol, 1 equiv.), **2** (2.0 equiv.), **3** (1.5 equiv.). [b] Isolated yield.

examined. All compounds proceeded smoothly under optimal conditions, achieving the corresponding azetidines with good yields. Overall, the current dual copper/photoredox catalysis protocol results in a robust and versatile strategy for the synthesis of azetidines with all-carbon quaternary centers.

The mechanism of this dual copper/photoredox catalysis coupling was investigated through a series of experiments (Scheme 3). A radical trapping experiment was conducted. The addition of the scavenger 2,2,6,6-tetramethylpiperidinooxy (TEMPO) under standard conditions completely inhibited the formation of azetidine **4a** (Scheme 3a). Interestingly, when ABB **1a** reacted without 1,3-butadiene and TMSCN, the radical-trapping adduct **8** was obtained in 87% yield (Scheme 3b). This result supports the involvement of radical **7** in this multicomponent coupling reaction. We observed that ABB **1a** readily underwent a transformation to form 3-brominated azetidine **9** through an SN_2-type process with bromide under the activation of Boc_2O (Scheme 3c).[12,17] To further confirm the presence of compound **9**, we utilized it as a reactant to replace ABB **1a** and the target product **4a** was

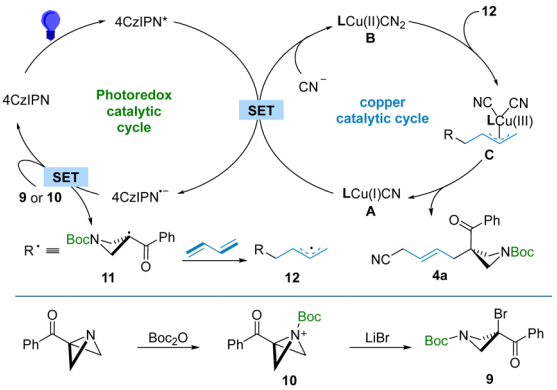


Scheme 3 Mechanism investigations.

successfully obtained with a significant yield (Scheme 3d). Stern–Volmer experiments revealed that $Cu(CH_3CN)_4PF_6$, ABB-Boc_2O adduct, and 3-brominated azetidine **9** all could quench the fluorescence of 4CzIPN (see ESI† for details, Fig. S2–S4).

Based on these results from previous reports,[12,18] we propose a catalytic cycle mechanism as shown in Scheme 4. Initially, the 4CzIPN photocatalyst is converted to a photoexcited 4CzIPN* under light irradiation. Subsequently, a single-electron transfer (SET) between the 4CzIPN* and the **L**Cu(I)CN **A** results in the formation of the radical anion $4CzIPN^{\bullet-}$ ($E_{1/2}[4CzIPN^*/4CzIPN^{\bullet-}]$ = +1.43 V *vs.* SCE) species and **L**Cu(II)CN_2 **B** intermediate.[18] The $4CzIPN^{\bullet-}$ species ($E_{1/2}[4CzIPN^{\bullet-}/4CzIPN]$ = −1.24 V *vs.* SCE) is oxidized by 3-brominated azetidine **9** (E_{red} = −1.54 V) or ABB-Boc_2O adduct **10** (E_{red} = −2.39 V) *via* SET to produce a radical species **11**.[12,18] Then radical species **11** undergoes intermolecular radical addition with the 1,3-butadiene and produces the allyl radicals species **12** that is readily captured by **L**Cu(II)CN_2 **B** to generate the key π-allylcopper **C** intermediates. Finally, the desired azetidine **4a** is obtained through an intramolecular *in situ* reductive elimination of π-allylcopper, and the **L**Cu(I) catalyst is regenerated for the next catalytic cycle.

In summary, we have developed a robust synthetic strategy for the photocatalytic tandem and elaborate reaction of ABBs to



Scheme 4 Proposed catalytic mechanism.

access allyl azetidines with all-carbon quaternary centers through dual copper and photoredox catalysis. The mildness of this strategy allows for the one-pot coupling of various ABBs with easily available 1,3-butadiene, TMSCN and Boc_2O. The significance of this approach is highlighted by its stability and broad functional group tolerance in late-stage drug molecular derivatization. The success of the reaction relies on the generation of 3-brominated azetidine and subsequent allylcopper complexes based on the ring strain-release strategy of ABBs. Altogether, given the significant value of azetidine scaffolds in pharmaceutical chemistry, we believe that this protocol will have the potential to be applied in both industrial and academic fields.

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Data availability

The data underlying this study are available in the published article and its ESI.†

Conflicts of interest

There are no conflicts to declare.

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