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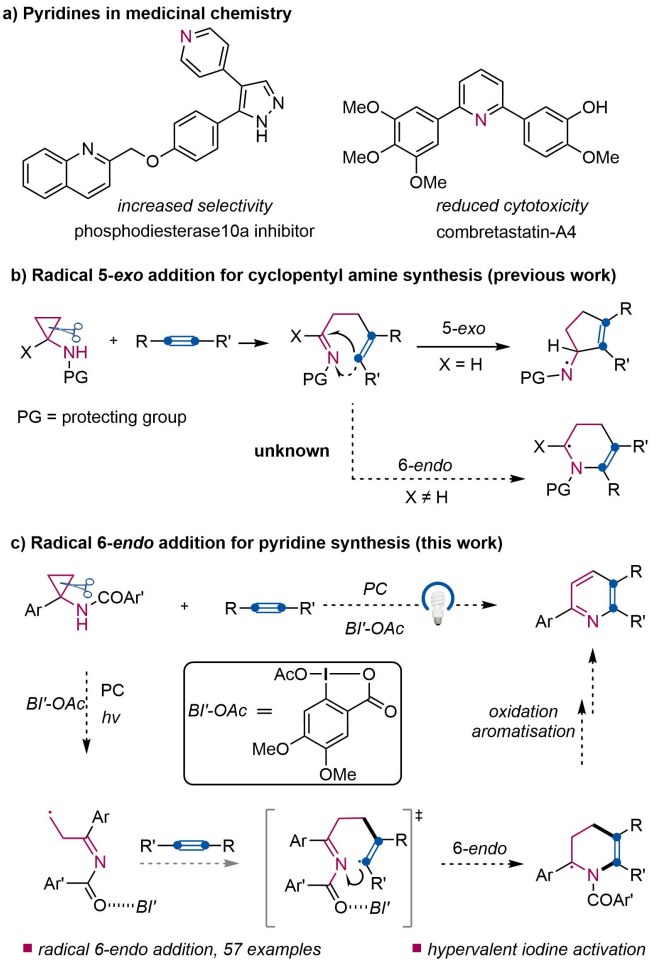
Hetereocyclic Chemistry

Radical 6-*Endo* Addition Enables Pyridine Synthesis under Metal-Free Conditions

Xiaojuan Dong[+], Yingbo Shao[+], Zhengyi Liu, Xia Huang, Xiao-Song Xue, and Yiyun Chen**

Abstract: Metal-free synthesis of heterocycles is highly sought after in the pharmaceutical industry and has garnered widespread attention due to eliminating the need to remove trace metal catalysts from the reaction. We report a radical 6-*endo* addition method for pyridine synthesis from cyclopropylamides and alkynes under metal-free conditions. Various terminal and substituted alkynes are inserted as C2 units into cyclopropylamides to synthesize versatile pyridines with 57 examples. Mechanistic investigations and computational studies indicate the unprecedented 6-*endo-trig* addition of vinyl radicals to the imine nitrogen atom rather than the conventional 5-*exo-trig* addition to the imine carbon atom, in which the hypervalent iodine(III) plays a critical role. This reaction easily scales up with excellent functional group compatibility and suits the late-stage pyridine installation on complex molecules.

Pyridine structure is one of the most frequently utilized heterocyclic pharmacophores in FDA-approved pharmaceuticals, and the pyridine installation improves their biological activity significantly.[1] Developing efficient methods for pyridine synthesis is highly sought after in the pharmaceutical industry and has garnered widespread attention (Scheme 1a).[2] Among various pyridine synthesis methods,[3] the catalytic systems that utilize cost-effective metals or operate entirely without metals are increasingly in high demand.[4] Traditional Chichibabin reactions and Bohlmann-Rahtz reactions operate under metal-free conditions, eliminating the need to remove trace metal catalysts from the reaction.[4a,5] The skeletal and molecular editing strategy has recently gained prominence due to the advantages of selectively inserting or deleting atoms in a given ring



Scheme 1. Radical 6-*endo* addition for pyridine synthesis.

[*] X. Dong,[+] X. Huang
Central China Normal University, 152 Luoyu Road, Wuhan, Hubei 430079, China

X. Dong,[+] Z. Liu, X. Huang, Y. Chen
State Key Laboratory of Bioorganic and Natural Products Chemistry, Shanghai Institute of Organic Chemistry, University of Chinese Academy of Sciences, Chinese Academy of Sciences
345 Lingling Road, Shanghai 200032 China
E-mail: yiyunchen@sioc.ac.cn

Y. Chen
School of Physical Science and Technology, Shanghai Tech University, 100 Haike Road, Shanghai 201210 China

X.-S. Xue, Y. Chen
School of Chemistry and Material Sciences, Hangzhou Institute for Advanced Study, University of Chinese Academy of Sciences, 1 Sublane Xiangshan, Hangzhou 310024, China
E-mail: xuexs@sioc.ac.cn

Y. Shao[+]
College of Chemistry, Nankai University, Tianjin 300071, China

X.-S. Xue
Key Laboratory of Fluorine and Nitrogen Chemistry and Advanced Materials, Shanghai Institute of Organic Chemistry, University of Chinese Academy of Sciences, Chinese Academy of Sciences, 345 Lingling Road, Shanghai 200032, China

[+] These authors contributed equally.

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structure.[6] In contrast to current metal-free pyridine synthesis methods with two-electron processes,[7] the single-electron strategy by radical cycloadditions is elusive, which may offer a unique opportunity to synthesize pyridines with distinct advantages in chemoselectivity and functional group compatibility.

Cyclopropylamines have the inherent ring strain enabling the efficient synthesis of a diverse array of nitrogen-containing compounds.[8] Recent advancements in photoredox catalysis have enabled the insertion of alkynes or alkenes into cyclopropylamines (where X = H) for cyclopentyl amine synthesis through a radical addition pathway (Scheme 1b).[9] The radical-initiated ring-opening of cyclopropylamines forms an alkyl radical tethered to a terminal imine, which may incorporate alkynes for further transformations. Traditionally, a preferential 5-*exo*-*trig* addition of the vinyl radical to the carbon atom of the terminal imine predominately formed the cyclopentyl amines.[10] In contrast, the 6-*endo*-*trig* addition for pyridine synthesis has not been reported. We hypothesize that substituted cyclopropylamines (where X ≠ H) may enable the 6-*endo*-*trig* addition to the nitrogen atom of imines.[11] Herein, we present the inaugural study for pyridine synthesis by an unconventional radical 6-*endo*-trig addition, in which the hypervalent iodine(III) reagent is critical for the transformation (Scheme 1c).

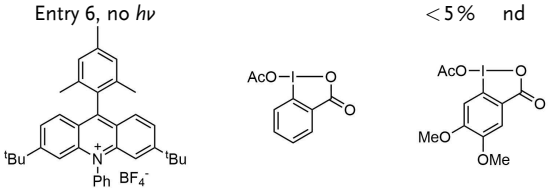
We commenced the preliminary investigation by examining aryl-substituted *N*-cyclopropylamides **1a**, easily prepared from arylnitriles.[12] The hypothetical ring-opening of **1a** was expected to yield an alkyl radical tethered to aryl-substituted imines, whose reactivity has not been explored before. With Ph-Acr-MesBF$_4$ (E^*_{red} = +2.10 V vs SCE in MeCN) as the photocatalyst,[13] *N*-cyclopropylamides **1a** and alkyne **1b** reacted to obtain a 40 % yield of **1** with acetoxylbenziodoxole (BI-OAc) as the additive (entry 1 in Table 1).[14] Photocatalysts exhibiting lower oxidation potentials such as [Ru(bpy)$_3$](PF$_6$)$_2$ (E^*_{red} = +0.77 V vs SCE in MeCN)[15] and Ir[*d*F(CF$_3$)ppy]$_2$(5,5'-*d*CF$_3$bpy)(PF$_6$) (E^*_{red} = +1.68 V vs SCE in MeCN)[16] failed to convert **1a** (entries 2–3). The electron-rich hypervalent iodine reagent (HIR) dimethoxy substituted acetoxylbenziodoxole (BI'OAc), namely 3,4-MeO-BI-OAc, produced **1** with an enhanced yield of 63 %, whereas the non-cyclic phenyliodine(III) diacetate (PIDA) failed to yield **1** (entries 4–5). The incorporation of acetic acid into this reaction delivered an optimal yield of 77 % of **1** (73 % isolated yield, entry 6), highlighting that acidic conditions favorably influence the reaction. Light irradiation and photocatalysts were essential for the reaction (entries 7–8, see Tables S4–S9 for detailed optimizations).

After establishing the optimal reaction conditions, the cyclopropylamide scope was explored (Scheme 2). The aryl-substituted cyclopropylamides **2a**–**4a** that possess electron-donating methyl or methoxyl groups afforded pyridine derivatives **2**–**4** smoothly in 61–70 % yields. Aryl-substituted *N*-cyclopropylamides with electron-withdrawing groups such as esters, trifluoromethyls, and trifluoromethoxyls reacted well with **1b** to give desired pyridines **5**–**8** in 59–65 % yields. The cyclopropylamides **9a**–**10a** reacted well to afford 60–61 % yields of **9**–**10** without over-oxidation on the highly electron-rich dimethoxyl-arenes.[17] The *para*, *meta*, and

Table 1: Reaction optimization.



Entry	Conditions[a]	Conv.[b]	Yield of **1**[b]
1	Acr-Mes-Ph$^+$BF$_4^-$, BI-OAc	89 %	40 %
2	Ru(bpy)$_3$(PF$_6$)$_2$, BI-OAc	< 5 %	nd
3	Ir[*d*F(CF$_3$)ppy]$_2$(5,5'*d*CF$_3$bpy)(PF$_6$), BI-OAc	< 5 %	nd
4	Entry 6, no AcOH	99 %	63 %
5	Acr-Mes-Ph$^+$BF$_4^-$, PIDA	14 %	trace
6	Acr-Mes-Ph$^+$BF$_4^-$, 3,4-MeO-BI-OAc	99 %	77(73)%
7	Entry 6, no photocatalyst	< 5 %	nd
8	Entry 6, no *hν*	< 5 %	nd



Ph-Acr-Mes$^+$BF$_4^-$ BI-OAc 3,4-MeO-BI-OAc = BI'-OAc

[a] Reaction conditions: **1a** (0.1 mmol), **1b** (0.2 mmol), photocatalyst (0.002 mmol), HIR (0.2 mmol), and AcOH (0.4 mmol) in 1.0 mL toluene under nitrogen with 20 W 456 nm blue LED (5 cm away from the vial) irradiation at r.t. for 12 h, unless otherwise noted. [b] Yields were determined by ^{1}H NMR analysis, and isolated yields were in parentheses.

ortho-substitutions on cyclopropylamides **11a**–**14a** were compatible to afford 50–66 % yields of **11**–**14**. This reaction was easily scaled up to 4 mmol to afford the unsymmetric 2,6-disubstituted pyridine **11** in 64 % yield in 0.83 g. The cyclopropylamides **15a**–**16a** with fused naphthalenes and heterocyclic thiophenes also reacted to give **15**–**16** in 35–59 % yields.

The scope of alkynes was next examined (Scheme 3). Alkynes **17b**–**22b** substituted with fluoro, chloro, or bromo groups at different aryl positions were all tolerated in the reaction to afford **17**–**22** in 56–63 % yields. The strongly electron-withdrawing trifluorosulfonyl, cyano, trifluoromethyl, and nitro groups on arenes were compatible to afford **23**–**26** in 46–62 % yields. The electron-rich phenyl, *t*-butyl, and methoxy groups on arenes did not affect the reaction to give 42–60 % yields of **27**–**31**. It is worth noting that cyclopropylamides **32a**–**37a** with different electronic properties consistently afforded good yields of pyridines **32**–**37** in 51–66 % yields, which is challenging for other cycloaddition reactions.[18] The *ortho*-methyl substitution in **38a** afforded 49 % of pyridine **38**, while the 4-methoxyl benzamide was observed in 16 % yield (see Scheme S2 for details). The aldehyde in **39a** was tolerated to give **39** in 55 % yield.[17b,19] The naphthalene at *α*- or *β*-substitutions gave consistently 59 % yields of **40**–**41**.

The reaction of heterocycle-conjugated alkynes (**42b**–**45b**) afforded diverse 2-substituted pyridine derivatives, including 2,2'-bipyridine (**42**), thiophenylpyridine (**43**), 2-(6-(4-chlorophenyl)pyridin-2-yl)quinoline (**44**), and benzothiophenylpyridine (**45**), in good yields (41–51 %). This reaction was not limited to terminal alkynes. Aryl-substituted

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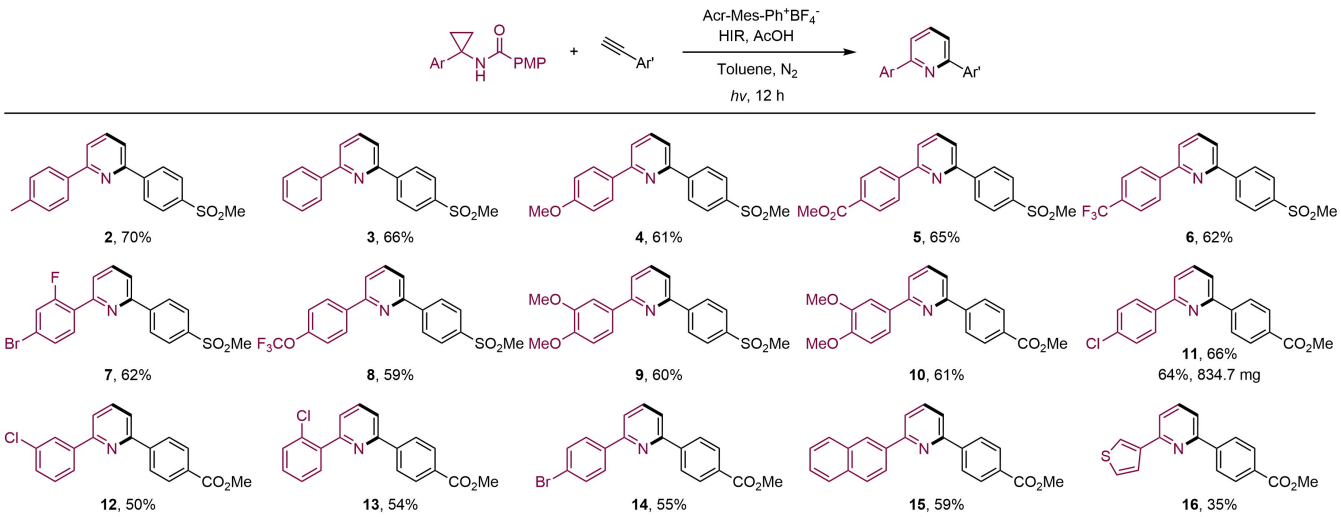

Scheme 2. Scope of cyclopropylamides. [a] Reaction conditions: cyclopropylamides (0.1 mmol), alkynes (0.2 mmol), Acr-Mes-Ph$^+$BF$_4^-$ (0.002 mmol), HIR = 3,4-MeO-BI-OAc (0.2 mmol), AcOH (0.4 mmol) in 1.0 mL toluene under nitrogen with 20 W 456 nm blue LED (5 cm away from the vial) irradiation at r.t. for 12 h, isolated yields.

alkynoates **46b**–**47b** reacted with excellent regioselectivity to afford 2,3,6-trisubstituted pyridines (**46**–**47**) in high yields (54–60 %). The structure of **47** was confirmed by X-ray crystallography,[20] which revealed 2-aryl substitution on the pyridine ring, further supporting the excellent regioselectivity of the radical 6-*endo* addition observed in this reaction.[18,21] Using a non-aryl alkyne substrate **48b** led to the preferential formation of the 2-ester substituted pyridine **48**, but with a lower yield (35 %). The reaction was also applicable for diynes **49b**–**50b** to afford 2,6-disubstitued and 2,5,6-trisubstituted **49**–**50** in 42–46 % yields. The reaction with an alkyl-substituted alkyne (**51b**) resulted in a lower yield (30 %) of the cyclopropyl-substituted pyridine **51**. This decrease in yield is likely attributed to the absence of an aryl group, which typically stabilizes the vinyl radical intermediate in this reaction.

We next conducted a series of mechanistic investigations to probe the reaction mechanism (Scheme 4). The addition of (2,2,6,6-tetramethylpiperidin-1-yl)oxyl (TEMPO) to the standard reaction conditions of cyclopropylamides **1a** and alkynes **1b** completely inhibited the formation of pyridine **1**, while the ring-opening TEMPO-addition imine product **52** was detected by HRMS (Scheme 4a). When dibutylhydroxytoluene (BHT) was subjected to the reaction of **1a** and **1b**, the BHT-trapped ketone product **53** was isolated in 41 % yield resulting from the hydrolysis of the imine intermediate, together with the hydrolysis adduct 4-methoxylbenzamide **54** in 38 % yield. Concurrently, the pyridine product **1** was not observed. When the reaction was carried out in deuterated chloroform ($CDCl_3$), the deuterium abstraction adduct **55** from the alkyl radical was detected in 10 % yield and the pyridine product **1** was obtained in 50 % yield. In contrast, the analysis of the standard reaction mixture between **1a** and **1b** indicated pyridine **1** and 4-methoxylbenzoic acid **56** in 73 % and 64 % yields, respectively, whereas the 4-methoxylbenzamide **54** was not observed (Scheme 4b).[22] These experimental investigations suggested that the radical cyclopropyl ring-opening yielded the critical aryl imine-tethered alkyl radical intermediate.

To further assess the fate of the aryl imine-tethered alkyl radical intermediate, we performed deuterium labeling experiments (Scheme 4c). Using **1a**–***d*** with full deuterium incorporation at the cyclopropyl ring, we found the deuterium retention (>99 % D) at the 3-, and 4-position of pyridine product **1-*d***. This result suggested the aryl imine-tethered alkyl radical did not isomerize to the enamine radical intermediate, which may lose the deuterium incorporation in the pyridine product. We further tested alkyne **11b-*d*** with deuterium incorporation at the terminal alkyne, and the complete deuterium retention (>99 % D) at the 5-position at pyridine **11-*d*** was observed. This result suggested that after the 6-membered ring formation, the isomerization did not occur to lose the deuterium during the elimination. We further subjected *N*-methyl cyclopropylamide **1a-Me** to the reaction conditions and found no conversion, which suggested free N–H was critical for the reaction (Scheme S1). In the fluorescence quenching experiment, we observed the quenching from 3,4-MeO-BI-OAc instead of cyclopropylamides **1a** (Figure S6). This observation was consistent with the oxidation potential (E_{ox} = 1.84 V) and reduction potential (E_{red} = −0.47 V) of 3,4-MeO-BI-OAc, which fall within the range of the excited Acr′s oxidation-reduction potentials ($E_{1/2}$ (Acr$^+$*/Acr) = 2.10 V, $E_{1/2}$ (Acr$^+$/Acr) = −0.56 V) (Figure S5).

To understand the unconventional radical 6-*endo-trig* addition rather than the well-explored radical 5-*exo-trig* addition,[9d,10a] we performed detailed DFT calculations using SMD[23](Toluene)/B3LYP-D3(BJ) /def2-TZVPP//B3LYP[24]-D3(BJ)[25]/def2-SVP[26] (Scheme 5a). These calculations revealed a significant difference in the two reaction pathways: In the case of 5-*exo* addition, the activation energy was 8.9 kcal/mol for the forward reaction and 7.2 kcal/mol for

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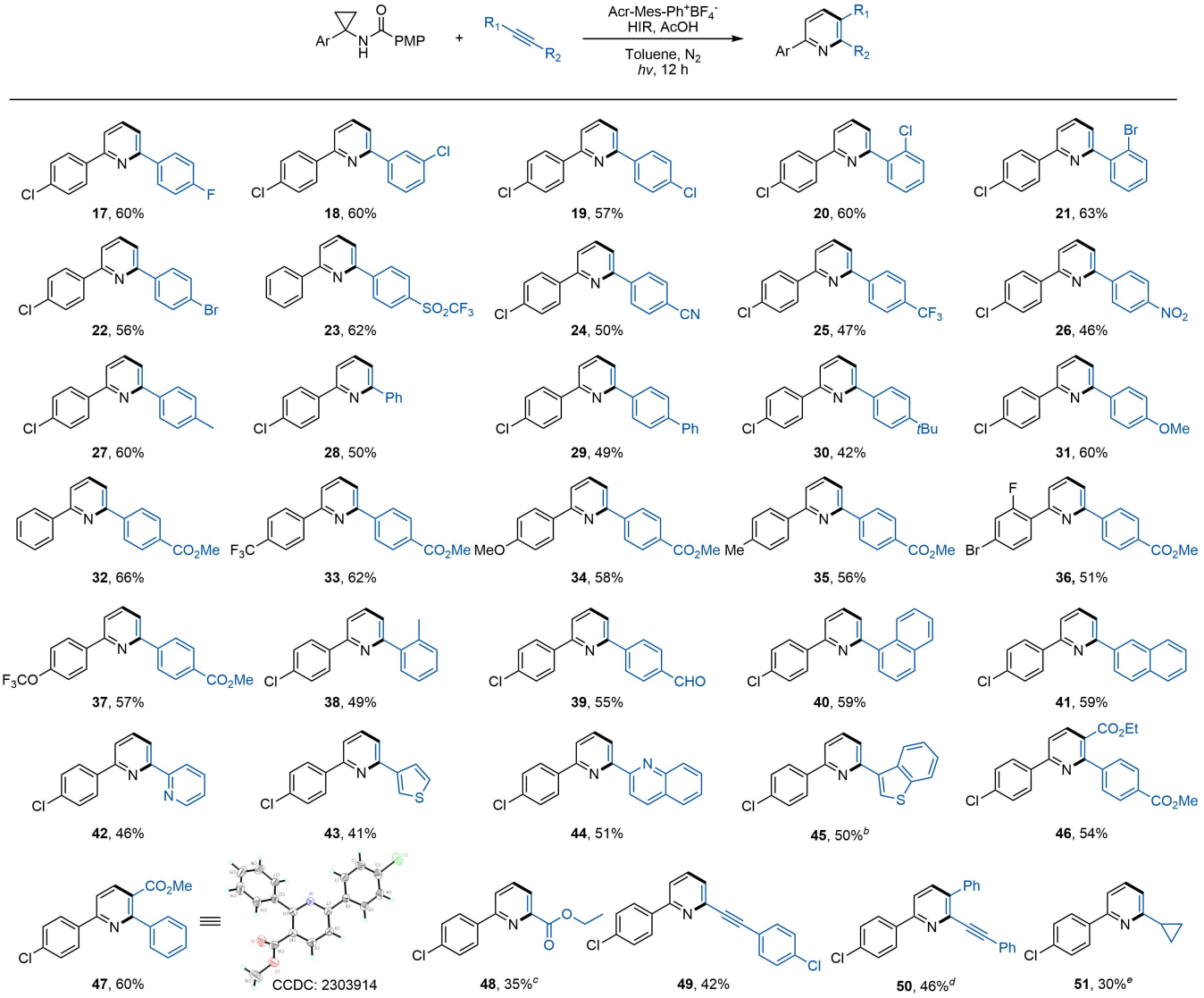

Scheme 3. Substrate scope of alkynes. [a] cyclopropylamides (0.1 mmol), alkynes (0.2 mmol), Acr-Mes-Ph$^+$BF$_4^-$ (0.002 mmol), HIR = 3,4-MeO-BI-OAc (0.2 mmol), AcOH (0.4 mmol) in 1.0 mL toluene under nitrogen with 20 W 456 nm blue LED (5 cm away from the vial) irradiation at r.t. for 12 h, isolated yields. [b] 40 W Kessil 456 nm. [c] alkynes (0.4 mmol). [d] 3,4-MeO-BI-OMe instead of 3,4-MeO-BI-OAc. [e] alkynes (0.6 mmol), 10 W Kessil 456 nm

the reverse reaction, suggesting a thermodynamically controlled pathway. Conversely, 6-*endo* addition has a 9.1 kcal/mol barrier for the forward reaction but a much higher 24.8 kcal/mol barrier for the reverse reaction, indicating a kinetically controlled pathway. Furthermore, charge density analysis suggests that the coordination of hypervalent iodine to the protected imine increases the electron density on the imine carbon atom, but not on the imine nitrogen atom (Scheme 5b). This, combined with the high *s*-orbital character of the vinyl radical,[21b] hinders the 5-*exo* addition.

Following the experimental and computational investigations above, we propose a plausible reaction mechanism (Scheme 5c). The visible light irradiation on Acr$^+$ afforded the excited-state Acr^{+}* formation, which oxidized hypervalent iodine(III) 3,4-MeO-BI-OAc (BI'-OAc) to afford the BI'-OAc$^{+\bullet}$ radical cation. The BI'-OAc$^{+\bullet}$ further oxidized cyclopropylamide **I** to its radical cation **II**.[27] The cyclopropyl ring-opening of the radical cation **II** led to an alkyl radical tethered to aryl imine **III**. The alkyl radical **III** then adds to alkyne **IV** to yield the vinyl radical **V**. Facilitated by the hypervalent iodine BI'-OAc coordination, the vinyl radical **V** underwent 6-*endo-trig* addition to the aryl imine nitrogen to yield the pyridine skeleton **VI**. After multi-step sequential oxidation with hypervalent iodines, the aromatic pyridine product **VII** was finally obtained.

With the mild reaction conditions and elucidated reaction mechanism, we last explored the synthetic potential for the late-stage pyridine installation on complex molecules.[28] Arising from the popular applications of copper-catalyzed click chemistry, terminal alkynes have been a widely utilized handle in bioactive molecules for further derivations, which have been increasingly crucial for lead compound optimiza-

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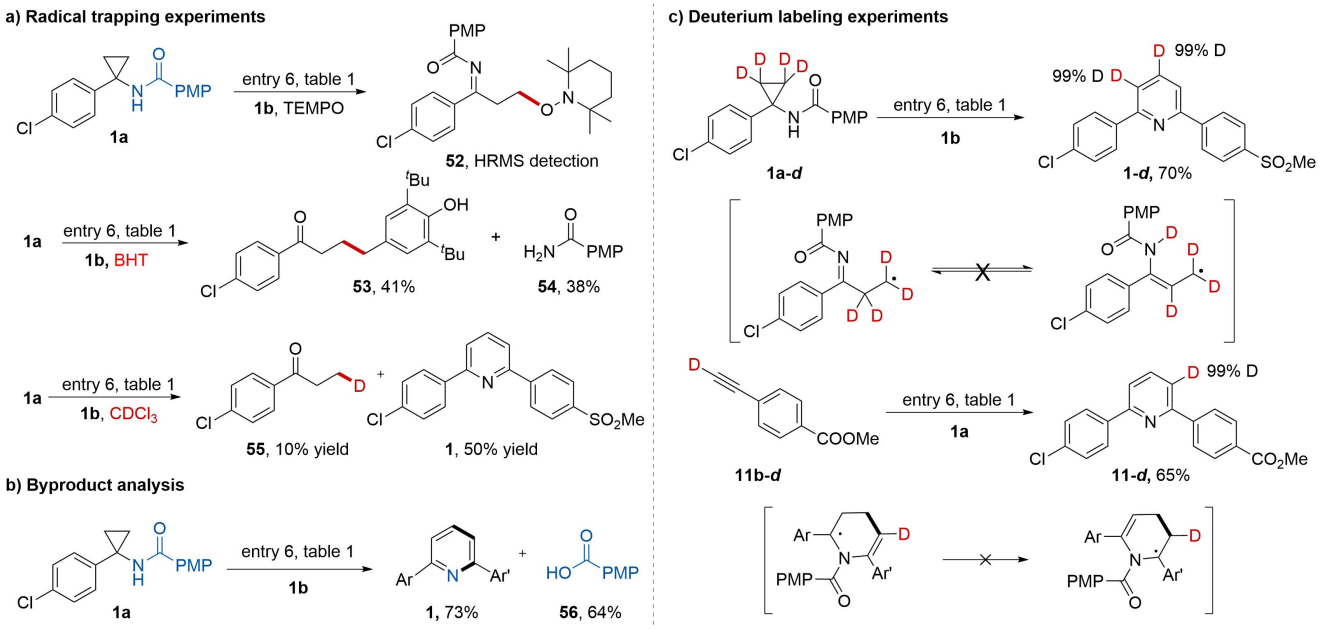
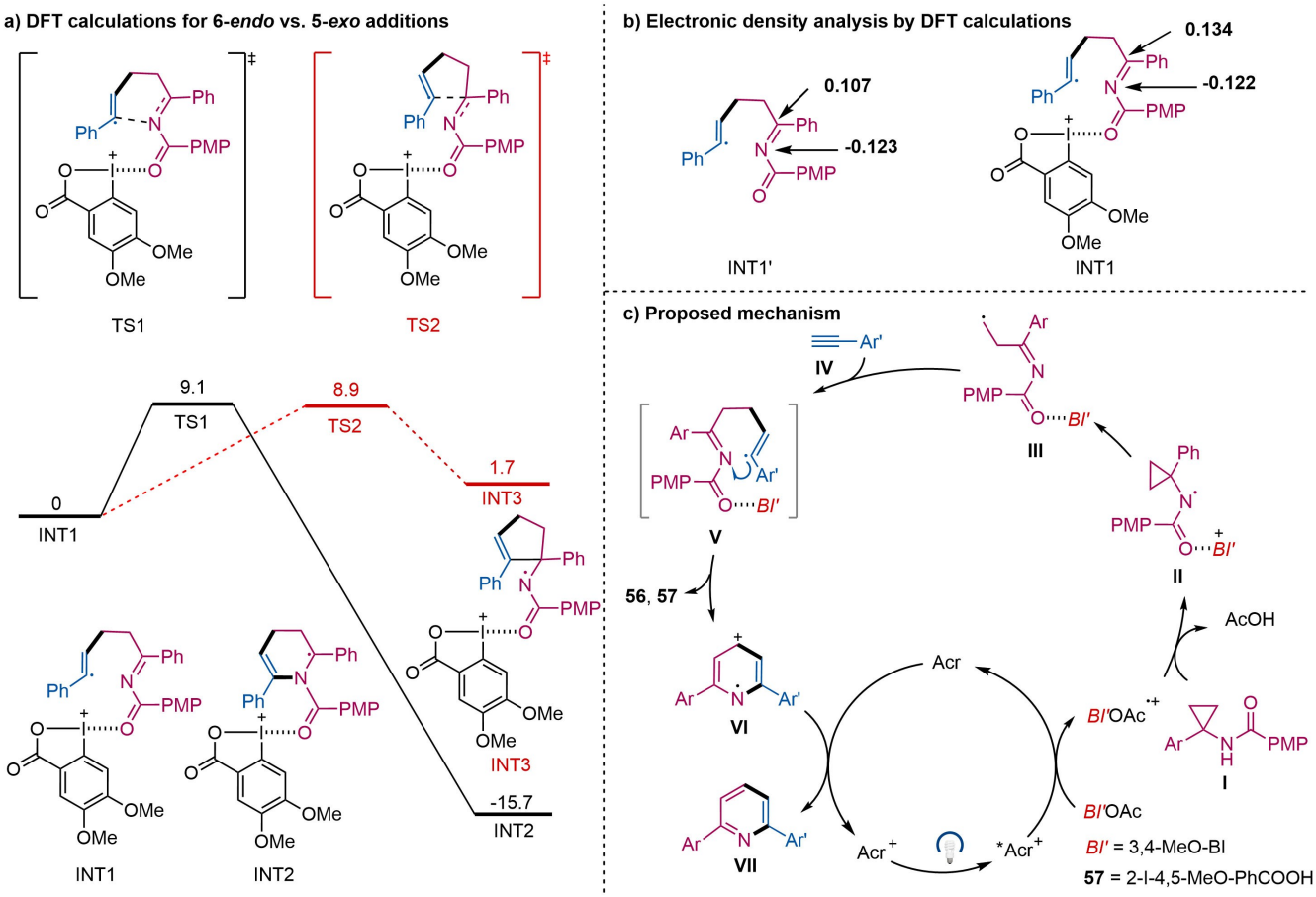


Scheme 4. Experimental investigations on the reaction mechanism. [a] cyclopropylamides (0.1 mmol), alkynes (0.2 mmol), Acr-Mes-Ph$^+$BF$_4^-$ (0.002 mmol), 3,4-MeO-BI-OAc (0.2 mmol), AcOH (0.4 mmol) in 1.0 mL toluene under nitrogen with 20 W 456 nm blue LED (5 cm away from the vial) irradiation at r.t. for 12 h, isolated yields.



Scheme 5. Computational studies and mechanistic proposal. DFT calculations using SMD (Toluene)/B3LYP-D3(BJ) /def2-TZVPP//B3LYP-D3(BJ) /def2-SVP. All energies are in kcal·mol^{-1}.

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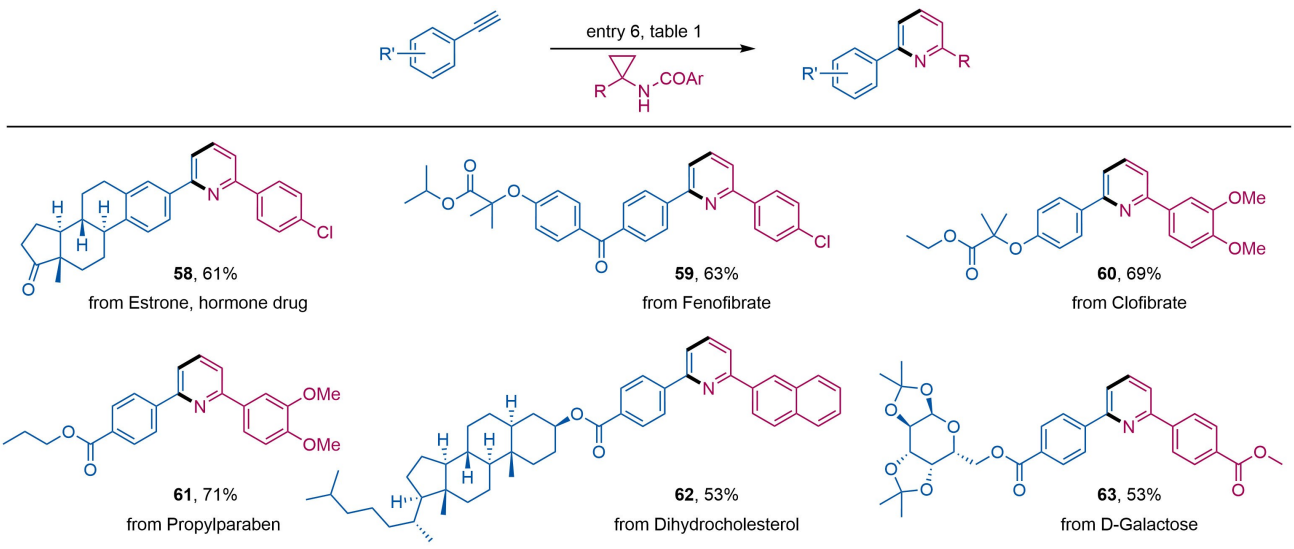

Scheme 6. Late-stage modification of bioactive molecules.

tion in drug discovery.[29] The hormone drug estrone with terminal alkyne **58b** could be easily inserted as the C2 unit to afford estrone-conjugated pyridine **58** in 61 % yield under standard reaction conditions. In this reaction, no trace metal residue remained and no functional group on steroids was affected (Scheme 6). The alkyne derivatives of antihyperlipidemic drug fenofibrate and clofibrate **59b** and **60b** underwent radical cycloaddition easily to their pyridine-conjugates **59** and **60** in 63–69 % yields. Furthermore, natural products such as propylparaben, dehydrocholesterol, and protected galactose were unaffected to afford **61**–**63** in 53 %–71 % yields. The introduction of the pyridine moiety significantly modulates the lipophilicity to improve its aqueous solubility, metabolic stability, and hydrogen bond capability.[2c,30]

In conclusion, we report the first radical 6-*endo* addition to synthesize substituted pyridines under metal-free conditions. Versatile pyridines with 57 examples are synthesized from terminal and substituted alkynes with excellent functional group compatibility, and the gram-scale reaction is easily achieved. Through mechanistic investigations and DFT calculations, the unprecedented 6-*endo-trig* addition of vinyl radicals to the imine nitrogen atom is enabled by the hypervalent iodine(III) activation. This strategy can be conveniently applied to structurally complex pharmaceutical molecules for late-stage pyridine incorporation.

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Conflict of Interest

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available in the supplementary material of this article.

Keywords: pyridine · organic radicals · hypervalent iodine · 6-*endo* additions · metal-free synthesis

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