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Research Article

Selective C(sp^3)-C(sp^3) Cleavage/Alkynylation of Cycloalkylamides Enables Aminoalkyne Synthesis with Hypervalent Iodine Reagents

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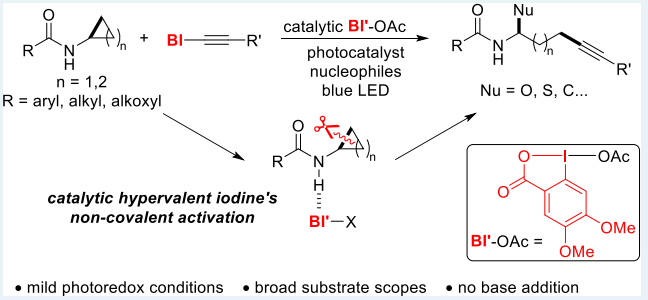
ABSTRACT: Here, we report the selective C(sp^3)-C(sp^3) cleavage/alkynylation of cycloalkylamides for the aminoalkyne synthesis under mild photoredox catalysis conditions. γ- and δ-Aminoalkynes with versatile alkyne and amine substituents are efficiently constructed from cyclopropylamides and cyclobutylamides via amidyl radicals enabled by hypervalent iodine(III) reagents. The catalytic amount of cyclic iodine(III) BI'-OAc facilitated the single-electron oxidation and ring-opening alkynylation of cycloalkylamides, which were investigated by a series of mechanistic probing experiments. Various α-amino substitutions from the oxygen, sulfur, or carbon nucleophile trapping can be performed in gram scale, and the aminoalkyne products easily derivatize to indolizidines, presenting in versatile bioactive fused azacycles.



KEYWORDS: *C−C bond cleavage, aminoalkynes, hypervalent iodine, nitrogen radical, photoredox catalysis*

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INTRODUCTION

Aminoalkynes are important bifunctional building blocks and can readily derivatize to bioactive fused azacycle natural products.[1] The indolizidine moiety is widely present in azacycle alkaloids, including lycorine, oxypalmatine, and rosettacin, which have demonstrated attractive biological and pharmacological activities (Scheme 1a).[2] Despite the valuable synthetic utilities of aminoalkynes, their preparation methods are limited. The current synthetic routes to aminoalkynes rely on the Gabriel synthesis or the N−H Mitsunobu reactions, which harsh reaction conditions and extra protection/deprotection sequences limit their synthetic utilities and functional group compatibilities. We envision that the entry to aminoalkynes with readily available cycloalkylamines provides an attractive synthetic manifold *via* the selective C−C bond cleavage and alkynylation.[3] The traditional ring-opening derivatization methods of cyclopropylamines include the polar reactions of donor−acceptor cyclopropylamines catalyzed by Lewis acids and the transition-metal-catalyzed C−C bond insertion of cyclopropylamines with directing groups.[4] The radical ring-opening reactions of cyclopropylamines provided unique synthetic opportunities: the ring-opening iodination and fluorination of cyclopropylamines were previously developed by Waser with N-iodosuccimide and Selectfluor.[5,6]

While effective, these radical ring-opening functionalizations were limited to halogenation, and the radical halogenation conditions were incompatible with the unsaturated functional groups such as alkynes. Zheng and Stephenson have pioneered the ring-opening cycloadditions of cyclopropylanilines with alkynes (Scheme 1b).[7] In these reactions, the cyclopropylanilines were photo-catalytically oxidized to yield the iminium radical, which was subsequently added to the alkyne to afford the alkenyl radical. Due to the high reactivity of the iminium cation, the alkenyl radical was readily trapped intramolecularly to afford the formal cycloaddition products. Similar strategies were accomplished for alkene cycloadditions and asymmetric cycloadditions.[8]

We hypothesize that the use of hypervalent iodine(III) alkyne reagents alkynylbenziodoxole (BI-alkyne) may switch the cycloaddition to the aminoalkyne synthesis with the facile BI elimination (Scheme 1b).[9] The use of the readily available cycloalkylamides and cycloalkylcarbamates may also provide more flexible nitrogen derivatizations compared to cycloalkylanilines. However, the higher oxidation potentials of cycloalkylamides (E > + 1.5 V) compared to cycloalkylanilines (E < + 1.0 V)[7a] require strong oxidative conditions. The base-promoted proton-coupled electron transfer (PCET) was shown to facilitate the amide oxidation for N radical generation under mild oxidative conditions; however, these basic conditions did not show compatibility with alkynylation.[10]

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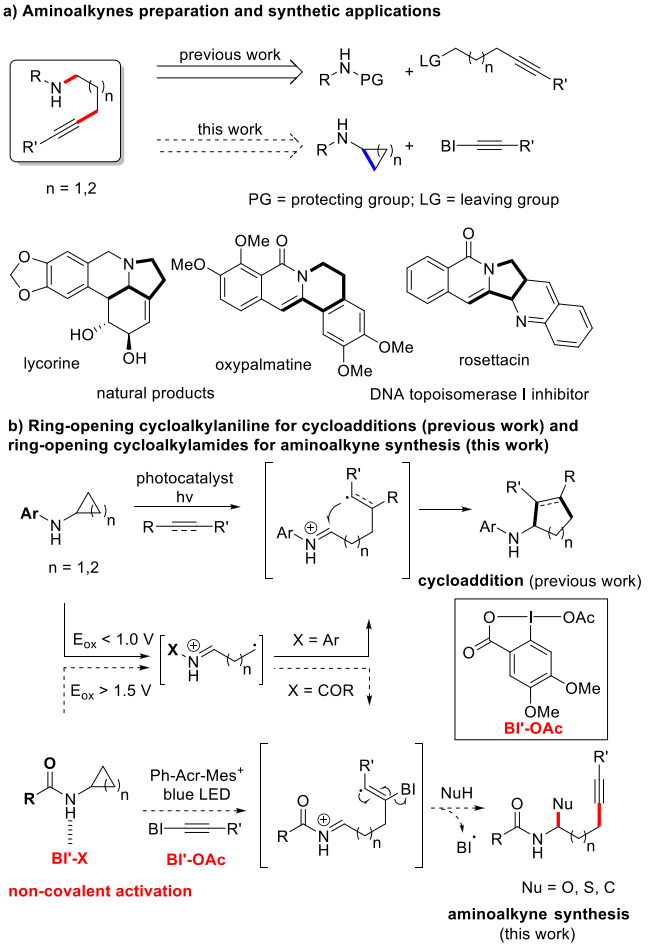
Scheme 1. Ring-Opening Alkynylation of Cycloalkylamines for Aminoalkyne Synthesis

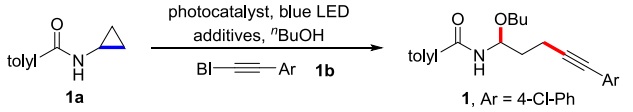


We previously discovered that the weakly oxidative cyclic iodine(III) reagents acetoxylbenziodoxole (BI-OAc) were compatible with the BI-alkyne for the radical alkynylation.[11] In these reactions, the covalent iodine−oxygen bond formation between BI-OAc and carboxylates[12]/alcohols[13] facilitated the oxygen-centered radical generation. However, compared to the carboxylate and alcohol activation by cyclic iodine(III) reagents, the amide activation by cyclic iodine(III) reagents has not been reported, and the activation mechanism remained unknown.[14] Herein, we report the first selective C(sp^3)-C(sp^3) cleavage/alkynylation of cyclopropylamides and cyclobutylamides to synthesize γ- and δ-amino-alkynes, which was enabled by the noncovalent hypervalent iodine(III) activation of cycloalkylamides for the first time.

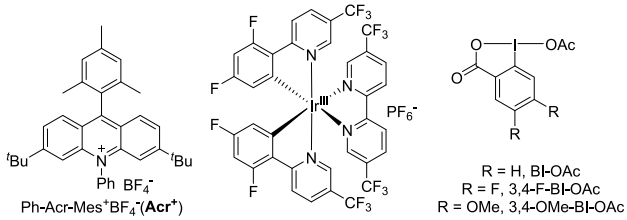
RESULTS AND DISCUSSION

Reaction Discovery and Optimization. We started the initial investigation with *N*-cyclopropyl-4-methylbenzamide **1a**, which was readily prepared by the one-step acylation of the commercially available cyclopropylamine. With BI-alkyne **1b** as the radical acceptor and *n*-butanol as the nucleophile to trap the iminium intermediate,[5,6,15] the use of $[Ru(bpy)_3](PF_6)_2$ (E^*_{red} = +0.77 V vs SCE in MeCN) as the photocatalyst gave no conversion of **1a** (E_p = +1.68 V vs SCE in MeCN, entry 1 in Table 1). The photocatalyst with higher oxidation potential Ph-Acr-MesBF$_4$ (E^*_{red} = +2.10 V vs SCE in MeCN) only afforded 7% yield of γ-amino-alkyne **1** in low conversions

Table 1. Optimization of Reaction Conditions[a,b,c,d]



entry	conditions[a]	additives	yield[b] (%)
1[c]	$Ru(bpy)_3(PF_6)_2$	-	0
2	Ph-Acr-MesBF$_4$	-	7
3	Ph-Acr-MesBF$_4$	BI-OAc	43
4	Ph-Acr-MesBF$_4$	PIDA	25
5	Ph-Acr-MesBF$_4$	3,4-F-BI-OAc	39
6	Ph-Acr-MesBF$_4$	3,4-OMe-BI-OAc	81(80)
7[d]	Ph-Acr-MesBF$_4$	3,4-OMe-BI-OAc	70
8	$Ir[dF(CF_3)ppy]_2$ (5,5'-dCF_3bpy)(PF_6)	3,4-OMe-BI-OAc	82(78)
9	Ph-Acr-MesBF$_4$	3,4-OMe-BI-OAc 0.1 equiv.	73
10	entry 6	3,4-OMe-BI-OAc + 1.0 equiv. TFA	78
11	entry 6	3,4-OMe-BI-OAc + 1.0 equiv. Na_2CO_3	78
12	entry 6, no hv	3,4-OMe-BI-OAc	0
13	entry 6, no PC	3,4-OMe-BI-OAc	0



[a]Reaction conditions: **1a** (0.15 mmol, 1.5 equiv), BI-alkyne **1b** (0.10 mmol, 1.0 equiv), ^{n}BuOH (0.2 mmol, 2.0 equiv), photocatalyst (0.002 mmol, 0.02 equiv), and additives (0.03 mmol, 0.3 equiv) in 1.0 mL DCE with 4 Å MS (40.0 mg) under nitrogen with 4 W blue LED irradiation at 25 °C for 2 h. [b]Yields were determined by ^{1}H NMR analysis, and isolated yields were in parentheses. [c]12 h. [d]No 4 Å MS addition.

(entry 2).[16] Gratifyingly, the catalytic amount (0.3 equiv) of cyclic iodine(III) acetoxylbenziodoxole (BI-OAc) significantly improved the reaction to afford 43% yield of **1** (entry 3); however, the extended irradiation did not further improve the conversions. The noncyclic phenyliodine(III) diacetate (PIDA) gave 25% yield of **1**, and the electron-deficient 3,4-F-BI-OAc afforded **1** in 39% yield (entries 4−5). In contrast, the use of electron-rich 3,4-OMe-BI-OAc (0.3 equiv) dramatically improved **1** in 81% optimal yield in 2 h (80% isolated yield, entry 6), and the use of 4 Å molecular sieves decreased the aldehyde formation from the imine hydrolysis (entry 7). $Ir[dF(CF_3)ppy]_2(5,5'\text{-}dCF_3bpy)(PF_6)$ (E^*_{red} = +1.68 V vs SCE in MeCN) with lower oxidation potentials also afforded **1** in 78% isolated yield (entry 8).[17] The use of 3,4-OMe-BI-OAc could be decreased to 0.1 equiv without significantly affecting the reaction to give 73% yield of **1** (entry 9). The addition of acids or bases did not affect the reaction yields, which suggested that the reaction did not proceed via the base-promoted PCET mechanism (entries 10−11).[10c,18] The light irradiation and photocatalysts were both critical for the reaction (entries 12−13; see Tables S7−S12 for detailed optimizations).

Substrate Scopes. The ring-opening alkynylation reaction could synthesize various amino-arylalkynes **2**−**12**, amino-silylalkynes **13**−**15**, and amino-alkylalkynes **16** using different

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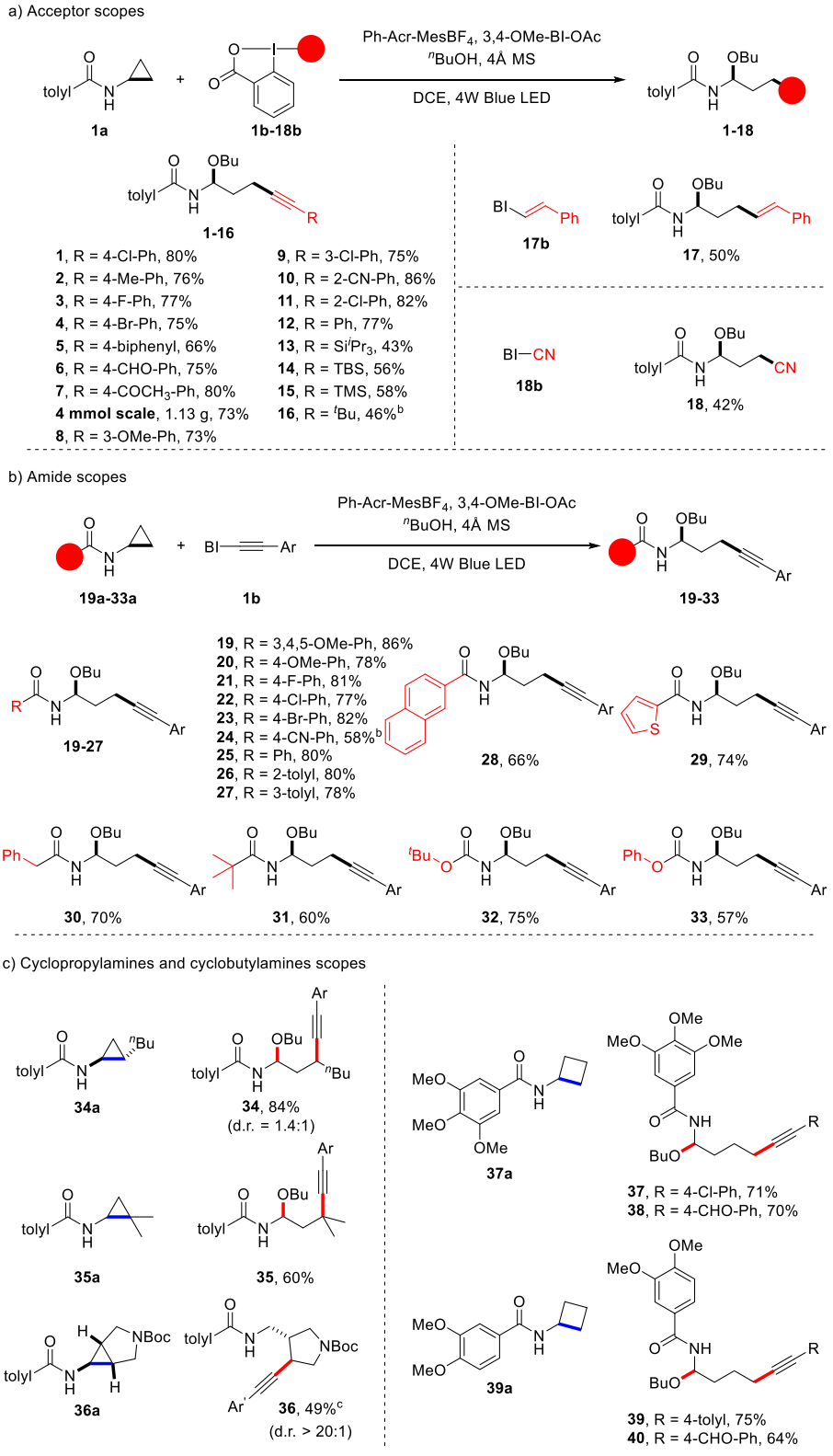
Scheme 2. Substrate Scopes of Radical Acceptors and Cycloalkylamides[a,b,c]



[a]Reaction conditions: Entry 6, Table 1. Isolated yields were reported. [b]Reaction time: 6 h. [c]Stepwise $NaBH_3CN$ treatment. Ar = 4-Cl-Ph. Ar′ = 2-CN-Ph.

BI-alkynes **2b-16b** (Scheme 2a). The electron-rich methoxy or electron-deficient halides, ketones, and nitriles were all tolerated on the arylalkynes, and the oxidation-sensitive aldehydes were not affected by the reaction conditions.[19]

The ring-opening alkynylation could be easily scaled up to 4 mmol to obtain 1.13 g of **7** in 73% yield. The silyl-substituted BI-alkynes were compatible with the reaction conditions to afford aminosilylalkynes **13**−**15** in 43−58% yields, and the

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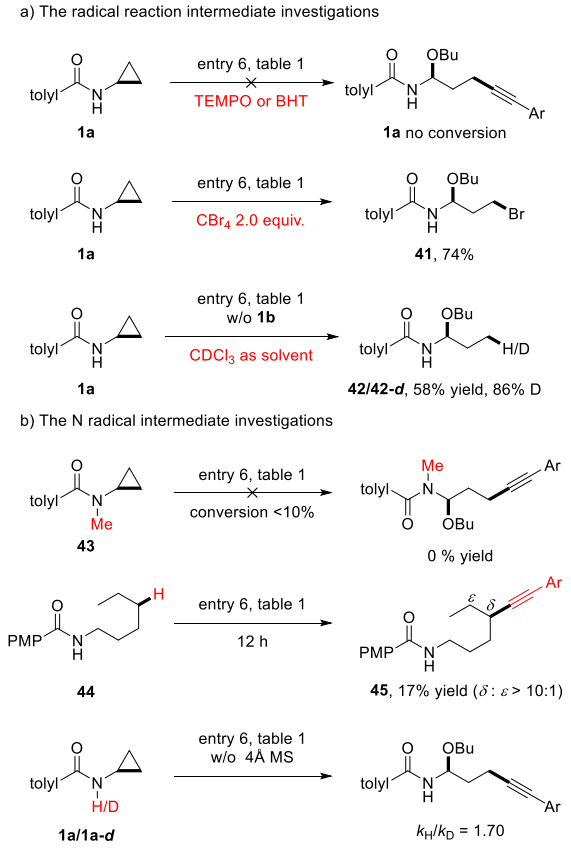
Scheme 3. Radical Reaction Mechanism Investigations



Si^iPr_3, *t*-butyldimethylsilyl (TBS), and trimethylsilyl (TMS) groups remained intact under the reaction conditions. The alkyl-substituted BI-alkyne **16b** gave a moderate 46% yield of **16** with a prolonged 6 h reaction time. The ring-opening functionalization of cycloalkylamide could extend to other hypervalent iodine(III) reagents: the BI-alkene **17b** afforded the alkenylation adduct aminoalkene **17** in 50% yield,[20] and BI-CN **18b** reacted to give the cyanation adduct aminonitrile **18** in 42% yield.[21] It is worth noting that neither the ring-opening alkenylation nor cyanation has been achieved by other methods.

We next explored if the ring-opening alkynylation was extendable to other cyclopropylamides (Scheme 2b). The cyclopropylamides **19a-20a** with electron-rich methoxylphenyl groups afforded **19**−**20** in 78−86% yields. The electron-deficient *p*-fluorophenyl-, *p*-chlorophenyl-, or *p*-bromophenyl-substituted cyclopropylamides **21a-23a** reacted smoothly to result in aminoalkynes **21**−**23** in 77−82% yields; even the strongly electron-deficient *p*-nitrilephenyl **24a** afforded **24** in 58% yield with a prolonged 6 h reaction time. The *o*- or *m*-substituents did not affect the reaction to give **25**−**27** in 78−80% yields. The cyclopropylamides **28a-29a** with naphthalene or heterocyclic thiophenes gave **28**−**29** in 66−74% yields. The reaction was not limited to aryl-substituted amides, and the benzyl-substituted or tert-butyl amides **30a-31a** effectively afforded **30**−**31** in 60−70% yields. In addition, the tert-butyl and phenyl carbamates **32a-33a** reacted to give **32**−**33** in 57−75% yield, which could easily yield the corresponding free aminoalkynes after the ready deprotection.[22] The substrate scope demonstrated by the hypervalent iodine(III) reagent method greatly expanded the cyclopropylamide scopes from the previously reported photocatalytic ring-opening fluorination with Selectfluor, in which the alkyl-substituted amides or carbamates were not applicable, and the electron-poor aryl-substituted amides gave decreased yields.[5b]

This reaction was not limited to unsubstituted cyclopropylamides that the 2-butyl cyclopropylamide **34a** afforded the secondary alkyl-substituted alkynes **34** in the excellent 84% yield (Scheme 2c). Further, the 2,2-dimethyl-cyclopropylamide **35a** resulted in the tertiary alkyl-substituted alkynes **35** in 60% yield. The bicyclic amide **36a** yielded the disubstituted tetrahydropyrrole **36** in 49% yield (d.r. > 20:1) after the sodium cyanoborate reduction. The cycloalkylamides could also extend to cyclobutylamides, and the electron-rich methoxylphenyl groups were required in **37a** and **39a** to afford *δ*-amino-alkynes **37**−**40** in 64−75% yields.[23]

Mechanistic Investigations. We next carried out the mechanistic probing experiments (Schemes 3 and 4). The (2,2,6,6-tetramethylpiperidin-1-yl)oxyl (TEMPO) or dibutylhydroxytoluene (BHT) addition to the reaction conditions completely inhibited the **1a** conversion (Scheme 3a). When CBr_4 was added to the reaction, the *γ*-bromo amide **41** was obtained in 74% yield.[24] In the deuterated $CDCl_3$ solvent, the deuterated **42** was observed in 58% yield in 86% deuterium incorporation in the absence of BI-alkyne **1b** as the radical acceptor (See Table S1). These results together confirmed the existence of the *γ*-aminoalkyl radical intermediate. The *N*-methyl cyclopropylamide **43** was next subjected to the standard reaction condition, and the lack of **43** conversion suggested the essential free N−H for the reaction (Scheme 3b). We also prepared amide **44** with the *δ*−C−H to test the amidyl radical intermediate. With BI-alkyne **1b** as the radical acceptor in the reaction conditions, the *δ*-alkynylation adduct **45** was obtained in 17% yield (*δ*: *ε* > 10:1) by the 1,5-hydrogen atom tranfer (HAT) reaction of amidyl radicals in 12 h.[14c] The parallel kinetic isotope effect (KIE) experiments with **1a** and **1a-*d*** were also performed to obtain the KIE (k_H/k_D) value as 1.70, and the weak primary isotope effect indicated that the N−H cleavage may be rate-determining for the reaction (Figures S1 and S2).[25]

As the previously reported photocatalytic ring-opening fluorination had limited cycloalkylamide scopes using Selectfluor,[5b] we were curious why this weakly oxidative 3,4-OMe-BI-OAc method could greatly expand the amide scopes. We first examined if 3,4-OMe-BI-OAc formed similar I−N covalent bonds with cycloalkylamides as with carboxylates and alcohols.[12,13] However, the NMR shifts between 3,4-OMe-BI-OAc and **1a** were minimal and no new peaks were observed (Figure S3).[26] The oxidation potentials of **1a** was measured and was not significantly affected by the addition of 3,4-OMe-BI-OAc either (Figures S4 and S5). Similarly, the addition of 3,4-OMe-BI-OAc to **1a** did not noticeably affect the fluorescence quenching of Ph-Acr-$MesBF_4$ (Figures S6−S9). We then tested if the addition of 3,4-OMe-BI-OAc affected the photocatalytic turnover of Ph-Acr-$MesBF_4$. The fluorescence lifetime of Ph-Acr-$MesBF_4$ measured by the time-correlated single photon counting indicated that 3,4-OMe-BI-OAc did not quench the excited Ph-Acr-$MesBF_4$. In addition, there was no conversion of **1a** with the stoichiometric amount of Ph-Acr-$MesBF_4$ (Table S3). These results were different from the covalent activation of carboxylates and alcohols by the hypervalent iodine, and together, they suggested the different activation mode of 3,4-OMe-BI-OAc on cycloalkylamides.

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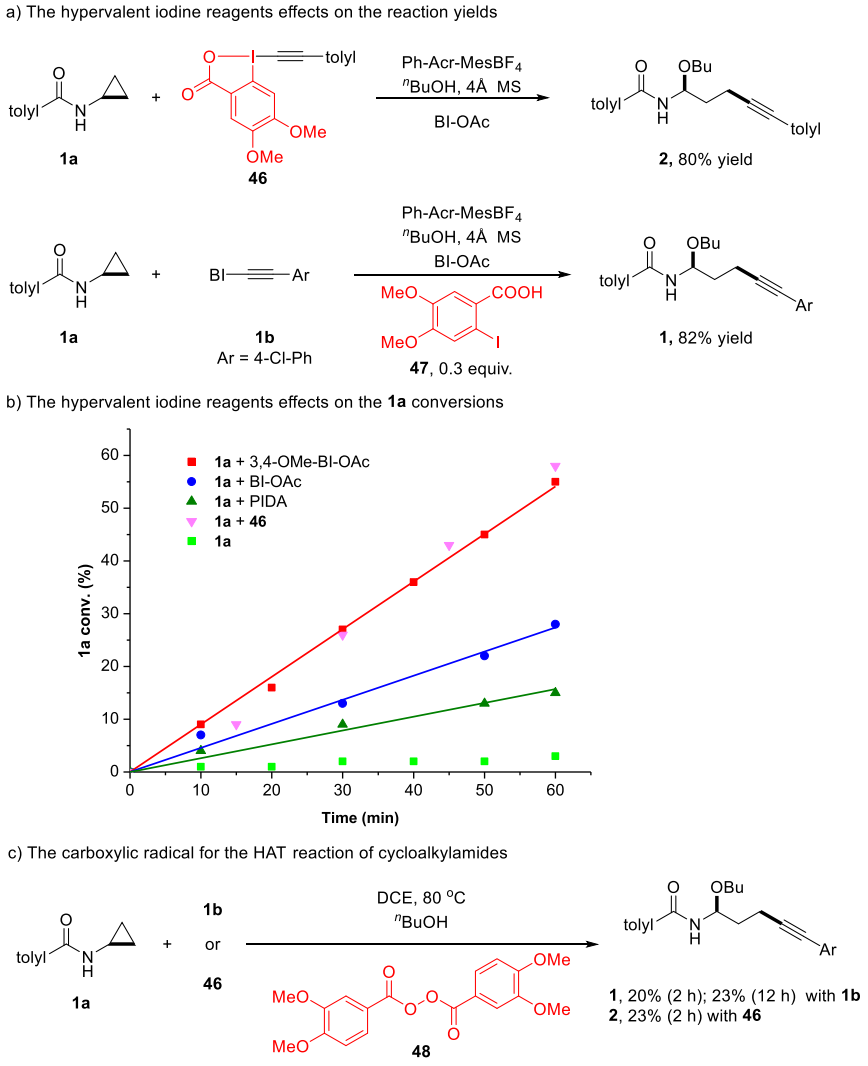
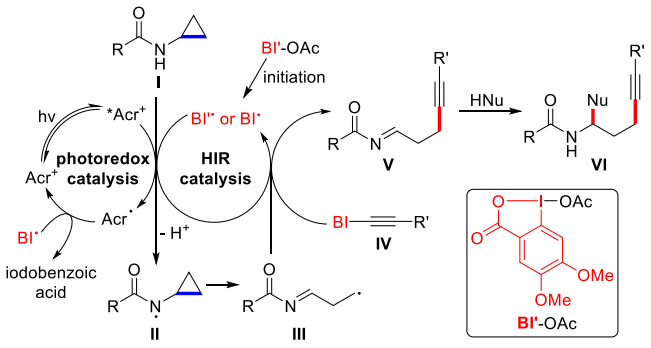
Scheme 4. Hypervalent Iodine(III) Activation of Cycloalkylamides



Scheme 5. Proposed Reaction Mechanism



As 3,4-OMe-BI-OAc dramatically improved the amino-alkyne synthesis compared to other hypervalent iodine(III) reagents as the additive, we envisioned that this vast difference provided a unique entry to probe the roles of hypervalent iodine in the reaction (Scheme 4a). Previous reports found that the substituted BI'-alkynes and unsubstituted BI-alkynes demonstrated similar alkyl radical addition reactivity for the radical alkynylation.[11b,27] We were curious if the substituted 3,4-OMe-BI-alkyne **46** would afford different reaction outcomes given the superior results from 3,4-OMe-BI-OAc. Using unsubstituted BI-alkyne **2b**, 32% yield of **2** was obtained with BI-OAc as the additive. In contrast, the use of 3,4-OMe-BI-alkyne **46** afforded 80% yield of **2**. Moreover, the removal of BI-OAc did not affect the reaction (Figure S10). We further injected 3,4-OMe-iodobenzoic acid **47** to the reaction with unsubstituted BI-OAc and BI-alkyne **1b** and observed the improved 82% yield of **1**. As the radical addition to BI'-alkynes and the photo-oxidation of the substituted iodobenzoic acids both resulted in the BI' radical, we hypothesized that the BI' radical was the critical component for the reaction improvement.[28] We also tested if the base-promoted PCET was suitable for the reaction (Table S4). In the absence of 3,4-OMe-BI-OAc, the addition of commonly used phosphate bases or collidines was ineffective for the transformation, which also resulted in the alkyne decomposition.[17,18,25,29]

We then examined how hypervalent iodine reagents changed the cycloalkylamide conversions (Scheme 4b). In the absence of 3,4-OMe-BI-OAc under otherwise standard reaction conditions, there was very little cyclopropylamide **1a** conversion (green squares). The addition of PIDA (green triangles) or BI-OAc (blue circles) accelerated the **1a** conversions. The rate acceleration by 3,4-OMe-BI-OAc (red squares) was most significant, which was two times that of BI-OAc and 3.7 times that of PIDA (Figure S11).[30] We also

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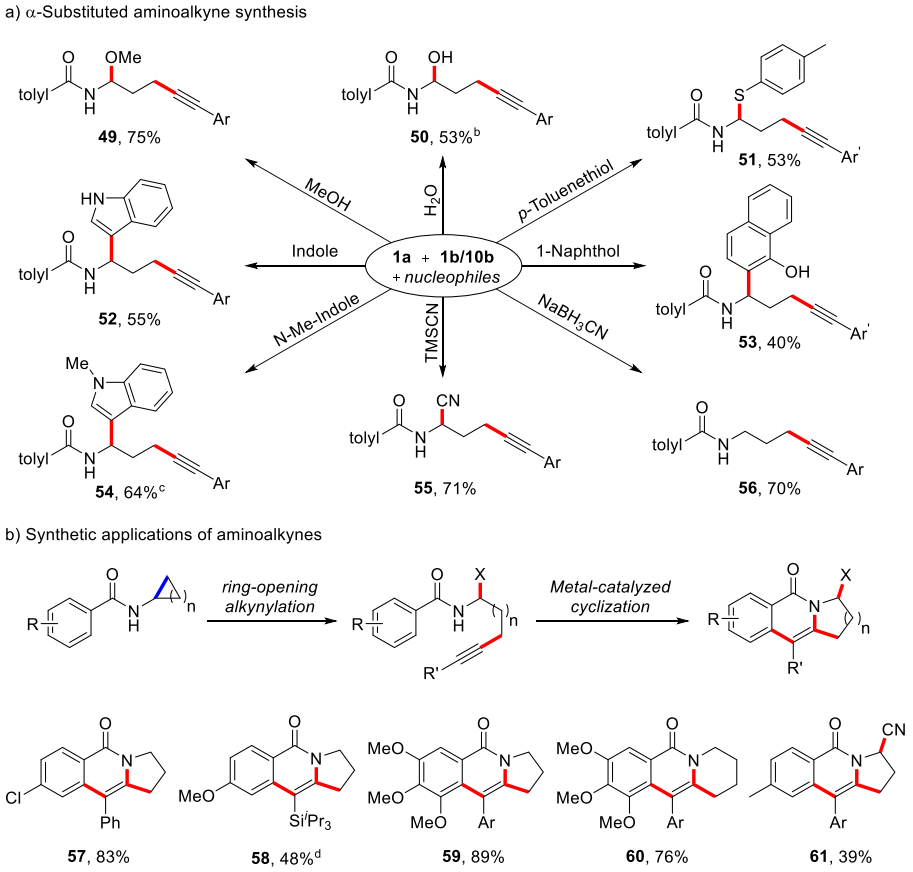
Scheme 6. Aminoalkyne Derivatizations and Synthetic Applications[a,b,c,d]



[a]See Supporting Information for the detailed procedures. Isolated yields. Ar = 4-Cl-Ph. Ar′ = 2-CN-Ph. [b]H_2O (0.1 mL) was added as the nucleophile without 4 Å MS. [c]$Zn(OTf)_2$ 10 mol % was added. [d]44% r.s.m.

tested the **1a** conversion in the absence of BI-alkynes and observed the similar rate acceleration by 3,4-OMe-BI-OAc (Figure S13). We next measured the cyclopropylamide **1a** conversion with substituted 3,4-OMe-BI-alkyne **46** (pink triangles) and observed an acceleration similar to 3,4-OMe-BI-OAc. These results further suggested that the use of 3,4-OMe-BI-OAc and 3,4-OMe-BI-alkyne shared the similar activation modes of cycloalkylamides in the reaction (Figure S14).[31]

We last measured the quantum yield of the reaction, and the 2.23 value indicated the existence of the chain reaction pathways (Table S5).[32] As the BI radical was generated from the radical addition to BI-alkynes, we also tested the HAT mechanism for amidyl radical generation by the BI radicals (Scheme 4c).[19,33] Using the carboxylic radical precursor 3,4-dimethoxybenzoic peroxyanhydride **48** as the BI radical surrogate, the ring-opening alkynylation adduct **1** or **2** was obtained in 20−23% yield after heating, with either BI-alkyne **1b** or BI′-alkyne **46** as the radical acceptor.[34] These results suggested that the HAT of cycloalkylamides to generate the amidyl radical was operative; however, it was not the main reaction pathway. In addition, the fact that the aldehyde **6** remained intact in the reaction conditions indicated that the HAT by the BI radical was not dominant. We also found that the addition of 3,4-OMe-BI-OAc to the 3,4-dimethoxybenzoic peroxyanhydride **48** reactions gave no reaction improvement, which suggested that the HAT of cycloalkylamides was not accelerated by 3,4-OMe-BI-OAc (Table S5).

From the mechanistic investigations mentioned above, the visible light irradiation on Acr^+ afforded the excited-state $*Acr^+$, and the reaction initiation resulted in the BI′ radical generation from BI′-OAc (Scheme 5).[9b,13a] The cycloalkylamide **I** was noncovalently activated by the BI′ radical to be oxidized by the excited-state $*Acr^+$, which was further deprotonated to afford the cycloalkylamide radical **II**. The N radical **II** then underwent the selective $C(sp^3)$-$C(sp^3)$ bond cleavage to afford the alkyl radical **III** with the pendent imine. The alkyl radical **III** added to BI-alkyne **IV** to afford the alkynyl imine **V** with the facile BI radical elimination. When BI′-alkyne **46** or 3,4-OMe-iodobenzoic acid **47** was used, the BI′ radical could also be obtained for the cycloalkylamide **I** activation. The imine **V** could be detected by high resolution mass spectrometry (HRMS) and was further trapped by various nucleophiles to afford the aminoalkyne **VI** product (See Figure S17 for HRMS-electrospray ionization results). As the quantum yield of the reaction was greater than 1, we speculate that the BI radical may also undergo HAT reaction with the cycloalkylamide **I** for the N radical **II** chain reactions; however, the efficiency was not high enough to be the main reaction pathway due to the light dependence.[32,35] Instead, the BI radical mainly oxidized the Acr radical to turn over the photocatalyst Acr^+.[36]

Synthetic Applications. After detailed mechanistic studies, we also investigated if the use of different nucleophiles could afford versatile α-substituted aminoalkynes (Scheme 6a). The oxygen nucleophiles methanol and water afforded the α-

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methoxyl and α-hydroxyl aminoalkynes **49**−**50** in 53−75% yields, and the sulfur nucleophile thiophenol obtained α-thioether **51** in 53% yield. The carbon nucleophiles naphthol, free indole, *N*-methylindole, and TMS-CN gave the α-carbon functionalization adducts **52**−**55** in 40−71% yields, which were challenging α-substituted aminoalkynes to prepare by traditional methods and may contribute to the diverse azacycle synthesis.[37] The sodium cyanoborohydride treatment afforded the unsubstituted aminoalkyne **56** in 70% yield.

We finally tested the synthetic applications of the bifunctional aminoalkyne products (Scheme 6b). The indolizidines presenting in various fused azacycles could be readily prepared under the $[RhCp^*Cl_2]_2$ and $Cu(OAc)_2$ conditions in one step.[38] The chlorophenyl-substituted and silyl-substituted isoquinolinone **57**−**58** were readily assembled from aminoalkynes in 48−83% yields, which were only a few synthetic steps away from the DNA topoisomerase I inhibitor rosettacin derivatives. It is worth noting that the starting aminoalkynes were originally prepared in many steps in low yields.[38b,39] The γ- and δ-aminoalkyne adducts derived from cyclopropylamide **19a** and cyclobutylamide **37a** afforded tricyclic isoquinolinone **59** and **60** effectively in 76−89% yields. The α-cyano dihydropyrrolo-isoquinolinone **61** was assembled from **55** in 39% unoptimized yield; the starting α-cyano aminoalkynes could not be prepared by other previous methods.

CONCLUSIONS

In conclusion, we have developed the first aminoalkyne synthesis from cycloalkylamides and hypervalent iodine(III) alkyne reagents under mild photoredox catalysis conditions. The γ- and δ-aminoalkynes with versatile alkyne and amine substituents are efficiently constructed by the selective $C(sp^3)$-$C(sp^3)$ cleavage/alkynylation of cyclopropylamides and cyclobutylamides *via* amidyl radicals. Various α-amino-substitutions on the aminoalkynes can be easily introduced by oxygen, sulfur, and carbon nucleophilic trapping, and the aminoalkyne products can readily derivatize to various fused azacycles with bioactivities. The noncovalent activation of hypervalent iodine(III) reagents on the cycloalkylamides was discovered for the first time, which shows vast difference compared to the covalent carboxylate/alcohol activation. The effects of the methoxyl substituents on the BI'-OAc catalytic reactivity is surprising and will be further investigated in our laboratory. While the details of the exact noncovalent activation of the hypervalent iodine(III) reagents on cycloalkylamides remains unknown, this method provides an attractive entry to amidyl radical generations under mild oxidative conditions without the use of bases and will be useful for the chemoselective complex molecule modifications and biocompatible applications.[40]

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acscatal.1c02981.

Experimental procedures, reaction optimizations, detailed mechanistic investigations, and new compound characterizations (PDF)

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This manuscript was written through the contributions of all authors.

Notes

The authors declare no competing financial interest.

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(31) The ring-opening bromination of cycloalkylamide **1a** with different hypervalent iodine reagents were performed, and the electron-rich 3,4-OMe-BI-OAc was the most effective to convert cycloalkylamides, which further confirmed the cycloalkylamide oxidation was rate determining, see Table S6.

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