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Research Article

Photocatalytic Oxyalkynylation of Unactivated Alkenes Enabled by Hypervalent Iodine(III) Reagents

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Cite This: *ACS Catal.* 2024, 14, 13202−13208

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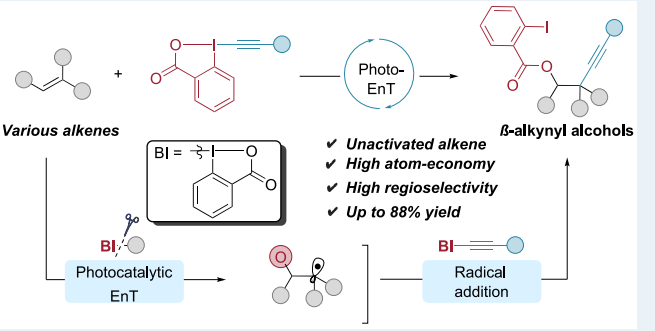
ABSTRACT: The oxyalkynylation of alkenes offers a valuable strategy for constructing C−C and C−O bonds, generating β-alkynyl alcohols frequently found in bioactive molecules. This work presents a photocatalytic approach for the oxyalkynylation of readily available unactivated alkenes using hypervalent iodine(III) reagents, acetoxylbenziodoxole (BI-OAc) and alkynylbenziodoxole (BI-alkyne), to afford anti-Markovnikov β-alkynyl alcohols. Mechanistic studies reveal a unique energy transfer process between BI-OAc and the photocatalyst, leading to the efficient generation of aryl carboxyl radicals. The aryl carboxyl radicals initiate atom-economical addition reactions with a broad range of commercially available mono-, di-, and trisubstituted alkenes, achieving anti-Markovnikov regioselectivity with BI-alkynes. The reaction can be readily scaled up to the gram scale, demonstrating its potential for late-stage modification of natural products and drug molecules. This method represents a significant advance in leveraging hypervalent iodine(III) reagents for radical generation and opens exciting avenues for future reaction design and development.



KEYWORDS: *hypervalent iodine, unactivated alkene, oxyalkynylation, carboxyl radical, photocatalysis*

INTRODUCTION

1,2-Difunctionalization of olefins offers a powerful and efficient way to build complex molecules quickly.[1] In particular, oxyalkynylation stands out for its ability to form both C−C and C−O bonds simultaneously, creating β-alkynyl alcohol structures often found in natural products and drugs (Scheme 1a). Examples include Lobetyolin, Petrosiol, and Capillarin, which possess fascinating biological activities.[2] However, these molecules are typically sourced from scarce medicinal plants, making them prime targets for total synthesis. Transition metal catalysis has been instrumental in advancing oxyalkynylation, but these methods often involve intramolecular reactions following Markovnikov's rule, where the oxygen atom attaches to the more substituted carbon (Scheme 1b).[3] Notably, it can also be achieved with hypervalent iodine(III) alkyne.[4] This preference arises due to the favorable 5-exo cyclization process.[5] While Patil achieved anti-Markovnikov oxyalkynylation of allenes using gold catalysts, the method was limited to N-allenamides.[6] Similarly, Liu's metal-free approach for unactivated olefins also followed anti-Markovnikov's rule but required excess strong oxidants (Scheme 1b).[7] Therefore, developing new methods for olefin oxyalkynylation under mild conditions to achieve desired products with anti-Markovnikov regioselectivity remains a significant challenge.

Photocatalysis offers a promising way to achieve anti-Markovnikov regioselectivity under mild conditions, as shown by its unique activation mode (Scheme 1c).[8] Pioneering work by Nicewicz involved photocatalytic alkene oxidation to generate electrophilic alkenyl radical cations, which then react with nucleophiles to yield anti-Markovnikov products.[9] Waser successfully achieved oxyalkynylation of enamides and enol ethers using organophotocatalysis with similar alkenyl radical cation intermediates, in which the alkene scope was limited to electron-rich alkenes.[10] In this work, the alkynylbenziodoxole acts as both an O-nucleophilic reagent and an alkynylation acceptor.[11] However, there is an urgent need for methods that effectively utilize readily available unactivated alkenes to create diverse products with high selectivity, which remains unknown.

Photocatalytic generation of O-centered radicals presents an attractive alternative for regioselective addition to unactivated alkenes.[12] Glorius demonstrated this approach by efficient oxyimination of unactivated alkenes using photocatalytic activation of bifunctional oxime carbonates.[13] The O-centered radicals, formed by the photocatalytic cleavage of the

Received: May 21, 2024
Revised: June 25, 2024
Accepted: June 26, 2024

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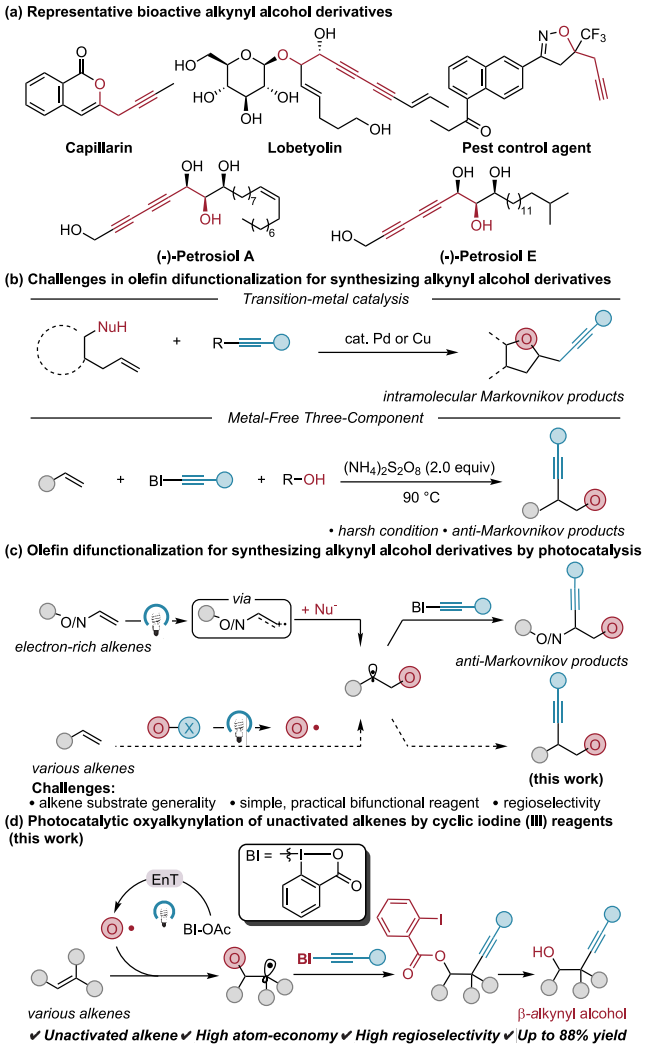
https://doi.org/10.1021/acscatal.4c02977
ACS Catal. 2024, 14, 13202−13208

Scheme 1. Oxyalkynylation of Alkenes



bifunctional reagents, were selectively added to unactivated alkenes before coupling with the simultaneously generated N-centered radicals. This process enables oxyimination of a wide range of alkenes with high regioselectivity. The key challenge of oxyalkynylation by photocatalysis is finding simple, practical bifunctional reagents that generate oxygen-centered radicals while forming C−O and C−C bonds with regioselectivity.[14] We propose that careful selection of bifunctional reagents allows for the synthesis of anti-Markovnikov oxyalkynylation products from various unactivated alkenes (Scheme 1c).

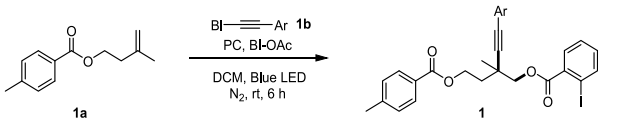
BI-alkynes (benziodoxole-alkyne reagents) offer promise as atom-efficient bifunctional reagents (Scheme 1d).[15] These reagents act as efficient radical acceptors, readily undergoing nucleophilic radical additions.[16] We and others have demonstrated that cyclic iodine(III) reagents like acetoxylbenziodoxole (BI-OAc), hydroxylbenziodoxole (BI−OH), and methoxylbenziodoxole (BI-OMe) generated BI radicals via single-electron transfer during photoredox catalysis.[16b,17] The BI radicals readily isomerize to *ortho*-iodobenzoic acid radicals, which *ortho*-iodo substitution stabilizes the aryl carboxyl radicals through resonance to facilitate selective hydrogen atom transfer. Given this stabilization effect, we hypothesized that olefins might intercept aryl carboxyl radicals as scavengers.[18]

We envisioned that hypervalent iodine(III) reagents could offer new avenues for photocatalytic difunctionalization to synthesize alkynyl alcohols. Here, we report the first photocatalytic oxyalkynylation of unactivated alkenes using BI-alkynes to create β-alkynyl alcohols with anti-Markovnikov selectivity. A photocatalytic energy transfer (EnT) process involving cyclic iodine(III) reagents generates aryl carboxyl radicals.[19] These radicals initiate the atom-economical addition of BI-alkynes to various alkenes with high regioselectivity (Scheme 1d).

RESULTS AND DISCUSSION

We began by exploring different reaction conditions using 2-methyl-1-butene derivative **1a**, BI-alkyne **1b**, various photocatalysts, and a catalytic amount (0.5 equiv) of BI-OAc to promote BI radical generation. While $Ru(bpy)_3(PF_6)_2$ is commonly used to generate BI radicals through oxidative quenching under blue LED light irradiation, it did not produce any desired product (Table 1, entry 1).[20] Similar lack of

Table 1. Optimization of Reaction Conditions



entry	conditions[a]	1a conv. (%)	Yield (%)[b]
1	$Ru(bpy)_3(PF_6)_2$	10	<5
2	$Ir(ppy)_2(dtbbpy)(PF_6)$	<5	<5
3	Ph-Acr-$MesBF_4$	<5	0
4	4CzIPN	25	32
5	$Ir(dFCF_3ppy)_2(5,5'\text{-}CF_3bpy)(PF_6)$	50	66(66)
6	entry 5, BI-OMe 0.5 equiv	20	35
7	entry 5, BI-OAc 0.1 equiv, 24 h	28	39
8	entry 5, BI-OAc 1.0 equiv	41	55
9	entry 5, no BI-OAc	<5	<5
10	entry 5, no photocatalyst	<5	<5
11	entry 5, no light	<5	0

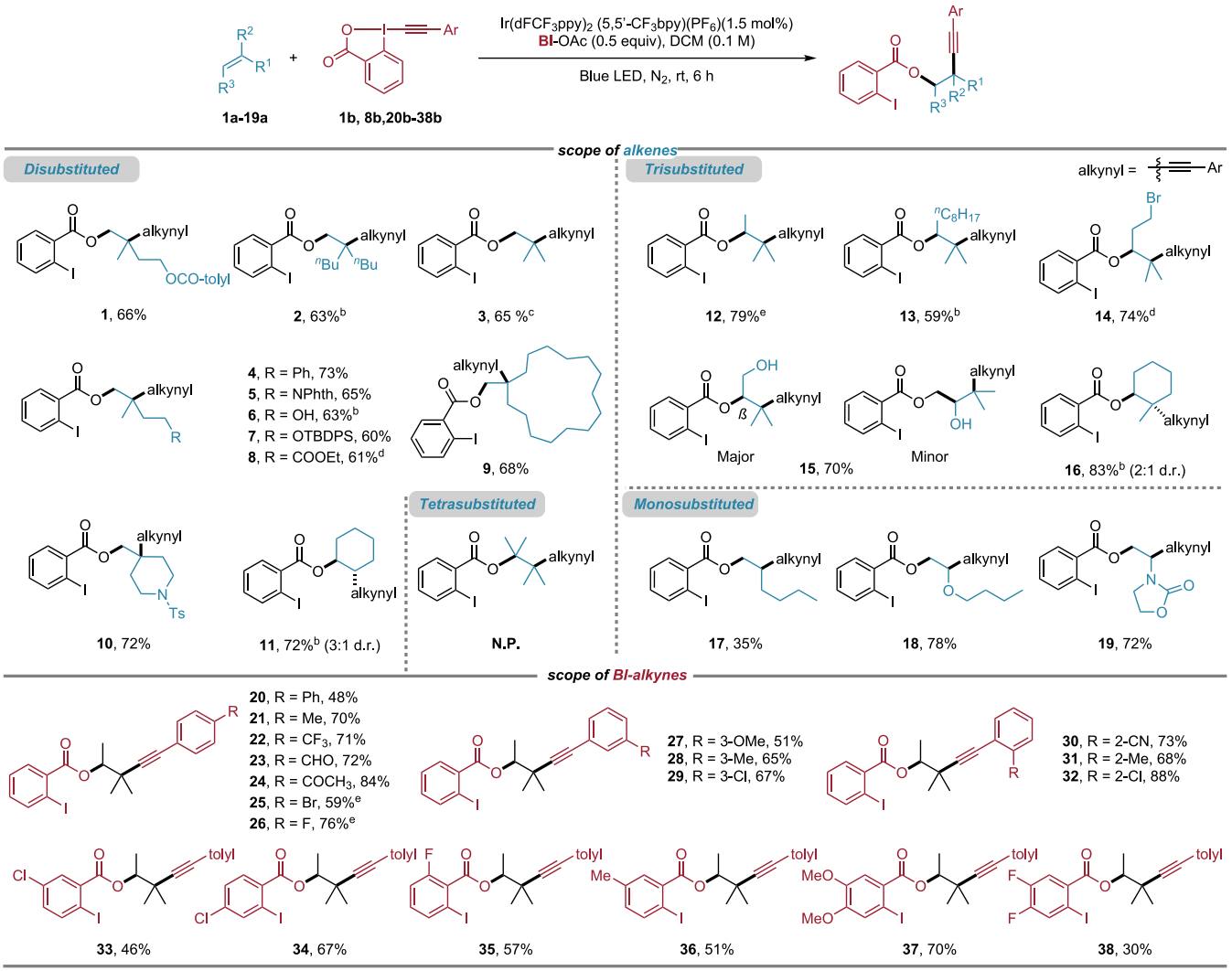
[a]Reaction conditions: **1a** (0.20 mmol, 2.0 equiv), **1b** (0.10 mmol, 1.0 equiv), photocatalyst (2.0 nmol, 0.02 equiv), and BI-OAc (0.05 mmol, 0.5 equiv) in 1.0 mL DCM under nitrogen with 20 W blue LED irradiation at 25 °C for 6 h, unless otherwise noted. [b]Yields were determined by ^{1}H NMR analysis, and isolated yields were in parentheses.

reactivity was observed with $Ir(ppy)_2(dtbbpy)(PF_6)$ and Ph-Acr-$MesBF_4$ (entries 2−3). Encouragingly, the organophotocatalyst 4CzIPN afforded the target product with the O-installation at the terminal alkene position (entry 4). Notably, $Ir(dFCF_3ppy)_2(5,5'\text{-}CF_3bpy)(PF_6)$ resulted in a regioselective 66% yield (entry 5).[21] BI-OMe was proved as an alternative cyclic iodine(III) reagent for generating BI radicals (entry 6).[16b] Reducing the BI-OAc amount to 0.1 equiv with an extended 24-h reaction time resulted in a 39% yield (entry 7). Conversely, increasing BI-OAc beyond 0.5 equiv did not improve the yield due to its limited solubility (entry 8). These findings indicate that only catalytic amounts of BI-OAc are necessary. As expected, the reaction failed in the absence of light irradiation, photocatalyst, or BI-OAc (entries 9−11; see Tables S1−S3 for detailed optimization).

We next investigated the versatility of this photocatalytic oxyalkynylation by exploring the reactivity of various alkenes under the optimized conditions (Scheme 2). Disubstituted

https://doi.org/10.1021/acscatal.4c02977
ACS Catal. 2024, 14, 13202−13208

Scheme 2. Substrate Scopes[a]



[a]Reaction conditions: **1a**–**19a** (0.20–0.30 mmol, 2.0-3.0 equiv), **1b**, **8b**, **20b**–**38b** (0.10 mmol, 1.0 equiv), BI-OAc (0.05 mmol, 0.5 equiv), and $Ir(dFCF_3ppy)_2$ (5,5'-CF_3bpy)(PF_6) (1.5 nmol, 0.015 equiv) in 1.0 mL DCM under nitrogen with 20 W blue LED irradiation at 25 °C for 6 h, unless otherwise noted. Isolated yields were recorded. [b]BI-OAc (0.03 mmol, 0.3 equiv). [c]**3a** (1.0 mmol, 10.0 equiv). [d]**8b** (0.10 mmol, 1.0 equiv) [e]40 W irradiation.

alkenes afforded excellent 60–73% yields of **1**–**10**, including various symmetrical and unsymmetrical 1,1-disubstituted substrates. Notably, unprotected hydroxyl groups, phthalimide, and piperidine heterocycles were well-tolerated. The regioselectivity in these reactions was dictated by the stability of the radical intermediate formed after aryl carboxyl radical addition to alkenes. This preference leads to preferential addition at the terminal alkene position. The 1,2-disubstituted cyclohexene yielded compound **11** as a mixture of diastereomers in a 72% yield with a 3:1 diastereomeric ratio.

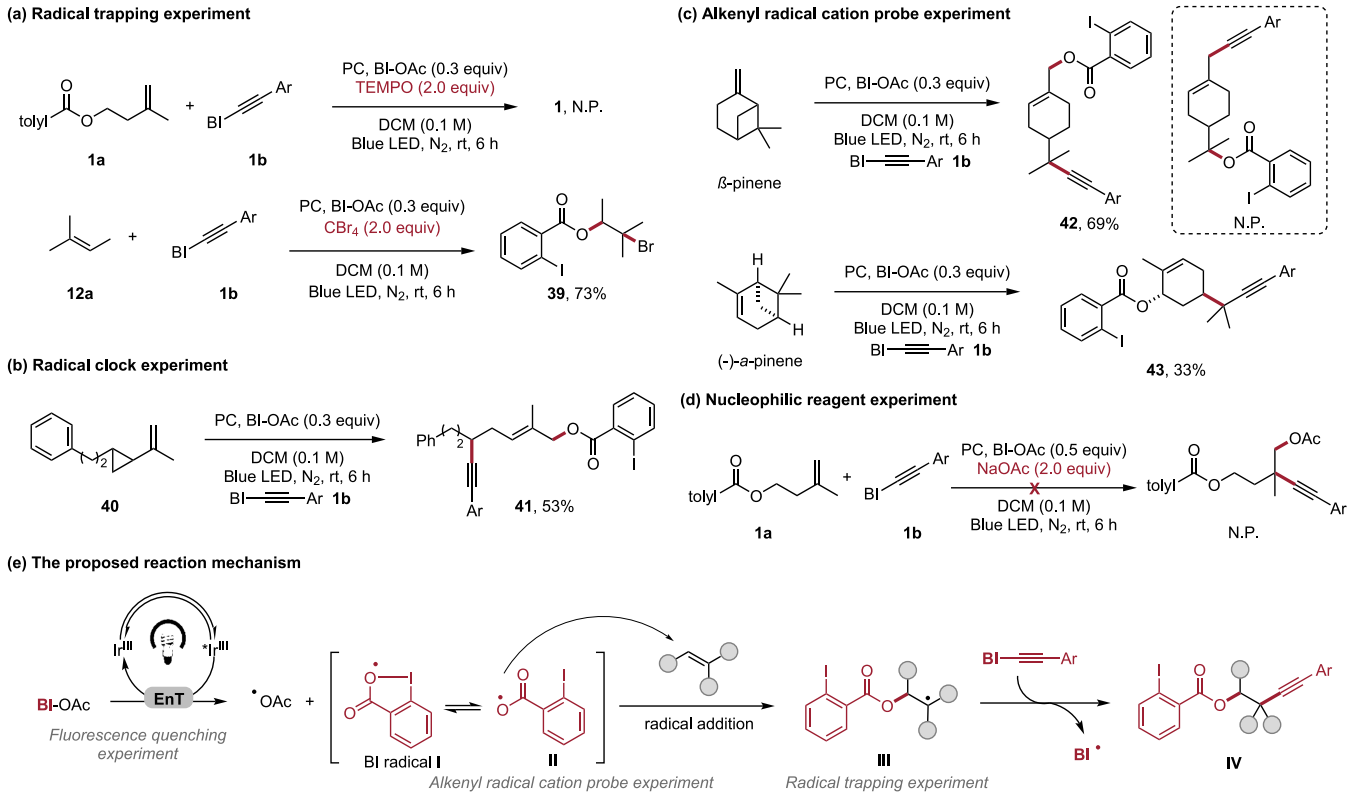
The reaction's versatility and regioselectivity were further evaluated with different trisubstituted alkenes. The oxyalkynylation proceeded smoothly to deliver products **12**–**16** in 59% to 83% yields. This included linear and cyclic alkenes, with compound **16** isolated as a 2:1 diastereomeric mixture (83% yield). 3-Methyl-2-butenol **15a** resulted in a 70% yield of a 2:1 mixture of product **15**, likely due to benzoyl group migration. Similar to disubstituted alkenes, the regioselectivity for trisubstituted substrates favored O-installation at the less hindered alkene position. The reaction also tolerated primary alkenes, affording product **17** in a 35% yield. This might be due to the moderate stability of the alkyl radical intermediate formed after aryl carboxyl radical addition. Finally, the reaction successfully converted electron-rich monosubstituted alkenes like enol ether **18a** and enamide **19a** into the desired products in 72–78% yields.[22] Tetrasubstituted alkenes did not yield the desired product, presumably due to steric hindrance.

This reaction tolerates a wide range of BI-alkyne reagents (Scheme 2). BI-alkynes with electron-rich or electron-poor substituents on the aryl alkyne moiety reacted efficiently to afford *β*-alkynyl alcohols **20**–**32** in 48–88% yields. The benziodoxole derivatization can also be tolerated to yield **33**–**38** in 30% to 70% yields. Among them, the dimethoxy substituents afforded the optimal 70% yield of **37**, while the difluoro substituents only gave 30% yield of **38**.[23]

We next carried out the mechanistic investigation experiments (Scheme 3). Cyclic voltammetry results (Figure S1) showed that the reduction potentials of BI-OAc ($E_{1/2red}$ = −0.45 V vs SCE in MeCN) and **1b** ($E_{1/2red}$ = −0.94 V vs SCE in MeCN) are lower than that of $Ir(dFCF_3ppy)_2$(5,5′-

https://doi.org/10.1021/acscatal.4c02977
ACS Catal. 2024, 14, 13202−13208

Scheme 3. Mechanistic Investigations



$CF_3bpy)(PF_6)$ ($PC^+/^*PC$ = −0.43 V vs SCE in MeCN). Additionally, the triplet energy of $Ir(dFCF_3ppy)_2(5,5'$-$CF_3bpy)(PF_6)$ (54.6 kcal/mol) is well-matched to the I(III)-O bond dissociation energy of BI-OAc (BDE_{O-I} ~58.7 kcal/mol), suggesting that BI radicals likely form through an energy transfer process between BI-OAc and the photocatalyst.[24] While $Ir(ppy)_3$ (58.1 kcal/mol) and $Ir(dFCF_3ppy)_2(dtbbpy)$-(PF_6) (61.8 kcal/mol) possess similar or slightly higher triplet energies, their lower oxidation potentials make them prone to being oxidatively quenched by BI-OAc, preventing the product formation (Table S1).

The addition of the radical scavenger (2,2,6,6-tetramethylpiperidin-1-yl)oxyl (TEMPO) completely inhibited the conversion of starting material **1a** (Scheme 3a).[25] Furthermore, the reaction with carbon tetrabromide (CBr_4) led to the oxybromination product **39** in 73% yield. Additionally, using the cyclopropyl-containing radical clock reagent **40** resulted in alkene product **41** (53% yield) via β-scission of the cyclopropane ring (Scheme 3b).[26] These results together confirm the involvement of a free radical process. We also tested β-pinenes and α-pinenes as radical cation probes, and the exclusive product formation from aryl carboxyl radical addition excluded the alkene oxidation to radical cations (Scheme 3c).[27] The products **42** and **43** are formed by carboxyl radical addition to olefin, followed by β-fragmentation of the bridge bond to generate tertiary carbon radical for the alkynylation. In contrast, a tertiary carbenium was not produced from olefin oxidation to radical cation to open the ring. Separately, we employed benzoyl peroxide (BPO), a common initiator for generating benzoate radicals, to initiate the radical addition with alkene **1a**.[17a] This reaction produced the desired β-alkynyl alcohol in 33% yield, supporting the oxygen-centered radical addition pathway (Scheme S6). We also performed the oxyalkynylation under standard conditions with sodium acetate as a nucleophilic reagent. No acetate incorporation was observed and confirmed the absence of a radical cation intermediate (Scheme 3d). We then measured the quantum yield of the reaction, and the 5.20 value indicated the existence of the chain reaction pathways (see Supporting Information for detailed optimization).

Fluorescence quenching experiments suggested BI-OAc quenched the photocatalyst (Figure S2). Furthermore, when BI-OAc was stirred with a photocatalyst under blue LED light for 6 h, 58% conversion of BI-OAc was observed (Scheme S4). However, due to a potential mismatch between BI-OAc's reduction potential and that of the photocatalyst, the oxidative quenching for the single electron transfer (SET) to generate BI radicals seems unlikely. Furthermore, using O_2 or pyrene as triplet quenchers significantly reduced or completely inhibited the alkene oxyalkynylation reaction (Table S4). These findings collectively suggest an energy transfer process between BI-OAc and the photocatalyst as the key step for BI radical generation.

Our experimental findings suggest the following mechanism for the oxyalkynylation of unactivated alkenes using hypervalent iodine(III) reagents (Scheme 3e). Light irradiation excites the photocatalyst $(Ir(dFCF_3ppy)_2(5,5'$-$CF_3bpy)(PF_6)$ to its triplet excited state (Ir^{III}*). This excited state then undergoes energy transfer with BI-OAc, leading to the formation of the BI radical (**I**) and the acetic acid radical. The instability of the acetic acid radical precludes the observation of an addition product.[28] The BI radical (**I**) readily isomerizes to intermediate (**II**), which selectively adds to the less substituted terminal position of the alkene. This regioselectivity can be attributed to the formation of a more stable carbon radical intermediate (**III**). Subsequently, the carbon radical (**III**) reacts with the BI-alkyne moiety to form

https://doi.org/10.1021/acscatal.4c02977
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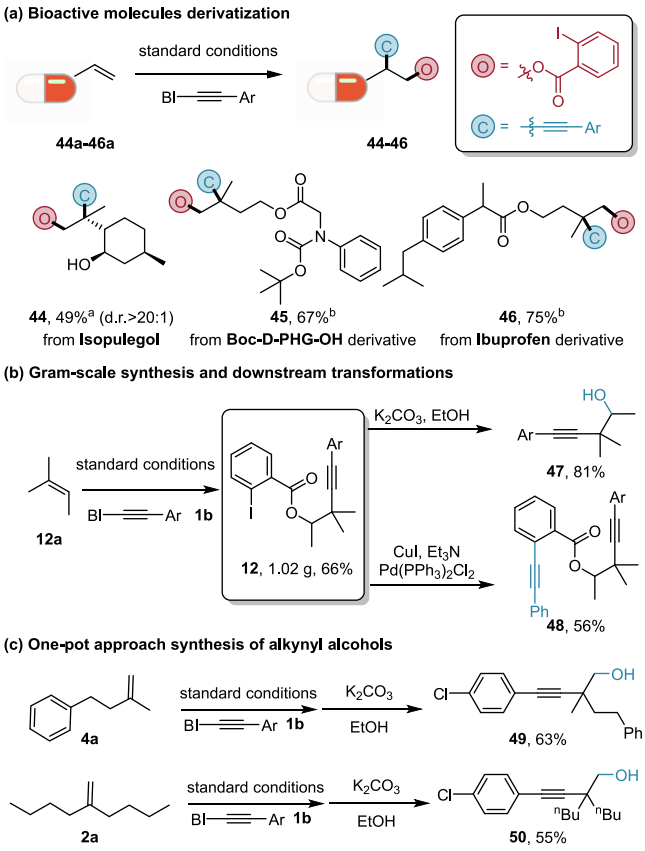
the C−C bond and generates a new BI radical. This process yielded the alkynyl alcohol product **IV**, while the eliminated BI radicals returned to the catalytic cycle to initiate the new alkene addition.

To demonstrate the synthetic utility of this oxyalkynylation method, we explored its application in the late-stage modifications of bioactive molecules (Scheme 4a). Isopulegol-based amino diol derivatives,[29] similar to other monoterpene-based diols, have shown promising antibacterial properties.[30] Gratifyingly, the oxyalkynylation of isopulegol provided a highly selective β-alkynyl alcohol derivative **44** in a 49% yield. The Boc-protected D-phenylglycine (Boc-D-PHG−OH) was further tested and resulted in product **45** in 67% yield. Ibuprofen, anti-inflammatory and analgesic drug, is known to enhance the therapeutic properties by derivatization.[31] The oxyalkynylation of the alkene-derived Ibuprofen provided the β-alkynyl alcohol **46** in 75% yield.

Highlighting the method's robustness, we successfully scaled up the reaction to a gram-scale synthesis of compound **12**, achieving a 66% yield (1.02 g) (Scheme 4b). The resulting product **12** readily underwent hydrolysis to afford β-alkynyl alcohol **47** in 81% yield. Additionally, Sonogashira cross-coupling with phenylacetylene yielded product **48** in 56% yield. To streamline the synthesis of β-alkynyl alcohols, we explored a one-pot strategy combining oxyalkynylation with in situ deprotection (Scheme 4c).[32] Standard photocatalytic conditions of **4a** and **2a** followed by the basic hydrolysis in the same reaction vessel provided alkynyl alcohols **49** and **50** in overall 55−63% yields.

Scheme 4. Synthetic Applications



[a]Reaction conditions: **44a−46a** (0.2-0.30 mmol, 2.0-3.0 equiv), **1b** (0.10 mmol, 1.0 equiv), BI-OAc (0.05 mmol, 0.5 equiv), and $Ir(dFCF_3ppy)_2$ (5,5'-CF_3bpy)(PF_6) (1.5 nmol, 0.015 equiv) in 1.0 mL DCM under nitrogen with 20 W blue LED irradiation at 25 °C for 6 h, unless otherwise noted. Isolated yields were recorded. [b]**32b** was used instead of **1b**.

CONCLUSION

In conclusion, we have developed a novel photocatalytic method for the oxyalkynylation of unactivated alkenes using BI-alkynes. Our mechanistic studies unveil, for the first time, an energy transfer process between cyclic iodine(III) reagents and the photocatalyst. This energy transfer efficiently generates aryl carboxyl radicals that initiate atom-economical addition reactions with a broad range of alkenes. The reaction delivers β-alkynyl alcohol products regioselectively with good functional group tolerance. Notably, the scalability of this reaction to the gram scale demonstrates its potential for natural product and drug modifications. This method presents a significant advancement in utilizing hypervalent iodine(III) reagents for radical generation and offers exciting possibilities for future reaction design and development, which are currently being explored in our laboratory.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acscatal.4c02977.

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

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Author Contributions

[‖]H.Q., Z.L., and Y.Z. contributed equally. The manuscript was written through the contributions of all authors. H.Q. and Z.L. performed experiments. All authors have given approval to the final version of the manuscript.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

The authors would like to acknowledge the financial support provided by National Natural Science Foundation of China 22337005, 22277133, 91753126, Youth Innovation Promotion Association CAS 2023266, CAS Interdisciplinary Innovation Team JCTD-2020-16, Program of Shanghai Academic/Technology Research Leader 21XD1424700.

■ REFERENCES

(1) (a) Li, Z.; Fang, G.; Gu, Q.; Liu, X. Recent advances in copper-catalysed radical-involved asymmetric 1,2-difunctionalization of alkenes. *Chem. Soc. Rev.* **2020**, *49*, 32−48. (b) Badir, S. O.; Molandert, G. A. Developments in photoredox/nickel dual-catalyzed 1,2-difunctionalizations. *Chem* **2020**, *6* (6), 1327−1339. (c) Luo, M.; Xiao, Q.; Li, J. Electro-/photocatalytic alkene-derived radical cation chemistry: recent advances in synthetic applications. *Chem. Soc. Rev.* **2022**, *51*, 7206−7237. (d) Wu, X.; Zhu, C. Radical-mediated remote functional group migration. *Acc. Chem. Res.* **2020**, *53*, 1620−1636.

(2) (a) Meepagala, K. M.; Sturtz, G.; Wedge, D. E. Antifungal constituents of the essential oil fraction of Artemisia dracunculus L. var. dracunculus. *J. Agric. Food Chem.* **2002**, *50*, 6989−6992. (b) Gangadhar, P.; Reddy, A. S.; Srihari, P. A facile approach for the total synthesis of neurotrophic diyne tetraol petrosiol A and petrosiol E. *Tetrahedron* **2016**, *72* (38), 5807−5817. (c) He, W.; Tao, W.; Zhang, F.; Jie, Q.; He, Y.; Zhu, W.; Tan, J.; Shen, W.; Li, L.; Yang, Y.; et al. Lobetyolin induces apoptosis of colon cancer cells by inhibiting glutamine metabolism. *J. Cell. Mol. Med.* **2020**, *24*, 3359−3369.

(3) (a) Huang, J.; Chen, Z.-M. The alkynylative difunctionalization of alkenes. *Chem. Eur. J.* **2022**, *28*, No. e202201519. (b) Orcel, U.; Waser, J. Palladium-catalyzed vicinal amino alcohols synthesis from allyl amines by in situ tether formation and carboetherification. *Angew. Chem., Int. Ed.* **2015**, *54*, 5250−5254.

(4) Waser, J. Recent progress in alkynylation with hypervalent iodine reagents. *Chem. Commun.* **2023**, *59*, 1589−1604.

(5) Beller, M.; Seayad, J.; Tillack, A.; Jiao, H. Catalytic Markovnikov and anti-Markovnikov functionalization of alkenes and alkynes: Recent developments and trends. *Angew. Chem., Int. Ed.* **2004**, *43*, 3368−3398.

(6) Banerjee, S.; Senthilkumar, B.; Patil, N. T. Gold-catalyzed 1,2-oxyalkynylation of N-allenamides with ethylnylbenziodoxolones. *Org. Lett.* **2019**, *21*, 180−184.

(7) Li, Y.; Lu, R.; Sun, S.; Liu, L. Metal-free three-component oxyalkynylation of alkenes. *Org. Lett.* **2018**, *20*, 6836−6839.

(8) (a) Prier, C. K.; Rankic, D. A.; MacMillan, D. W. Visible light photoredox catalysis with transition metal complexes: applications in organic synthesis. *Chem. Rev.* **2013**, *113*, 5322−5363. (b) Romero, N. A.; Nicewicz, D. A. Organic photoredox catalysis. *Chem. Rev.* **2016**, *116*, 10075−10166.

(9) (a) Margrey, K. A.; Nicewicz, D. A. A general approach to catalytic alkene anti-markovnikov hydrofunctionalization reactions via acridinium photoredox catalysis. *Acc. Chem. Res.* **2016**, *49*, 1997−2006. (b) Perkowski, A. J.; Nicewicz, D. A. Direct catalytic anti-Markovnikov addition of carboxylic acids to alkenes. *J. Am. Chem. Soc.* **2013**, *135*, 10334−10337.

(10) Amos, S. G. E.; Nicolai, S.; Waser, J. Photocatalytic Umpolung of N- and O-substituted alkenes for the synthesis of 1,2-amino alcohols and diols. *Chem. Sci.* **2020**, *11*, 11274−11279.

(11) The hypervalent iodine reagent alkynylbenziodoxole (BI-alkyne) is also referred to as ethynylbenziodoxolones (EBXs).

(12) (a) Jia, K.; Chen, Y. Visible-light-induced alkoxyl radical generation for inert chemical bond cleavage/functionalizations. *Chem. Commun.* **2018**, *54*, 6105−6112. (b) Zhang, J.; Liu, D.; Chen, Y. *Science of Synthesis: Free Radicals: Fundamentals and Applications in Organic Synthesis*. Fensterbank, L.; Ollivier, D., Ed.; Thieme: Stuttgart, 2021; Vol. *1*, pp. 323380;. (c) Barthelemy, A. L.; Tuccio, B.; Magnier, E.; Dagousset, G. Alkoxyl radicals generated under photoredox catalysis: A strategy for anti-Markovnikov alkoxylation reactions. *Angew. Chem., Int. Ed.* **2018**, *57*, 13790−13794.

(13) Patra, T.; Das, M.; Daniliuc, C. G.; Glorius, F. Metal-free photosensitized oxyimination of unactivated alkenes with bifunctional oxime carbonates. *Nat. Catal.* **2021**, *4*, 54−61.

(14) (a) Huang, H. M.; Bellotti, P.; Ma, J.; Dalton, T.; Glorius, F. Bifunctional reagents in organic synthesis. *Nat. Rev. Chem.* **2021**, *5*, 301−321. (b) Wang, M.; Zhang, H.; Liu, J. G.; Wu, X. X.; Zhu, C. Radical monofluoroalkylative alkynylation of olefins by a Docking-Migration Strategy. *Angew. Chem., Int. Ed.* **2019**, *58*, 17646−17650.

(15) (a) Yoshimura, A.; Zhdankin, V. V. Advances in synthetic applications of hypervalent iodine compounds. *Chem. Rev.* **2016**, *116*, 3328−3435. (b) Jia, K.; Chen, Y., Photochemistry of Hypervalent Iodine Compounds. In *Patai's Chemistry of Functional Groups*, Marek, I.; Olofsson, B.; Rappoport, Z., Ed.; Wiley: 2018; pp. 142.

(16) (a) Liu, X.; Wang, Z.; Cheng, X.; Li, C. Silver-catalyzed decarboxylative alkynylation of aliphatic carboxylic acids in aqueous solution. *J. Am. Chem. Soc.* **2012**, *134*, 14330−14333. (b) Huang, H.; Zhang, G.; Gong, L.; Zhang, S.; Chen, Y. Visible-light-induced chemoselective deboronative alkynylation under biomolecule-compatible conditions. *J. Am. Chem. Soc.* **2014**, *136*, 2280−2283.

(17) (a) Li, G.; Morales-Rivera, C. A.; Wang, Y.; Gao, F.; He, G.; Liu, P.; Chen, G. Photoredox-mediated Minisci C-H alkylation of N-heteroarenes using boronic acids and hypervalent iodine. *Chem. Sci.* **2016**, *7*, 6407−6412. (b) Jia, K.; Zhang, F.; Huang, H.; Chen, Y. Visible-Light-Induced alkoxyl radical generation enables selective C(sp3)−C(sp3) bond cleavage and functionalizations. *J. Am. Chem. Soc.* **2016**, *138*, 1514−1517. (c) Li, G.; Hu, X.; He, G.; Chen, G. Photoredox-mediated minisci-type alkylation of N-heteroarenes with alkanes with high methylene selectivity. *ACS Catal* **2018**, *8*, 11847−11853. (d) Mukherjee, S.; Garza-Sanchez, R. A.; Tlahuext-Aca, A.; Glorius, F. Alkynylation of sp2 C(O)−H bonds enabled by photoredox-mediated hydrogen atom transfer. *Angew. Chem., Int. Ed.* **2017**, *129*, 14915−14919. (e) Wu, S.; Chen, Y. Selective C−H acyloxylation of sulfides/disulfides enabled by hypervalent iodine reagents. *Adv. Synth. Catal.* **2023**, *365*, 2690−2696.

(18) (a) Li, Y.; Zhang, J.; Li, D.; Chen, Y. Metal-free C(sp3)-H allylation via aryl carboxyl radicals enabled by donor-acceptor complex. *Org. Lett.* **2018**, *20*, 3296−3299. (b) Li, J.; Yuan, Y.; Bao, X.; Sang, T.; Yang, J.; Huo, C. Visible-light-induced intermolecular oxyimination of alkenes. *Org. Lett.* **2021**, *23*, 3712−3717.

(19) Strieth-Kalthoff, F.; James, M. J.; Teders, M.; Pitzer, L.; Glorius, F. Energy transfer catalysis mediated by visible light: principles, applications, directions. *Chem. Soc. Rev.* **2018**, *47*, 7190−7202.

(20) Jia, K.; Pan, Y.; Chen, Y. Selective Carbonyl-C(sp3) bond cleavage to construct ynamides, ynoates, and ynones by photoredox catalysis. *Angew. Chem., Int. Ed.* **2017**, *56*, 2478−2481.

(21) Liu, Z.; Wu, S.; Chen, Y. Selective C(sp3)-C(sp3) cleavage/alkynylation of cycloalkylamides enables aminoalkyne synthesis with hypervalent iodine reagents. *ACS Catal.* **2021**, *11*, 10565−10573.

(22) We added the nucleophilic reagent NaOAc to the photochemical reaction of substrate **18a** to capture the alkenyl radical cation intermediate. Only the target product **18** was obtained, with no nucleophilic addition product.

(23) Reactions with TBS-substituted (**51b**), n-butyl-substituted (**52b**), and diyne BI-alkyne (**55b**) resulted in low conversions of the BI-alkyne substrates (around 10% for **51** and **52**, 6% for **55**) . Aryl-substituted BI-alkynes exhibited significantly higher reactivity compared to alkyl and silyl-substituted analogs in our system.

https://doi.org/10.1021/acscatal.4c02977
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(24) (a) Kwon, K.; Simons, R. T.; Nandakumar, M.; Roizen, J. L. Strategies to generate nitrogen-centered radicals that may rely on photoredox catalysis: developmennt in reaction methodology and applications in organic synthesis. *Chem. Rev.* **2022**, *122*, 2353−2428. (b) Yang, J.; Li, M.; Xue, X. Computational I(III)-X BDEs for benziodoxol(on)e-based hypervalent iodine reagents: Implications for their functional group transfer abilities. *Chin. J. Chem.* **2019**, *37*, 359−363.

(25) (a) Vogler, T.; Studer, A. Applications of TEMPO in synthesis. *Synthesis* **2008**, *13*, 1979−1993. (b) Xu, Y.; Wu, Z.; Jiang, J. X.; Ke, Z. F.; Zhu, C. Merging distal alkynyl migration and photoredox catalysis for radical trifluoromethylative alkynylation of unactivated olefins. *Angew. Chem., Int. Ed.* **2017**, *56*, 4545−4548.

(26) Yang, X. K.; Tsui, G. C. Silver-catalyzed trifluoromethylalkynylation of unactivated alkenes with hypervalent Iodine reagents. *Org. Lett.* **2019**, *21*, 8625−8629.

(27) (a) Donald, R. A.; Xin, D. The photochemical nucleophile-olefin combination, aromatic substitution reaction: methanol-alpha- and beta-pinene-1,4-dicyanobenzene. *J. Am. Chem. Soc.* **1989**, *111*, 7666−7667. (b) Jiang, H.; Studer, A. Transition-metal-free three-component radical 1,2-amidoalkynylation of unactivated alkenes. *Chem* **2019**, *25*, 516−520.

(28) (a) Barton, D. H. R.; Lacher, B.; Zard, S. Z. Radical decarboxylative bromination and iodination of aromatic acids. *Tetrahedron* **1987**, *43*, 4321−4328. (b) Minisci, F.; Vismara, E.; Fontana, F.; Barbosa, M. C. N. A new general method of homolytic alkylation of protonated heteroaromatic bases by carboxylic acids and iodosobenzene diacetate. *Tetrahedron Lett.* **1989**, *30* (34), 4569−4572. (c) Aryl carboxyl radicals are much more stable than alkyl carboxyl radicals, with stability differences of about four or more orders of magnitude due to resonance stabilization in the arene π-system. In contrast, acetic acid radicals are unstable in radical reactions.

(29) Orhan, I. E.; Özçelik, B.; Kartal, M.; Kan, Y. Antimicrobial and antiviral effects of essential oils from selected Umbelliferae and Labiatae plants and individual essential oil components. *Turk. J. Biol.* **2012**, *36*, 239−246.

(30) Le, T. M.; Huynh, T.; Endre, G.; Szekeres, A.; Fülöp, F.; Szakonyi, Z. Stereoselective synthesis and application of isopulegol-based bi- and trifunctional chiral compounds. *RSC Adv.* **2020**, *10*, 38468−38477.

(31) Chen, S.; Hang, Q.; Ao, G.; Hou, B.; Xu, G. Synthesis and Anti-inflammatory activities of novel Ibuprofen derivatives. *Chin. J. Syn. Chem.* **2014**, *22*, 781−784.

(32) Broadwater, S. J.; Roth, S. L.; Price, K. E.; Kobaslija, M.; McQuade, D. T. One-pot multi-step synthesis: a challenge spawning innovation. *Org. Biomol. Chem.* **2005**, *3*, 2899−2906.

https://doi.org/10.1021/acscatal.4c02977
ACS Catal. 2024, 14, 13202−13208