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Letter

Hypervalent Iodine Reagents Enable C−H Alkynylation with Iminophenylacetic Acids via Alkoxyl Radicals

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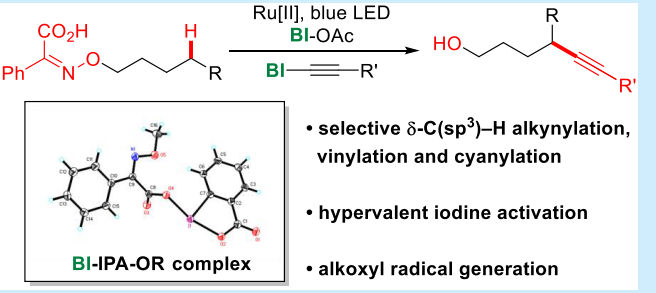
ABSTRACT: Here we report δ-C−H alkynylation to synthesize various δ-alkynols from iminophenylacetic acids. The hypervalent iodine-coordinated benziodoxole-alkoxyl-iminophenylacetic acid complex was the key intermediate and was characterized by X-ray crystallography for the first time. δ-C−H alkynylation is compatible with sensitive functional groups, including azides, aldehydes, and free alcohols, for the synthesis of δ-alkynols with diversified substituents in excellent regioselectivity. This reaction extends to δ-hydroxylalkene and δ-hydroxylnitrile synthesis, and the δ-alkynol products are easily derivatized to other valuable bifunctional building blocks.



Alkoxyl radicals are advantageous for C−H functionalization because of the strong O−H bond energies compared to the C−H bond energies.[1] The 1,5-HAT reactions of alkoxyl radicals enable δ-C(sp^3)−H functionalization of alcohols,[2] which provide complementary reactivity to β- and γ-C(sp^3)−H functionalization of alcohols by transition-metal catalysis.[3] The recently emergent photoredox catalysis has witnessed the development of various alkoxyl radical precursors with readily cleavable N−O bonds by single-electron reduction (Scheme 1a).[4] Recently, Yu and co-workers generated the alkoxyl radicals by single-electron oxidation from α-iminoacetic acids with SelectFluor for δ-C(sp^3)−H fluorination of alcohols.[5] However, δ-C(sp^3)−H alkynylation remains underexplored,[6] which alkynol products present in many bioactive natural products and may easily derivatize to other valuable bifunctional building blocks (Scheme 1b).[7]

Hypervalent iodine reagents acetoxylbenziodoxoles (BI-OAc) demonstrate mild single-electron oxidation reactivity and transition-metal-like properties in photoredox catalysis.[8] We and other groups previously discovered that BI-OAc activated alcohols via covalent iodine−oxygen bond formation for alkoxyl radical generation;[9] however, δ-C(sp^3)−H alkynylation could not be achieved. We speculate that the hypothetical coordination of BI to α-iminoacetic acids may reduce their oxidation potentials by forming the BI-iminoacetic acid complex.[10] The alkoxyl radicals may then be produced under mild single-electron oxidation conditions without the use of strong oxidants and compatible with alkynylation. In this Letter, we report the first hypervalent iodine(III) activation of phenyl-substituted iminophenylacetic acids for selective δ-C(sp^3)−H alkynylation via alkoxyl radicals.

We started the investigation of δ-C−H alkynylation by preparing pentanol-derived iminoacetic acids **1** and **2** from bromopentanes, which were derived from pyruvic acid and phenyl glyoxylic acid, respectively (Table 1). With alkynyl-benziodoxole (BI-alkyne) **3** as the radical acceptor and $Ru(bpy)_3(PF_6)_2$ as the photocatalyst ($E^{III/II}$ = 1.29 V vs SCE in MeCN),[11] methyl-substituted alkoxyl-iminoacetic acid IMA-OR **1** gave no conversion, which was reactive under the C−H fluorination conditions reported by Yu (entry 1).[5] In contrast, phenyl-substituted alkoxyl-iminophenylacetic acid IPA-OR **2** gave the desired δ-alkynol **5** product in 78% yield with acetoxylbenziodoxole (BI-OAc) **4** as the additive (76% isolated yield, entry 2). The change in the photocatalyst to $Ir(dFCF_3ppy)_2(dtbbpy)PF_6$ ($E^{IV/III}$ = 1.69 V) or Acr-$MesClO_4$ (E^*_{red} = 2.06 V vs SCE in MeCN) with a higher oxidation potential did not benefit the reaction but did result in many side products (entries 3 and 4).[12] The addition of CF_3CO_2H (1.0 equiv) inhibited the reaction (entry 5). The catalytic use of BI-OAc **4** (0.2 equiv) did not significantly affect the reaction, giving a 68% yield of **5** (entry 6).[9b,11b] The photocatalyst, BI-OAc, and light irradiation were all critical for the reaction as determined by control experiments (entries 7−9).[13]

With IPA-OR as the alkoxyl radical precursor, we next tested if δ-C(sp^3)−H alkynylation was general to other substrates (Scheme 2). The electron-rich phenyl or electron-deficient halide groups on BI-alkynes **6b−10b** were all tolerated to

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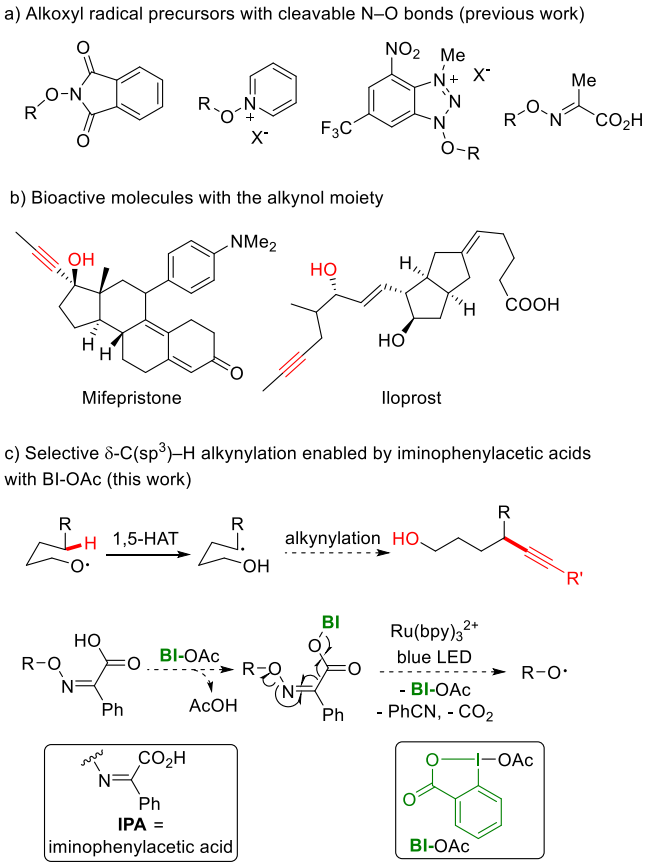
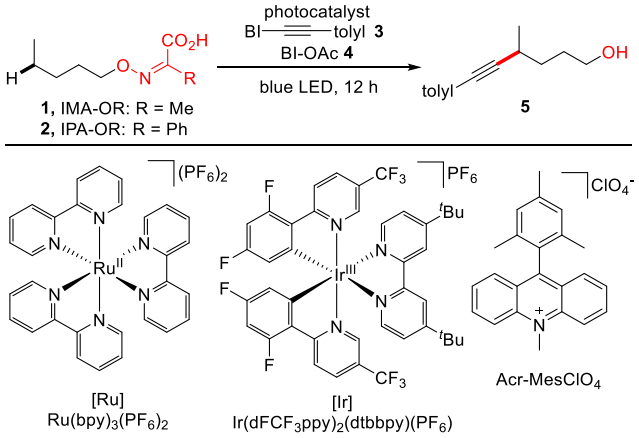
Scheme 1. Hypervalent Iodine(III) Reagents Enable C−H Alkynylation with Iminophenylacetic Acid Derivatives via Alkoxyl Radicals



afford δ-alkynols **6**−**10**, respectively, in 48−73% yields. BI-alkynes bearing different *o*-, *m*-, or *p*-aryl substituents did not affect the reaction, giving **11**−**17** in 62−75% yields. The nitrile, ketone, and aldehyde functional groups were all compatible with the reaction conditions. We also carried out the gram-scale reaction and observed **10** in 74% yield (1.18 g). Silyl-substituted BI-alkyne **18b** reacted smoothly to afford TBS-substituted δ-alkynol **18** in 74% yield, which could easily be deprotected to yield δ-hydroxyl terminal alkyne **19** in 85% yield. *tert*-Butyl-substituted BI-alkyne **20b** gave *tert*-butyl-substituted δ-alkynol **20** in 32% yield in low conversions, and the main byproducts were non-alkynylated alcohols generated from the alkoxyl radicals.[14] With BI-alkene **21b** as the radical acceptor,[15] regioselective δ-C(sp^3)−H alkenylation afforded δ-alkenol **21** in 66% yield. Similarly, BI-CN **22b** afforded δ-hydroxylnitrile **22** in 64% yield via δ-C(sp^3)−H cyanylation.[16]

The primary, secondary, and tertiary δ-C(sp^3)−H all reacted smoothly to give **23**−**25**, respectively, in 56−71% yields. The primary, secondary, and tertiary alkyl alkoxyl radicals underwent selective 1,5-HAT reaction to give **26**−**28**, respectively, in 75−80% yields, and the β-fragmentation side products were not observed.[17] Notably, the secondary δ-C−H in **26** outcompeted the tertiary ε-C−H to afford selective δ-alkynylation adduct **25** in a >15:1 δ:ε ratio. The substitution at the β- and γ-positions of alcohols did not affect the reaction, affording **29** and **30**, respectively, in 70−74% yields with exclusive δ-alkynylation, and a 5:1 *trans*:*cis* ratio was observed for **30**. When chemically equivalent δ-C−H and ε-C−H bonds

Table 1. Optimization of δ-C(sp^3)−H Alkynylation with Alkoxyl-Iminoacetic Acids



entry	conditions[a]	additive	conversion of **3** (%)	yield[b] (%)
1	**1**, [Ru]	**4**	<5	<5
2	**2**, [Ru]	**4**	>95	78 (76)
3	**2**, [Ir]	**4**	19	6
4	**2**, Acr-MesClO$_4$	**4**	75	10
5	entry 2	**4** and CF_3CO_2H	<5	0
6	entry 2	0.2 equiv of **4**	>95	68
7	entry 2, no [Ru]	**4**	0	0
8	entry 2	N/A	<5	0
9	entry 2, no *hv*	**4**	0	0

[a]Reaction conditions: iminoacetic acid **1** or **2** (0.15 mmol, 1.5 equiv), BI-alkyne **3** (0.10 mmol, 1.0 equiv), photocatalyst (0.002 mmol, 0.02 equiv), and BI-OAc **4** (0.1 mmol, 1.0 equiv) in 2.0 mL of 1,2-dichloroethane (DCE) under nitrogen with 4 W blue LED irradiation at 25 °C for 12 h, unless otherwise noted. [b]Yields were determined by ^{1}H NMR analysis using 1,3,5-trimethoxybenzene as the internal standard, and an isolated yield is given in parentheses. BI = benziodoxole.

were both present in **31**−**34**, only the selective δ-alkynylation adducts were observed in 46−79% yields. The reactive azide and free alcohol were not affected in the reaction, which further indicated the functional group tolerance of the reaction.

To further investigate the critical role of hypervalent iodine BI-OAc in the reaction, we prepared methoxy-iminophenylacetic acids (IPA-OMe) **35** and characterized their structure by X-ray crystallography (Scheme 3a).[18] We monitored the interaction of IPA-OMe **35** with BI-OAc **4** by NMR spectrometry (see Figure S1), and the formation of the new peaks suggested coordination of the hypervalent iodine to iminophenylacetic acids.[19] BI-IPA-OMe complex **36** was isolated and characterized by X-ray crystallography (CCDC 2009402), which showed a 2.08 Å I−O(IPA) bond and was the first hypervalent iodine(III)-coordinated iminoacetic acid or ketoacid isolated and characterized to date (Scheme 3a).[9a] We then investigated the intermolecular C−H alkynylation of cyclohexane **37** with BI-IPA-OMe **36**. Using BI-alkyne **3** as the radical acceptor, the addition of BI-IPA-OMe **36** afforded alkyne **38** in an unoptimized 35% yield (Scheme 3b). The *in situ* formation of **36** from IPA-OMe **35** and BI-OAc **4** resulted in a 57% yield of **38**, which suggested methoxyl radical generation under the reaction conditions.[20]

From the cyclic voltammetry measurement, the oxidation potential of hypervalent iodine-coordinated complex **36** (E_p = 1.25 V vs SCE in MeCN) was significantly decreased

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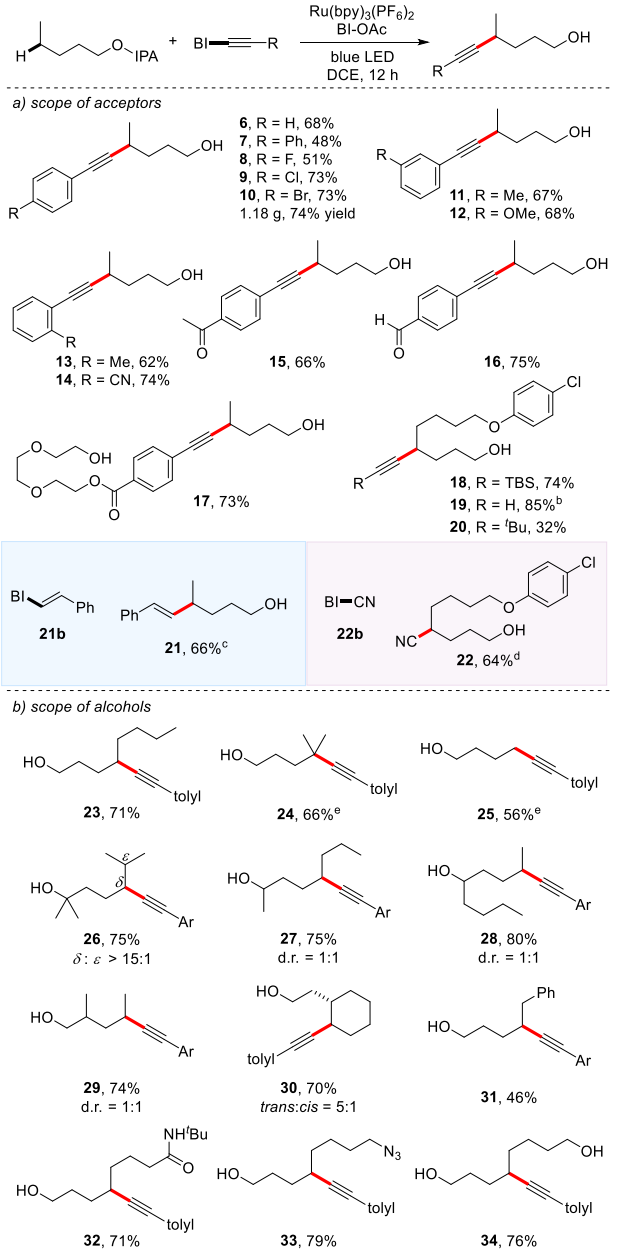
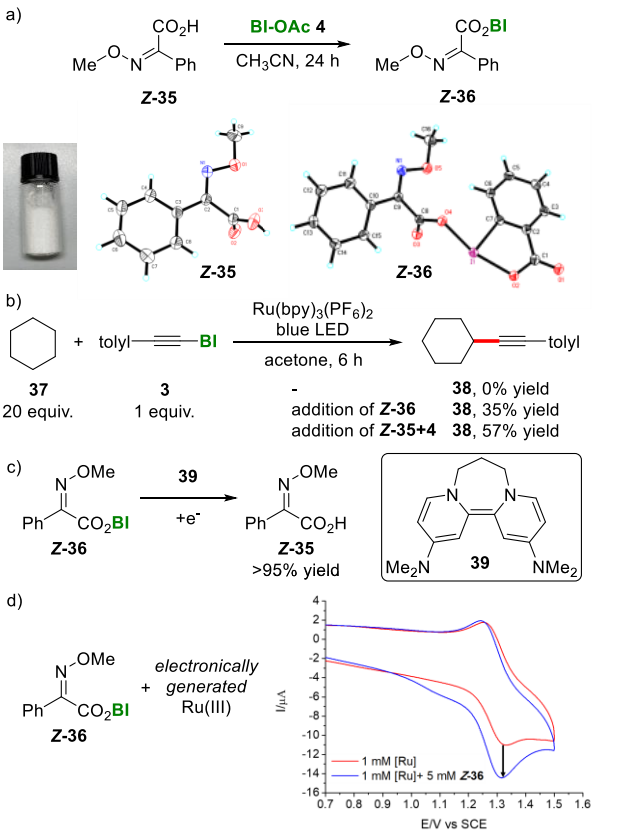
Scheme 2. Substrate Scope of δ-C(sp^3)−H Alkynylation with Alkoxyl-Iminophenylacetic Acids[a]



[a]For the reaction conditions, see entry 2 of Table 1. [b]After TBAF treatment. The yield was based on **18**. [c]BI-alkene was used as the acceptor. [d]BI-CN was used as the acceptor. [e]With 3.0 equiv of IPA-OR and 1.5 equiv of BI-OAc. Ar = 4-CHO-C_6H_4.

compared to that of IPA-OMe **35** (E_p = 1.71 V vs SCE in MeCN), falling in the redox potential range of various photocatalysts.[21] In fact, BI-IPA-OMe **36** quenched the fluorescence of the excited ruthenium photocatalyst effectively; however, IPA-OMe **35** afforded no quenching (Figure S10).[22] With **39** as the organic electron donor (E_{ox} = −1.24 V vs SCE in MeCN),[23] the single-electron reduction of BI-IPA-OMe **36** (E_{re} = −0.26 V vs SCE in MeCN) merely yielded 2-iodobenzoic acid in >95% yield, together with the recovery of methoxy-iminophenylacetic acid IPA-OMe **35** in >95% yield (Scheme 3c). The lack of fragmentation and methoxy radical generation in the reaction suggested the single-electron

Scheme 3. Discovery of the BI-IPA-OMe Complex and Reactivity



reduction on BI-IPA-OMe **36** did not yield the methoxy radical. In contrast, the addition of BI-IPA-OMe **36** to the electrochemically generated Ru(III) led to a significant increase in the anodic current, suggesting that BI-IPA-OMe **36** could be oxidized by Ru(III) (Scheme 3d).

We further carried out mechanistic investigations of C−H alkynylation with alkoxyl-iminophenylacetic acids (Scheme 4). Iminophenylacetic methyl ester **40** without the free carboxylic acid group was not converted under the reaction conditions, suggesting the coordination of BI to IPA was critical and further indicating the direct N−O bond cleavage by single-electron reduction was unlikely (Scheme 4a).[24] When the radical quencher TEMPO was added to the reaction mixture, the formation of **5** was completely inhibited. We also prepared iminophenylacetic acid **41** with a tethered alkene, and 5-exo cyclization/alkynylation adduct **42** was obtained smoothly in 60% yield under the standard reaction conditions, which confirmed the presence of the alkoxyl radical and expanded the synthetic utility of the reaction (Scheme 4b).[25] The quantum yield of the reaction was measured to be 0.50, indicating the long radical chain was unlikely.[26] The generally used photocatalytic decarboxylation conditions were not applicable for the reaction. The use of photocatalyst Ir-($dFCF_3ppy$)$_2$(dtbbpy)PF_6 or 4CzIPN under basic conditions afforded very poor product formation from IPA-OR **2** and resulted in BI-alkyne decomposition. These results together indicated the critical role of hypervalent iodine for the reaction (see Table S5).[27]

From the mechanistic investigations described above, the proposed catalysis cycle for C−H alkynylation is initiated via the oxidative quenching of the excited-state Ru(II)* by BI-

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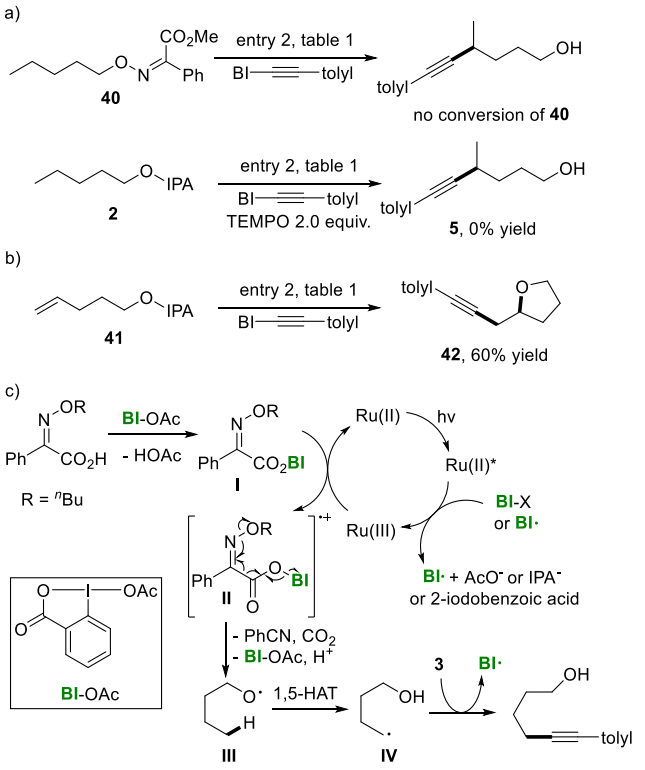
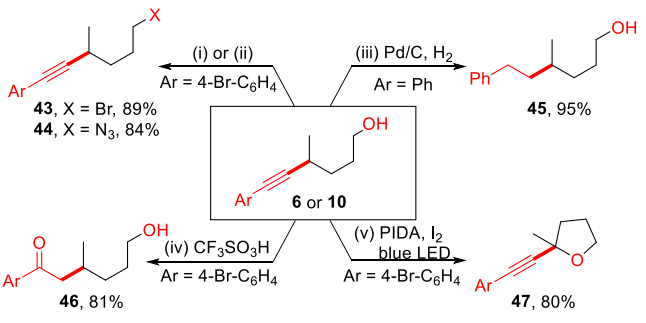
Scheme 4. Mechanistic Investigations of C−H Alkynylation



OAc or BI-IPA-OR to afford Ru(III) (Scheme 4c).[11b] The coordination of the iminophenylacetic acid with BI-OAc affords BI-IPA-OR complex **I**, which has a significantly reduced oxidation potential.[10a−d] The oxidation of BI-IPA-OR complex **I** by Ru(III) yields alkoxyl radical **III** after the concerted elimination of carbon dioxide and benzonitrile. Alkoxyl radical **III** then undergoes 1,5-HAT and alkynylation with BI-alkyne to afford the δ-C(sp^3)−H alkynylation adduct, and the released BI radical may also oxidatively quench the photoexcited Ru(II)* for catalytic turnover.[28]

Various alkynols from δ-C(sp^3)−H alkynylation are readily derivatized to bifunctional building blocks (Scheme 5). The alcohol moiety in δ-alkynol **10** was easily transformed into bromide **43** in 89% yield by the Appel reaction, and azido derivative **44** could be synthesized in two steps in a combined 84% yield. The palladium-catalyzed hydrogenation of **6** afforded branched aliphatic alcohol **45** in 95% yield, and alkyne hydration with trifluorosulfonic acids gave ϵ-hydroxylketone **46** in 81% yield. Under blue light irradiation conditions, δ-alkynol **10** underwent 1,5-HAT followed by smooth cyclization to produce alkynyl tetrahydropyran **47** in 80% yield, which is widely present in many bioactive natural products.

Scheme 5. Synthetic Applications of Hydroxylalkynes[a]



[a]Reaction conditions: (i) CBr_4, PPh_3, DCM, overnight; (ii) TsCl, Et_3N, DCM, overnight, then NaN_3, DMF, 80 °C, 8 h; (iii) 5% Pd/C, 1 atm of H_2, MeOH, 8 h; (iv) CF_3SO_3H, HFIP, overnight; (v) PIDA, I_2, DCM, blue LED, 6 h.

In conclusion, we have developed iminophenylacetic acid derivatives to generate alkoxyl radicals enabled by hypervalent iodine(III) reagents. The key alkoxyl benziodoxole-iminophenylacetic acid (BI-IPA-OR) complex was characterized by X-ray crystallography for the first time, and the decreased oxidation potentials were suitable for the facile single-electron oxidation. Various δ-alkynols can be synthesized by chemoselective δ-C(sp^3)−H alkynylation, and its products are useful bifunctional building blocks and could be prepared on gram scales.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.2c02210.

Mechanistic studies, substrate preparations and characterizations, crystal data, and NMR spectra of new compounds (PDF)

Accession Codes

CCDC 2009402 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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