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Selective Carbonyl–C(sp³) Bond Cleavage To Construct Ynamides, Ynoates, and Ynones by Photoredox Catalysis

Kunfang Jia, Yue Pan, and Yiyun Chen*

Abstract: Carbon–carbon bond cleavage/functionalization is synthetically valuable, and selective carbonyl– $C(sp^3)$ bond cleavage/alkynylation presents a new perspective in constructing ynamides, ynoates, and ynones. Reported here is the first alkoxyl-radical-enabled carbonyl– $C(sp^3)$ bond cleavage/alkynylation reaction by photoredox catalysis. The use of novel cyclic iodine(III) reagents are essential for β -carbonyl alkoxyl radical generation from β -carbonyl alcohols, including alcohols with high redox potential ($E_p^{ox} > 2.2 V$ vs. SCE in MeCN). β -Amide, β -ester, and β -ketone alcohols yield ynamides, ynoates, and ynones, respectively, for the first time, with excellent regio- and chemoselectivity under mild reaction conditions.

he carbonyl group is an important functional group in organic molecules, of which selective manipulation is valuable in organic synthesis. Compared to many synthetic efforts to construct carbonyl–C(sp³) (OC–alkyl) bonds,^[1] it is challenging to cleave the OC–alkyl bond selectively (Scheme 1 a).^[2] A traditional Norrish type-I reaction cleaves the OC–alkyl bond



b) Carbonyl–C(sp³) bond cleavage by β-alkoxyl radical with cyclic iodine(III) reagents in photoredox catalysis (this work)

c) Ynamide, ynoate, ynone formation from β-carbonyl alcohols (this work)

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CIR = cyclic Iodine(III) reagents

Scheme 1. Carbonyl– $C(sp^3)$ bond cleavage/functionalization for ynamide, ynoate, and ynone formation. TM = transition metal.

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by UV light irradiation to generate the acyl radical, however unselective OC–alkyl bond cleavage usually occurs and no further functionalization of the acyl radical has been reported.^[2a,b] Transition-metal catalysis requires very strong heating for unstrained OC–alkyl bond cleavage to generate the acyl metal intermediate, and limits the chemoselectivity and functional-group compatibility of the reaction.^[2c-f]

The alkoxyl radical is a versatile reactive intermediate for carbon-carbon bond-cleavage reactions.^[3] However, the OCalkyl bond cleavage/β-carbonyl functionalization of the alkoxyl radical is unknown.^[3a-c] Our group previously discovered that the cyclic iodine(III) reagent^[4] acetoylbenziodoxole enables alkoxyl radical generation from cyclic and linear alcohols by photoredox catalysis,^[3f] and provides a unique entry for studying unprecedented β-carbonyl alkoxyl radical reactivity with β-carbonyl alcohols (Scheme 1b).^[5] Ynones, ynamides, and ynoates are versatile synthons for natural product and heterocycles syntheses.^[6] While the syntheses of ynones are widely carried out using aldehydes and ketoacids as acyl precursors, the syntheses of ynamides and ynoates are challenging using the corresponding aldehyde and ketoacid derivatives as carbamoyl and alkoxylcarbonyl precursors, respectively.^[1a,4e] Herein, we report the first selective carbonyl-C(sp³) bond cleavage/alkynylation reactions of β -amide, β -ester, and β -ketone alcohols to construct ynamides, ynoates, and ynones, respectively (Scheme 1c).

We chose the β -amide alcohol **1** as the model substrate, as the amide $-C(sp^3)$ bond-cleavage reaction is not applicable through either Norrish type-I or transition-metal-catalysis reactions (Table 1).^[7] We initially tested acetoylbenziodoxole (BI-OAc; 4) with an alkynyl benziodoxole (BI-alkyne; 2) as the radical acceptor.^[8] Under blue LED ($\lambda_{max} = 468 \pm 25 \text{ nm}$) irradiation with $[Ru(bpy)_3](PF_6)_2$ as the photocatalyst, the OC-alkyl bond cleavage/alkynylation adduct 3 was obtained in 34% yield (entry 1). Unfortunately, with extensive screening of solvents and additives, we could not further improve the reaction.^[9] We then turned to CIR derivatives which have not been investigated in photoredox catalysis before.^[10] Using the F-BI-OAc derivatives 5 and 6, with an electron-withdrawing fluoro substituent, we found an improved yield of 3 (entries 2 and 3). When 3,4-F-BI-OAc (7), having two fluoro substituents, was used, the yield increased to 61% (entry 4). With 2,3,4,5-F-BI-OH (8), bearing four fluoro substituents, the reaction yield was satisfyingly optimized to 74% (entry 5). In comparison, using 3,4-MeO-BI-OAc (9), having two electronrich methoxy groups, a decreased yield was observed (entry 6). The noncyclic iodine(III) reagents PhI(OAc)₂ and PhI(OCOCF₃)₂ were ineffective (entries 7 and 8). The photocatalyst and light irradiation were both critical for the reaction (entries 9 and 10).

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We next tested different β -amide alcohols using the CIR/ photoredox catalytic system of entry 5 in Table 1. Anilinederived amide alcohols with either a free NH or N-alkylsubstituents underwent carbonyl-C(sp³) bond cleavage to deliver carbamoyl radicals smoothly, and subsequently yielded the ynamides 10 and 11 (Scheme 2).^[11] Dialkylsubstituted amide alcohols led to the ynamides 12 and 13 in 79% and 89% yield, respectively. BI-alkynes substituted with electron-rich methoxy and electron-deficient chloride groups reacted well to give 14 and 15, respectively. For β -ester alcohols which are resistant to both Norrish type-I and transition-metal catalysis reactions,^[12] the ynoates **16** and **17** were obtained, via alkoxylcarbonyl radical intermediates. uneventfully in 70% and 73% yield, respectively. For a β-ester alcohol derived from tert-butyl alcohol, the tert-butyl alkyne 18 was obtained in 73% yield after both ketone and carbon dioxide elimination.[13]

The β -ketone alcohols with various electron-deficient or electron-rich aryl substitutions were then tested (Scheme 2).^[11] The carbonyl-C(sp³) bond cleavage/alkynylation adducts 19-27 were obtained selectively in 72-91% yields without carbonyl-C(sp²) bond cleavage.^[14] The heterocyclic N-methylindole reacted without indole oxidation to give 28 in 67% yield. For alkyl-substituted ketone derivatives, the carbonyl–C(sp³) bond β to the alcohol was selectively cleaved to give 29 and 30. Various aryl substituents on BIalkynes were compatible, including electron-rich phenyl and methoxy groups, as well as electron-deficient fluorides, chlorides, ketones, or nitriles (31-38). n-Hexyl- or silylsubstituted BI-alkynes reacted smoothly to give the corresponding ynones 39 and 40 in 64% and 77% yield, respectively.



Scheme 2. Substrate scope with respect to β -amide, β -ester, and β -ketone alcohols. Reaction conditions a: entry 5 in Table 1, 24 h. Reaction condition b: entry 5 in Table 1, 5 h. Reaction condition c: entry 1 in Table 1, 24 h.^[11] Yields of isolated products were reported. $Ar = 4-MeOC_6H_4$.

To gain mechanistic insights into the reactivity of the β-carbonyl substrate under the CIR/photoredox catalytic system, we mixed the β -ketone cyclohexanol 41 (peaks marked with circles; Scheme 3a) with 4 and observed a new set of ¹H NMR signals (triangles; Scheme 3a). These characteristic peaks belong to the unprecedented β-ketone cvclohexanol/benziodoxole complex 42, which is an air-stable white solid.^[15] X-ray crystallography of 42 shows a long iodine-oxygen bond within the benziodoxole moiety (I-O3 = 2.18 Å), and a short iodine-oxygen bond $(I-O1 = 2.01 \text{ \AA})$ connecting the benziodoxole and the cyclohexanol moiety.^[3f,4d] We next measured the oxidation potential of 42 ($E_p^{ox} =$ 1.06 V vs. SCE in MeCN) by cyclic voltammetry and found a significant decrease compared to that of **41** ($E_{p}^{ox} = 1.69$ V vs. SCE in MeCN), and it explains the benziodoxole activation of the β -carbonyl alcohols (Scheme 3b). We then tested the CIR-alcohol complexes between different CIR derivatives and 41. The oxidation potential of the complex 44, with two electron-withdrawing fluoro substituents on the benziodoxole moiety, further decreased ($E_p^{ox} = 0.93$ V vs. SCE in MeCN),^[16] while the oxidation potential of the complex 45, with two electron-rich methoxy substituents, decreased to a lesser extent ($E_p^{ox} = 1.21 \text{ V}$ vs. SCE in MeCN). The complex between $4\hat{1}$ and $\hat{8}$ was too unstable to isolate, but the optimal

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Scheme 3. Discovery of the cyclic iodine(III) reagent/ β -ketone alcohol complex.

77% yield (74% isolated) of **43** suggested its superior β -carbonyl alcohol activation.

With these mechanistic insights, we tested β -carbonyl alcohols without electron-rich *p*-methoxyphenyl groups, as such compounds would significantly expand the substrate scope to alcohols with higher redox potentials ($E_p^{ox} > 2 V vs$. SCE in MeCN; Scheme 3c).^[3f,9] For phenyl- (**48**) and tolyl-substituted β -carbonyls (**49**) ($E_p^{ox} \approx 2 V vs$. SCE in MeCN), the use of **8** improved the OC–alkyl bond-cleavage/alkynylation reaction to 71–74 % yield, respectively. For the alcohols **50** and **51**, with very high redox potentials ($E_p^{ox} \approx 2.2 V vs$. SCE in MeCN), yields of 51 and 57 %, respectively, were obtained when using **8**.

We next carried out the TEMPO radical quenching experiment with the β -ketone alcohol **22a** (Scheme 4a). The alkynylation was inhibited and only the acyl-TEMPO adduct **52** was obtained in 21 % yield.^[17] When potassium persulfate was used to replace the cyclic iodine(III) reagent, the desired product **22** was not obtained (Scheme 4b). The cyclic iodine-(III) reagent is catalytic in the reaction as 0.3 equivalents of **8** is effective for obtaining **22** in 77 % yield. These results collectively suggest that the β -carbonyl alcohol/CIR complex is the key reaction intermediate, which is oxidized in the photocatalytic system to generate the β -carbonyl alkoxyl radical.^[18] Based on the mechanistic investigations described



Scheme 4. Mechanistic investigations and proposals.

above, we propose that the reaction is initiated by oxidation of the photoexcited Ru(bpy)_3^{2+*} to Ru(bpy)_3^{3+} by either the CIR or its decomposing CIR radical adduct (Scheme 4c).^[8f] The Ru(bpy)_3^{3+} then oxidizes the β -carbonyl alcohol/CIR complex formed in situ and releases the CIR cation (CIR⁺) for a new CIR catalytic cycle. The alkoxyl radical undergoes a β -carbonyl–C(sp³) bond-cleavage reaction to yield either the carbamoyl, alkoxylcarbonyl, or acyl radical, which does a radical addition to the alkynyl benziodoxole to form ynamides, ynoates, or ynones, respectively.

In conclusion, we have developed the first regio- and chemoselective carbonyl–C(sp³) bond-cleavage/alkynylation reaction of β -amide, β -ester, and β -ketone alcohols^[19] under mild photoredox catalysis conditions. Novel cyclic iodine(III) reagents are essential for alkoxyl radical generation from β -carbonyl alcohols, including alcohols with high redox potentials ($E_p^{ox} > 2.2$ V vs. SCE in MeCN). We envision this novel photoredox catalytic system with CIRs, bearing different electronic properties, will find various applications in chemoselective synthesis and biomolecule studies.

Acknowledgments

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Conflict of interest

The authors declare no conflict of interest.

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Keywords: acyl compounds · hypervalent compounds · photochemistry · radicals · reaction mechanisms

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- [11] For β -ester and β -amide alcohols with free NH groups, the reaction yields are significantly improved when using **8** for a reaction time of 24 h (conditions a), and much lower yields are obtained with **4** within 24 h (conditions c). For β -ketone and β -amide alcohols without a free NH group, the reaction yields are similar when using either **8** or **4**. However, the reactions are complete within 5 h with **8** (conditions b), and 24 h with **4** (conditions c).
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- [15] CCDC 1513742 (42) and 1520184 (44) contain the supplementary crystallographic data for this paper. These data are provided free of charge by The Cambridge Crystallographic Data Centre.
- [16] We also performed luminescence quenching experiments and found electron-deficient cyclic iodine(III) reagents quenched Ru(bpy)₃^{2+*} luminescence more effectively; see the Supporting Information for details. Both the decreased oxidation potential of the CIR-alcohol complex and increased oxidative quenching efficiency for photoexcited Ru^{II}* are responsible for the improved reaction kinetics and yields when using 8.
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- [19] The preparations of β-amide, β-ester, and β-ketone alcohols are straightforward and proceeds in two steps from simple starting materials; see the Supporting Information for details.

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Communications



K. Jia, Y. Pan, Y. Chen* _____

Selective Carbonyl–C(sp³) Bond Cleavage To Construct Ynamides, Ynoates, and Ynones by Photoredox Catalysis



Aye, aye CIR: Novel cyclic iodine reagents (CIRs) are essential for β -carbonyl alkoxyl radical generation from β -carbonyl alcohols in carbonyl–C(sp³) bond cleavage/ alkynylation reactions under photoredox catalysis. β -Amide, β -ester, and β -ketone alcohols yield ynamides, ynoates, and ynones, respectively, with excellent regioand chemoselectivity.