Hypervalent Iodine

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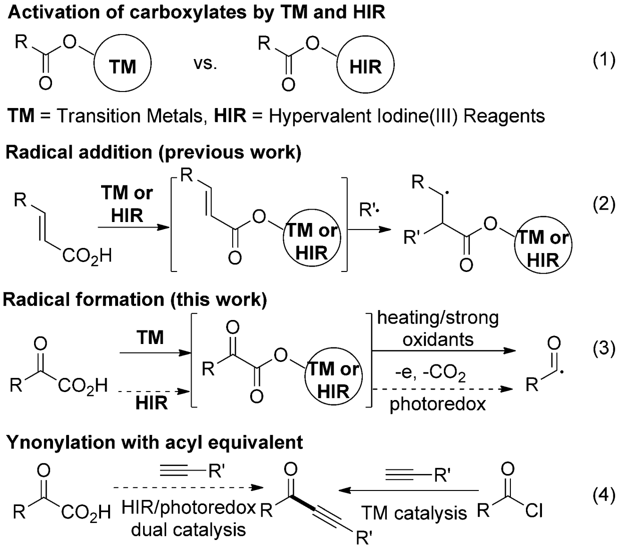
Dual Hypervalent Iodine(III) Reagents and Photoredox Catalysis Enable Decarboxylative Ynonylation under Mild Conditions**

*Hanchu Huang, Guojin Zhang, and Yiyun Chen**

Abstract: *A combination of hypervalent iodine(III) reagents (HIR) and photoredox catalysis with visible light has enabled chemoselective decarboxylative ynonylation to construct ynones, ynamides, and ynoates. This ynonylation occurs effectively under mild reaction conditions at room temperature and on substrates with various sensitive and reactive functional groups. The reaction represents the first HIR/photoredox dual catalysis to form acyl radicals from α-ketoacids, followed by an unprecedented acyl radical addition to HIR-bound alkynes. Its efficient construction of an mGlu5 receptor inhibitor under neutral aqueous conditions suggests future visible-light-induced biological applications.*



Organic carboxylates are readily available and stable, and a removable carboxylate acts as a latent activating group for organic synthesis.[1] Transition metals are widely used to activate carboxylates through formation of a transition-metal/carboxylate complex which facilitates extrusion of carbon dioxide.[2] Hypervalent iodine(III) reagents (HIR) demonstrate reactivity similar to transition metals, however, the analogous reactivity of HIR–carboxylate complexes has been less explored [Eq. (1)].[3] Our group recently discovered that HIR activated vinyl carboxylates similar to transition metals, which enabled radical addition followed by decarboxylation [Eq. (2)].[4] α-Ketoacids are important acyl synthons in organic synthesis; however, transition-metal-mediated decarboxylation requires activation by a transition metal followed by heating or strong oxidants.[2,5] We speculate that by forming the hypothetical HIR–ketoacid intermediate and subsequent photoredox catalysis, the decarboxylative acyl radical formation might be possible under mild reaction conditions [Eq. (3)].[6]

Ynones, ynamides, and ynoates are important structural motifs for the syntheses of natural products and heterocyclic molecules.[7] Although the transition-metal-catalyzed ynonylation by cross-coupling the acyl equivalent and the alkyne equivalent has been reported, such an ynonylation approach is limited and has poor functional-group tolerance because of the instability of the acyl halides used [Eq. (4)].[8,9] By using the readily available and stable α-ketoacids, we herein report the first decarboxylative ynonylation to construct ynones, ynamides, and ynoates by a HIR/photoredox dual catalysis [Eq. (4)].

We started our investigation with benzoylformic acid (**1**) by using the hypervalent iodine photoredox system[4,10] under irradiation with blue light-emitting diodes (LEDs, $\lambda_{max} = 468 \pm 25$ nm). Although terminal alkynes gave no ynonylation adducts, alkynyl bromides and alkynyl sulfones with acetoxybenziodoxole (BI-OAc) as additives gave the desired ynone **3** in low yields (Table 1, entries 1–3). To our delight, an alkynyl benziodoxole (BI-alkyne) gave ynone **3** in 81% yield. BI-alkyne was known as an electrophilic alkyne acceptor, but its tendency for acyl radical addition was unprecedented (entries 4).[10–12] Cyclic HIR reagents[13] including BI-OAc, hydroxybenziodoxole (BI-OH), and methoxybenziodoxole (BI-OMe) were all effective, among which BI-OAc was the most efficient with a yield of 85% (77% yield of isolated product; entries 5–7). Photosensitizer, light, and BI-OAc were all critical for this reaction (see Table S3 in the Supporting Information).[14]

We evaluated the substrate scope of the reaction under the optimized reaction conditions (Table 1, entry 5). Benzoylformic acids bearing an electron-rich 4-methyl or 4-methoxyl group yielded ynones **4** and **5** smoothly, and

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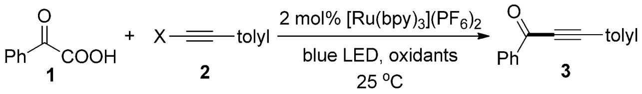
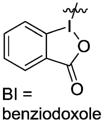
Table 1: Optimization of the ynonylation reaction.



Entry	Conditions	*t* [h]	Conversion	Yield
1	X = H, CH$_2$Cl$_2$/H$_2$O	10	91%	< 5%
2	X = Br, CH$_2$Cl$_2$/H$_2$O	10	82%	15%
3	X = Ts, CH$_2$Cl$_2$/H$_2$O	10	> 95%	39%
4	X = BI, CH$_2$Cl$_2$/H$_2$O	10	> 95%	81%
5	BI-OAc (1.0 equiv)	5	> 95%	85% (77%)
6	entry 5, BI-OH	5	87%	69%
7	entry 5, BI-OMe	5	> 95%	74%

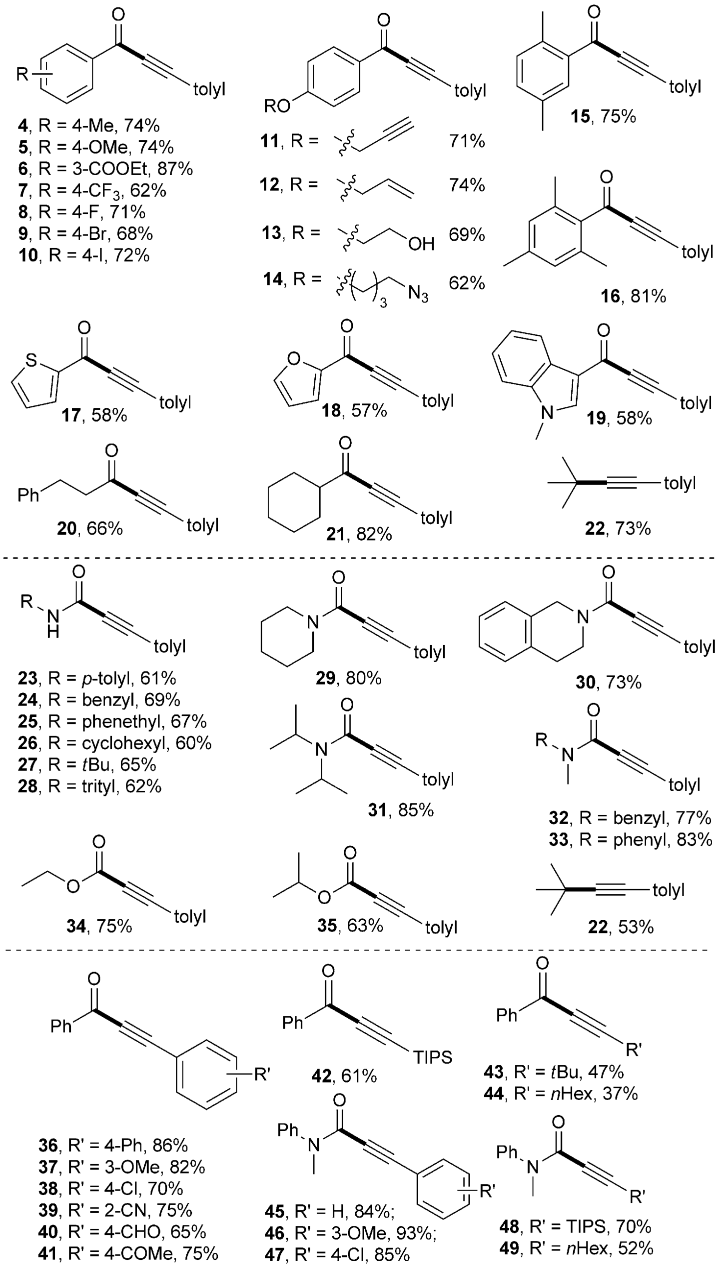
[a] Reaction conditions: **1** (0.15 mmol), **2** (0.10 mmol), BI-OAc (0.15 mmol), and [Ru(bpy)$_3$](PF$_6$)$_2$ (0.002 mmol) in 2.0 mL CH$_2$Cl$_2$ under nitrogen gas with 4 W LED irradiation at 468 nm at 25 °C, unless otherwise noted. [b] Conversions and yields were determined by ^{1}H NMR analysis, yields of isolated products are given in parentheses.



electron-deficient 3-ester, 4-trifluomethyl, or 4-fluoro derivatives yielded ynones **6**–**8** in yields of 62–87% (Scheme 1). Functional groups sensitive to transition-metal catalysis remained intact in the reaction, including aryl bromides and aryl iodides, which could be readily used as synthetic handles for further derivatizations (**9** and **10**). Substrates with allyl esters, propargyl esters, alcohols, and azides (**11**–**14**), which were not tolerated in other transition-metal-catalyzed reactions,[9a] all performed uneventfully. Steric bulk did not affect the reaction, with ynones **15** and **16** obtained in yields of 75 and 81%, respectively. Heterocyclic thiophenes, furans, and indoles reacted smoothly to give ynones **17**–**19**. Notably, alkyl-substituted ketoacids decarboxylated to give coupling adducts: Primary and secondary alkyl ketoacids gave ynones without decarbonylation in 66% and 82% yields, respectively (**20, 21**), while the tertiary alkyl ketoacid gave the dual decarboxylative-decarbonylative alkyne coupling adduct **22** in 73% yield.[15]

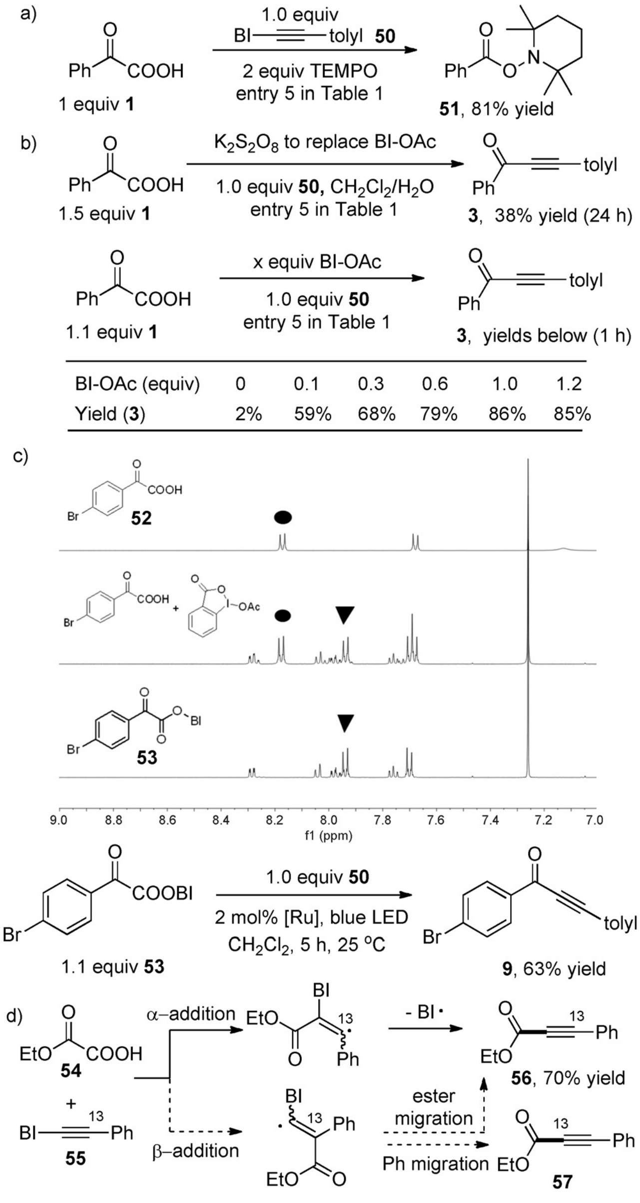
In addition to aryl- and alkyl-substituted α-ketoacids, carbamoyl ketoacids readily reacted to give ynamides: Primary carbamoyl ketoacids reacted to give, in yields of 61–69%, primary ynamide products, which could not be obtained by transition-metal-catalyzed aminocarbonylation because of the catalytic inhibition of primary amines by transition metals (**23**–**28**).[9b] Secondary carbamoyl ketoacids including aliphatic amines and aniline substitutions all showed excellent reactivity (**29**–**33**). Alkoxycarbonyl ketoacids reacted to give ynoates: Primary and secondary alkoxycarbonyl ketoacids gave ynones **34** and **35** in yields of 75% and 63%, respectively, while tertiary alkoxycarbonyl ketoacid interestingly gave the dual-decarboxylative alkyne coupling product **22** in 53% yield.[16] We also investigated the reactivity of different BI-alkynes and found that aryl-, alkyl-, and silyl-substituted ynones were all obtained smoothly. Various aryl substituents were tolerated on the BI-alkynes including electron-rich methoxy and phenyl groups, as well as electron-deficient chlorides, ketones, aldehydes, and nitriles (**36**–**41**, **45**–**47**). Alkyl-substituted BI-alkynes including bulky *tert*-butyl and linear hexyl groups resulted in slightly lower yields (**43**, **44**, **49**). The silyl-substituted BI-alkynes gave **42** and **48** in yields of 61 and 70%, respectively, which could be easily deprotected to give terminal ynones.

This observed broad substrate scope is unprecedented due to the mild reaction conditions for the dual HIR/photoredox catalysis, which prompted us to investigate the mechanism of the reaction. The radical quencher 2,2,6,6-tetramethylpiper-



Scheme 1. Substrate scope of the ynonylation reaction.

idinoxyl (TEMPO)[17] inhibited the ynonylation reaction and yielded the TEMPO addition adduct **51** in 81 % yield (Scheme 2 a). When benzoylformic acid (**1**) was injected into the reaction condition in the absence of BI-alkyne **50**, the formation of the decarboxylative diketone adduct through dimerization further confirmed the acyl radical intermediate (see Scheme S3 in the Supporting Information).[18] We next tested another effective oxidative quencher of photoexcited $Ru^{II}*$ species to study the role of BI-OAc. Interestingly, with 1.0 equivalent of potassium persulfates,[19] ynone **3** was obtained only in 38 % yield with side products after an extended 24 h reaction time (Scheme 2 b). In contrast, BI-OAc greatly accelerated the reaction, and a catalytic amount (0.1–0.6 equivalent) of BI-OAc was sufficient to yield ynone **3** in 59–79 % yield in 1 h with clean conversions. When the reaction time was extended to 8 h, 0.1 equivalent of BI-OAc was sufficient to yield ynone **3** in 81 % yield, which implied the catalytic role of BI-OAc (Scheme 2 b).[20] These results collectively suggested that HIR was not simply an oxidant for the photoexcited $Ru^{II}*$ species but also selectively activated the ketoacid.



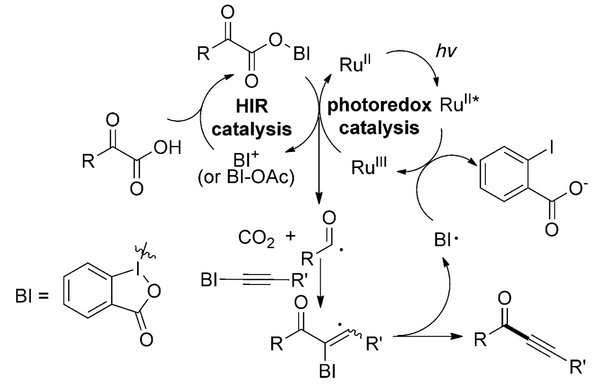
BI-OAc (equiv)	0	0.1	0.3	0.6	1.0	1.2
Yield (**3**)	2%	59%	68%	79%	86%	85%

Scheme 2. Mechanistic investigation of the ynonylation reaction.

We next mixed the ketoacid **52** (circles in Scheme 2 c) with BI-OAc and observed a new set of signals (triangles in Scheme 2 c) in the ^1H NMR spectrum, thus indicating the formation of a new ketoacid/benziodoxole complex. We further developed methods to prepare the stable, but previously unknown, BI–ketoacid complex **53**, and found the identical signals in the ^1H NMR spectrum (labeled with triangles, see the Supporting Information for details). This BI–ketoacid complex **53** could substitute ketoacid **52** and BI-OAc in the ynonylation reaction to yield ynone **9** in 63 % yield, which additionally confirmed the BI–ketoacid complex as the reaction intermediate (Scheme 2 c). We also carried out ^{13}C isotopic-labeling experiments to explore how the acyl radical added to the BI-alkyne. By using the ^{13}C-labled BI-alkyne **55**, we found exclusive ^{13}C retention in **56**, which was formed in 70 % yield. As the migration of the ester group was generally difficult,[21] a β-addition followed by an exclusive ester migration was unlikely (bottom equation in Scheme 2 d), thus an α-addition[22] accompanied by benziodoxole radical elimination was suggested (top equation in Scheme 2 d).

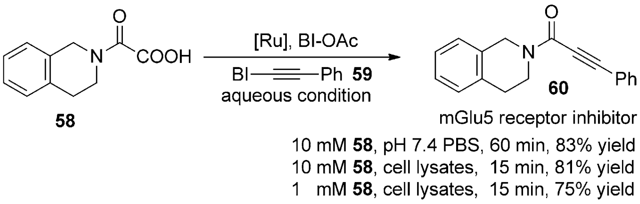
Based on the mechanistic investigations above, we propose that the ketoacid and BI-OAc generated a benziodoxole/ketoacid complex (BI–O_2CCOR') in situ, which was subsequently oxidized by $[Ru(bpy)_3]^{3+}$ to the acyl radical after decarboxylation (Scheme 3).[23] The resulting benziodoxole cation (BI^+ or the BI-OAc) and $[Ru(bpy)_3]^{2+}$ were regenerated for new HIR catalysis and photoredox catalysis cycle.[13] The acyl radical undergoes α-addition to BI-alkyne to yield the ynone, and the eliminated benziodoxole radical oxidizes the photoexcited $[Ru(bpy)_3]^{2+}*$ to complete the photoredox cycle.[10]

We next aimed to construct ynamide **60**, the structural motif of which represents an effective inhibitor for the metabotropic glutamate receptor 5 (mGlu5 receptor) and has therapeutic potential for disorders of both the peripheral and central nervous system.[24] Under the standard ynonylation conditions, ynamide **60** can be obtained in 75 % yield on a gram scale (see the Supporting Information for details). As the hypervalent-iodine reagent/photoredox system was shown



Scheme 3. Mechanistic proposal of the ynonylation reaction.

to be compatible with biomolecules,[10] we were curious if this ynonylation could be run under neutral aqueous reaction conditions. To our delight, the carbamoyl ketoacid **58** in pH 7.4 phosphate buffered saline (PBS) gave ynone **60** in 83 % yield (Scheme 4). The addition of cell lysates as complex biomolecule mixtures did not inhibit the reaction[25] and the ynonylation could be run at a 1 mM concentration in 75 % yield within 15 min, with reaction kinetics sufficient for biomolecule studies.[26] We envision this visible-light-induced construction of bioactive molecules under neutral aqueous conditions will be useful for biological studies.[27]



Scheme 4. Construction of an mGlu5 receptor inhibitor under neutral aqueous reaction conditions.

In conclusion, we have developed the first decarboxylative ynonylation by dual hypervalent iodine(III) reagents/photoredox catalysis, where the HIR demonstrates reactivity similar to or even superior to transition metals. This novel ynonylation method constructs ynones, ynamides, and ynoates with broad substrate scope, excellent chemoselectivity, and under mild reaction conditions at room temperature. The further reactivity and biological applications of this dual HIR/photoredox system is under investigation in our laboratory.

Keywords: decarboxylation · homogeneous catalysis · hypervalent compounds · photochemistry · ynonylation

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[1] L. J. Gooßen, N. Rodríguez, K. Gooßen, *Angew. Chem. Int. Ed.* **2008**, *47*, 3100–3120; *Angew. Chem.* **2008**, *120*, 3144–3164.

[2] N. Rodríguez, L. J. Gooßen, *Chem. Soc. Rev.* **2011**, *40*, 5030–5048.

[3] a) V. V. Zhdankin, *Hypervalent Iodine Chemistry: Preparation, Structure, and Synthetic Applications of Polyvalent Iodine Compounds*, Wiley, Weinheim, **2013**; b) P. J. Stang, V. V. Zhdankin, *Chem. Rev.* **1996**, *96*, 1123–1178; c) V. V. Zhdankin, P. J. Stang, *Chem. Rev.* **2008**, *108*, 5299–5358.

[4] H. Huang, K. Jia, Y. Chen, *Angew. Chem. Int. Ed.* **2015**, *54*, 1881–1884; *Angew. Chem.* **2015**, *127*, 1901–1904.

[5] a) L. J. Gooßen, F. Rudolphi, C. Oppel, N. Rodríguez, *Angew. Chem. Int. Ed.* **2008**, *47*, 3043–3045; *Angew. Chem.* **2008**, *120*, 3085–3088; b) J. Miao, H. Ge, *Synlett* **2014**, 911–919.

[6] The HIR-ketoacid complex was reported before; however, only the oxidative reactivity of HIR was demonstrated, see H. Togo, M. Katohgi, *Synlett* **2001**, 565–581.

[7] a) M. C. Bagley, C. Glover, E. A. Merritt, *Synlett* **2007**, 2459–2482; b) T. J. J. Müller, *Top. Heterocycl. Chem.* **2010**, *25*, 25–94.

[8] a) Y. Tohda, K. Sonogashira, N. Hagihara, *Synthesis* **1977**, 777–778; b) C. Boersch, E. Merkul, T. J. J. Müller, *Angew. Chem. Int. Ed.* **2011**, *50*, 10448–10452; *Angew. Chem.* **2011**, *123*, 10632–10636.

[9] The alternative approach is the transition-metal-catalyzed carbonylative ynonylation between organic halides and terminal alkynes at a high carbon monoxide pressure; however, the undesired Sonogashira reaction and toxic carbon monoxide limited its wide applications; see a) X. Wu, H. Neumann, M. Beller, *Chem. Soc. Rev.* **2011**, *40*, 4986–5009; b) Q. Liu, H. Zhang, A. Lei, *Angew. Chem. Int. Ed.* **2011**, *50*, 10788–10799; *Angew. Chem.* **2011**, *123*, 10978–10989.

[10] H. Huang, G. Zhang, L. Gong, S. Zhang, Y. Chen, *J. Am. Chem. Soc.* **2014**, *136*, 2280–2283.

[11] For selected reviews on alkynyl benziodoxoles, see a) V. V. Zhdankin, P. J. Stang, *Tetrahedron* **1998**, *54*, 10927–10966; b) J. P. Brand, J. Waser, *Chem. Soc. Rev.* **2012**, *41*, 4165–4179; for early studies, see c) M. Ochiai, Y. Masaki, M. Shiro, *J. Org. Chem.* **1991**, *56*, 5511–5513; d) V. V. Zhdankin, C. J. Kuehl, A. P. Krasutsky, J. T. Bolz, A. J. Simonsen, *J. Org. Chem.* **1996**, *61*, 6547–6551; for selected examples on electrophilic alkynylations, see e) J. P. Brand, J. Charpentier, J. Waser, *Angew. Chem. Int. Ed.* **2009**, *48*, 9346–9349; *Angew. Chem.* **2009**, *121*, 9510–9513; f) C. Feng, T. P. Loh, *Angew. Chem. Int. Ed.* **2014**, *53*, 2722–2726; *Angew. Chem.* **2014**, *126*, 2760–2764; g) F. Xie, Z. S. Qi, S. J. Yu, X. W. Li, *J. Am. Chem. Soc.* **2014**, *136*, 4780–4787; h) K. D. Collins, F. Lied, F. Glorius, *Chem. Commun.* **2014**, *50*, 4459–4461; i) Z. Wang, L. Li, Y. Huang, *J. Am. Chem. Soc.* **2014**, *136*, 12233–12236; for selected examples on alkyl radical alkynylations, see j) X. S. Liu, Z. T. Wang, X. M. Cheng, C. Z. Li, *J. Am. Chem. Soc.* **2012**, *134*, 14330–14333; k) R. Y. Zhang, L. Y. Xi, L. Zhang, S. Liang, S. Y. Chen, X. Q. Yu, *RSC Adv.* **2014**, *4*, 54349–54353.

[12] For reviews on acyl radicals, see a) C. Chatgilialoglu, D. Crich, M. Komatsu, I. Ryu, *Chem. Rev.* **1999**, *99*, 1991–2069; b) G. J. Rowlands, *Tetrahedron* **2009**, *65*, 8603–8655; c) G. J. Rowlands, *Tetrahedron* **2010**, *66*, 1593–1636.

[13] V. V. Zhdankin, *Curr. Org. Synth.* **2005**, *2*, 121–145.

[14] See the Supporting Information for detailed optimizations.

[15] Tertiary alkyl substituted acyl radicals decarbonylated readily to produce tertiary alkyl radicals, see C. Chatgilialoglu, C. Ferreri, M. Lucarini, P. Pedrielli, G. F. Pedulli, *Organometallics* **1995**, *14*, 2672–2676.

[16] a) D. H. R. Barton, D. Crich, *Tetrahedron Lett.* **1985**, *26*, 757–760; b) P. A. Simakov, F. N. Martinez, J. H. Horner, M. Newcomb, *J. Org. Chem.* **1998**, *63*, 1226–1232.

[17] T. Vogler, A. Studer, *Synthesis* **2008**, 1979–1993.

[18] The dimer formation was the result of radical combinations, see M. J. Gibian, R. C. Corley, *Chem. Rev.* **1973**, *73*, 441–464.

[19] a) F. Bolletta, A. Juris, M. Maestri, D. Sandrini, *Inorg. Chim. Acta* **1980**, *44*, L175–L176; b) W. J. Miao, *Chem. Rev.* **2008**, *108*, 2506–2553.

[20] The addition of BI-OAc in the dark also facilitated oxidation of the ketoacid, see Scheme S7 in the Supporting Information for the use of TEMPO as oxidants.

[21] a) U. Aeberhard, R. Keese, E. Stamm, U. C. Vogeli, W. Lau, J. K. Kochi, *Helv. Chim. Acta* **1983**, *66*, 2740–2759; b) D. A. Lindsay, J. Lusztyk, K. U. Ingold, *J. Am. Chem. Soc.* **1984**, *106*, 7087–7093.

[22] J. Gong, P. L. Fuchs, *Tetrahedron Lett.* **1997**, *38*, 787–790.

[23] In another reported photoredox example using ketoacids, the reductive Ru^{I} intermediate was proposed, and the superoxide rather than Ru^{III} was suggested to oxidize the ketoacid, see J. Liu, Q. Liu, H. Yi, C. Qin, R. Bai, X. Qi, Y. Lan, A. Lei, *Angew. Chem. Int. Ed.* **2014**, *53*, 502–506; *Angew. Chem.* **2014**, *126*, 512–516.

[24] a) G. Jaeschke, J. G. Wettstein, R. E. Nordquist, W. Spooren, *Expert Opin. Ther. Pat.* **2008**, *18*, 123–142; b) S. Kuehnert, M. Reich, S. Zemolka, M. Haurand, K. Schiene (Grunenthal

GmbH), U.S. Patent 2009/0075978A1, **2009**; c) S. T. Gadge, M. V. Khedkar, S. R. Lanke, B. M. Bhanage, *Adv. Synth. Catal.* **2012**, *354*, 2049 – 2056.

[25] K. D. Collins, F. Glorius, *Nat. Chem.* **2013**, *5*, 597 – 601.

[26] E. M. Sletten, C. R. Bertozzi, *Angew. Chem. Int. Ed.* **2009**, *48*, 6974; *Angew. Chem.* **2009**, *121*, 7108.

[27] a) T. Fehrentz, M. Schonberger, D. Trauner, *Angew. Chem. Int. Ed.* **2011**, *50*, 12156 – 12182; *Angew. Chem.* **2011**, *123*, 12362 – 12390; b) R. K. V. Lim, Q. Lin, *Acc. Chem. Res.* **2011**, *44*, 828 – 839; c) Q. Y. Liu, A. Deiters, *Acc. Chem. Res.* **2014**, *47*, 45 – 55; d) C. Hu, Y. Chen, *Tetrahedron Lett.* **2015**, *56*, 884.

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