JACS
JOURNAL OF THE AMERICAN CHEMICAL SOCIETY

Communication

pubs.acs.org/JACS

Visible-Light-Induced Chemoselective Deboronative Alkynylation under Biomolecule-Compatible Conditions

Hanchu Huang, Guojin Zhang, Li Gong, Shuaiyan Zhang, and Yiyun Chen*

State Key Laboratory of Bioorganic and Natural Products Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 345 Lingling Road, Shanghai 200032 People's Republic of China

Supporting Information

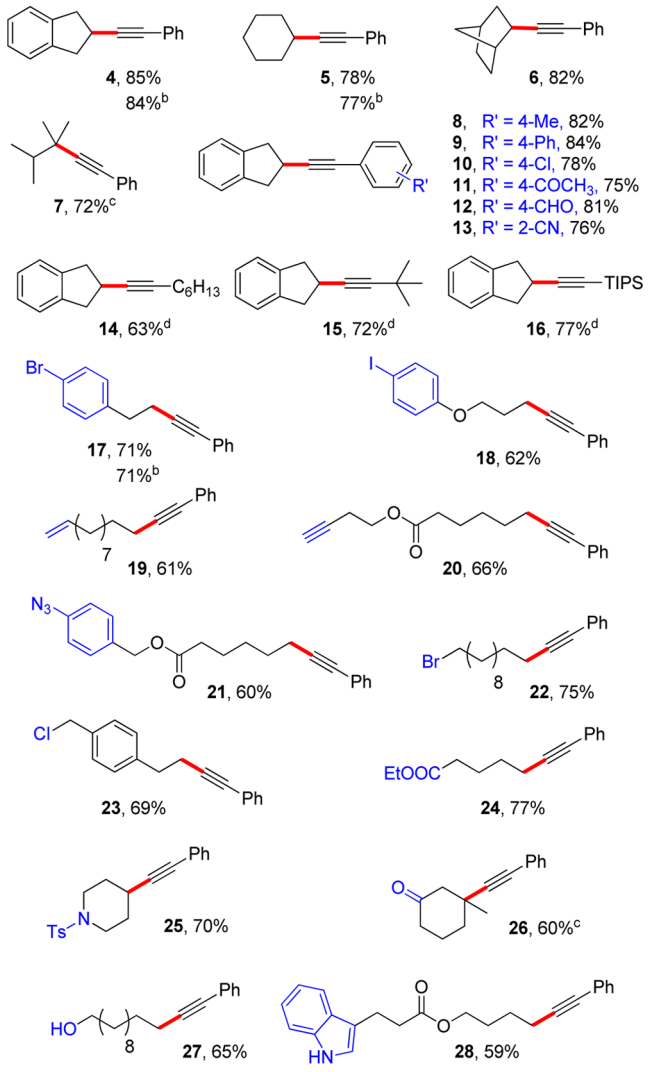
ABSTRACT: Here, we report a visible-light-induced deboronative alkynylation reaction, which is redox-neutral and works with primary, secondary and tertiary alkyl trifluoroborates or boronic acids to generate aryl, alkyl and silyl substituted alkynes. This reaction is highly chemoselective and performs well on substrates containing alkenes, alkynes, aldehydes, ketones, esters, nitriles, azides, aryl halides, alkyl halides, alcohols, and indoles, with no detectable occurrence of side reactions. The mechanism of this novel C(sp^3)−C(sp) bond coupling reaction was investigated by luminescence quenching, radical trapping, on−off light, and ^{13}C-isotopic-labeling experiments. This reaction can be performed in neutral aqueous conditions, and it is compatible with amino acids, nucleosides, oligosaccharides, nucleic acids, proteins, and cell lysates.

Chemoselective bond formations and cleavages are useful for manipulating molecules with sensitive functional groups.[1,2] For biomolecule studies in particular, neutral aqueous conditions are required.[3,4] In aqueous conditions, solvent-insensitive radical reactions performed well compared to cationic or anionic reactions.[5,6] However, its functional group compatibility was limited by radical initiation methods such as high temperature or UV light. Recently, visible light catalysis has resurged in the organic synthesis community[7−9] and appears promising for radical initiations under mild conditions.[10,11] Some limited examples on oxidative coupling of phenols[12,13] and reduction of azides[14,15] have shown visible light catalysis could be biomolecule-compatible and applicable in vitro and in cellulo.

The boronate is stable in neutral aqueous conditions, and its small size is suitable for biomolecule applications.[16] Previous reports used strong oxidants to couple alkyl boronates with quinones[17], alkenes[18,19], arenes[20,21], or isocyanides[22]. Recently, some alkyl boronates were shown to couple with 2,2,6,6-tetramethylpiperidin-1-yl)oxy (TEMPO) or Michael acceptors under visible light catalysis conditions.[23,24] As the visible-light-induced C(sp^3)−C(sp) bond coupling using boronates was unprecedented and the resulting alkyne was biomolecule-compatible,[25] we aimed to develop a novel visible-light-induced deboronative alkynylation and to further explore its biomolecule compatibility under neutral aqueous conditions.

We first studied alkyl trifluoroborate **1** with various alkynes under blue LED (λ_{max} = 468 ± 25 nm) irradiation using [Ru(bpy)$_3$](PF$_6$)$_2$ as the photocatalyst. Terminal alkynes or alkynyl

Scheme 1. Substrates Scope and Functional Group Compatibility of the Deboronative Alkynylation Reaction

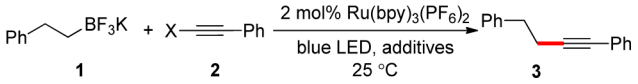


[a]Reaction conditions: entry 6 in Table 1, trifluoborates were used, unless otherwise noted. [b]Reaction conditions: entry 12 in Table 1, boronic acids were used. [c]3 equiv. of trifluoborates and 4 equiv. of Na_2CO_3 were used, [d]3 equiv. of trifluoborates were used.

Received: December 29, 2013
Published: February 3, 2014

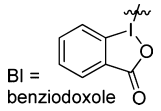
   dx.doi.org/10.1021/ja413208y | J. Am. Chem. Soc. 2014, 136, 2280−2283

Table 1. Optimization of the Deboronative Alkynylation Reaction



entry	conditions[a]	time	conversion	yield[b]
1	$K_2S_2O_8$ (2.0 equiv.), X = H	15 h	<5%	0
2	$K_2S_2O_8$ (2.0 equiv.), X = BF_3K	15 h	<5%	0
3	$K_2S_2O_8$ (2.0 equiv.), X = SO_2Ph	15 h	21%	10%
4	$K_2S_2O_8$ (2.0 equiv.), X = BI	15 h	57%	28%
5	BI−OH (2.0 equiv.), X = BI	15 h	42%	34%
6	BI−OH (0.5 equiv.), X = BI Na_2CO_3 (2.0 equiv.)	5 h	>95%	76% (73%)
7	entry 6, no $Ru(bpy)_3(PF_6)_2$	12 h	<5%	0
8	entry 6, no blue LED	12 h	<5%	0
9	entry 6, no BI−OH	12 h	<5%	0
10	BI−OMe (0.5 equiv.), X = BI Na_2CO_3 (2.0 equiv.)	8 h	>95%	77%
11	entry 6, BI−OH (0.05 equiv.)	5 h	>95%	77%
12	entry 6, $PhCH_2CH_2B(OH)_2$ as **1**	12 h	>95%	78% (71%)
13	entry 6, air	12 h	>95%	71%

[a]Reaction conditions: **1** (0.30 mmol, 1.5 equiv.), **2** (0.20 mmol, 1 equiv.), and $Ru(bpy)_3(PF_6)_2$ (0.004 mmol, 0.02 equiv.) in 2.0 mL (1:1) CH_2Cl_2/H_2O under nitrogen with 4 W blue LED irradiation at 25 °C, unless otherwise noted. [b]Conversions and yields were determined by ^1H NMR analysis, and isolated yields were in parentheses.



boronates gave no oxidative coupling products (entries 1 and 2 in Table 1). Interestingly, alkynyl sulfones[26−29] or alkynyl benziodoxoles (BI−alkyne)[30−32] yielded alkynylation **3** in the presence of persulfates (entries 3 and 4). As this deboronative alkynylation between trifluoroborates and electrophilic alkyne equivalents was redox-neutral, the stoichiometric strong oxidant persulfates should not be required and could contribute to side reactions. After examining various oxidants (Supporting Information Table S1), we found the mild oxidant hydroxybenziodoxole (BI−OH) mediated the reaction with suppressed side reactions (entry 5).[33−35] Further screening (Supporting Information Tables S2−4) revealed that Na_2CO_3 improved the reaction yield to 76% in 5 h at 25 °C (isolated yield 73%, entry 6).[36] Photocatalyst and light irradiation were both critical (entries 7 and 8). BI−OH was necessary but could be substituted by methoxybenziodoxole (BI−OMe) (entries 9 and 10). As expected, 5 mol % BI−OH was sufficient for this transformation (entry 11). Trifluoroborates could be substituted by boronic acids with little decrease in reaction yields and the air atmosphere was operative for the reaction (entries 12 and 13).

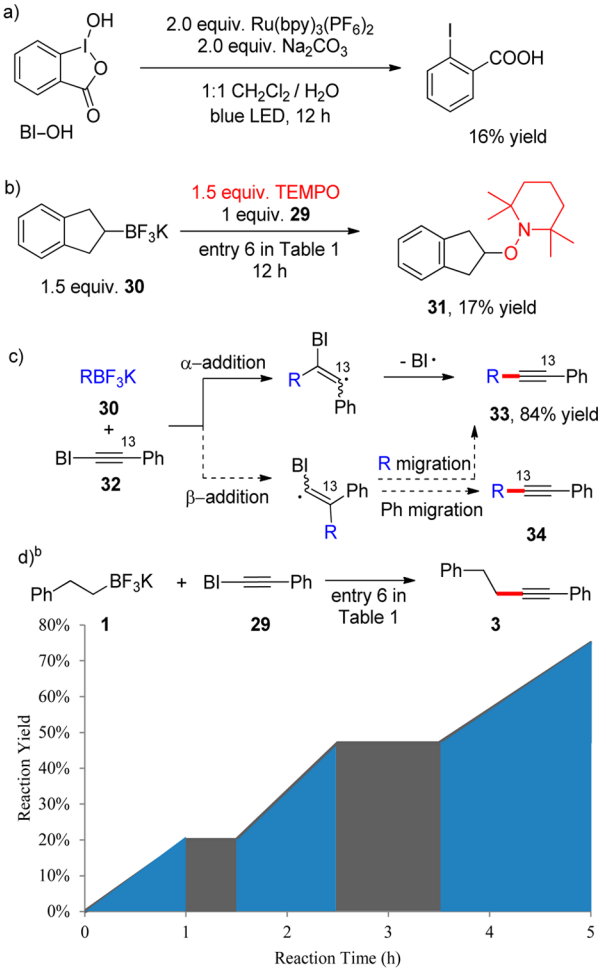
With this newly developed $[Ru(bpy)_3](PF_6)_2$/BI−OH catalytic system, the deboronative alkynylation was tested on broad substrate variations and demonstrated excellent chemoselectivity. Primary, secondary, and tertiary alkyl trifluoroborates (or boronic acids) bearing different substitutions all gave good to excellent results (products **4**−**7** in Scheme 1; see entry 6 in Table 1 for conditions). Various aryl substituents were tolerated on BI−alkyne including electron-rich methyl and phenyl groups, as well as electron-deficient chlorides, ketones, aldehydes, and nitriles (products **8**−**13**). Alkyl substituted BI−alkyne including linear hexyl and bulky *tert*-butyl groups performed well with the addition of three equivalents of trifluoroborates (products **14** and **15**). The silyl-substituted BI−alkyne gave 77% yield (product **16**). Functional groups typically sensitive to transition metal catalysis were tolerated, which included aryl bromides, aryl iodides, unactivated alkenes, unactivated alkynes, and azides (products **17**−**21**). Functional groups prone to nucleophilic or electrophilic side reactions also remained intact, which included alkyl bromides, benzyl chlorides, esters, sulfonamides, ketones, alcohols, and indoles (products **22**−**28**).

To gain insights on the $[Ru(bpy)_3](PF_6)_2$/BI−OH catalytic system, we carried out luminescence quenching experiments. We observed a decrease of $Ru(bpy)_3(PF_6)_2$ luminescence in the presence of BI−OH (or BI−OMe), but not in the presence of trifluoroborates or BI−alkyne (Supporting Information Schemes S1−4). This was in sharp contrast to previous reports, where trifluoroborates reductively quenched the photoexcited iridium(III) complex.[23,24] In addition, when BI−OH was mixed with two equivalents of $Ru(bpy)_3(PF_6)_2$ under the blue LED irradiation for 12 h, *o*-iodobenzoic acid was observed in 16% yield amid low conversions (Scheme 2a). These observations suggested BI−OH (or BI−OMe) interacted with the photoexcited $Ru(bpy)_3^{2+*}$ and generated $Ru(bpy)_3^{3+}$ for reaction initiation. We also recovered 87% yield of *o*-iodobenzoic acid along with the alkynylation adduct when 5 mol % BI−OH was used (entry 11 in Table 1), which confirmed BI−alkyne's role as an internal oxidant and this reaction was redox-neutral (Supporting Information Scheme S6).[37]

To test if this visible-light-induced reaction underwent the radical process, we added the radical quencher TEMPO[38] to the optimized reaction condition (entry 6 in Table 1). After 12 h, neither the desired alkynylation adduct **4** nor the alkyne−TEMPO adduct was observed, only the alkyl−TEMPO adduct **31** was isolated in 17% yield amid low conversions, which indicated the presence of alkyl R radical (Scheme 2b). To explore how the alkyl R radical reacted with BI−alkyne, we prepared ^{13}C isotope-labeled BI−alkyne **32.** With exclusive ^{13}C retention adduct **33,** an α addition followed by benziodoxole radical

dx.doi.org/10.1021/ja413208y | J. Am. Chem. Soc. 2014, 136, 2280−2283

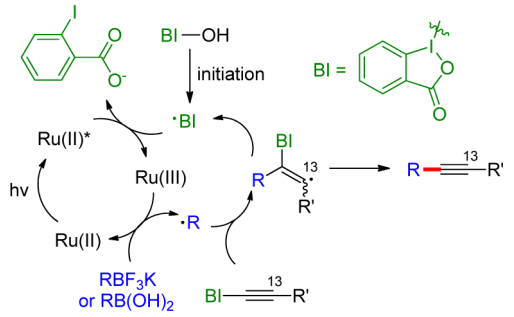
Scheme 2. Mechanistic Investigations of the Deboronative Alkynylation Reaction



[a]Reaction conditions: entry 6 in Table 1, unless otherwise noted. [b]The blue area indicates the blue LED irradiation, while the grey area indicates the dark treatment. The x axis is the reaction time, and the y axis is the reaction yield of **3**.

elimination was suggested (top equation in Scheme 2c).[30,39] In contrast, a β addition followed by an unpreferential alkyl R group migration was unlikely (bottom equation in Scheme 2c).[40−42] To explore if benziodoxole radicals could oxidize trifluoroborates for radical propagation, we performed on−off light experiments and observed the light dependence (Scheme 2d). We further tested the conditions known to generate alkyl R radical[17] and observed no alkynylation (Supporting Information Scheme S10). Taken together, radical propagation from benziodoxole radicals was unlikely.[43]

Scheme 3. Mechanistic Proposal of the Deboronative Alkynylation Reaction

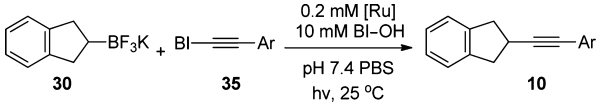


Based on mechanistic investigations above, we proposed that $Ru(bpy)_3^{2+}$ was photoexcited[44] to $Ru(bpy)_3^{2+*}$ and oxidized by the benziodoxole radical (or its precursor BI−OH) to $Ru(bpy)_3^{3+}$ (Scheme 3). The resulting $Ru(bpy)_3^{3+}$ oxidized alkyl trifluoroborate (or boronic acid) to alkyl R radical and regenerated $Ru(bpy)_3^{2+}$. The alkyl R radical did α−addition to BI−alkyne and yielded the alkyne. The eliminated benziodoxole radical oxidized $Ru(bpy)_3^{2+*}$ to generate the *o*-iodobenzoic acid, which was removed by the addition of bases.

To enable the biomolecule compatibility of this deboronative alkynylation, it was required to remove the base Na_2CO_3 from the reaction condition. Gladly, in buffered (pH 6, 7.4, and 8) CH_2Cl_2/H_2O mixed solvents, 71−75% yields of alkynylation adduct were obtained (Supporting Information Table S5).[45] We further searched for reactivity with minimal organic solvents and found 100% neutral aqueous buffer was applicable for this reaction (pH 7.4 phosphate saline buffers, entry 1 in Table 2).

With this mild neutral aqueous condition and excellent chemoselectivity, we tested the compatibility of deboronative alkynylation with various biomolecules.[46] In standard neutral aqueous conditions (entry 1), the addition of stoichiometric

Table 2. Deboronative Alkynylation Reaction in Neutral Aqueous Conditions and in the Presence of Biomolecules



entry	conditions[a]	time	conversion	yield[b]
1	100% pH 7.4 10X PBS	5 h	>95%	76%
2	entry 1, 1.0 equiv. L-tyrosine	5 h	>95%	75% (70%)
3	entry 1, 1.0 equiv. L-cysteine	12 h	>95%	73%
4	entry 1, 1.0 equiv. L-methionine	5 h	>95%	83%
5	entry 1, 1.0 equiv. guanosine	5 h	>95%	74%
6	entry 1, 1.0 equiv. naringin	5 h	>95%	68%
7	entry 1, 6.4 mg/mL ss DNA	8 h	>95%	78% (69%)
8	entry 1, 10 mg/mL bovine serum albumin	12 h	>95%	72%
9	entry 1, 2 mg/mL bacterial cell lysates	12 h	>95%	86%

[a]Reaction conditions: **30** (0.075 mmol, 16.8 mg, 1.5 equiv.), **35** (Ar = *p*-chlorophenyl, 0.05 mmol, 19.1 mg, 1.0 equiv.), $Ru(bpy)_3(PF_6)_2$ (0.001 mmol, 0.86 mg, 0.02 equiv.), and BI−OH (0.05 mmol, 13.2 mg, 1.0 equiv.) in 5 mL of 10X PBS buffers for 5−12 h under nitrogen with blue LED irradiation at 25 °C, unless otherwise noted. [b]Conversions and yields were determined by ^{1}H NMR analysis, and isolated yields were in parentheses.

dx.doi.org/10.1021/ja413208y | J. Am. Chem. Soc. 2014, 136, 2280−2283

(mole or mass) amount of biomolecules including amino acids, nucleosides, oligosaccharides, nucleic acids, or proteins did not significantly affect the reaction (entries 2−8). We also tested bacterial cell lysates, which contained various endogenous biomolecules, and found the uncompromised alkynylation in 86% yield (entry 9).

In conclusion, we have developed a visible-light-induced deboronative alkynylation reaction with the $[Ru(bpy)_3](PF_6)_2$/BI−OH catalytic system. This reaction works with primary, secondary, and tertiary alkyl trifluoroborates or boronic acids to generate aryl, alkyl, and silyl substituted alkynes. Its broad substrate scope, excellent chemoselectivity, and mild reaction conditions bring a useful new addition to $C(sp^3)$−C(sp) bond coupling reactions. Its compatibility with amino acids, nucleosides, oligosaccharides, nucleic acids, proteins, and cell lysates suggests future biomolecule applications. The further reactivity and mechanism of this $[Ru(bpy)_3](PF_6)_2$/BI−OH catalytic system is under investigation in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

Complete mechanistic experiments, optimization tables, experimental methods, and additional experimental data. This material is available free of charge via the Internet at http://pubs.acs.org

■ AUTHOR INFORMATION

Corresponding Author

yiyunchen@sioc.ac.cn

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This paper is dedicated to Professor David R. Liu on the occasion of his 40th birthday. Financial support was provided by the National Basic Research Program of China 2014CB910304, National Natural Science Foundation of China 21272260, "Thousand Talents Program" Young Investigator Award, Shanghai Pujiang Investigator Award 12PJ1410700, the start-up fund from State Key Laboratory of Bioorganic and Natural Products Chemistry, and Chinese Academy of Sciences.

■ REFERENCES

(1) Shenvi, R. A.; O'Malley, D. P.; Baran, P. S. *Acc. Chem. Res.* **2009**, *42*, 530.
(2) Afagh, N. A.; Yudin, A. K. *Angew. Chem., Int. Ed.* **2010**, *49*, 262.
(3) Kolb, H. C.; Finn, M. G.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **2001**, *40*, 2004.
(4) Sletten, E. M.; Bertozzi, C. R. *Angew. Chem., Int. Ed.* **2009**, *48*, 6974.
(5) Rowlands, G. J. *Tetrahedron* **2009**, *65*, 8603.
(6) Li, C.-J. *Chem. Rev.* **2005**, *105*, 3095.
(7) Ischay, M. A.; Anzovino, M. E.; Du, J.; Yoon, T. P. *J. Am. Chem. Soc.* **2008**, *130*, 12886.
(8) Nicewicz, D. A.; MacMillan, D. W. C. *Science* **2008**, *322*, 77.
(9) Narayanam, J. M. R.; Tucker, J. W.; Stephenson, C. R. J. *J. Am. Chem. Soc.* **2009**, *131*, 8756.
(10) Yoon, T. P.; Ischay, M. A.; Du, J. N. *Nature Chem.* **2010**, *2*, 527.
(11) Prier, C. K.; Rankic, D. A.; MacMillan, D. W. C. *Chem. Rev.* **2013**, *113*, 5322.
(12) Fancy, D. A.; Kodadek, T. *Proc. Natl. Acad. Sci. U. S. A.* **1999**, *96*, 6020.
(13) Sato, S.; Nakamura, H. *Angew. Chem., Int. Ed.* **2013**, *52*, 8681.
(14) Chen, Y.; Kamlet, A. S.; Steinman, J. B.; Liu, D. R. *Nature Chem.* **2011**, *3*, 146.
(15) Sadhu, K. K.; Eierhoff, T.; Römer, W.; Winssinger, N. *J. Am. Chem. Soc.* **2012**, *134*, 20013.
(16) *Boronic Acids: Preparation and Applications in Organic Synthesis, Medicine and Materials*, 2 ed.; Wiley-VCH: Weinheim, Germany, 2011.
(17) Fujiwara, Y.; Domingo, V.; Seiple, I. B.; Gianatassio, R.; Del Bel, M.; Baran, P. S. *J. Am. Chem. Soc.* **2011**, *133*, 3292.
(18) Liwosz, T. W.; Chemler, S. R. *Org. Lett.* **2013**, *15*, 3034.
(19) Sorin, G.; Mallorquin, R. M.; Contie, Y.; Baralle, A.; Malacria, M.; Goddard, J. P.; Fensterbank, L. *Angew. Chem., Int. Ed.* **2010**, *49*, 8721.
(20) Molander, G. A.; Colombel, V.; Braz, V. A. *Org. Lett.* **2011**, *13*, 1852.
(21) Neufeldt, S. R.; Seigerman, C. K.; Sanford, M. S. *Org. Lett.* **2013**, *15*, 2302.
(22) Tobisu, M.; Koh, K.; Furukawa, T.; Chatani, N. *Angew. Chem., Int. Ed.* **2012**, *51*, 11363.
(23) Yasu, Y.; Koike, T.; Akita, M. *Adv. Synth. Catal.* **2012**, *354*, 3414.
(24) Miyazawa, K.; Yasu, Y.; Koike, T.; Akita, M. *Chem. Commun.* **2013**, *49*, 7249.
(25) Kolb, H. C.; Sharpless, K. B. *Drug Discovery Today* **2003**, *8*, 1128.
(26) Gong, J. C.; Fuchs, P. L. *J. Am. Chem. Soc.* **1996**, *118*, 4486.
(27) Back, T. G. *Tetrahedron* **2001**, *57*, 5263.
(28) Schaffner, A. P.; Darmency, V.; Renaud, P. *Angew. Chem., Int. Ed.* **2006**, *45*, 5847.
(29) Brand, J. P.; Waser, J. *Chem. Soc. Rev.* **2012**, *41*, 4165.
(30) Liu, X. S.; Wang, Z. T.; Cheng, X. M.; Li, C. Z. *J. Am. Chem. Soc.* **2012**, *134*, 14330.
(31) Ochiai, M.; Masaki, Y.; Shiro, M. *J. Org. Chem.* **1991**, *56*, 5511.
(32) Zhdankin, V. V.; Kuehl, C. J.; Krasutsky, A. P.; Bolz, J. T.; Simonsen, A. J. *J. Org. Chem.* **1996**, *61*, 6547.
(33) Zhdankin, V. V. *Curr. Org. Synth.* **2005**, *2*, 121.
(34) Stang, P. J.; Zhdankin, V. V. *Chem. Rev.* **1996**, *96*, 1123.
(35) Zhdankin, V. V.; Stang, P. J. *Chem. Rev.* **2008**, *108*, 5299.
(36) Pure CH_2Cl_2 or the mixable solvents (MeCN/H_2O, DMF/H_2O) did not give good results; however, when boronic acids were used, either CH_2Cl_2/H_2O or pure CH_2Cl_2 gave excellent results (Supporting Information Table S2).
(37) As BI−OH and BI−alkyne were prepared from o-iodobenzoic acid, this catalytic alkynylation was sustainable.
(38) Vogler, T.; Studer, A. *Synthesis−Stuttgart* **2008**, 1979.
(39) Xiang, J. S.; Fuchs, P. L. *Tetrahedron Lett.* **1996**, *37*, 5269.
(40) Ochiai, M.; Kunishima, M.; Nagao, Y.; Fuji, K.; Shiro, M.; Fujita, E. *J. Am. Chem. Soc.* **1986**, *108*, 8281.
(41) Stang, P. J. *Angew. Chem., Int. Ed.* **1992**, *31*, 274.
(42) Frei, R.; Waser, J. *J. Am. Chem. Soc.* **2013**, *135*, 9620.
(43) The on−off light experiment alone was not sufficient to indicate that no radical chain process was occurring. For example, see Wallentin, C. J.; Nguyen, J. D.; Finkbeiner, P.; Stephenson, C. R. J. *J. Am. Chem. Soc.* **2012**, *134*, 8875. Also see Espelt, L. R.; Wiensch, E. M.; Yoon, T. P. *J. Org. Chem* **2013**, *78*, 4107.
(44) Juris, A.; Balzani, V.; Barigelletti, F.; Campagna, S.; Belser, P.; Vonzelewsky, A. *Coordin. Chem. Rev.* **1988**, *84*, 85.
(45) The resulting *o*-iodobenzoic acid (pK_a 2.85, ref 32) was detrimental to the reaction, which could be removed either by addition of bases or by pH 6−8 buffers.
(46) Collins, K. D.; Glorius, F. *Nature Chem.* **2013**, *5*, 597.