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Synthesis of Isoquinolones Using Visible-Light-Promoted Denitrogenative Alkyne Insertion of 1,2,3-Benzotriazinones

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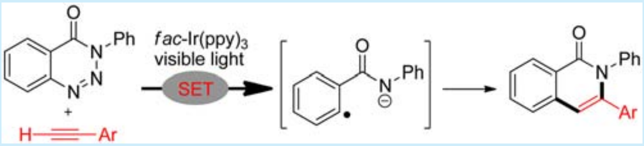
S *Supporting Information*

ABSTRACT: A visible-light-promoted regioselective denitrogenative insertion of terminal alkynes into 1,2,3-benzotriazinones is reported. This mechanistically novel process allows the synthesis of substituted isoquinolones in satisfactory isolated yields (24 examples, 46−84% yield) at room temperature under visible-light irradiation with the assistance of a photocatalyst. The proposed single-electron-transfer pathway was supported by TEMPO trapping, radical clock experiments, and Stern−Volmer analysis.



Isoquinolones, an important class of heterocycles, exist in many natural products and biologically active molecules,[1] such as the natural product antinoplanone A[2] and the anticancer polyketide (−)-kibdelone C.[3] Therefore, the development of efficient methods for the synthesis of isoquinolones has attracted intense interest from synthetic chemists.[4−7] One of the most popular strategies recently developed for the construction of these heterocycles is the transition-metal-catalyzed annulation of benzamides with alkynes (Figure 1a).[5] Mechanistically, oxidative annulation of benzamides with a transition metal-based catalyst through C−H/N−H bond cleavage gives metallocycles **A** as the key intermediates, followed by alkyne insertion and reductive elimination. Elevated temperature and oxidants (internal or external) are normally necessary for these transformations. When unsymmetrical internal alkynes or terminal alkynes are employed, a mixture of regioisomers is frequently produced.[5a,d,p,q]

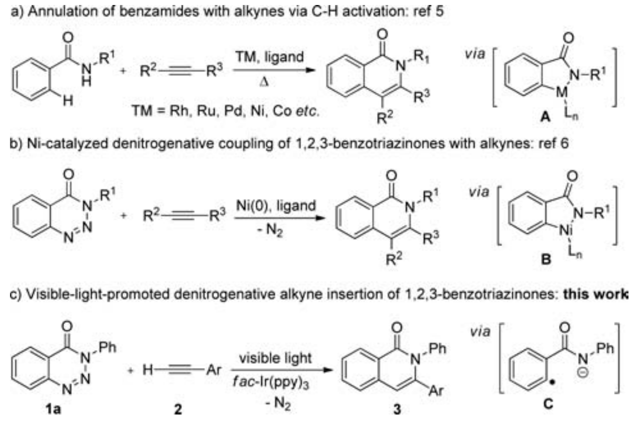


Figure 1. Syntheses of isoquinolones.

In 2008, a nickel-catalyzed alkyne insertion reaction of 1,2,3-benzotriazin-4(3*H*)-ones to synthesize substituted isoquinolones was reported (Figure 1b).[6,8] Nickelacyles **B** generated from the denitrogenative annulation of 1,2,3-benzotriazin-4(3*H*)-ones with the nickel catalyst were proposed as the key intermediates. A mixture of regioisomers was also produced with unsymmetrical alkynes, especially terminal alkynes.

Our group is currently engaged in the de novo synthesis of (hetero)arenes using visible-light-promoted radical alkyne or isocyanide insertions.[9] These sustainable and eco-friendly transformations are enabled by photoredox catalysis, which takes advantage of the redox potential of photocatalysts under visible-light irradiation.[10] The cyclic voltammogram of 1,2,3-benzotriazone **1a** contains a reversible reduction wave at −0.812 V vs SCE (for details, see the Supporting Information), which indicates that **1a** is easily reduced by an excited-state photocatalyst, such as *fac*-Ir(ppy)$_3$* ($E_{1/2}^{\mathrm{IV}/*\mathrm{III}}$ = −1.73 V vs SCE).[10a] On the basis of these observations, a mechanistically novel strategy was proposed for the construction of isoquinolones (Figure 1c). The reduced 1,2,3-benzotriazinone **1a** could prompt the extrusion of molecular dinitrogen, giving the key radical anion intermediate **C**, which can then undergo radical alkyne insertion followed by cyclization and oxidation to give isoquinolone **3**. As we previously observed,[9d] these visible-light-promoted radical alkyne insertions are regioselective even when terminal alkynes are employed. Herein we report our efforts on the regioselective synthesis of isoquinolones using the denitrogenative alkyne insertion of 1,2,3-benzotriazinones under visible-light photoredox catalysis.

Our rationale was evaluated by selecting 1,2,3-benzotriazinone **1a** and *p*-methoxyphenylacetylene (**2a**) as the reaction partners. When a solution of **1a** (1.0 equiv) and **2a** (1.5 equiv) in DMSO was irradiated using blue LEDs in the presence of the photocatalyst *fac*-Ir(ppy)$_3$ for 15 h, the desired product **3a** was obtained in 53% isolated yield, together with a 32% yield of the

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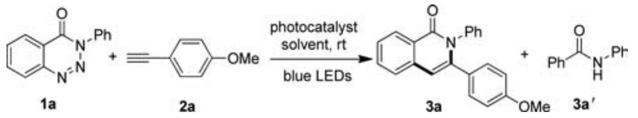
denitrogenation product **3a′** as a major byproduct (Table 1, entry 1). Control experiments verified the necessity of the photocatalyst and visible-light irradiation, as there was no reaction and the starting materials **1a** and **2a** were fully recovered without visible light irradiation or *fac*-Ir(ppy)$_3$ (entries 2 and 3). The reaction could not proceed when *fac*-Ir(ppy)$_3$ was replaced by other photocatalysts such as Ru(bpy)$_3$(PF$_6$)$_2$, Ru(Phen)(PF$_6$)$_2$, Ir(dFCF$_3$ppy)$_2$(dtbbpy)PF$_6$, and Ir(ppy)$_2$(dtbbpy)PF$_6$ (entries 4–7) because of their lower reduction potentials in their excited states compared with *fac*-Ir(ppy)$_3$. The solvent effect was then investigated. When DMF was used as the solvent, less of the desired product **3a** (12%) and more of the denitrogenation product **3a′** (55%) were produced (entry 8). Other solvents such as THF, acetone, DCM, CH$_3$CN, and MeOH could not promote this reaction (entries 9–13). Finally, the dosage of alkyne **2a** was examined. When 2.0 equiv of **2a** was used, more of the desired product **3a** (63%) and less of the denitrogenation product **3a′** (20%) were produced (entry 14). The yield of **3a** further increased to 83% with as little as 13% yield of **3a′** when 3.0 equiv of **2a** was used (entry 15).

Table 1. Optimization of the Reaction Conditions[a]

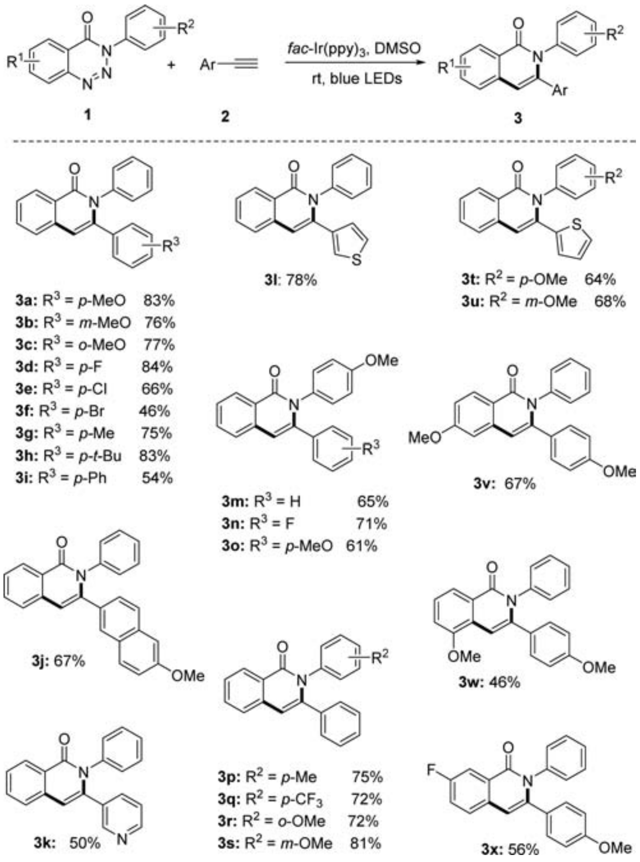


entry	photocatalyst	solvent	3a/%[b]	3a′/%[b]
1	Ir(ppy)$_3$	DMSO	53	32
2	none	DMSO	0	0
3[c]	Ir(ppy)$_3$	DMSO	0	0
4	Ru(bpy)$_3$(PF$_6$)$_2$	DMSO	0	0
5	Ru(Phen) (PF$_6$)$_2$	DMSO	0	0
6	Ir(dFCF$_3$ppy)$_2$(dtbbpy)PF$_6$	DMSO	0	0
7	Ir(ppy)$_2$(dtbbpy)PF$_6$	DMSO	0	0
8	Ir(ppy)$_3$	DMF	12	55
9	Ir(ppy)$_3$	THF	0	0
10	Ir(ppy)$_3$	acetone	0	0
11	Ir(ppy)$_3$	DCM	0	0
12	Ir(ppy)$_3$	CH$_3$CN	0	0
13	Ir(ppy)$_3$	MeOH	0	0
14[d]	Ir(ppy)$_3$	DMSO	63	20
15[e]	Ir(ppy)$_3$	DMSO	83	13

[a]Reaction conditions: A solution of **1a** (0.2 mmol), **2a** (0.3 mmol), and catalyst (0.002 mmol, 1.0 mol %) in the indicated solvent (2.0 mL) was irradiated using blue LED strips at rt for 15 h. [b]Isolated yields. [c]In the dark. [d]2.0 equiv of **2a** (0.4 mmol) was used. [e]3.0 equiv **2a** (0.6 mmol) was used.

With the optimized reaction conditions in hand, the synthetic potential of this visible-light-promoted denitrogenative alkyne insertion was then investigated, and the results are summarized in Scheme 1. First, different terminal alkynes were tested using 1,2,3-benzotriazinone **1a** as the reaction partner. Steric effects did not affect this transformation significantly, as *p*-, *m*-, and *o*-methoxyphenylacetylenes gave similar yields of isoquinolones **3a–c** (76–83%). The electronic properties of the phenylacetylene were then investigated. Substituted phenylacetylenes with electron-donating and electron-neutral groups on the benzene ring worked smoothly to produce the corresponding isoquinolones **3d–I** in good yields (46–84%). Naphthalene-, pyridine-, and thiophene-derived terminal alkynes could also frequently undergo this transformation to provide isoquinolones **3j–l** in 50–78% yield. The nonterminal alkynes and aliphatic terminal alkynes we tested thus far could not undergo this transformation; the starting material was recovered. The substituent on the nitrogen atom of the 1,2,3-benzotriazinone was then examined. Different substituted phenyl groups on the nitrogen atom could be employed, providing *N*-arylisoquinolones **3m–u** in 61–81% yield. Isoquinolones **3v–x** with different substituents on the benzene ring could also be prepared in 46–67% yield.

Scheme 1. Substrate Scope of the Reaction[a]

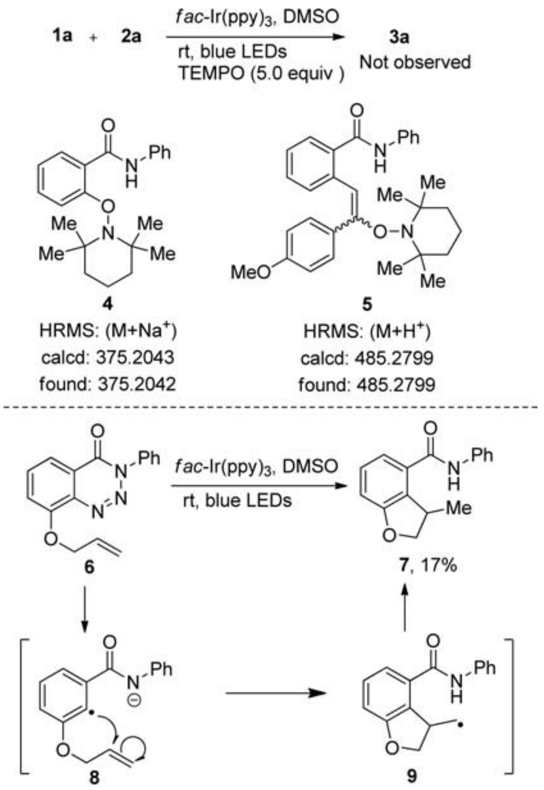


[a]Reaction conditions: A mixture of **1** (0.2 mmol), **2** (0.6 mmol), and *fac*-Ir(ppy)$_3$ (0.002 mmol, 1.0 mol %) in dry DMSO (2.0 mL) was irradiated using blue LED strips. Yields of isolated products are shown.

To gain insight into the mechanism of this reaction, a series of control reactions were conducted, as shown in Scheme 2. Addition of the radical trap 2,2,6,6-tetramethylpiperidin-1-oxyl (TEMPO) to the model reaction terminated the desired reaction completely. Instead, the radical-trapped products **4** and **5** could be observed by high-resolution mass spectrometry. These results suggested that this reaction involves a single-electron-transfer (SET) pathway. The radical nature of this transformation was further supported by a radical clock experiment.[11] When 1,2,3-benzotriazinone **6** was subjected to the standard conditions without addition of an alkyne, 2,3-dihydrobenzofuran derivative **7** was isolated in 17% yield. This experiment also suggested that the reduction of a 1,2,3-benzotriazinone gave a carbon-centered radical instead of a nitrogen-centered radical.

Furthermore, the luminescence of *fac*-Ir(ppy)$_3$ with excitation at 350 nm could be readily quenched by **1a** following

Scheme 2. TEMPO Trapping and Radical Clock Experiments



Stern–Volmer kinetics (Figure 2). This luminescence quenching is most likely due to photoinduced electron transfer.

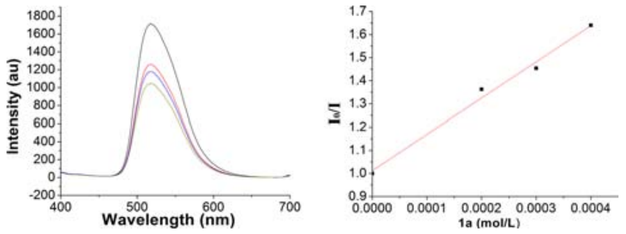


Figure 2. (left) Luminescence quenching of *fac*-Ir(ppy)$_3$ with excitation at 350 nm by **1a**. (right) The Stern–Volmer plot.

On the basis of these experimental observations and literature precedents,[9,10] a plausible mechanism is proposed (Figure 3). First, the Ir^{III} photocatalyst is irradiated to the excited state Ir^{III}* ($E_{1/2}^{IV/*III}$ = −1.73 V vs SCE) using blue LEDs, and this excited state is then oxidatively quenched by **1a** ($E_p^{1a/1a^{-\bullet}}$ = −0.812 V vs SCE) with concomitant generation of Ir^{IV} and radical anion **10**. Radical anion **10** adds to alkyne **2a** to produce radical anion **11**, followed by intramolecular addition to form radical anion **13**. Finally, radical anion **13** is oxidized by Ir^{IV} to yield isoquinolone **3a** with regeneration of the photocatalyst. Radical anion **10** can also abstract a hydrogen atom following protonation, which can give the side product *N*-phenylbenzamide (**3a′**).

In summary, we have described a visible-light-promoted regioselective denitrogenative insertion of terminal alkynes into 1,2,3-benzotriazinones. This mechanistically novel process can provide substituted isoquinolones in satisfactory isolated yields (24 examples, up to 84% yield) at room temperature under visible-light irradiation with the assistance of a photocatalyst. Control experiments supported the proposed SET pathway. Further explorations of the mechanistic details and additional visible-light-promoted denitrogenative insertions are underway in our laboratory.

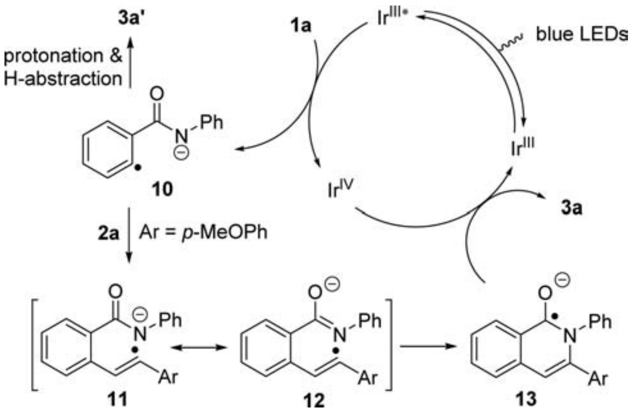


Figure 3. Proposed mechanism.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b01960.

Experimental procedures and spectral data (PDF)

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) (a) Lewis, J. R. *Nat. Prod. Rep.* **1994**, *11*, 329. (b) González, M. C.; Zafra-Polo, M. C.; Blázquez, M. A.; Serrano, A.; Cortes, D. *J. Nat. Prod.* **1997**, *60*, 108. (c) Chen, C.-Y.; Chang, F.-R.; Pan, W.-B.; Wu, Y.-C. *Phytochemistry* **2001**, *56*, 753. (d) Zhang, Z.; Li, S.; Zhang, S.; Liang, C.; Gorenstein, D.; Beasley, R. S. *Planta Med.* **2004**, *70*, 1216. (e) Ruchelman, A. L.; Houghton, P. J.; Zhou, N.; Liu, A.; Liu, L. F.; LaVoie, E. J. *J. Med. Chem.* **2005**, *48*, 792. (f) Cappelli, A.; Mohr, G. P.; Giuliani, G.; Galeazzi, S.; Anzini, M.; Mennuni, L.; Ferrari, F.; Makovec, F.; Kleinrath, E. M.; Langer, T.; Valoti, M.; Giorgi, G.; Vomero, S. *J. Med. Chem.* **2006**, *49*, 6451. (g) Giri, P.; Kumar, G. S. *Mini-Rev. Med. Chem.* **2010**, *10*, 568. (h) Bhadra, K.; Kumar, G. S. *Mini-Rev. Med. Chem.* **2010**, *10*, 1235. (i) Larsson, E. A.; Jansson, A.; Ng, F. M.; Then, S. W.; Panicker, R.; Liu, B.; Sangthongpitag, K.; Pendharkar, V.; Tai, S. J.; Hill, J.; Dan, C.; Ho, S. Y.; Cheong, W. W.; Poulsen, A.; Blanchard, S.; Lin, G. R.; Alam, J.; Keller, T. H.; Nordlund, P. *J. Med. Chem.* **2013**, *56*, 4497.

(2) Ratnayake, R.; Lacey, E.; Tennant, S.; Gill, J. H.; Capon, R. J. *Chem. - Eur. J.* **2007**, *13*, 1610.

(3) (a) Kobayashi, K.; Nishino, C.; Ohya, J.; Sato, S.; Mikawa, T.; Shiobara, Y.; Kodama, M. *J. Antibiot.* **1988**, *41*, 741. (b) Butler, J. R.;

Wang, C.; Bian, J.; Ready, J. M. *J. Am. Chem. Soc.* **2011**, *133*, 9956. (c) Sloman, D. L.; Bacon, J. W.; Porco, J. A., Jr. *J. Am. Chem. Soc.* **2011**, *133*, 9952.

(4) For a review of the synthesis of isoquinolones, see: Glushkov, V. A.; Shklyaev, Y. V. *Chem. Heterocycl. Compd.* **2001**, *37*, 663.

(5) For rhodium-catalyzed syntheses of isoquinolones, see: (a) Hyster, T. K.; Rovis, T. *J. Am. Chem. Soc.* **2010**, *132*, 10565. (b) Guimond, N.; Gouliaras, C.; Fagnou, K. *J. Am. Chem. Soc.* **2010**, *132*, 6908. (c) Guimond, N.; Gorelsky, S. I.; Fagnou, K. *J. Am. Chem. Soc.* **2011**, *133*, 6449. (d) Mochida, S.; Umeda, N.; Hirano, K.; Satoh, T.; Miura, M. *Chem. Lett.* **2010**, *39*, 744. (e) Wang, H.; Grohmann, C.; Nimphius, C.; Glorius, F. *J. Am. Chem. Soc.* **2012**, *134*, 19592. (f) Huckins, J. R.; Bercot, E. A.; Thiel, O. R.; Hwang, T.-Li; Bio, M. M. *J. Am. Chem. Soc.* **2013**, *135*, 14492. (g) Song, G.; Chen, D.; Pan, C.-L.; Crabtree, R. H.; Li, X. *J. Org. Chem.* **2010**, *75*, 7487. (h) Xu, X.; Liu, Y.; Park, C.-M. *Angew. Chem., Int. Ed.* **2012**, *51*, 9372. For ruthenium-catalyzed syntheses of isoquinolones, see: (i) Ackermann, L.; Lygin, A. V.; Hofmann, N. *Angew. Chem., Int. Ed.* **2011**, *50*, 6379. (j) Ackermann, L.; Fenner, S. *Org. Lett.* **2011**, *13*, 6548. (k) Li, B.; Feng, H.; Xu, S.; Wang, B. *Chem. - Eur. J.* **2011**, *17*, 12573. For palladium-catalyzed syntheses of isoquinolones, see: (l) Zhang, N.; Li, B.; Zhong, H.; Huang, J. *Org. Biomol. Chem.* **2012**, *10*, 9429. (m) Zhong, H.; Yang, D.; Wang, S.; Huang, J. *Chem. Commun.* **2012**, *48*, 3236. (n) Peng, X.; Wang, W.; Jiang, C.; Sun, D.; Xu, Z.; Tung, C.-H. *Org. Lett.* **2014**, *16*, 5354. (o) Shu, Z.; Li, W.; Wang, B. *ChemCatChem* **2015**, *7*, 605. For a nickel-catalyzed synthesis of isoquinolones, see: (p) Shiota, H.; Ano, Y.; Aihara, Y.; Fukumoto, Y.; Chatani, N. *J. Am. Chem. Soc.* **2011**, *133*, 14952. For a cobalt-catalyzed synthesis of isoquinolones, see: (q) Grigorjeva, L.; Daugulis, O. *Angew. Chem., Int. Ed.* **2014**, *53*, 10209.

(6) Miura, T.; Yamauchi, M.; Murakami, M. *Org. Lett.* **2008**, *10*, 3085.

(7) For other methods for the synthesis of isoquinolones, see: (a) Manna, S.; Antonchick, A. P. *Angew. Chem., Int. Ed.* **2014**, *53*, 7324. (b) Chen, Z.-W.; Zhu, Y.-Z.; Ou, J.-W.; Wang, Y.-P.; Zheng, J.-Y. *J. Org. Chem.* **2014**, *79*, 10988. (c) Kajita, Y.; Matsubara, S.; Kurahashi, T. *J. Am. Chem. Soc.* **2008**, *130*, 6058. (d) Zeng, R.; Dong, G. *J. Am. Chem. Soc.* **2015**, *137*, 1408.

(8) For other selected examples of denitrogenative couplings of triazoles, see: (a) Yamauchi, M.; Morimoto, M.; Miura, T.; Murakami, M. *J. Am. Chem. Soc.* **2010**, *132*, 54. (b) Miura, T.; Morimoto, M.; Yamauchi, M.; Murakami, M. *J. Org. Chem.* **2010**, *75*, 5359. (c) Miura, T.; Nishida, Y.; Morimoto, M.; Yamauchi, M.; Murakami, M. *Org. Lett.* **2011**, *13*, 1429. (d) Miura, T.; Yamauchi, M.; Kosaka, A.; Murakami, M. *Angew. Chem., Int. Ed.* **2010**, *49*, 4955. (e) Chuprakov, S.; Hwang, F. W.; Gevorgyan, V. *Angew. Chem., Int. Ed.* **2007**, *46*, 4757. (f) Horneff, T.; Chuprakov, S.; Chernyak, N.; Gevorgyan, V.; Fokin, V. V. *J. Am. Chem. Soc.* **2008**, *130*, 14972. (g) Chuprakov, S.; Kwok, S. W.; Zhang, L.; Lercher, L.; Fokin, V. V. *J. Am. Chem. Soc.* **2009**, *131*, 18034. (h) Grimster, N.; Zhang, L.; Fokin, V. V. *J. Am. Chem. Soc.* **2010**, *132*, 2510. (i) Chuprakov, S.; Malik, J. A.; Zibinsky, M.; Fokin, V. V. *J. Am. Chem. Soc.* **2011**, *133*, 10352. (j) Selander, N.; Worrell, B. T.; Chuprakov, S.; Velaparthi, S.; Fokin, V. V. *J. Am. Chem. Soc.* **2012**, *134*, 14670. (k) Zibinsky, M.; Fokin, V. V. *Angew. Chem., Int. Ed.* **2013**, *52*, 1507. (l) Gulevich, A. V.; Gevorgyan, V. *Angew. Chem., Int. Ed.* **2013**, *52*, 1371. (m) Chuprakov, S.; Gevorgyan, V. *Org. Lett.* **2007**, *9*, 4463. (n) Fang, Z.-J.; Zheng, S.-C.; Guo, Z.; Guo, J.-Y.; Tan, B.; Liu, X.-Y. *Angew. Chem., Int. Ed.* **2015**, *54*, 9528. (o) Hey, D. H.; Rees, C. W.; Todd, A. R. *J. Chem. Soc. C* **1968**, 1028. (p) Barker, A. J.; Paterson, T. M.; Smalley, R. K.; Suschitzky, H. *J. Chem. Soc., Perkin Trans. 1* **1979**, 2203. (q) Cirrincione, G.; Almerico, A. M.; Dattolo, G.; Aiello, E.; Diana, P.; Mingoia, F. *J. Heterocycl. Chem.* **1992**, *29*, 1309. For a related review, see: (r) Chattopadhyay, B.; Gevorgyan, V. *Angew. Chem., Int. Ed.* **2012**, *51*, 862.

(9) (a) Jiang, H.; Cheng, Y.; Wang, R.; Zheng, M.; Zhang, Y.; Yu, S. *Angew. Chem., Int. Ed.* **2013**, *52*, 13289. (b) Jiang, H.; Cheng, Y.; Wang, R.; Zhang, Y.; Yu, S. *Chem. Commun.* **2014**, *50*, 6164. (c) Cheng, Y.; Yuan, X.; Jiang, H.; Wang, R.; Ma, J.; Zhang, Y.; Yu, S. *Adv. Synth. Catal.* **2014**, *356*, 2859. (d) Jiang, H.; Cheng, Y.; Zhang, Y.; Yu, S. *Org. Lett.* **2013**, *15*, 4884. (e) Sun, X.; Yu, S. *Org. Lett.* **2014**, *16*, 2938. (f) Cheng, Y.; Jiang, H.; Zhang, Y.; Yu, S. *Org. Lett.* **2013**, *15*, 5520.

(10) For selected reviews of visible-light photoredox catalysis, see: (a) Prier, C. K.; Rankic, D. A.; MacMillan, D. W. C. *Chem. Rev.* **2013**, *113*, 5322. (b) Xi, Y.; Yi, H.; Lei, A. *Org. Biomol. Chem.* **2013**, *11*, 2387. (c) Xuan, J.; Xiao, W.-J. *Angew. Chem., Int. Ed.* **2012**, *51*, 6828. (d) Narayanam, J. M. R.; Stephenson, C. R. J. *Chem. Soc. Rev.* **2011**, *40*, 102. (e) Yoon, T. P.; Ischay, M. A.; Du, J. *Nat. Chem.* **2010**, *2*, 527. (f) Zeitler, K. *Angew. Chem., Int. Ed.* **2009**, *48*, 9785.

(11) (a) Bowry, V. W.; Lusztyk, J.; Ingold, K. U. *J. Am. Chem. Soc.* **1991**, *113*, 5687. (b) Griller, D.; Ingold, K. U. *Acc. Chem. Res.* **1980**, *13*, 317.