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Stereoselective Radical Cyclization Cascades Triggered by Addition of Diverse Radicals to Alkynes To Construct 6(5)−6−5 Fused Rings

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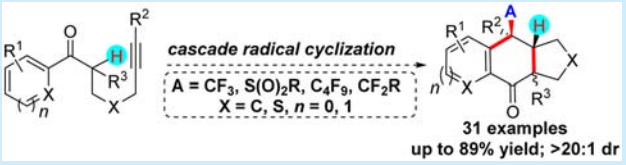
Supporting Information

ABSTRACT: Cascade radical cyclization of alkynyl ketones with various carbon- and heteroatom-centered radical precursors via a sequential radical addition/1,5-H radical shift/5-*exo*-*trig*/radical cyclization process was realized for the first time. This method provides a strategically novel and step-economical protocol for diversity-oriented synthesis of a wide range of carbocyclic and heterocyclic 6(5)−6−5 fused ring systems with three contiguous stereocenters, including a quaternary carbon in high yields with excellent chemo- and diastereoselectivity.



Complex carbon- or heteroatom-containing *n*−6−5 fused ring systems (*n* = 5 or 6) with multiple stereocenters are privileged structural motifs found in natural products and pharmaceutical compounds with important biological properties (Figure 1). For example, pycnanthuquinones A−C display

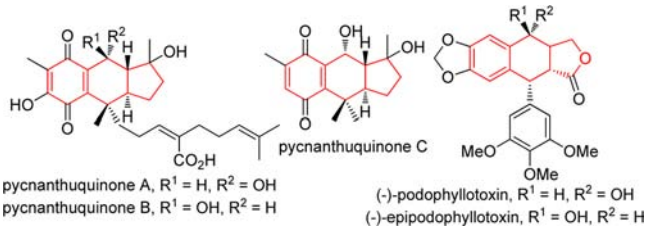
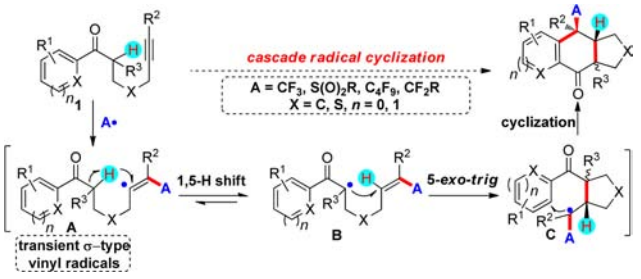


Figure 1. Representative natural products with a 6−6−5 fused ring.

antihyperglycemic activity in mice.[1] (−)-Epipodophyllotoxin represents the aglycon of the potent clinical antitumor drugs etoposide and teniposide for the treatment of small cell lung cancer and Kaposi's sarcoma.[2] Therefore, considerable efforts have been devoted to the development of new and simple methods for the construction of such fused tricyclic frameworks.[3] Although significant progress has been made, some crucial and challenging issues are far from being fully addressed, such as limited product scope, step-economy and starting material accessibility, and achievement of high degrees of stereocontrol in these stereocenter-abundant systems. Development of a new and efficient protocol for diversity-oriented synthesis of functionally, skeletally, and stereochemically diverse tricyclic scaffolds is highly desired.

Ingenious design and applications of radical cascade cyclizations have emerged as a powerful strategy to construct complex molecular scaffolds.[4] Note that several cascade cyclizations have been efficiently applied to the total synthesis of complex natural products, such as scholarisine A,[5a] barbiturates,[5b] and ophiobolin sesterterpene.[5c] However, addition of carbon- and heteroatom-centered radicals to unactivated alkynes is an especially attractive approach for the direct functionalization of alkynes as the alkyne is an easily accessible building block.[6] In this context, initiated by pioneering works of Heiba and Dessau,[7d] Curran,[7e−g] Renaud,[7h−j] and others, the tandem H atom translocation/cyclization process triggered by vinyl radical intermediates[7] has attracted considerable attention for constructing a wide range of five-membered rings. Inspired by these seminal works and driven by our continued interest in the area of radical chemistry,[8] we envisioned that such inherently high-energy σ-type vinyl radicals,[7] which could be in situ generated from addition of a variety of radicals to unactivated alkynes, would provide a driving force to undergo cascade 1,5-H radical shift/5-*exo*-*trig*/radical cyclization process (Scheme 1).

Scheme 1. Synthetic Strategy



Herein, we report a new, efficient, and general cascade radical cyclization protocol for diversity-oriented synthesis of carbocyclic and heterocyclic fused tricyclic frameworks with three contiguous stereocenters, including a quaternary carbon from readily available alkynyl ketones, in which three new carbon−carbon bonds and two rings are simultaneously formed in a cascade process in high yields with excellent chemo- and

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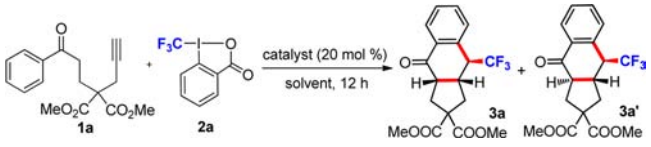
diastereoselectivity. In the context of a diversity-oriented synthesis of fused tricyclic frameworks, the current protocol displays some exceptional advantages. (1) *Functional group diversity*: a variety of carbon- and heteroatom-centered radical sources, including trifluoromethyl, difluoromethyl, perfluoroalkyl, and sulfonyl radical, are compatible. (2) *Skeleton diversity*: various carbocyclic and heterocyclic 6(5)−6−5 fused ring systems are easily collected. (3) Efficient control of chemo- and diastereoselectivity of multiple stereocenters is realized under mild synthetic conditions from easily available acyclic precursors.

Selective incorporation of a CF_3 group into drug molecules may lead to significant improvement in the drug's pharmacokinetic properties, binding selectivity, and metabolic stability.[9] We began our investigation by exploring a radical trifluoromethylation system[6b,d,f] using the model reaction of alkynyl ketone **1a** with Togni's reagent **2a** (Scheme 2; see Table S1 for details).[10]

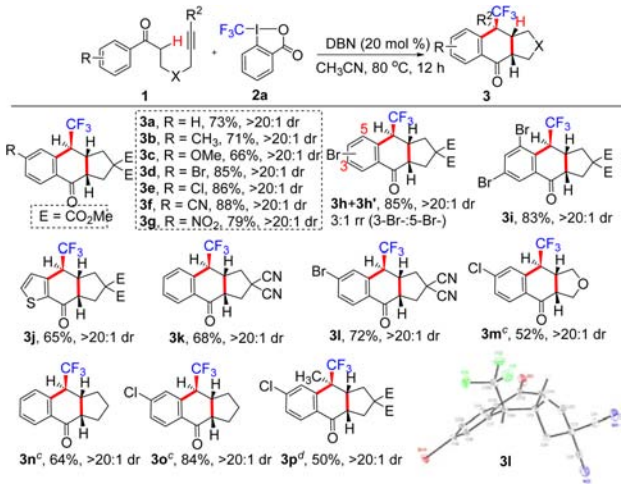
Scheme 2. Optimization of Model Reaction



Since copper salts were used to activate **2a** to generate the CF_3 radical, different Cu(I) salts were first examined as the catalysts. In the presence of these catalysts, reaction of **1a** with **2a** gave the desired products **3a** and **3a**′ in 78−81% total yields with almost complete chemoselectivity after 24 h. However, only poor diastereoselectivity was observed in all cases. To improve the diastereoselectivity, we evaluated different pyridine-based bidentate ligands but with little improvement. Finally, inspired by the success of our recently developed organic base-catalyzed radical trifluoromethylation of alkenes,[8b,d] we envisioned that an organic base may be a suitable catalyst to realize such cyclizations via a SET process to activate **2a**. We screened a series of phosphines and amines under otherwise identical conditions. Use of DBN resulted in a significantly increased diastereoselectivity of up to 14:1 with 73% yield. Furthermore, an obvious solvent effect was observed, and the best results (81% yield with >20:1 dr) were obtained with CH_3CN as the solvent. The observed excellent diastereoselectivity using DBN might be attributed to its strong basicity, which could epimerize **3a**′ to give the more stable *cis*-fused **3a**.

With the optimized conditions, we next investigated the substrate scope of alkynyl ketones with diverse substituents (Scheme 3). A variety of alkynyl aryl ketones, bearing either electron-donating groups (R = CH_3, OMe) or electron-withdrawing groups (R = Br, Cl, CN, NO_2) at the *para* position of the phenyl ring, reacted smoothly with **2a**, affording **3b**−**3g** in 66−88% yields with excellent diastereoselectivity. Substrate with *meta*-substituent (3-Br) in the phenyl ring gave two regioisomers, **3h** and **3h**′, in 85% yield with a regioselectivity of 3:1. This reaction shows excellent compatibility with disubstituted phenyl and heteroaromatic groups, yielding the 6−6−5 fused ring **3i** and 5−6−5 fused ring **3j** in 83 and 65% yields. Furthermore, substrates bearing other tethered groups, such as malononitrile- and oxygen-tethered **1k**−**1m**, were also well-tolerated to give final products **3k**−**3m** in 52−72% yields. Most importantly, **1n** and **1o** without any tether were also applicable to this process, affording **3n** and **3o** in 64 and 84% yields, respectively, even with

Scheme 3. Substrate Scope of Alkynyl Ketones[a,b]

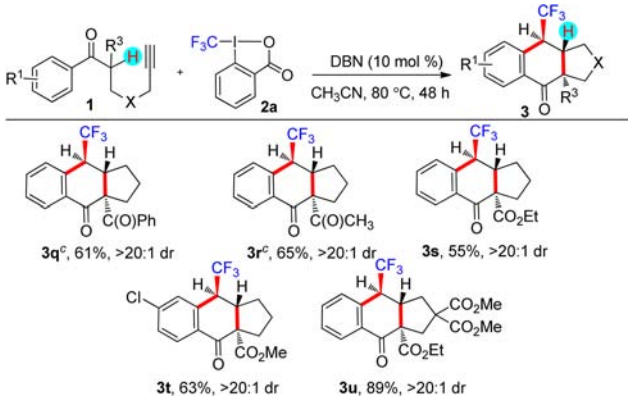


[a]Reaction conditions: **1** (0.2 mmol), **2a** (0.3 mmol), DBN (20 mol %), solvent (4 mL) at 80 °C for 12 h under argon. [b]Yield of isolated product. [c]DBN (10 mol %) for 24 h. [d]DBN (20 mol %) for 24 h; 20% of **1p** was recovered.

only 10 mol % of DBN as the catalyst. Notably, internal alkyne **1p** bearing a methyl group proved to be a suitable substrate, giving **3p** in 50% yield along with 20% recovery of **1p**. The structure and relative configuration of **3l** were further confirmed by X-ray crystallographic analysis (Scheme 3).

To expand the synthetic utility of this methodology, we next focused on other more sterically hindered alkynyl 1,3-dicarbonyl substrates, which would offer a novel and promising method to synthesize cyclopenta[*b*]hydronaphthalenes with three contiguous stereocenters including a quaternary carbon (Scheme 4).

Scheme 4. Substrate Scope of Alkynyl 1,3-Dicarbonyls[a,b]



[a]Reaction conditions: **1** (0.2 mmol), **2a** (0.3 mmol), DBN (10 mol %), solvent (4 mL) at 80 °C for 48 h under argon. [b]Yield of isolated product. [c]TBD (10 mol %) for 48 h. TBD = 1,5,7-triazabicyclo[4.4.0]-dec-5-ene.

After systematic optimization of different reaction parameters, we found that **1q** with a 1,3-diketone group was efficiently converted to **3q** in 61% yield with excellent diastereoselectivity with 10 mol % of TBD. A variety of functional groups including 1,3-diketone (**1r**) and *β*-ketone ester (**1s**,**1t**) were also compatible with the current system in the presence of TBD or DBN, affording **3r**−**3t** in 55−65% yield with excellent diastereoselectivity. Most importantly, **1u** with a diester-tethered

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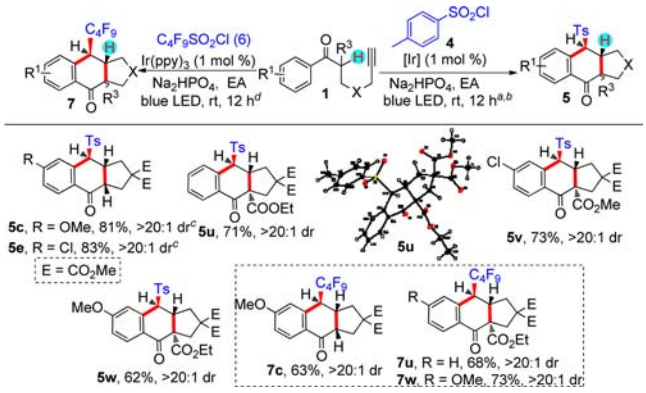
group was also suitable, and **3u** bearing densely multiple substituents was isolated in 89% yield.

We next extended other radical precursors. In recent years, visible-light-driven photoredox catalysis has become an eco-friendly and powerful tool for the generation of various radical species.[11] As expected, reaction of **1c** and **1e** with *p*-toluenesulfonyl chloride (**4**) under visible light photoredox catalysis conditions[12] delivered sulfonyl-containing fused rings in good yields with poor diastereoselectivity. Diastereoselectivity was significantly improved to >20:1 after in situ treatment of the reaction mixture with DBN at 60 °C for 6 h (Scheme 5). For

Scheme 5. Substrate Scope with Sulfonyl Chlorides

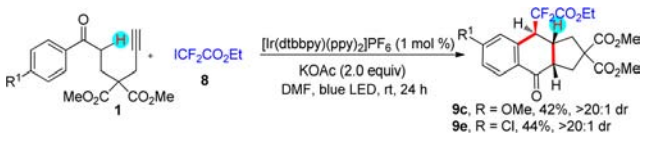


[a]Reaction conditions: **1** (0.2 mmol), **4** (0.4 mmol), Na_2HPO_4 (0.4 mmol), [Ir] = [Ir(dtbbpy)(ppy)$_2$]PF_6 (1 mol %)], EA (4 mL), blue LED at rt for 12 h under argon. [b]Yield of isolated product. [c]The dr ratio was obtained when the crude mixture was further treated with DBN (1.2 mmol) at 60 °C for 6 h. [d]Reaction conditions: **1** (0.2 mmol), **6** (0.4 mmol), Na_2HPO_4 (0.4 mmol), lr(ppy)$_3$ (1 mol %), EA (4 mL), blue LED at rt for 12 h under argon. Yield of isolated product.

sterically hindered alkynyl 1,3-dicarbonyl substrates **1u**−**1w**, fused ring compounds **5u**−**5w** were obtained in 62−73% yields with excellent diastereoselectivity under standard conditions without any organic base. The structure and relative configuration of **5u** were further confirmed by X-ray crystallographic analysis (Scheme 5). Success of C_4F_9 radical installation to generate **7c**, **7u**, and **7w** in 63−73% yields with >20:1 dr achieved with perfluorobutanesulfonyl chloride (**6**)[13] via extrusion of sulfur dioxide under similar reaction conditions demonstrates the utility of the present methodology to introduce a perfluoroalkyl group to fused ring systems via a radical process (Scheme 5).

To further expand this methodology and in light of the increasing importance of the difluoromethylene group (CF_2) in drug and agrochemical design,[9] we investigated the reaction of alkynyl ketones with EtO_2CCF_2I **8** as the radical precursor[14] under visible light photoredox catalysis conditions. Gratifyingly, under the reaction conditions similar to those of Scheme 5, the CF_2-incorporated cyclopenta[*b*]hydronaphthalenes **9c** and **9e** were obtained via CF_2 radical-initiated cascade cyclization in moderate yields with excellent diastereoselectivity (Scheme 6).

Scheme 6. Substrate Scope with EtO_2CCF_2I

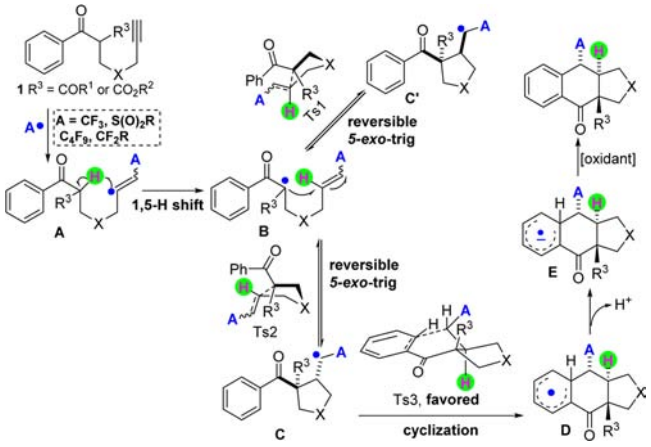


To further evaluate the practicality of the process, reaction was carried out on a gram scale. There was no change in reactivity and almost no influence on the chemical yield and stereoselectivity (1.24 g, 86% yield along with >20:1 dr for **3d**) (Scheme S1, eq 1). Reduction of **3e** by $NaBH_4$ generated the desired product with four contiguous stereocenters (Scheme S1, eq 2), an important structural motif presented in biologically active pycnanthuquinones A−C (Figure 1).

To gain more insight into the reaction mechanism, a series of control experiments were performed. We recently developed *N*-hydroxyphthalimide for reduction of **2a** to generate CF_3 and short-lived phthalimide-*N*-oxyl radical (PINO).[8e] The reaction of PINO with alkyl radical **C** (Scheme 1) provides **13** in 94% yield with PINO−CF_3 **14** in 36% yield (Scheme S2) when alkynyl ketone **11** with a methyl group was used as the substrate under the standard conditions. These results also support that **C** was generated through a cascade radical process triggered by addition of radicals to alkyne. An isotopic experiment supported that the 1,5-H radical shift process, established by Renaud,[7h−j] might be involved in this transformation (Scheme S3).

On the basis of these results and previous reports,[7,8] a proposed pathway for the formation of fused rings including a quaternary carbon is depicted in Scheme 7. Initially, a variety of

Scheme 7. Plausible Catalytic Cycle



radicals could be generated in situ under different reaction conditions. *In situ* generated radical species attack alkyne, affording a nascent σ-type vinyl radical intermediate **A**, followed by 1,5-H radical shift to generate a lower-energy carbonyl-stabilized radical **B**.[8] Once formed, **B** undergoes 5-*exo*-*trig* cyclization via Ts1 or Ts2 to form **C**′ or **C**, respectively. As 5-*exo*-*trig* cyclization is expected to be rapid and reversible in the presence of multiple radical-stabilizing carbonyl groups,[15] **C** having a pseudoequatorial **A** group would undergo an radical cyclization via Ts3 due to less steric reasons, which enables excellent diastereocontrol to give intermediate **D**. Finally, deprotonation of **D** to give **E** followed by single-electron oxidation takes place to furnish the final product.[6e,16] An alternative pathway via single-electron oxidation and deprotonation cannot be ruled out.[6] However, the origin of excellent diastereoselectivity observed in this reaction remains unclear and deserves further detailed studies.

In conclusion, we have successfully developed the first cascade radical cyclization of easily available alkynyl ketones via a sequential 1,5-H radical shift/5-*exo*-*trig*/radical cyclization process triggered by radical trifluoromethylation, sulfonylation,

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perfluoroalkylation, or difluoromethylation of alkynes. The reaction provides a new facile and straightforward approach for the diversity-oriented synthesis of carbocyclic and heterocyclic fused tricyclic frameworks with three contiguous stereocenters, including a quaternary carbon in high yields, with excellent chemo- and diastereoselectivity. To the best of our knowledge, this is the first example using in situ generated vinyl radicals as the key intermediate in cascade radical cyclizations for the construction of 6(5)−6−5 fused rings, which would provide a particularly advantageous alternative to the traditional tandem H atom translocation/cyclization process triggered by vinyl radicals.[7]

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b02599.

Experimental procedures, characterization of all new compounds, Table S1, Schemes S1−S3 (PDF)
X-ray data for **3l** (CIF)
X-ray data for **5u** (CIF)

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Author Contributions

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) (a) Fort, D. M.; et al. *J. Org. Chem.* **2000**, *65*, 6534. (b) Laird, D. W.; Poole, R.; Wikström, M.; van Altena, I. A. *J. Nat. Prod.* **2007**, *70*, 671.

(2) (a) Issell, B. F.; Muggia, F. M.; Carter, S. K. Etoposide(VP-16). *Current Status and New Developments*; Academic Press: New York, 1984. (b) Stähelin, H. F.; von Wartburg, A. *Cancer Res.* **1991**, *51*, 5. (c) Imbert, T. F. *Biochimie* **1998**, *80*, 207. (d) Damayanthi, Y.; Lown, J. W. *Curr. Med. Chem.* **1998**, *5*, 205.

(3) (a) Andrews, R. C.; Teague, S. J.; Meyers, A. I. *J. Am. Chem. Soc.* **1988**, *110*, 7854. (b) Bush, E. J.; Jones, D. W. *J. Chem. Soc., Chem. Commun.* **1993**, *15*, 1200. (c) Berkowitz, D. B.; Choi, S.; Maeng, J.-H. *J. Org. Chem.* **2000**, *65*, 847. (d) Barluenga, J.; Fernández-Rodríguez, M. A.; Aguilar, E. *Org. Lett.* **2002**, *4*, 3659. (e) Engelhardt, U.; Sarkar, A.; Linker, T. *Angew. Chem., Int. Ed.* **2003**, *42*, 2487. (f) Nieto-Oberhuber, C.; Pérez-Galán, P.; Herrero-Gómez, E.; Lauterbach, T.; Rodríguez, C.; López, S.; Bour, C.; Rosellón, A.; Cárdenas, D. J.; Echavarren, A. M. *J. Am. Chem. Soc.* **2008**, *130*, 269. (g) Xie, J.; Ma, Y.; Horne, D. A. *J. Org. Chem.* **2011**, *76*, 6169. (h) Wong, Y.-C.; Tseng, C.-T.; Kao, T.-T.; Yeh, Y.-C.; Shia, K.-S. *Org. Lett.* **2012**, *14*, 6024.

(4) (a) Malacria, M. *Chem. Rev.* **1996**, *96*, 289. (b) Curran, D. P. *Aldrichimica Acta* **2000**, *33*, 104. (c) Zard, S. Z. *Radical Reactions in Organic Synthesis*; Oxford University Press: Oxford, UK, 2003. (d) Togo, H. *Advanced Free Radical Reactions for Organic Synthesis*; Elsevier: Amsterdam, 2004. (e) Snider, B. B. Oxidative Free-Radical Cyclizations and Additions with Mono and β-Dicarbonyl Compounds. In *Handbook of C−H Transformations: Applications in Organic Synthesis*; Dyker, G., Ed.; Wiley-VCH: Weinheim, 2005; Vol. 2, p 371. (f) Renaud, P.; Sibi, M. P. *Radicals in Organic Synthesis*; Wiley-VCH: Weinheim, 2008. (g) Godineau, E.; Landais, Y. *Chem. - Eur. J.* **2009**, *15*, 3044. (h) Hata, S.; Sibi, M. P. *Science of Synthesis-Stereoselective Reactions of C−C Double Bonds*; de Vries, J. G., Ed.; Georg Thieme Verlag: Stuttgart, 2011; p 873.

(5) (a) Smith, M. W.; Snyder, S. A. *J. Am. Chem. Soc.* **2013**, *135*, 12964. (b) Huang, H.; Procter, D. J. *J. Am. Chem. Soc.* **2016**, *138*, 7770. (c) Brill, Z. G.; Grover, H. K.; Maimone, T. J. *Science* **2016**, *352*, 1078.

(6) (a) Wille, U. *Chem. Rev.* **2013**, *113*, 813. (b) Besset, T.; Poisson, T.; Pannecoucke, X. *Chem. - Eur. J.* **2014**, *20*, 16830. (c) Pan, X.-Q.; Zou, J.-P.; Yi, W.-B.; Zhang, W. *Tetrahedron* **2015**, *71*, 7481. (d) Gao, P.; Song, X.-R.; Liu, X.-Y.; Liang, Y.-M. *Chem. - Eur. J.* **2015**, *21*, 7648. (e) Studer, A.; Curran, D. P. *Angew. Chem., Int. Ed.* **2016**, *55*, 58. (f) Zeng, Y.; Ni, C.; Hu, J. *Chem. - Eur. J.* **2016**, *22*, 3210.

(7) (a) Dénès, F.; Beaufils, F.; Renaud, P. *Synlett* **2008**, *2008*, 2389. (b) Dénès, F.; Pichowicz, M.; Povie, G.; Renaud, P. *Chem. Rev.* **2014**, *114*, 2587. (c) Dreessen, T.; Jargstorff, C.; Lietzau, L.; Plath, C.; Stademann, A.; Wille, U. *Molecules* **2004**, *9*, 480. (d) Heiba, E. I.; Dessau, R. M. *J. Am. Chem. Soc.* **1967**, *89*, 3772. (e) Curran, D. P.; Kim, D.; Liu, H.-T.; Shen, W. *J. Am. Chem. Soc.* **1988**, *110*, 5900. (f) Curran, D. P.; Kim, D.; Ziegler, C. *Tetrahedron* **1991**, *47*, 6189. (g) Curran, D. P.; Shen, W. *J. Am. Chem. Soc.* **1993**, *115*, 6051. (h) Renaud, P.; Beaufils, F.; Feray, L.; Schenk, K. *Angew. Chem., Int. Ed.* **2003**, *42*, 4230. (i) Beaufils, F.; Dénès, F.; Renaud, P. *Angew. Chem., Int. Ed.* **2005**, *44*, 5273. (j) Lamarque, C.; Beaufils, F.; Dénès, F.; Schenk, K.; Renaud, P. *Adv. Synth. Catal.* **2011**, *353*, 1353. (k) Sannigrahi, M.; Mayhew, D. L.; Clive, D. L. J. *J. Org. Chem.* **1999**, *64*, 2776. (l) Wille, U.; Lietzau, L. *Tetrahedron* **1999**, *55*, 10119.

(8) (a) Yu, P.; Lin, J.-S.; Li, L.; Zheng, S.-C.; Xiong, Y.-P.; Zhao, L.-J.; Tan, B.; Liu, X.-Y. *Angew. Chem., Int. Ed.* **2014**, *53*, 11890. (b) Yu, P.; Zheng, S.-C.; Yang, N.-Y.; Tan, B.; Liu, X.-Y. *Angew. Chem., Int. Ed.* **2015**, *54*, 4041. (c) Huang, L.; Lin, J.-S.; Tan, B.; Liu, X.-Y. *ACS Catal.* **2015**, *5*, 2826. (d) Yang, N.-Y.; Li, Z.-L.; Ye, L.; Tan, B.; Liu, X.-Y. *Chem. Commun.* **2016**, *52*, 9052. (e) Huang, L.; Zheng, S.-C.; Tan, B.; Liu, X.-Y. *Org. Lett.* **2015**, *17*, 1589.

(9) (a) Müller, K.; Faeh, C.; Diederich, F. *Science* **2007**, *317*, 1881. (b) Purser, S.; Moore, P. R.; Swallow, S.; Gouverneur, V. *Chem. Soc. Rev.* **2008**, *37*, 320. (c) Nie, J.; Guo, H.-C.; Cahard, D.; Ma, J.-A. *Chem. Rev.* **2011**, *111*, 455.

(10) Eisenberger, P.; Gischig, S.; Togni, A. *Chem. - Eur. J.* **2006**, *12*, 2579.

(11) Recent reviews on photoredox catalysis: (a) Yoon, T. P.; Ischay, M. A.; Du, J. *Nat. Chem.* **2010**, *2*, 527. (b) Narayanam, J. M. R.; Stephenson, C. R. J. *Chem. Soc. Rev.* **2011**, *40*, 102. (c) Xuan, J.; Xiao, W. *Angew. Chem., Int. Ed.* **2012**, *51*, 6828. (d) Tucker, J. W.; Stephenson, C. R. J. *J. Org. Chem.* **2012**, *77*, 1617. (e) Prier, C. K.; Rankic, D. A.; MacMillan, D. W. C. *Chem. Rev.* **2013**, *113*, 5322. (f) Xi, Y.; Yi, H.; Lei, A. *Org. Biomol. Chem.* **2013**, *11*, 2387. (g) Xie, J.; Jin, H.; Xu, P.; Zhu, C. *Tetrahedron Lett.* **2014**, *55*, 36.

(12) (a) Deng, G.-B.; Wang, Z.-Q.; Xia, J.-D.; Qian, P.-C.; Song, R.-J.; Hu, M.; Gong, L.-B.; Li, J.-H. *Angew. Chem., Int. Ed.* **2013**, *52*, 1535. (b) Pagire, S. K.; Paria, S.; Reiser, O. *Org. Lett.* **2016**, *18*, 2106.

(13) (a) Tang, X. J.; Thomoson, C. S., Jr.; Dolbier, W. R. *Org. Lett.* **2014**, *16*, 4594. (b) Tang, X. J., Jr.; Dolbier, W. R. *Angew. Chem., Int. Ed.* **2015**, *54*, 4246.

(14) (a) Nguyen, J. D.; Tucker, J. W.; Konieczynska, M. D.; Stephenson, C. R. J. *J. Am. Chem. Soc.* **2011**, *133*, 4160. (b) Wallentin, C. J.; Nguyen, J. D.; Finkbeiner, P.; Stephenson, C. R. J. *J. Am. Chem. Soc.* **2012**, *134*, 8875. (c) Feng, Z.; Min, Q.-Q.; Xiao, Y.-L.; Zhang, B.; Zhang, X. *Angew. Chem., Int. Ed.* **2014**, *53*, 1669.

(15) Julia, M. *Acc. Chem. Res.* **1971**, *4*, 386.

(16) Zhang, B.; Mück-Lichtenfeld, C.; Daniliuc, C. G.; Studer, A. *Angew. Chem., Int. Ed.* **2013**, *52*, 10792.

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