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Visible Light Driven Photocascade Catalysis: $Ru(bpy)_3(PF_6)_2$/TBHP-Mediated Synthesis of Fused β-Carbolines in Batch and Flow Microreactors

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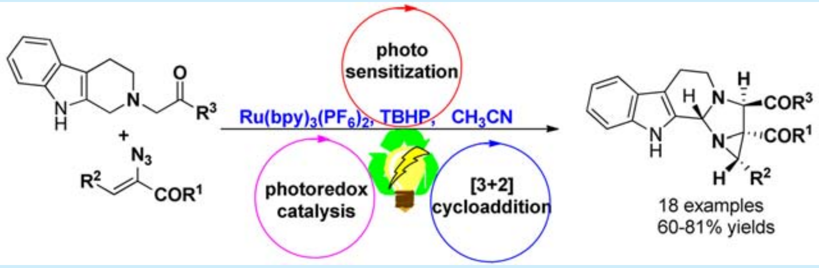
Supporting Information



ABSTRACT: 1,2,3,4-Tetrahydro-β-carbolines were coupled with α-keto vinyl azides through an unprecedented visible light-$Ru(bpy)_3(PF_6)_2$/TBHP mediated photocascade strategy that involves photosensitization, photoredox catalysis and [3 + 2] cycloaddition reaction. The scope and scale-up feasibility of the photocascade strategy was demonstrated by synthesizing 18 different fused β-carbolines in moderate to good yields using batch and continuous flow microreactor. This operationally simple synthetic protocol allows the formation of one C−C and two C−N new bonds in the overall transformation.

N-Heterocycles are frequently found in a huge number of pharmaceutical drugs, natural products, agrochemicals, functional materials and fine chemicals. Among them, β-carbolines, a subgroup of the indole alkaloid family, which consist of a plethora of synthetic and natural products of wide structural diversity, showed rich medicinal properties.[1] Molecules containing a β-carboline core unit exhibit numerous biological activities such as antitumor, antileishmanial, antihypertensive, antitrypanosomal, anti-HIV, anti-inflammatory and many others.[1,2] Harmine (antileishmanial), harmicine (antispasmodic, antipyretic, and anticancer), arborescidine B (anticancer), fumitremorgin C (anticancer), eburnamonine (vasodilator), reserpine (antihypertensive), and tadalafil (a top selling drug for erectile dysfunction) are among the most important β-carboline derivatives. Due to their importance and utility, β-carbolines have attracted considerable interest among synthetic organic chemists for decades. This manuscript deals with an unprecedented, efficient photochemical pathway to construct structurally novel, strained β-carboline derivatives.

Recently, visible-light driven organic transformations have attracted much attention because of their green and sustainable perspectives. They provide novel modes of reactivity that enable otherwise difficult construction of complex molecular architectures.[3] Most of the visible light-driven photochemical reactions generally proceed via energy transfer (photosensitization) or electron transfer (photoredox catalysis) pathways and are well studied. The scope of visible light-driven photochemical reactions has been further expanded by merging photo- and metal/organo-catalysis.[4] Attempts have also been made to devise a synthetic strategy, namely photocascade catalysis, that combines both energy transfer and redox pathways, though only three such examples are in the literature to the best of our knowledge.[5] Initial trials of photocascade catalysis were performed by Xiao and co-workers who studied a visible-light driven [3 + 2] cycloaddition to synthesize pyrroles.[5a] In this context, recently we reported a combination of visible-light photosensitization and photoredox catalysis for the construction of various imidazoles.[5b] In continuation of our work on visible light photocatalysis, herein we report an efficient photocascade strategy for the synthesis of structurally novel β-carboline derivatives that utilizes [3 + 2] cycloaddition reaction of *in situ* generated azomethine ylides (visible light photoredox catalysis) and 2*H*-azirines (visible light photosensitization).

Direct sp^3 C−H activation adjacent to a nitrogen atom is one of the most synthetically useful reactions to synthesize nitrogen containing molecules.[6] In the presence of visible light and Ru/Ir polypyridyl complexes, *tert*-amines **I** get oxidized to iminium ion **IV** or azomethine ylide **V** (when there is an acidic α-H) through the intermediates **II** and **III** (Scheme 1).[6,7] We envisioned that the azomethine ylide **V** generated under visible light photoredox catalysis might be trapped by vinyl azides to yield various N-

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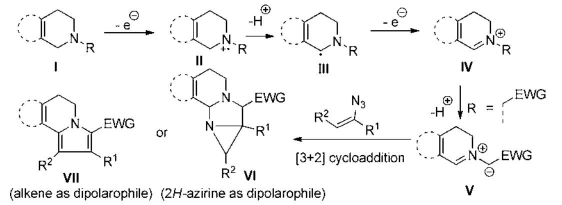
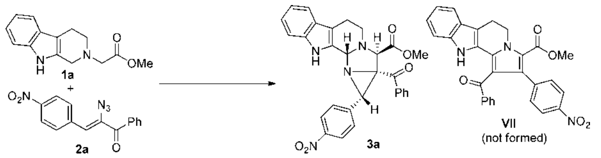
Scheme 1. Proposed Coupling of *tert*-Amines with Vinyl Azides under Visible-Light Photoredox Catalysis



heterocycles (Scheme 1). To test the feasibility of the concept and optimize reaction conditions, coupling of 1,2,3,4-tetrahydro-β-carboline **1a** and vinyl azide **2a** was taken as a model reaction, and the effect of light, catalyst, oxidant and solvent was studied (Table 1).

Table 1. Optimization of the Coupling of 1,2,3,4-Tetrahydro-β-carboline 1a with Vinyl Azide 2a[a]



entry	light[b]	catalyst	solvent	yield of **3a**[c] (%)
1	X		CH_3CN	ND
2	√		CH_3CN	ND
3	X	$Ru(bpy)_3(PF_6)_2$	CH_3CN	ND
4	√	$Ru(bpy)_3(PF_6)_2$	CH_3CN	65
5	√	$Ru(bpy)_3(PF_6)_2$	CH_3CN	65[d]
6	√	$Ru(bpy)_3(PF_6)_2$	CH_3CN	55[e]
7	√	$Ru(bpy)_3(PF_6)_2$	CH_3CN	25[f]
8	√	$Ru(bpy)_3(PF_6)_2$	CH_3CN	45[f,g]
9	√	$Ru(bpy)_3(PF_6)_2$	CH_3CN	51[h]
10	√	$Ru(bpy)_3(PF_6)_2$	CH_3CN	66[h,i]
11	√	$Ru(bpy)_3Cl_2.6H_2O$	CH_3CN	58
12	√	$[Ir(dtbbpy)(ppy)_2]PF_6$	CH_3CN	ND
13	√	Rose Bengal	CH_3CN	trace
14	√	eosin Y	CH_3CN	ND
15	√	$Ru(bpy)_3(PF_6)_2$	THF	22
16	√	$Ru(bpy)_3(PF_6)_2$	$CHCl_3$	25
17	√	$Ru(bpy)_3(PF_6)_2$	DMF	12
18[f,h]	√	$Ru(bpy)_3(PF_6)_2$	CH_3CN	ND

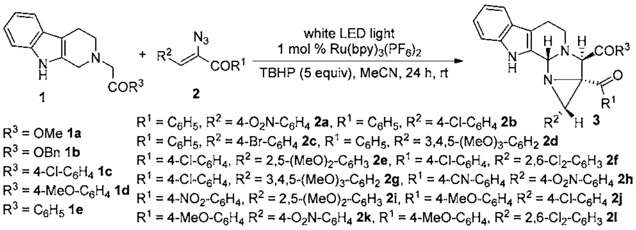
[a] Reaction conditions: **1a** (0.2 mmol), **2a** (0.2 mmol), TBHP (1.0 mmol), catalyst 1 mol %, solvent (5 mL), stir, 24 h. [b] 17 W white LED kept at a distance of 10 cm (approx) from the reaction flask. [c] Isolated yields. [d] Catalyst 2 mol %. [e] Catalyst 0.5 mol %. [f] TBHP was not used. [g] The reaction was carried out using an oxygen balloon. [h] The reaction was carried out in a nitrogen atmosphere. [i] 2.0 mmol of TBHP was used. ND = product **3a** was not detected on TLC.

No reaction between **1a** and **2a** was observed in the absence of the light and photocatalyst (Table 1, entries 1−3). The reaction of **1a** and **2a** proceeded smoothly using 1 mol % of $Ru(bpy)_3(PF_6)_2$ as a photocatalyst in acetonitrile yielding a clean spot on TLC, which was characterized as **3a** (Table 1, entry 4). The chemical structure of **3a** was assigned by analyzing its ^1H, ^{13}C, MS/HRMS spectra. The relative stereochemical assignments of **3a** were made by single crystal X-ray crystallography (for crystal details, see Supporting Information). The yield of **3a** was not increased by increasing the catalyst loading. However, lowering the same decreased the yield (Table 1, entries 5−6).

The desired product **3a** was obtained in a low yield when the reaction was carried out in air without *tert*-butyl hydroperoxide (TBHP) (Table 1, entry 7). However, an improved yield of **3a** was observed using an oxygen balloon (Table 1, entry 8). The reaction was also successful in a nitrogen atmosphere using higher loading of THBP (Table 1, entries 9−10). When the reaction was performed in absence of TBHP in a nitrogen atmosphere, the desired product **3a** was not formed (Table 1, entry 18). Among several photocatalysts and organic dyes screened, $Ru(bpy)_3(PF_6)_2$ was found the best for the formation of **3a** (Table 1, entries 4, 11−14). The reaction was also tried in several other solvents such as THF, $CHCl_3$ and DMF but none of them improved the product yields (Table 1, entries 15−17).

Excellent regio- and diastereoselective formation of **3a** indicated the potential application of the photochemical strategy to construct a library of β-carboline derivatives. The pentacyclic N-heterocycle **3a** contains a strained aziridine ring as a part of its structure and could be of various pharmaceutical interests. We, therefore, explored the scope of the visible-light driven coupling of 1,2,3,4-tetrahydro-β-carbolines with vinyl azides in detail (Table 2). For our investigations, we prepared five different β-carboline substrates **1a** (methyl ester), **1b** (benzyl ester), **1c** (*p*-chlorophenyl ketone), **1d** (*p*-methoxyphenyl ketone), and **1e** (phenyl ketone) by reacting 2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole with methyl 2-bromoacetate, benzyl 2-bromoacetate, 2-bromo-1-(4-chlorophenyl)ethanone, 2-bromo-1-(4-methoxyphenyl)ethanone and 2-bromo-1-phenylethanone, respectively. All the ester (**1a**−**b**) and ketone (**1c**−**e**) containing β-carboline substrates worked well, giving good yields (60−71%)

Table 2. Scope of the Coupling of 1,2,3,4-Tetrahydro-β-carbolines with Vinyl Azides to Yield Strained β-Carboline Derivatives 3a−r



entry	β-carboline	vinyl azide	product	yield of **3**[a] (%)
1	**1a**	**2a**	**3a**	65
2	**1a**	**2b**	**3b**	67
3	**1a**	**2c**	**3c**	63
4	**1a**	**2d**	**3d**	65
5	**1a**	**2e**	**3e**	67
6	**1a**	**2f**	**3f**	68
7	**1a**	**2g**	**3g**	60
8	**1a**	**2h**	**3h**	62
9	**1a**	**2i**	**3i**	67
10	**1a**	**2j**	**3j**	71
11	**1a**	**2k**	**3k**	69
12	**1b**	**2j**	**3l**	67
13	**1b**	**2l**	**3m**	60
14	**1b**	**2c**	**3n**	64
15	**1b**	**2a**	**3o**	68
16	**1c**	**2d**	**3p**	63
17	**1d**	**2g**	**3q**	64
18	**1e**	**2b**	**3r**	66

[a] Isolated yields.

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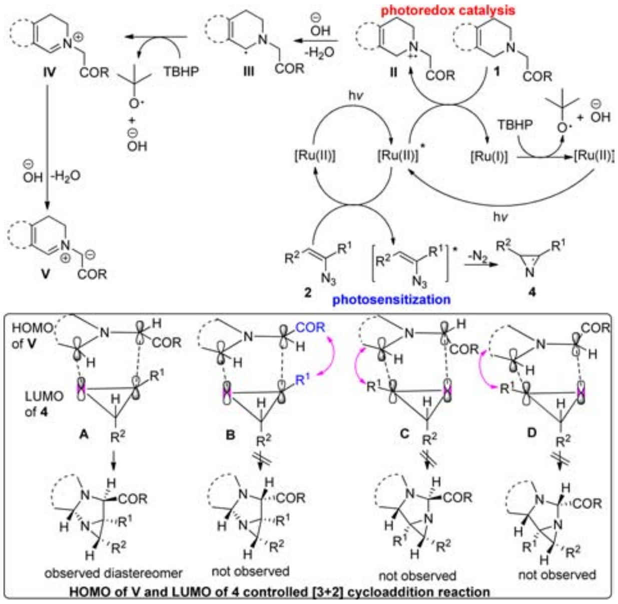
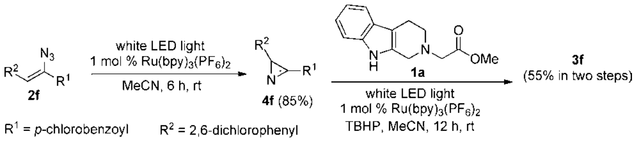
of the desired products **3a−r**. Notably, the NH functional group of the *β*-carboline substrates was tolerated in the reaction, which offers the possibilities of further functionalization of these products. However, it was disappointing that despite screening many reaction conditions, the reaction did not work with structurally similar 1,2,3,4-tetrahydroisoquinoline substrates. Both the substrates 1,2,3,4-tetrahydroisoquinolines and vinyl azides were fully consumed but the corresponding aziridine product was not isolated or detected on TLC. The reaction was found to be compatible with a large number of vinyl azides containing halogen, and electron releasing as well as electron withdrawing groups in their aromatic rings. The product yield was not much influenced by electron donating or withdrawing groups present in the aromatic rings of *α*-keto vinyl azides. The reaction did not work with the corresponding vinyl azides derived from heteroaromatic (furfural) or aliphatic (*n*-propanal) aldehydes. Using the optimized reaction conditions, 18 different compounds **3a−r** were synthesized in good yields, and a single diastereomer of the products was observed in most of the cases.

Formation of the fused *β*-carboline derivatives **3a−r** via visible light-driven coupling of 1,2,3,4-tetrahydro-*β*-carbolines **1** and *α*-keto vinyl azides **2** can be explained by a plausible mechanism depicted in Scheme 2. In the presence of visible light and $Ru(bpy)_3(PF_6)_2$, vinyl azide **2** undergoes photosensitized decomposition to yield 2*H*-azirine **4** with the liberation of nitrogen.[5b,8] $Ru(bpy)_3(PF_6)_2$ catalyzes the oxidation of *tert*-amine **1** to a radical cation **II** in the presence of visible light, which further gets oxidized to an azomethine ylide **V**. Fused *β*-carboline derivatives **3a−r** seem to be derived from a regio- and diastereoselective 1,3-dipolar cycloaddition reaction of the azomethine ylide **V** with 2*H*-azirine **4**. Compound **3** has 4 stereocenters, thereby allowing the possibility of the formation of $2^4 = 16$ stereoisomers (8 pairs of diastereomers). Since the [3 + 2] cycloaddition reaction is stereospecific, the stereochemical information on the dipolorophile **4** remains intact in the final product, which cuts the possibility of the formation of four pairs of diastereomers. Four possible transition states (A, B, C and D) of the highest occupied molecular orbital (HOMO) of **V** and lowest unoccupied molecular orbital (LUMO) of **4** controlled cycloaddition reaction are shown in Scheme 2. The azomethine ylide **V** approaches the least hindered (top) face of 2*H*-azirine **4**, maintaining the *anti*-orientation (minimum steric crowding) between the COR group of **V** and R^1 of **4** (Scheme 2, transition state A). Remaining other possible transition states B, C, and D suffer from steric crowding as shown in Scheme 2. Therefore, a single diastereomer of the product **3** was observed in most of the cases. Involvement of the photocascade catalysis (visible light photosensitization, photoredox oxidation, and 1,3-dipolar cycloaddition) was established by performing a stepwise synthesis of **3f** (Scheme 3). Visible light/$Ru(bpy)_3(PF_6)_2$-mediated photosensitized decomposition of **2f** yielded 2*H*-azirine **4f** in 85% yield. In another experiment, when the decomposition of **2f** was complete, the reaction flask was charged with *β*-carboline **1a** and TBHP, and irradiated with visible light for 12 h. After the usual workup, the desired product **3f** was isolated in 55% yield.

Scheme 2. Mechanistic Rationalization for the Formation of Fused *β*-Carboline Derivatives 3a−r via Visible Light Driven Photocascade Catalysis



Scheme 3. Photosensitized Generation of 2*H*-Azirine 4f and Its Coupling with 1,2,3,4-Tetrahydro-*β*-carboline 1a in a Photoredox/[3 + 2] Cycloaddition Reaction Cascade



Recently, continuous flow microreactors gained much interest for performing organic transformations due to increased product selectivity, yield, safety and scale-up possibilities.[9] Microreactors are particularly usable in photochemical reactions because of their high surface to volume ratio, heat and mass transfer capability, and increased illumination homogeneity.[10] Considering these advantages of the flow microreactors for photochemical reactions, we tried to translate the coupling of 1,2,3,4-tetrahydro-*β*-carbolines **1** and *α*-keto vinyl azides **2** from batch to a photochemical flow microreactor (Figure 1). The flow microreactor setup was assembled by wrapping visible light transparent PFA (perfluoroalkoxy) tubing (i.d. = 0.76 mm, length = 15 m, volume = 6.8 mL) over a glass column fitted with a white LED light source, and connections were made as depicted in Figure 1. The coupling of 1,2,3,4-tetrahydro-*β*-carboline **1a** and *α*-keto vinyl azide **2b** was carried out in the flow microreactor setup. After relative flow rates were optimized, an 81% yield of **3b** was obtained in a residence time of 43 min. The productivity of the microreactor was calculated as 3.2 mg/min of the fused *β*-carboline **3b**, which shows the synthetic competence of the microfluidic strategy (for details of the microreactor and optimization, see the Supporting Information). It is notable

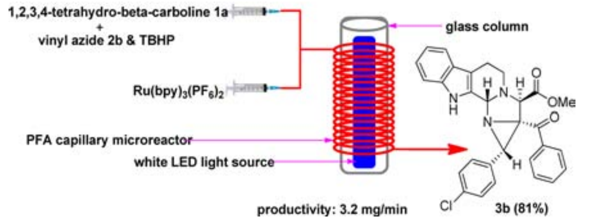


Figure 1. Visible light-driven coupling of *β*-carboline **1a** and vinyl azide **2b** to yield **3b** in a flow microreactor.

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that performing a reaction for the synthesis of **3b** in a batch reactor for 43 min under the optimized reaction conditions (Table 1) gave **3b** in 36% yield. The improved product yield (65% in batch vs 81% in flow) and decreased reaction time (24 h in batch vs 43 min in flow) can be explained by considering the short length scale and increased illumination homogeneity, which led to a high photon flux in the microreactor.

In conclusion, we have developed an unprecedented visible light-driven photocascade catalysis that utilizes dual photocatalysis to synthesize structurally novel, strained β-carbolines. It involves highly regio- and diastereoselective [3 + 2] cycloaddition reactions of in situ generated 2*H*-azirines and azomethine ylides from visible light-mediated photosensitized decomposition of vinyl azides and photoredox oxidation of 1,2,3,4-tetrahydro-β-carbolines, respectively. The scope of the reaction was studied by performing visible light-driven coupling of several 1,2,3,4-tetrahydro-β-carbolines and vinyl azides in batch and continuous flow microreactors using Ru(bpy)$_3$(PF$_6$)$_2$ as a photocatalyst and TBHP as an oxidant. This successful demonstration of photocascade catalysis opens the door for exploring the possibilities of generating structurally novel molecular libraries of biological importance and provides a potential tool for the direct utilization of visible light for constructing otherwise difficult molecular architectures.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b01321.

> Full experimental details, characterization data for all products, copies of ^{1}H and ^{13}C spectra, and single-crystal X-ray analysis (PDF)

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) (a) Cao, R.; Peng, W.; Wang, Z.; Xu, A. *Curr. Med. Chem.* **2007**, *14*, 479. (b) Higuchi, K.; Kawasaki, T. *Nat. Prod. Rep.* **2007**, *24*, 843. (c) Cabrera, G. M.; Seldes, A. M. *J. Nat. Prod.* **1999**, *62*, 759. (d) Boursereau, Y.; Coldham, I. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 5841. (e) Uskokovic, M. R.; Grethe, G. *The Alkaloids*; Manske, R. H. F., Ed.; Academic Press: New York, 1973; Vol. *14*, p 181.

(2) (a) Beghyn, T. B.; Charton, J.; Leroux, F.; Laconde, G.; Bourin, A.; Cos, P.; Maes, L.; Deprez, B. *J. Med. Chem.* **2011**, *54*, 3222. (b) Zhao, M.; Bi, L.; Bi, W.; Wang, C.; Yang, Z.; Ju, J.; Peng, S. *Bioorg. Med. Chem.* **2006**, *14*, 4761. (c) Biggio, G.; Concas, A.; Mele, S.; Corda, M. G. *Brain Res. Bull.* **1987**, *19*, 301. (d) Dorey, G.; Poissonnet, G.; Potier, M. C.; De Carvalho, L. P.; Venault, P.; Chapouthier, G.; Rossier, J.; Potier, P.; Dodd, R. H. *J. Med. Chem.* **1989**, *32*, 1799. (e) Deveau, A. M.; Labroli, M. A.; Dieckhaus, C. M. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 1251.

(3) For selected recent reviews over visible-light photocatalysis, see: (a) Brimioulle, R.; Lenhart, D.; Maturi, M. M.; Bach, T. *Angew. Chem., Int. Ed.* **2015**, *54*, 3872. (b) Hari, D. P.; Konig, B. *Chem. Commun.* **2014**, *50*, 6688. (c) Prier, C. K.; Rankic, D. A.; MacMillan, D. W. C. *Chem. Rev.* **2013**, *113*, 5322. (d) Ravelli, D.; Fagnoni, M.; Albini, A. *Chem. Soc. Rev.* **2013**, *42*, 97. (e) Xuan, J.; Xiao, W.-J. *Angew. Chem., Int. Ed.* **2012**, *51*, 6828. (f) Narayanam, J. M. R.; Stephenson, C. R. J. *Chem. Soc. Rev.* **2011**, *40*, 102. (g) Angnes, R. A.; Li, Z.; Correia, C. R. D.; Hammond, G. B. *Org. Biomol. Chem.* **2015**, *13*, 9152. (h) Reckenthaler, M.; Griesbeck, A. G. *Adv. Synth. Catal.* **2013**, *355*, 2727.

(4) (a) Meggers, E. *Chem. Commun.* **2015**, *51*, 3290. (b) Rueping, M.; Vila, C.; Koenigs, R. M.; Poscharny, K.; Fabry, D. C. *Chem. Commun.* **2011**, *47*, 2360. (c) Chu, L.; Lipshultz, J. M.; MacMillan, D. W. C. *Angew. Chem., Int. Ed.* **2015**, *54*, 7929. (d) Tlahuext-Aca, A.; Hopkinson, M. N.; Sahoo, B.; Glorius, F. *Chem. Sci.* **2016**, *7*, 89. (e) Ruiz Espelt, L.; McPherson, I. S.; Wiensch, E. M.; Yoon, T. P. *J. Am. Chem. Soc.* **2015**, *137*, 2452.

(5) (a) Xuan, J.; Xia, X.-D.; Zeng, T.-T.; Feng, Z.-J.; Chen, J.-R.; Lu, L.-Q.; Xiao, W.-J. *Angew. Chem., Int. Ed.* **2014**, *53*, 5653. (b) Tiwari, D. K.; Maurya, R. A.; Nanubolu, J. B. *Chem. - Eur. J.* **2016**, *22*, 526. (c) Xia, X.-D.; Ren, Y.-L.; Chen, J.-R.; Yu, X.-L.; Lu, L.-Q.; Zou, Y.-Q.; Wan, J.; Xiao, W.-J. *Chem. - Asian J.* **2015**, *10*, 124.

(6) (a) Shi, L.; Xia, W. *Chem. Soc. Rev.* **2012**, *41*, 7687. (b) Muhmel, S.; Alpers, D.; Hoffmann, F.; Brasholz, M. *Chem. - Eur. J.* **2015**, *21*, 12308. (c) Nakajima, M.; Fava, E.; Loescher, S.; Jiang, Z.; Rueping, M. *Angew. Chem., Int. Ed.* **2015**, *54*, 8828. (d) Xie, J.; Shi, S.; Zhang, T.; Mehrkens, N.; Rudolph, M.; Hashmi, A. S. K. *Angew. Chem., Int. Ed.* **2015**, *54*, 6046. (e) Beatty, J. W.; Stephenson, C. R. J. *Acc. Chem. Res.* **2015**, *48*, 1474. (f) Kohls, P.; Jadhav, D.; Pandey, G.; Reiser, O. *Org. Lett.* **2012**, *14*, 672. (g) Condie, A. G.; Gonzalez-Gomez, J. C.; Stephenson, C. R. J. *J. Am. Chem. Soc.* **2010**, *132*, 1464.

(7) (a) Zou, Y.-Q.; Lu, L.-Q.; Fu, L.; Chang, N.-J.; Rong, J.; Chen, J.-R.; Xiao, W.-J. *Angew. Chem., Int. Ed.* **2011**, *50*, 7171. (b) Rueping, M.; Leonori, D.; Poisson, T. *Chem. Commun.* **2011**, *47*, 9615. (c) Huang, L.; Zhao, J. *Chem. Commun.* **2013**, *49*, 3751. (d) Guo, S.; Zhang, H.; Huang, L.; Guo, Z.; Xiong, G.; Zhao, J. *Chem. Commun.* **2013**, *49*, 8689. (e) Chandrasekhar, D.; Borra, S.; Kapure, J. S.; Shivaji, G. S.; Srinivasulu, G.; Maurya, R. A. *Org. Chem. Front.* **2015**, *2*, 1308.

(8) Hu, B.; DiMagno, S. G. *Org. Biomol. Chem.* **2015**, *13*, 3844.

(9) (a) Gutmann, B.; Cantillo, D.; Kappe, C. O. *Angew. Chem., Int. Ed.* **2015**, *54*, 6688. (b) Maurya, R. A.; Park, C. P.; Lee, J. H.; Kim, D.-P. *Angew. Chem., Int. Ed.* **2011**, *50*, 5952. (c) Sharma, S.; Maurya, R. A.; Min, K.-I.; Jeong, G.-Y.; Kim, D.-P. *Angew. Chem., Int. Ed.* **2013**, *52*, 7564. (d) Basavaraju, K. C.; Sharma, S.; Maurya, R. A.; Kim, D.-P. *Angew. Chem., Int. Ed.* **2013**, *52*, 6735. (e) Mueller, S. T. R.; Wirth, T. *ChemSusChem* **2015**, *8*, 245. (f) Wiles, C.; Watts, P. *Green Chem.* **2014**, *16*, 55. (g) Pastre, J. C.; Browne, D. L.; Ley, S. V. *Chem. Soc. Rev.* **2013**, *42*, 8849.

(10) (a) Su, Y.; Straathof, N. J. W.; Hessel, V.; Noel, T. *Chem. - Eur. J.* **2014**, *20*, 10562. (b) Park, C. P.; Maurya, R. A.; Lee, J. H.; Kim, D.-P. *Lab Chip* **2011**, *11*, 1941. (c) Wang, X.; Cuny, G. D.; Noel, T. *Angew. Chem., Int. Ed.* **2013**, *52*, 7860. (d) Asano, K.; Uesugi, Y.; Yoshida, J.-i. *Org. Lett.* **2013**, *15*, 2398. (e) Neumann, M.; Zeitler, K. *Org. Lett.* **2012**, *14*, 2658. (f) Maurya, R. A.; Park, C. P.; Kim, D.-P. *Beilstein J. Org. Chem.* **2011**, *7*, 1158. (g) Tucker, J. W.; Zhang, Y.; Jamison, T. F.; Stephenson, C. R. J. *Angew. Chem., Int. Ed.* **2012**, *51*, 4144. (h) Lumley, E. K.; Dyer, C. E.; Pamme, N.; Boyle, R. W. *Org. Lett.* **2012**, *14*, 5724. (i) Cambie, D.; Bottecchia, C.; Straathof, N. J. W.; Hessel, V.; Noel, T. *Chem. Rev.* **2016**, DOI: 10.1021/acs.chemrev.5b00707. (j) Beatty, J. W.; Stephenson, C. R. J. *J. Am. Chem. Soc.* **2014**, *136*, 10270. (k) Cantillo, D.; de Frutos, O.; Rincon, J. A.; Mateos, C.; Kappe, C. O. *Org. Lett.* **2014**, *16*, 896.