JOC The Journal of Organic Chemistry

Featured Article

pubs.acs.org/joc

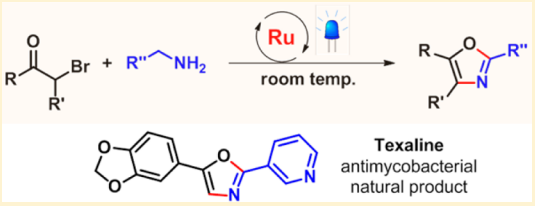
Synthesis of Substituted Oxazoles by Visible-Light Photocatalysis

Tanmay Chatterjee, Ji Young Cho, and Eun Jin Cho*

Department of Chemistry, Chung-Ang University, 84 Heukseok-ro, Dongjak-gu, Seoul 06974, Republic of Korea

Supporting Information

ABSTRACT: A simple and practical method for the synthesis of substituted oxazoles has been developed using readily available α-bromoketones and benzylamines by visible-light photocatalysis at room temperature. The process, which requires 1 mol % of $[Ru(bpy)_3]Cl_2$ photocatalyst with K_3PO_4 and CCl_3Br, is effective for accessing a variety of valuable oxazole compounds. The synthetic utility of our protocol was also demonstrated by preparing a natural product, texaline.



INTRODUCTION

The oxazole motif is one of the most widely occurring heterocycles in biologically active molecules and natural products and has attracted interest from both industry and academia.[1] In particular, 2,5-disubstituted and 2,4,5-trisubstituted oxazoles[2] are found in numerous natural products and pharmacologically active molecules such as the antimycobacterial natural product texaline,[2b,3] antipancreatic cancer agent PC-046,[2e] potent monoamine oxidase inhibitor pimpirinine,[2f] antidiabetic agent AD-5061,[4] and peptide alkaloid (−)-muscoride A[5] (Figure 1). Oxazoles also have applications as important structural motifs in fluorescent dyes[2f,6] and polymers.[7]

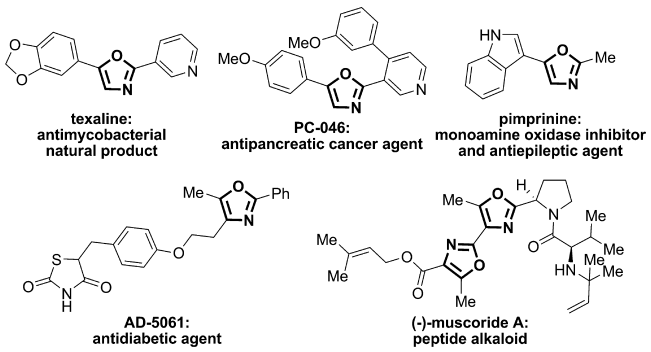
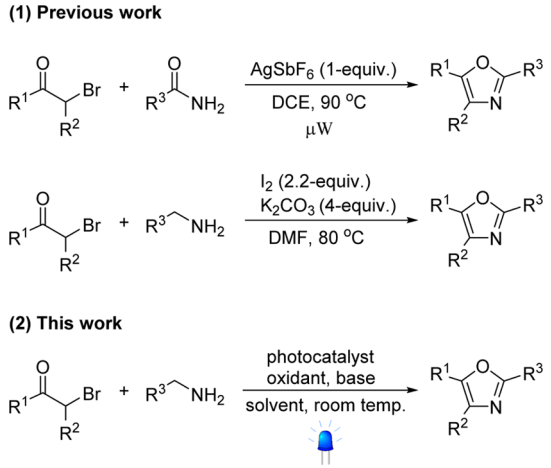


Figure 1. Biologically active molecules containing the oxazole structural motif.

Due to their significant importance, several methodologies have been developed to construct functionalized oxazole skeletons.[8] In general, the motif is generated by cyclization of acyclic precursors[9] and oxidation of oxazolines.[10] However, there is still significant scope for the development of a single-step method from readily available starting materials under mild reaction conditions. Recently, easily accessible α-bromoketones were utilized by Moses et al.[11] and Zhang et al.[12] for the synthesis of substituted oxazoles [Scheme 1 (1)]. Despite their efficiency and broad substrate scope, these methods suffer from limitations associated with the use of a stoichiometric amount of silver reagent or oxidants at high reaction temperature by microwave or conventional heating.

Scheme 1. Synthesis of Oxazoles from α-Bromoketones



In another arena, visible-light photoredox catalysis has attracted significant attention.[13] In continuation of our previous studies for the visible-light-induced synthesis of heterocycles,[14] we developed a practical method for the synthesis of substituted oxazoles from α-bromoketones and benzylamine derivatives utilizing a Ru photocatalyst under visible light irradiation at room temperature [Scheme 1 (2)].

RESULTS AND DISCUSSION

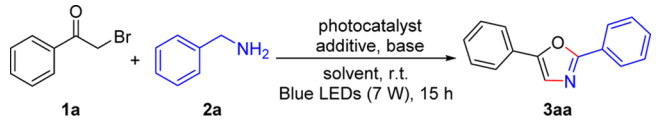
We started the investigation by using 2-bromoacetophenone **1a** and benzylamine **2a** as model substrates in the presence of 2 mol % of $[Ru(bpy)_3]Cl_2$ photocatalyst, 2 equiv of CCl_3Br, and 3 equiv of K_3PO_4 in 0.2 M DMF at room temperature. The desired 2,5-diphenyloxazole **3aa** was formed in 70% yield under

Special Issue: Photocatalysis

Received: April 29, 2016
Published: June 21, 2016

DOI: 10.1021/acs.joc.6b00989
J. Org. Chem. 2016, 81, 6995−7000

Table 1. Optimization of Reaction Conditions[a]



1a 2a 3aa

entry	photocatalyst (mol %)	additive (equiv)	base (equiv)	solvent (conc)	yield[b] (%)
1	$[Ru(bpy)_3]Cl_2$ (2)	CCl_3Br (2)	K_3PO_4 (3)	DMF (0.2 M)	70
2[c]	$[Ru(bpy)_3]Cl_2$ (2)	CCl_3Br (2)	K_3PO_4 (3)	DMF (0.2 M)	trace
3		CCl_3Br (2)	K_3PO_4 (3)	DMF (0.2 M)	
4	$[Ru(bpy)_3]Cl_2$ (2)	CCl_3Br (2)		DMF (0.2 M)	
5	$[Ru(bpy)_3]Cl_2$ (2)		K_3PO_4 (3)	DMF (0.2 M)	
6	Eosin Y (5)	CCl_3Br (2)	K_3PO_4 (3)	DMF (0.2 M)	32
7	$[Ru(phen)_3]Cl_2$ (2)	CCl_3Br (2)	K_3PO_4 (3)	DMF (0.2 M)	63
8	*fac*-lr(ppy)$_3$	CCl_3Br (2)	K_3PO_4 (3)	DMF (0.2 M)	65
9	$[lr(dtbbpy)\ (ppy)_2]PF_6$	CCl_3Br (2)	K_3PO_4 (3)	DMF (0.2 M)	60
10	$[Ru(bpy)_3]Cl_2$ (2)	CCl_3Br (2)	K_2CO_3 (3)	DMF (0.2 M)	56
11	$[Ru(bpy)_3]Cl_2$ (2)	CCl_3Br (2)	Cs_2CO_3 (3)	DMF (0.2 M)	50
12	$[Ru(bpy)_3]Cl_2$ (2)	CCl_3Br (2)	Et_3N (3)	DMF (0.2 M)	trace
13	$[Ru(bpy)_3]Cl_2$ (2)	CCl_3Br (2)	2,6-luitidine (3)	DMF (0.2 M)	42
14	$[Ru(bpy)_3]Cl_2$ (2)	TBHP (2)	K_3PO_4 (3)	DMF (0.2 M)	trace
15	$[Ru(bpy)_3]Cl_2$ (2)	$(PhS)_2$ (2)	K_3PO_4 (3)	DMF (0.2 M)	trace
16	$[Ru(bpy)_3]Cl_2$ (2)	CCl_3Br (2)	K_3PO_4 (3)	DMSO (0.2 M)	66
17	$[Ru(bpy)_3]Cl_2$ (2)	CCl_3Br (2)	K_3PO_4 (3)	MeCN (0.2 M)	53
18	$[Ru(bpy)_3]Cl_2$ (2)	CCl_3Br (2)	K_3PO_4 (3)	THF (0.2 M)	trace
19	$[Ru(bpy)_3]Cl_2$ (2)	CCl_3Br (2)	K_3PO_4 (3)	MeOH (0.2 M)	trace
20	$[Ru(bpy)_3]Cl_2$ (5)	CCl_3Br (2)	K_3PO_4 (3)	DMF (0.2 M)	70
21	$[Ru(bpy)_3]Cl_2$ (1)	CCl_3Br (2)	K_3PO_4 (3)	DMF (0.2 M)	70
22	$[Ru(bpy)_3]Cl_2$ (0.5)	CCl_3Br (2)	K_3PO_4 (3)	DMF (0.2 M)	61
23	$[Ru(bpy)_3]Cl_2$ (1)	CCl_3Br (2)	K_3PO_4 (4)	DMF (0.2 M)	70
24	$[Ru(bpy)_3]Cl_2$ (1)	CCl_3Br (2)	K_3PO_4 (2)	DMF (0.2 M)	61
25	$[Ru(bpy)_3]Cl_2$ (1)	CCl_3Br (1.5)	K_3PO_4 (3)	DMF (0.2 M)	71
26	$[Ru(bpy)_3]Cl_2$ (1)	CCl_3Br (1.1)	K_3PO_4 (3)	DMF (0.2 M)	59
27[d]	$[Ru(bpy)_3]Cl_2$ (1)	CCl_3Br (1.5)	K_3PO_4 (3)	DMF (0.2 M)	80
28[e]	$[Ru(bpy)_3]Cl_2$ (1)	CCl_3Br (1.5)	K_3PO_4 (3)	DMF (0.2 M)	80
29[d]	**$[Ru(bpy)_3]Cl_2$ (1)**	**CCl_3Br (1.5)**	**K_3PO_4 (3)**	**DMF (0.1 M)**	**90**
30[d]	$[Ru(bpy)_3]Cl_2$ (1)	CCl_3Br (1.5)	K_3PO_4 (3)	DMF (0.4 M)	65
31[d,f]	$[Ru(bpy)_3]Cl_2$ (1)	CCl_3Br (1.5)	K_3PO_4 (3)	DMF (0.1 M)	
32[d,f]	$[Ru(bpy)_3]Cl_2$ (1)		K_3PO_4 (3)	DMF (0.1 M)	

[a]Reaction conditions: **1a** (0.1 mmol), **2a** (1.2 equiv) unless otherwise stated, argon atmosphere. [b]Yield was determined by ^1H NMR spectroscopy using bromoform as the internal standard. [c]No blue LEDs. [d]**2a** (1.5 equiv). [e]**2a** (2 equiv). [f]Oxygen atmosphere.

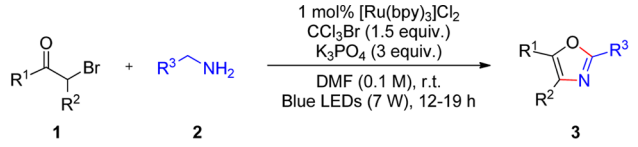
visible-light irradiation (Table 1, entry 1). Blank experiments in the absence of any one of visible light, $[Ru(bpy)_3]Cl_2$, CCl_3Br, or K_3PO_4 did not provide **3aa**, confirming that all of the reagents are essential for oxazole synthesis (Table 1, entries 2−5). Among various Ru- and Ir-based photocatalysts and an organophotocatalyst (Eosin Y), $[Ru(bpy)_3]Cl_2$ showed the highest activity (Table 1, entries 1 and 6−9). Several inorganic and organic bases were also tested, but K_3PO_4 was found to be optimal (Table 1, entries 1 and 10−13). Notably, the use of other radical mediators such as TBHP or diphenyl disulfide instead of CCl_3Br was ineffective for the transformation (Table 1, entries 14 and 15). Among various solvents, including DMF, DMSO, MeCN, THF, and MeOH, DMF worked best (Table 1, entries 1 and 16−19). Photocatalyst loading was optimized to 1 mol % (Table 1, entries 1 and 20−22). Next, the stoichiometry of K_3PO_4, CCl_3Br, and **2a** was investigated; the use of 3 equiv of K_3PO_4, and 1.5 equiv of CCl_3Br and **2a** was found to be optimal (Table 1, entries 1 and 23−28). Finally, the effect of reagent concentration was investigated, and the best yield of **3aa** was obtained under dilute (0.1 M) conditions (Table 1, entries 1, 29, and 30). The presence of molecular oxygen prevented the formation of the desired oxazole in presence or absence of CCl_3Br (Table 1, entries 31 and 32).

Under the optimized conditions, the α-bromoketone substrate scope of the method was investigated (Table 2). 2-Bromoacetophenones containing both electron-donating and electron-withdrawing substituents underwent cyclization with benzylamine **2a** to afford the corresponding 2,5-disubstuted oxazoles in moderate-to-excellent yields (Table 2, **3aa**−**ka**). An aliphatic α-bromoketone, 1-bromo-3,3-dimethyl-2-butanone (**1l**), and a conjugated α-bromoketone, (*E*)-1-bromo-4-phenyl-but-3-en-2-one (**1m**), were also suitable substrates to give 5-*tert*-butyl-2-phenyloxazole (**3la**) and (*E*)-2-phenyl-5-styryloxazole (**3ma**), respectively. In addition, a trisubstituted oxazole, 2,4,5-triphenyloxazole (**3na**), could be synthesized by using 2-bromo-2-phenylacetophenone (**1n**) with benzylamine despite the low yield. On the other hand, α-bromoesters such as ethyl 2-bromoacetate (**1o**) and diethyl 2-bromomalonate (**1p**) were found to be poor substrates for the transformation.

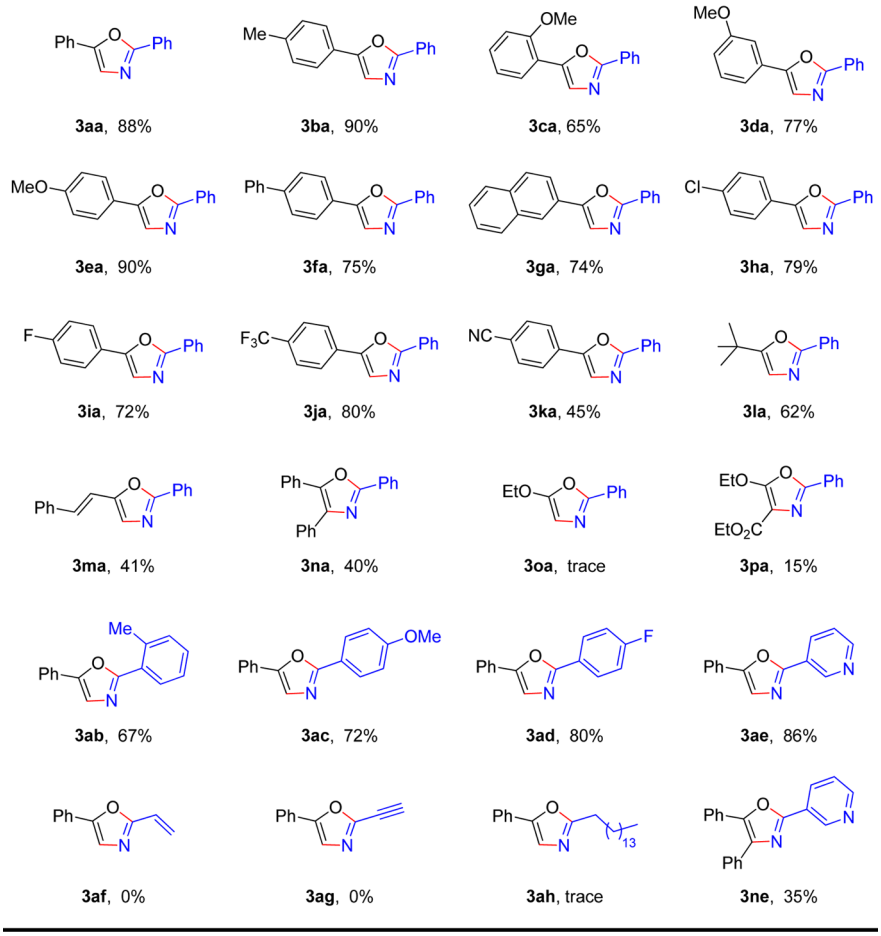
Next, we explored the substrate scope using various benzylamine derivatives with 2-bromoacetophenone **1a** (Table 2, **3ab**−**ae**). The reactions proceeded smoothly to

DOI: 10.1021/acs.joc.6b00989
J. Org. Chem. 2016, 81, 6995−7000

Table 2. Substrate Scope for Oxazole Synthesis[a,b]



1 2 3

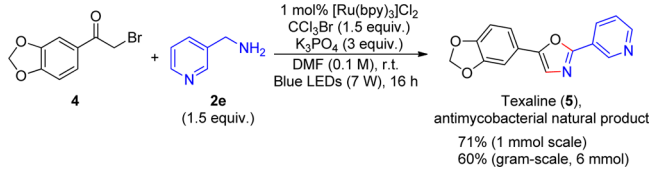


[a]Reaction scale: **1** (1 mmol), **2** (1.5 mmol), argon atmosphere. [b]Yield of isolated product.

afford the corresponding oxazoles in high yields. Notably, heteroaryl compound 3-(aminomethyl)pyridine (**2e**) was also an excellent substrate, providing 5-phenyl-2-(pyridin-3-yl)-oxazole (**3ae**), which is known to be highly active against *Mycobacterium tuberculosis*.[2b] However, reactions of allylamine (**2f**), propargylamine (**2g**), and alkylamines such as hexadecylamine (**2f**) did not furnish the desired oxazoles (**3af**–**ah**). In the case of the reaction between 2-bromo-2-phenylacetophenone (**1n**) and 3-(aminomethyl)pyridine (**2e**), the desired trisubstituted oxazole, 4,5-diphenyl-2-(pyridin-3-yl)oxazole (**3ne**), was generated in 35% yield.

Furthermore, to verify the applicability of the methodology to the synthesis of biologically active natural products, we attempted to synthesize texaline. The reaction between readily available **4** and **2e** under the optimized conditions furnished texaline **5** in 71% yield, and even this valuable natural product was synthesized in gram scale, indicating that scale-up of the transformation is straightforward (Scheme 2). This process could be considered the mildest, most practical, and cost-effective method compared to previously reported multistep reactions for the synthesis of texaline.[15]

Scheme 2. Synthesis of Texaline



4 **2e** (1.5 equiv.) Texaline (**5**), antimycobacterial natural product

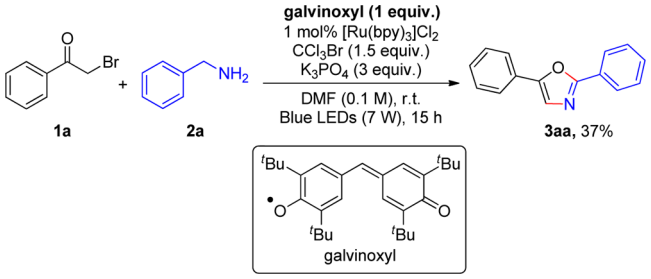
71% (1 mmol scale)
60% (gram-scale, 6 mmol)

To gain insight into the reaction mechanism, **1a** and **2a** were reacted in the presence of stoichiometric amounts of a radical scavenger, galvinoxyl under the optimized conditions (Scheme 3). The yield of **3aa** was reduced drastically to 37%, indicating the involvement of radical species in the transformation.

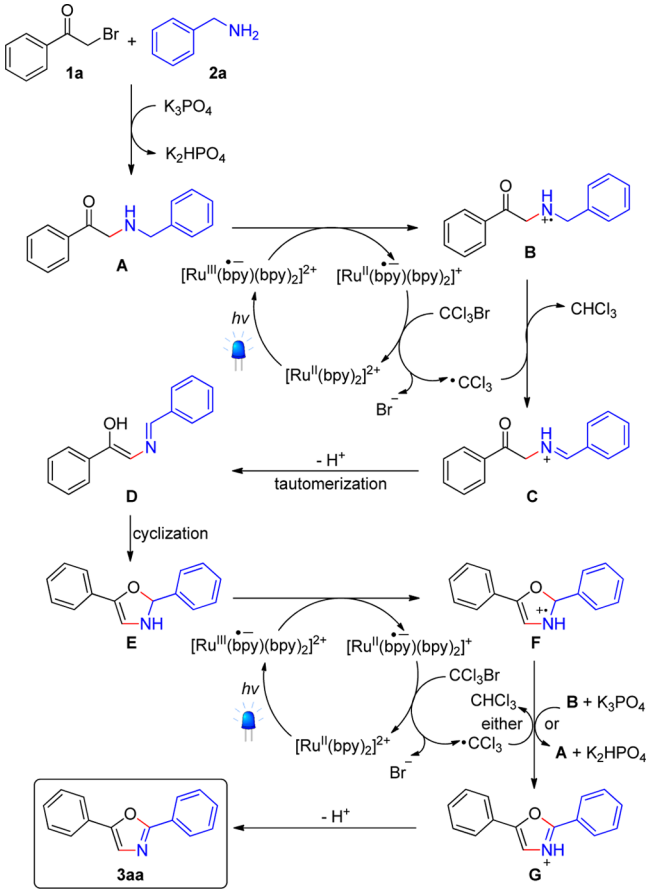
We propose a reaction mechanism for the synthesis of oxazole using **1a** and **2a** as substrates (Scheme 4). The reaction is initiated by simple nucleophilic substitution of **1a** by **2a** to produce α-aminoketone **A**. Then the species **A** transfers a single electron to $[Ru^{III}(bpy)^{\bullet-}(bpy)_2]^{2+}$, formed by metal-to-ligand charge transfer of $[Ru^{II}(bpy)_3]^{2+}$ under visible-light irradiation, resulting in the formation of radical cation **B** and reduced $[Ru^{II}(bpy)^{\bullet-}(bpy)_2]^{+}$. Next, $[Ru^{II}(bpy)^{\bullet-}(bpy)_2]^{+}$ is trans-

DOI: 10.1021/acs.joc.6b00989
J. Org. Chem. 2016, 81, 6995−7000

Scheme 3. Reaction of 1a and 2a in the Presence of Radical Scavenger



Scheme 4. Proposed Reaction Mechanism



formed back to the $[Ru^{II}(bpy)_3]^{2+}$ photocatalyst by reducing CCl_3Br to produce the $CCl_3^{\bullet}$ radical, which subsequently abstracts a H atom from the benzylic position of **B** to furnish iminium ion **C**.[16] Deprotonation of **C** followed by tautomerization provides key intermediate **D**. Base-mediated cyclization of **D** provides the corresponding oxazoline intermediate **E**. As the reaction did not produce the desired oxazole **3aa** under oxygen atmosphere both in the presence or absence of CCl_3Br (Table 1, entries 31 and 32), it is likely that the oxidation of oxazoline (**E**) to oxazole (**3aa**) is not operative by molecular oxygen. For the transformation of **E** to **3aa**, the similar photocatalytic pathway to give the intermediate **G** followed by its deprotonation might involve. In this pathway, **G** can be generated either by reaction with $^{\bullet}CCl_3$ radical or intermediate **B**.

In conclusion, we have developed a method for the synthesis of substituted oxazoles by visible-light photocatalysis under mild reaction conditions at room temperature. 2,5-Diaryl-, aryl−alkyl-, heteroaryl−aryl-, and 2,4,5-tri(hetero)aryl-substituted oxazoles were prepared in moderate-to-excellent yields. The applicability of the method was also successfully extended to the synthesis of texaline. Thus, we believe that the methodology is an important addition to those previously reported.

EXPERIMENTAL SECTION

General Information. All reagents including DMF and $[Ru(bpy)_3]Cl_2$ were purchased from commercial sources. Benzylamines were purified by distillation. Flash column chromatography was performed using silica gel 60 (70−230 mesh). The oxazole products were characterized by ^1H, ^{13}C NMR and FT-IR spectroscopy. NMR spectra were recorded on a 600 MHz instrument (600 MHz for ^1H NMR and 151 MHz for ^{13}C NMR). Copies of ^1H and ^{13}C NMR spectra can be found in the Supporting Information. ^1H NMR experiments are reported in units, parts per million (ppm), and were measured relative to residual chloroform (7.26 ppm) in the deuterated solvent. ^{13}C NMR spectra are reported in ppm relative to deuterochloroform (77.23 ppm), and all were obtained with ^1H decoupling. Coupling constants were reported in Hz. FT-IR spectra were recorded on a FT-IR spectrometer.

General Experimental Procedure for the Synthesis of 2,5-Disubstituted Oxazoles (3). *Representative Experimental Procedure for the Synthesis of 2,5-Diphenyloxazole (**3aa**).* A flame-dried resealable tube equipped with a magnetic stirrer bar was filled with 2-bromoacetophenone **1a** (1 mmol), benzylamine **2a** (1.5 mmol), $[Ru(bpy)_3]Cl_2$ (1 mol %, 0.01 mmol), CCl_3Br (1.5 mmol), and K_3PO_4 (3 mmol) in DMF (10 mL, 0.1 M). Then argon gas was bubbled through the reaction mixture for 10 min, and the tube was sealed with a silicone septum screw cap. The test tube was then placed under blue LEDs (7 W; 430−490 nm) at room temperature. The progress of the reaction was monitored by TLC or ^1H NMR of the crude reaction mixture using bromoform ($CHBr_3$) as the internal standard. The reaction mixture was then diluted with ethyl acetate (EtOAc) and washed with water and brine. The organic layer was dried over $MgSO_4$, filtered, concentrated under vacuum, and purified by flash column chromatography (hexane/EtOAc = 95:5) to furnish pure 2,5-diphenyloxazole **3aa** in 88% yield.

*2,5-Diphenyloxazole (**3aa**):*[9d] white solid (194 mg, 88%); ^1H NMR (600 MHz, $CDCl_3$) δ 8.13 (dd, J = 7.8, 1.2 Hz, 2H), 7.73 (dd, J = 7.8, 1.2 Hz, 2H), 7.52−7.42 (m, 6H), 7.35 (tt, J = 7.8, 1.2 Hz, 1H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 161.4, 151.47, 130.53, 129.2, 129.0, 128.7, 128.3, 127.7, 126.5, 124.4, 123.7; IR (neat) ν_{max} = 2926, 1727, 1684, 1482, 1241, 710, 689 cm^{-1}; R_f 0.45 (hex/EtOAc, 5/1).

*2-Phenyl-5-(p-tolyl)oxazole (**3ba**):*[9d] off-white solid (211 mg, 90%); ^1H NMR (600 MHz, $CDCl_3$) δ 8.11 (dd, J = 7.8, 1.8 Hz, 2H), 7.62 (d, J = 8.4 Hz, 2H), 7.51−7.44 (m, 3H), 7.40 (s, 1H), 7.25 (dd, J = 7.8, 1.8 Hz, 2H), 2.40 (s, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 160.8, 151.5, 138.5, 130.2, 129.6, 128.8, 127.5, 126.2, 125.3, 124.2, 122.8, 21.4; IR (neat) ν_{max} = 2920, 1683, 1502, 1245, 814, 713 cm^{-1}; R_f 0.43 (hex/EtOAc, 5/1).

*5-(2-Methoxyphenyl)-2-phenyloxazole (**3ca**):*[9a] off-white solid (163 mg, 65%); ^1H NMR (600 MHz, $CDCl_3$) δ 8.13 (dd, J = 7.8, 1.2 Hz, 2H), 7.90 (dd, J = 7.8, 1.8 Hz, 1H), 7.66 (s, 1H), 7.52−7.43 (m, 3H), 7.31 (dd, J = 7.8, 1.8 Hz, 1H), 7.08 (td, J = 7.2, 1.2 Hz, 1H), 7.00 (d, J = 8.4 Hz, 1H), 3.99 (s, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 160.2, 155.9, 148.0, 130.3, 129.2, 129.0, 127.84, 127.83, 126.5, 126.0, 121.0, 117.5, 111.1, 55.7; IR (neat) ν_{max} = 2924, 1567, 1490, 1249, 1130, 1023, 750, 708 cm^{-1}; R_f 0.45 (hex/EtOAc, 3/1).

*5-(3-Methoxyphenyl)-2-phenyloxazole (**3da**):*[9a] pale yellow solid (193 mg, 77%); ^1H NMR (600 MHz, $CDCl_3$) δ 8.11 (dd, J = 8.1, 1.5 Hz 2H), 7.50−7.45 (m, 3H), 7.44 (s, 1H), 7.36 (dd, J = 8.0, 7.8 Hz, 1H), 7.31 (ddd, J = 7.8, 1.5, 1.1 Hz, 1H), 7.25 (dd, J = 2.6, 1.5 Hz, 1H), 6.89 (ddd, J = 8.1, 2.6, 1.1 Hz, 1H), 3.88 (s, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 161.3, 160.2, 151.3, 130.5, 130.3, 129.4, 129.0, 127.6, 126.5, 123.9, 116.9, 114.2, 109.9, 55.6; IR (neat) ν_{max} = 2939, 2835,

DOI: 10.1021/acs.joc.6b00989
J. Org. Chem. 2016, 81, 6995−7000

1593, 1487, 1219, 1041, 775, 709, 686 cm^{-1}; R_f 0.43 (hex/EtOAc, 3/1).

*5-(4-Methoxyphenyl)-2-phenyloxazole (**3ea**):*[9a] pale yellow solid (226 mg, 90%); ^1H NMR (300 MHz, $CDCl_3$) δ 8.1 (d, J = 7.4 Hz, 2H), 7.64 (d, J = 8.8 Hz, 2H), 7.48−7.41 (m, 3H), 7.31 (s, 1H), 6.96 (d, J = 8.8 Hz, 2H), 3.82 (s, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 160.6, 159.9, 151.4, 130.2, 128.9, 127.7, 126.2, 125.8, 122.1, 121.0, 114.5, 55.4; IR (neat) ν_{max} = 2957, 2836, 1616, 1500, 1252, 1026, 823, 707 cm^{-1}; R_f 0.38 (hex/EtOAc, 3/1).

*5-Biphenyl-4-yl-2-phenyloxazole (**3fa**):*[9h] white solid (223 mg, 75%); ^1H NMR (600 MHz, $CDCl_3$) δ 8.14 (dd, J = 8.1, 1.5 Hz, 2H), 7.80 (ddd, J = 8.5, 6.6, 1.9 Hz, 2H), 7.69 (ddd, J = 8.5, 6.6, 1.9 Hz, 2H), 7.64 (dd, J = 8.2, 1.3 Hz, 2H), 7.52−7.46 (m, 6H), 7.38 (tt, J = 7.4, 1.3 Hz, 1H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 161.4, 151.3, 141.4, 140.5, 130.6, 129.1, 129.0, 127.9, 127.8, 127.7, 127.18, 127.13, 126.5, 124.8, 123.8; IR (neat) ν_{max} = 3033, 1728, 1484, 908, 766, 687 cm^{-1}; R_f 0.46 (hex/EtOAc, 3/1).

*5-(Naphthalen-2-yl)-2-phenyloxazole (**3ga**):*[9a] white solid (201 mg, 74%); ^1H NMR (600 MHz, $CDCl_3$) δ 8.20 (s, 1H), 8.17 (ddd, J = 6.7, 4.6, 1.7 Hz, 2H), 7.90 (dd, J = 8.3, 7.4 Hz, 2H), 7.85 (d, J = 7.9 Hz, 1H), 7.78 (dd, J = 8.5, 1.7 Hz, 1H), 7.56 (s, 1H), 7.55−7.46 (m, 5H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 161.6, 151.6, 133.6, 133.3, 130.6, 129.1, 129.0, 128.4, 128.1, 127.7, 127.0, 126.7, 126.6, 125.5, 124.2, 123.1, 122.3; IR (neat) ν_{max} = 3056, 1728, 1485, 1128, 814, 710, 690 cm^{-1}; R_f 0.48 (hex/EtOAc, 3/1).

*5-(4-Chlorophenyl)-2-phenyloxazole (**3ha**):*[9a] pale yellow solid (202 mg, 79%); ^1H NMR (600 MHz, $CDCl_3$) δ 8.10 (dd, J = 7.9, 1.8 Hz, 2H), 7.65 (d, J = 8.5 Hz, 2H), 7.52−7.45 (m, 3H), 7.44 (s, 1H), 7.42 (d, J = 8.5 Hz, 2H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 161.6, 150.5, 134.4, 130.7, 129.4, 129.1, 127.5, 126.7, 126.5, 125.6, 124.1; IR (neat) ν_{max} = 3057, 1542, 1480, 1090, 951, 819, 706, 689 cm^{-1}; R_f 0.49 (hex/EtOAc, 4/1).

*5-(4-Fluorophenyl)-2-phenyloxazole (**3ia**):*[9a] white solid (172 mg, 72%); ^1H NMR (600 MHz, $CDCl_3$) δ 8.10 (dd, J = 8.0, 1.7 Hz, 2H), 7.72−7.67 (dd, J = 8.8, $^4J_{H-F}$ = 5.2 Hz, 2H), 7.50−7.46 (m, 3H), 7.39 (s, 1H), 7.14 (dd, J = 8.8, $^3J_{H-F}$ = 8.6 Hz, 2H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 162.9 (d, $^1J_{C-F}$ = 249.2 Hz), 161.3, 150.5, 130.6, 129.0, 127.6, 126.5, 126.3 (d, $^3J_{C-F}$ = 8.2 Hz), 124.6 (d, $^4J_{C-F}$ = 3.4 Hz), 123.3, 116.3 (d, $^2J_{C-F}$ = 22.1 Hz); IR (neat) ν_{max} = 3063, 2928, 1724, 1498, 1231, 824, 707, 690 cm^{-1}; R_f 0.48 (hex/EtOAc, 4/1).

*5-(4-Trifluoromethylphenyl)-2-phenyloxazole (**3ja**):*[15b] white solid (231 mg, 80%); ^1H NMR (600 MHz, $CDCl_3$) δ 8.11 (dd, J = 7.8, 2.0 Hz, 2H), 7.80 (d, J = 8.2 Hz, 2H), 7.69 (d, J = 8.2 Hz, 2H), 7.54 (s, 1H), 7.50−7.48 (m, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 162.2, 151.9, 150.0, 131.3, 130.9, 130.2 (q, J_{C-F} = 32.8 Hz), 129.1, 127.3, 126.7, 126.2 (q, J_{C-F} = 3.8 Hz), 125.4, 124.4; IR (neat) ν_{max} = 3063, 2931, 1734, 1618, 1321, 1109, 1071, 833, 711, 686 cm^{-1}; R_f 0.51 (hex/EtOAc, 4/1).

*4-(2-Phenyloxazol-5-yl)benzonitrile (**3ka**):*[9e] off-white solid (111 mg, 45%); ^1H NMR (600 MHz, $CDCl_3$) δ 8.13 (dd, J = 7.2, 1.8 Hz, 2H), 7.81 (dd, J = 9.0, 1.2 Hz, 2H), 7.73 (dd, J = 9.0, 1.2 Hz, 2H), 7.60 (s, 1H), 7.53−7.49 (m, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 162.7, 149.6, 133.0, 132.2, 131.2, 129.2, 127.1, 126.8, 126.5, 124.6, 118.8, 111.7; IR (neat) ν_{max} = 2925, 1734, 1365, 1217, 839, 731, 686 cm^{-1}; R_f 0.34 (hex/EtOAc, 3/1).

*5-tert-Butyl-2-phenyloxazole (**3la**):*[12] pale yellow liquid (125 mg, 62%); ^1H NMR (600 MHz, $CDCl_3$) δ 8.09 (dd, J = 7.8, 1.2 Hz, 2H), 7.50−7.37 (m, 3H), 6.79 (s, 1H), 1.36 (s, 9H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 161.2, 160.6, 130.0, 128.9, 128.2, 126.2, 121.2, 31.8, 29.0; IR (neat) ν_{max} = 2968, 2930, 1736, 1480, 1366, 1117, 972, 716, 690 cm^{-1}; R_f 0.57 (hex/EtOAc, 5/1).

*(E)-2-Phenyl-5-styryloxazole (**3ma**):*[12] yellow solid (101 mg, 41%); ^1H NMR (600 MHz, $CDCl_3$) δ 8.11 (d, J = 8.4 Hz, 2H), 7.52−7.46 (m, 5H), 7.38 (t, J = 7.8 Hz, 2H), 7.30 (t, J = 7.2 Hz, 1H), 7.17 (d, J = 16.2 Hz, 1H), 7.17 (s, 1H), 6.95 (d, J = 16.2 Hz, 1H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 161.3, 150.6, 136.6, 130.6, 129.7, 129.0, 128.5, 127.6, 126.8, 126.7, 126.6, 113.3; R_f 0.31 (hex/EtOAc, 20/1).

*2,4,5-Triphenyloxazole (**3na**):*[12] white solid (118 mg, 40%); ^1H NMR (600 MHz, $CDCl_3$) δ 8.21−8.12 (d, J = 8.4 Hz, 2H), 7.74 (d, J = 7.2 Hz, 2H), 7.69 (d, J = 7.2 Hz, 2H), 7.51−7.46 (m, 3H), 7.44−7.33 (m, 6H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 160.4, 145.8, 137.0, 132.8, 130.6, 129.2, 129.0, 128.9, 128.84, 128.77, 128.5, 128.4, 127.6, 126.8, 126.7; IR (neat) ν_{max} = 3058, 1488, 1449, 965, 776, 692 cm^{-1}; R_f 0.50 (hex/EtOAc, 20/1).

*5-Phenyl-2-o-tolyloxazole (**3ab**):*[9e] pale yellow solid (157 mg, 67%); ^1H NMR (600 MHz, $CDCl_3$) δ 8.10 (d, J = 7.7 Hz, 1H), 7.73 (d, J = 7.7 Hz, 2H), 7.49 (s, 1H), 7.45 (t, J = 7.7 Hz, 2H), 7.38−7.31 (m, 4H), 2.77 (s, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 161.8, 151.1, 137.5, 131.9, 130.1, 129.1, 129.0, 128.6, 128.3, 126.6, 126.2, 124.4, 123.4, 22.3; IR (neat) ν_{max} = 3106, 2970, 2922, 1735, 1487, 1449, 1121, 953, 724, 689 cm^{-1}; R_f 0.44 (hex/EtOAc, 8/1).

*2-(4-Methoxyphenyl)-5-phenyloxazole (**3ac**):*[9e] pale yellow solid (181 mg, 72%); ^1H NMR (600 MHz, $CDCl_3$) δ 8.05 (d, J = 8.8 Hz, 2H), 7.70 (d, J = 7.5 Hz, 2H), 7.43 (t, J = 7.5 Hz, 2H), 7.40 (s, 1H), 7.32 (t, J = 7.5 Hz, 1H), 6.99 (d, J = 8.8 Hz, 2H), 3.86 (s, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 161.5, 161.4, 150.9, 129.1, 128.4, 128.4, 128.1, 124.2, 123.5, 120.5, 114.4, 55.6; IR (neat) ν_{max} = 2939, 2836, 1609, 1495, 1249, 1171, 1025, 834, 738, 686 cm^{-1}; R_f 0.36 (hex/EtOAc, 3/1).

*2-(4-Fluorophenyl)-5-phenyloxazole (**3ad**):*[9e] pale yellow solid (191 mg, 80%); ^1H NMR (600 MHz, $CDCl_3$) δ 8.09 (dd, J = 8.6 Hz, $^4J_{H-F}$ = 5.3 Hz, 2H), 7.70 (d, J = 7.8 Hz, 2H), 7.44 (dd, J = 7.8, 7.5 Hz, 2H), 7.42 (s, 1H), 7.34 (t, J = 7.5 Hz, 1H), 7.17 (dd, J = 8.6 Hz, $^3J_{H-F}$ = 8.2 Hz, 2H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 164.2 (d, $^1J_{C-F}$= 250.7 Hz), 160.5, 151.5, 129.1, 128.7, 128.6(d, $^3J_{C-F}$= 7.6 Hz), 128.1, 124.4, 124.0, 123.6, 116.2(d, $^2J_{C-F}$= 22.7 Hz); IR (neat) ν_{max} = 3040, 1739, 1605, 1494, 1218, 838, 731, 686 cm^{-1}; R_f 0.36 (hex/EtOAc, 6/1).

*5-Phenyl-2-(pyridin-3-yl)oxazole (**3ae**):*[9h] yellow solid (191 mg, 86%); ^1H NMR (600 MHz, $CDCl_3$) δ 9.32 (s, 1H), 8.67 (s, 1H), 8.33 (d, J = 7.8 Hz, 1H), 7.70 (d, J = 7.3 Hz, 2H), 7.47−7.41 (m, 3H), 7.39 (dd, J = 8.3, 4.5 Hz, 1H), 7.34 (dd, J = 7.8, 4.5 Hz, 1H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 158.9, 152.2, 151.1, 147.7, 133.5, 129.2, 129.0, 127.8, 124.5, 123.8, 123.8, 123.8; IR (neat) ν_{max} = 3038, 2925, 1738, 1409, 1021, 952, 811, 761, 720, 689 cm^{-1}; R_f 0.52 (in EtOAc).

*4,5-Diphenyl-2-(pyridin-3-yl)oxazole (**3ne**).* colorless viscous oil (104 mg, 35%); ^1H NMR (600 MHz, $CDCl_3$) δ 9.38 (s, 1H), 8.70 (d, J = 4.8 Hz, 1H), 8.41 (d, J = 7.8 Hz, 1H), 7.72 (d, J = 7.2 Hz, 2H), 7.68 (d, J = 7.2 Hz, 2H), 7.44−7.36 (m, 7H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 158.0, 151.2, 147.9, 146.5, 137.2, 133.8, 132.4, 129.1, 129.0, 128.9, 128.8, 128.7, 128.3, 126.9, 123.9, 123.8; IR (neat) ν_{max} = 3057, 2924, 1605, 1482, 965, 764, 693 cm^{-1}; R_f 0.22 (hex/EtOAc, 4/1); MS m/z (EI) calcd for $C_{20}H_{14}N_2O$ [M^+] 298.1106, found 298.1.

*5-(Benzo[d][1,3]dioxol-5-yl)-2-(pyridin-3-yl)oxazole, Texaline (**5**):*[15b] pale yellow solid (1 mmol scale:189 mg, 71%; 6 mmol scale: 0.96 g, 60%); ^1H NMR (600 MHz, $CDCl_3$) δ 9.31 (s, 1H), 8.68 (dd, J = 4.8, 1.8 Hz, 1H), 8.33 (dd, J = 8.4, 1.8 Hz, 1H), 7.41 (dd, J = 8.4, 4.8 Hz, 1H), 7.34 (s, 1H), 7.25 (dd, J = 8.4, 1.8 Hz, 1H), 7.17 (s, 1H), 6.89 (d, J = 8.4 Hz, 1H), 6.03 (s, 2H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 158.4, 152.1, 151.0, 148.5, 148.4, 147.7, 133.5, 123.9, 123.8, 122.7, 122.0, 118.9, 109.2, 105.1, 101.7; IR (neat) ν_{max} = 2917, 1733, 1685, 1482, 1448, 1232, 1038, 933, 812, 723 cm^{-1}; R_f 0.64 (in EtOAc).

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b00989.

^1H and ^{13}C NMR spectra for all oxazoles **3** and texaline **5** (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: ejcho@cau.ac.kr.

Notes

The authors declare no competing financial interest.

DOI: 10.1021/acs.joc.6b00989
J. Org. Chem. 2016, 81, 6995−7000

■ ACKNOWLEDGMENTS

We acknowledge grants from the National Research Foundation of Korea (NRF-2014R1A1A1A05003274, NRF-2014-011165, and NRF-2012M3A7B4049657).

■ REFERENCES

(1) (a) *Oxazoles: Synthesis, Reactions and Spectroscopy, Part A*; Palmer, D. C., Ed.; John Wiley & Sons: Hoboken, NJ, 2003. (b) *Oxazoles: Synthesis, Reactions and Spectroscopy, Part B*; Palmer, D. C., Ed.; John Wiley & Sons: Hoboken, NJ, 2004. (c) Yeh, V. S. C. *Tetrahedron* **2004**, *60*, 11995. (d) Nicolaou, K. C.; Hao, J.; Reddy, M. V.; Rao, P. B.; Rassias, G.; Snyder, S. A.; Huang, X.; Chen, D. Y. K.; Brenzovich, W. E.; Giuseppone, N.; Giannakakou, P.; O'Brate, A. *J. Am. Chem. Soc.* **2004**, *126*, 12897. (e) Jin, Z. *Nat. Prod. Rep.* **2011**, *28*, 1143. (f) Zhang, J.; Ciufolini, M. A. *Org. Lett.* **2011**, *13*, 390.

(2) For some selected examples, see: (a) Brown, P.; Davies, D. T.; O'Hanlo, P. J.; Wilson, J. M. *J. Med. Chem.* **1996**, *39*, 446. (b) Giddens, A. C.; Boshoff, H. I. M.; Franzblau, S. G.; Barry, C. E., III; Copp, B. R. *Tetrahedron Lett.* **2005**, *46*, 7355. (c) Bey, E.; Marchais-Oberwinkler, S.; Kruchten, P.; Frotscher, M.; Werth, R.; Oster, A.; Algül, O.; Neugebauer, A.; Hartmann, R. W. *Bioorg. Med. Chem.* **2008**, *16*, 6423. (d) Zhao, Q.; Liu, S.; Li, Y.; Wang, Q. *J. Agric. Food Chem.* **2009**, *57*, 2849. (e) Shaw, A. Y.; Henderson, M. C.; Flynn, G.; Samulitis, B.; Han, H.; Stratton, S. P.; Chow, H.-H. S.; Hurley, L. H.; Dorr, R. T. *J. Pharmacol. Exp. Ther.* **2009**, *331*, 636. (f) Grotkopp, O.; Ahmad, A.; Frank, W.; Muller, T. J. J. *Org. Biomol. Chem.* **2011**, *9*, 8130. (g) Yang, W. S.; Shimada, K.; Delva, D.; Patel, M.; Ode, E.; Skouta, R.; Stockwell, B. R. *ACS Med. Chem. Lett.* **2012**, *3*, 35.

(3) (a) de la Fuente, G.; Domínguez, X. A.; Gonzalez, A. G.; Reina, M.; Timon, I. *Heterocycles* **1988**, *27*, 35. (b) Rastogi, N.; Abaul, J.; Goh, K. S.; Devallois, A.; Philogène, E.; Bourgeois, P. *FEMS Immunol. Med. Microbiol.* **1998**, *20*, 267.

(4) Momose, Y.; Maekawa, T.; Yamano, T.; Kawada, M.; Odaka, H.; Ikeda, H.; Sohda, T. *J. Med. Chem.* **2002**, *45*, 1518.

(5) Nagatsu, A.; Kajitani, H.; Sakakibara, J. *Tetrahedron Lett.* **1995**, *36*, 4097.

(6) (a) Min, J.; Lee, J. W.; Ahn, Y.-H.; Chang, Y.-T. *J. Comb. Chem.* **2007**, *9*, 1079. (b) Iliashenko, R. Y.; Gorobets, N. Y.; Doroshenko, A. O. *Tetrahedron Lett.* **2011**, *52*, 5086.

(7) (a) Maier, G.; Schneider, J. M. *Macromolecules* **1998**, *31*, 1798. (b) Gong, Z.-H.; Leu, C.-M.; Wu, F.-I.; Shu, C.-F. *Macromolecules* **2000**, *33*, 8527.

(8) Turchi, I. J.; Dewar, M. J. S. *Chem. Rev.* **1975**, *75*, 389.

(9) For some recent examples, see: (a) Jiang, H.; Huang, H.; Cao, H.; Qi, C. *Org. Lett.* **2010**, *12*, 5561. (b) Cano, I.; Álvarez, E.; Nicasio, M. C.; Pérez, P. J. *J. Am. Chem. Soc.* **2011**, *133*, 191. (c) He, W.; Li, C.; Zhang, L. *J. Am. Chem. Soc.* **2011**, *133*, 8482. (d) Cheung, C. W.; Buchwald, S. L. *J. Org. Chem.* **2012**, *77*, 7526. (e) Xu, Z.; Zhang, C.; Jiao, N. *Angew. Chem., Int. Ed.* **2012**, *51*, 11367. (f) Xue, W.-J.; Li, Q.; Zhu, Y.-P.; Wang, J.-G.; Wu, A.-X. *Chem. Commun.* **2012**, *48*, 3485. (g) Xie, J.; Jiang, H.; Cheng, Y.; Zhu, C. *Chem. Commun.* **2012**, *48*, 979. (h) Gao, Q.-H.; Fei, Z.; Zhu, Y.-P.; Lian, M.; Jia, F.-C.; Liu, M.-C.; She, N.-F.; Wu, A.-X. *Tetrahedron* **2013**, *69*, 22. (i) Li, J.-l.; Wang, Y.-c.; Li, W.-z.; Wang, H.-s.; Mo, D.-l.; Pan, Y.-m. *Chem. Commun.* **2015**, *51*, 17772.

(10) (a) Meyers, A. I.; Tavares, F. X. *J. Org. Chem.* **1996**, *61*, 8207. (b) Phillips, A. J.; Uto, Y.; Wipf, P.; Reno, M. J.; Williams, D. R. *Org. Lett.* **2000**, *2*, 1165. (c) Wang, Y.; Li, Z.; Huang, Y.; Tang, C.; Wu, X.; Xu, J.; Yao, H. *Tetrahedron* **2011**, *67*, 7406.

(11) Ritson, D. J.; Spiteri, C.; Moses, J. E. *J. Org. Chem.* **2011**, *76*, 3519.

(12) Gao, W.-C.; Wang, R.-L.; Zhang, C. *Org. Biomol. Chem.* **2013**, *11*, 7123.

(13) (a) Narayanam, J. M. R.; Stephenson, C. R. J. *Chem. Soc. Rev.* **2011**, *40*, 102. (b) Prier, C. K.; Rankic, D. A.; MacMillan, D. W. C. *Chem. Rev.* **2013**, *113*, 5322. (c) Schultz, D. M.; Yoon, T. P. *Science* **2014**, *343*, 1239176. (d) For a review on visible-light-induced synthesis of heterocycles, see: Xuan, J.; Lu, L.-Q.; Chen, J.-R.; Xiao, W.-J. *Eur. J. Org. Chem.* **2013**, *2013*, 6755.

(14) (a) Yu, C.; Lee, K.; You, Y.; Cho, E. J. *Adv. Synth. Catal.* **2013**, *355*, 1471. (b) Park, S.; Jung, J.; Cho, E. J. *Eur. J. Org. Chem.* **2014**, *2014*, 4148. (c) Choi, S.; Chatterjee, T.; Choi, W. J.; You, Y.; Cho, E. J. *ACS Catal.* **2015**, *5*, 4796. (d) Chatterjee, T.; Choi, M. G.; Kim, J.; Chang, S.-K.; Cho, E. J. *Chem. Commun.* **2016**, *52*, 4203.

(15) (a) Verrier, C.; Martin, T.; Hoarau, C.; Marsais, F. *J. Org. Chem.* **2008**, *73*, 7383. (b) Ohnmacht, S. A.; Mamone, P.; Culshaw, A. J.; Greaney, M. F. *Chem. Commun.* **2008**, 1241. (c) Besselièvre, F.; Mahuteau-Betzer, F.; Grierson, D. S.; Piguel, S. *J. Org. Chem.* **2008**, *73*, 3278. (d) Yamamoto, T.; Muto, K.; Komiyama, M.; Canivet, J.; Yamaguchi, J.; Itami, K. *Chem. - Eur. J.* **2011**, *17*, 10113. (e) Bellina, F.; Lessi, M.; Manzini, C. *Eur. J. Org. Chem.* **2013**, *2013*, 5621.

(16) Freeman, D. B.; Furst, L.; Condie, A. G.; Stephenson, C. R. J. *Org. Lett.* **2012**, *14*, 94.

DOI: 10.1021/acs.joc.6b00989
J. Org. Chem. 2016, 81, 6995−7000