Advanced Synthesis & Catalysis

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To be cited as: *Adv. Synth. Catal.* 10.1002/adsc.201800037

Link to VoR: http://dx.doi.org/10.1002/adsc.201800037

COMMUNICATION

DOI: 10.1002/adsc.201 ((will be filled in by the editorial staff))

Visible Light Photocatalytic Radical Addition/Cyclization Reaction of *o*-Vinyl-*N*-alkoxybenzamides for Synthesis of CF_3-Containing Iminoisobenzofurans

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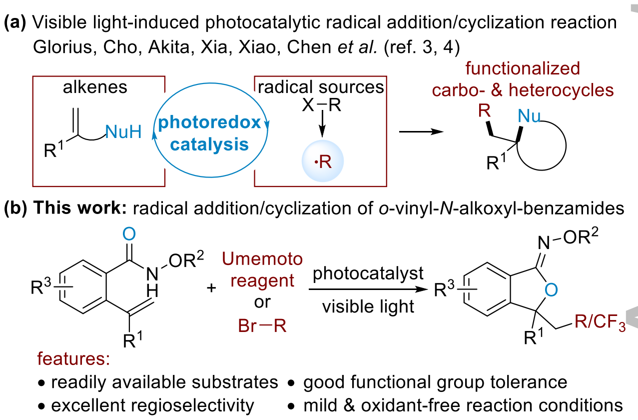
Received :((will be filled in by the editorial staff))

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/adsc.201######.

Abstract: A visible light-induced photocatalytic radical addition/cyclization reaction of *o*-vinyl-*N*-alkoxybenzamides has been accomplished for efficient synthesis of diversely functionalized CF_3-containing iminoisobenzofurans. This external oxidant-free and mild protocol features ready availability of starting materials, excellent regioselectivity, good substrate scope and functional group tolerance.

Keywords: visible light; photoredox catalysis; iminoisobenzofurans; radical cascade; heterocycles

Visible light-driven photoredox catalyzed radical addition/cyclization reaction has received a great deal of attention from the synthetic community during the past decade,[1] owing to the unique redox properties of photocatalysts and their prominent performances in generation of various radicals.[2] Employing this reaction mode, a wide range of alkenes bearing a nucleophilic moiety could undergo facile radical addition and subsequent intramolecular heteroatom attack to enable construction of diversely functionalized heterocycles at mild conditions. In contrast to their traditional thermal variants, these photo-induced reactions always displayed distinct chemo- and regioselectivity. In this context, a series of works from the groups of Glorius, Cho, Akita, Xia, Xiao, and Chen disclosed that photogenerated aryl and trifluoromethyl radicals enabled efficient cascade radical addition/cyclization reactions, providing access to various structurally diverse oxygen and nitrogen heterocycles (Scheme 1a).[3,4] Our research group has also developed a series of visible light-driven photocatalytic arylation/lactonization of olefinic carboxylic acids, as well as oxy- and aminotrifluoromethylative cyclization reactions of *N*-allylamides and unsaturated hydrazones.[4] These transformations allowed for convenient synthesis of various synthetically and biologically important arylated γ,γ-disubstituted butyrolactones, CF_3-containg oxazolines and pyrazolines. Despite these advances, it is still highly desirable to expand the reaction mode of photoredox-catalyzed radical addition/cyclization to include olefinic amides, which would enable assembly of novel structurally diverse heterocyclic scaffolds because of their inherent two different nucleophilic sites.



Scheme 1. Visible light-driven photocatalytic radical addition/cyclization cascade of alkenes for heterocycle synthesis.

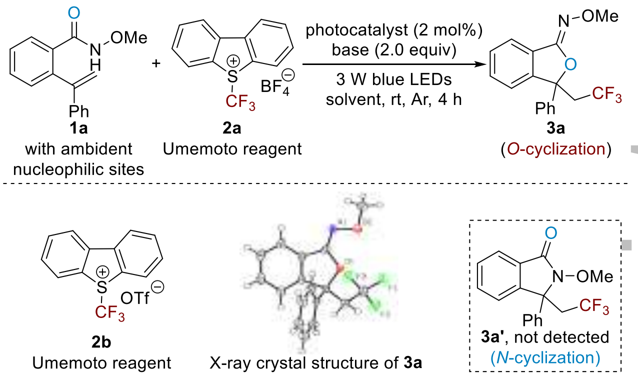
Isobenzofurans are an important class of heterocyclic scaffolds that are prevalent in numerous natural products and biologically active compounds.[5]

They can also serve as versatile building blocks and precursors for formation of reactive intermediates. In particular, iminoisobenzofurans have recently become increasingly attractive synthetic targets.[6] Representative synthetic methods toward these compounds include Pd-catalyzed three-component coupling of *in situ*-formed arynes,[7] Pd-catalyzed cyclization/coupling of *o*-alkynylbenzamides,[8] Ag- and Au-catalyzed cycloisomerization of *o*-alkynylbenzohydroxamic acid derivatives,[9] as well as transition metal-free oxyfluorination and thiocyanooxygenation of olefinic amides.[10] Despite these advances, to our knowledge, there is no report on the practical, general, and catalytic synthesis of fluoroalkylated iminoisobenzofurans.[1,11] On the basis of our continued interest in the photoredox-catalyzed synthesis of heterocycles,[4,12] herein, we disclosed a visible light-driven photocatalytic radical addition/cyclization of *o*-vinyl-*N*-alkoxybenzamides (Scheme 1b). The reaction provides an external oxidant-free, and practical approach to diversely functionalized iminoisobenzofurans.

It has been well documented that the introduction of fluorinated functional group, such as CF_3, into carbo- and heterocycles can bring about significant improvement of their lipophilicity, metabolic stability and bioavailability.[13] Thus, our optimization study began by investigating the radical addition/cyclization cascade of the readily accessible *o*-vinyl-*N*-methoxyl-benzamide **1a** using Umemoto's reagent[14] **2a** as a CF_3 radical precursor (Table 1).[15]

Under our previous conditions that enabled a successful visible light-induced photocatalytic radical oxytrifluoromethylation of *N*-allylamides,[4b] the model reaction of **1a** and **2a** proceeded smoothly through a highly regioselective *O*-cyclization mode, giving rise to iminoisobenzofuran **3a** in 84% yield (Table 1, entry 1). The (*Z*)-configuration of the product **3a** was unambiguously determined based on its X-ray crystal structure.[16] Notably, we did not detect any *N*-cyclization product, isoindolin-1-one **3a'**. Then, we continued to screen other reaction parameters to improve the yield. A brief evaluation of several other commonly used photocatalysts showed that $Ru(bpy)_3(PF_6)_2$ was still superior over others (Table 1, entries 1 *vs* 2-4). In accordance with our previous studies,[4] the addition of base is also critical to the reaction. An array of weak bases, such as Na_2CO_3, K_2CO_3 and K_2HPO_4 all proved to be compatible with the reaction with the exception of strong base NaOH (entries 5-8); and $NaHCO_3$ still proved to be the best one of choice. With the combination of photocatalyst $Ru(bpy)_3(PF_6)_2$ and base $NaHCO_3$, we further examined a series of solvents including $CHCl_3$, MeOH and toluene; however, significant decrease of yield was observed in these cases (Table 1, entries 9-11). Without base, the reaction also proceeded well, but resulting in a slight decrease of yield (entry 12). As expected, control experiments that were carried out in the absence of photocatalyst or visible light irradiation led to none of the desired product (entries 13 and 14), suggesting that the observed reactivity was due to the visible light-driven photoredox catalyzed activation of substrates. Notably, in the presence of stoichiometric radical scavenger TEMPO, the reaction was completely suppressed (entry 15); this finding implies that the reaction involves a radial process.[15] Notably, Umemoto reagent **2b** was also proved to be suitable for the reaction, giving **3a** in 75% yield (entry 16).

Table 1. Identification of optimal conditions.[a]



Entry	Photocatalyst	Base	Solvent	Yield [%][b]
1	$Ru(bpy)_3(PF_6)_2$	$NaHCO_3$	CH_3CN	84
2	*fac*-Ir(ppy)$_3$	$NaHCO_3$	CH_3CN	80
3	[Ir][c]	$NaHCO_3$	CH_3CN	54
4	$MesAcrClO_4$	$NaHCO_3$	CH_3CN	54
5	$Ru(bpy)_3(PF_6)_2$	Na_2CO_3	CH_3CN	81
6	$Ru(bpy)_3(PF_6)_2$	NaOH	CH_3CN	trace
7	$Ru(bpy)_3(PF_6)_2$	K_2CO_3	CH_3CN	59
8	$Ru(bpy)_3(PF_6)_2$	K_2HPO_4	CH_3CN	75
9	$Ru(bpy)_3(PF_6)_2$	$NaHCO_3$	$CHCl_3$	48
10	$Ru(bpy)_3(PF_6)_2$	$NaHCO_3$	MeOH	22
11	$Ru(bpy)_3(PF_6)_2$	$NaHCO_3$	toluene	17
12[d]	$Ru(bpy)_3(PF_6)_2$	-	CH_3CN	81
13[e]	-	$NaHCO_3$	CH_3CN	trace
14[f]	$Ru(bpy)_3(PF_6)_2$	$NaHCO_3$	CH_3CN	trace
15[g]	$Ru(bpy)_3(PF_6)_2$	$NaHCO_3$	CH_3CN	trace
16[h]	$Ru(bpy)_3(PF_6)_2$	$NaHCO_3$	CH_3CN	75

[a] Reaction conditions: **1a** (0.1 mmol), **2a** (0.11 mmol), photocatalyst (2 mol%), base (2.0 equiv., 0.2 mmol) in solvent (2.0 mL) under irradiation of 3 W blue LEDs at room temperature under Ar atmosphere. N.R. = no reaction.

[b] Isolated yield after flash chromatography.

[c] [Ir] = $Ir[dF(CF)_3(ppy)]_2(dtbbpy)PF_6$.

[d] Without $NaHCO_3$.

[e] Without photocatalyst.

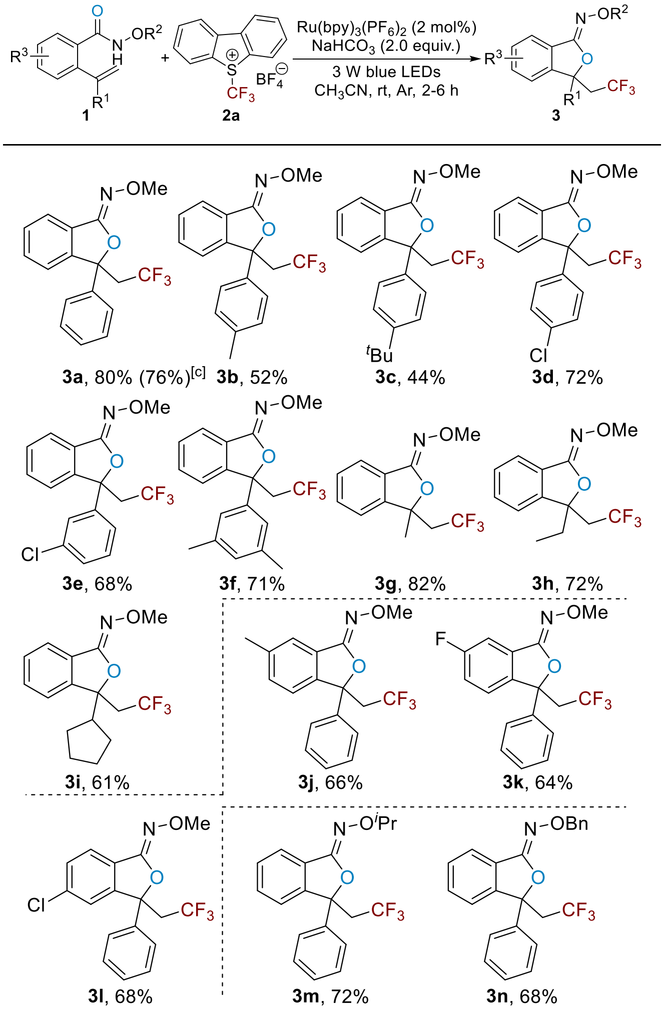
[f] Without visible light irradiation.

[g] With addition of TEMPO (2.0 equiv).

[h] Using **2b** as a CF_3 radical precursor.

With the optimal conditions established (Table 1, entry 1), we proceeded to investigate the substrate generality and limitation of our reaction by reacting a representative set of *o*-vinyl-*N*-alkoxybenzamides **1** with **2a** on a 0.3 mmol scale. As highlighted in Table 2, the protocol demonstrated broad substrate scope and good functional group tolerance. For instance, as for the R^1 group in the vinyl moiety, in addition to **1a**, a range of substrates **1b-1e** bearing a weak electron-donating (e.g., Me, ^{t}Bu) or withdrawing substituents (e.g., Cl) at the *para*- or *meta*-position of the aryl group worked well to give the corresponding products **3b-3e** in 44-72% yield. The steric hindrance of the phenyl ring has no influence on the reaction either; the reaction of multi-substituted substrate **1f** proceeded smoothly to furnish a 71% yield of **3f**. Moreover, substrates **1g-1i** with R^1 group as linear or cyclic aliphatic functional group proved to be suitable for the reaction, affording **3g-3i** in good yields (61-82%). As shown in the cases of substrates **1j-1l**, the presence of a methyl or fluoro group in the *para*-position or a chloro group in the *meta*-position with respect to the vinyl substituent did not affect the reaction either, and the expected iminoisobenzofurans **3j-3l** were isolated in 64-68% yields.

Table 2. Scope of the o-Vinyl-N-alkoxybenzamides.[a,b]



1 **2a** **3**

3a, 80% (76%)[c] **3b**, 52% **3c**, 44% **3d**, 72%

3e, 68% **3f**, 71% **3g**, 82% **3h**, 72%

3i, 61% **3j**, 66% **3k**, 64%

3l, 68% **3m**, 72% **3n**, 68%

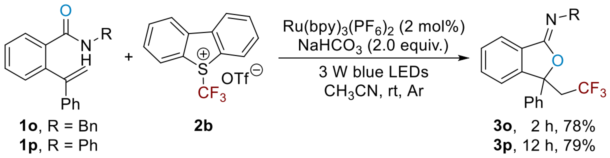
[a] Reaction conditions: **1** (0.3 mmol), **2a** (0.33 mmol), Ru(bpy)$_3$(PF$_6$)$_2$ (2 mol%), NaHCO$_3$ (2.0 equiv., 0.6 mmol) in CH$_3$CN (6.0 mL) under irradiation of 3 W blue LEDs at room temperature under Ar atmosphere.

[b] Isolated yield after flash chromatography.

[c] Under sunlight irradiation.

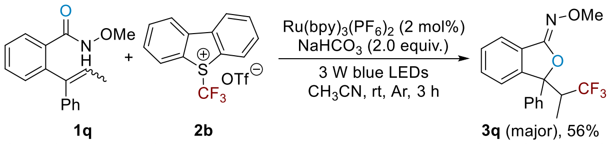
Finally, structural variation of the amide moiety was also simply studied. Replacing the methyl ether with a isopropyl (**1m**) or benzyl (**1n**) group was well tolerated, as the desired products **3m** and **3n** were obtained in 72% and 68% yields, respectively. It should be noted that sunlight could also be used as the light source instead of blue LEDs; efficient synthesis of **3a** could be achieved with 76% yield after 2 h of total sunlight exposure.[15]

Notably, the reaction was also tolerant of other simple alkyl and aryl groups on the benzamide nitrogen atom. For instance, both of the normal amides **1o** (N-Bn) and **1p** (N-Ph) reacted well with Umemoto reagent **2b** under the standard conditions, giving the corresponding products **3o** and **3p** in 78% and 79% yields, respectively [Eq. 1]. Moreover, the reaction of substrate **1q** bearing an internal alkene moiety also proceeded smoothly to give the desired product **3q** with moderate diastereoselectivity; and the major isomer could be obtained in 56% yield by column chromatographic purification [Eq. 2].



(1)

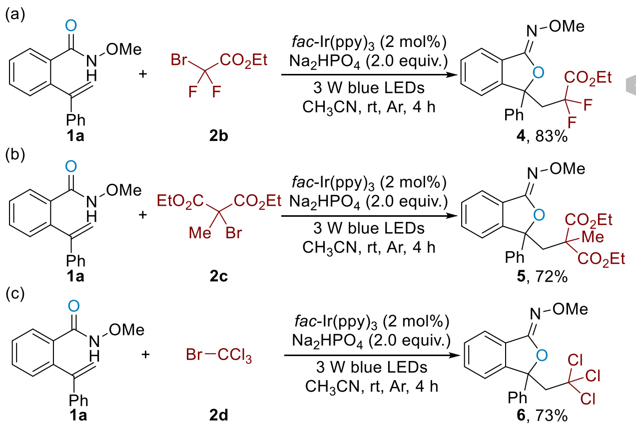
1o, R = Bn
1p, R = Ph
2b
3o, 2 h, 78%
3p, 12 h, 79%



(2)

1q (major/minor = 1.5:1)
2b
3q (major), 56% (major/minor: 4:1)

To further demonstrate the potential of our protocol, we examined a series of other commercially available radical precursors (Scheme 2). For example, 2-bromo-2,2-difluoroacetate ester **2b** could serve as a competitive fluoroalkyl source to participate in the desired reaction efficiently, when using *fac*-Ir(ppy)$_3$ as the photocatalyst and Na$_2$HPO$_4$ as the base, furnishing the difluoroalkylation product **4** in 83% yield (Scheme 2a). Moreover, the reaction with other haloalkane **2c** and bromochloroform **2d** also reacted well with **1a** to give products **5** and **6** in 72% and 73% yields, respectively (Scheme 2b and 2c).



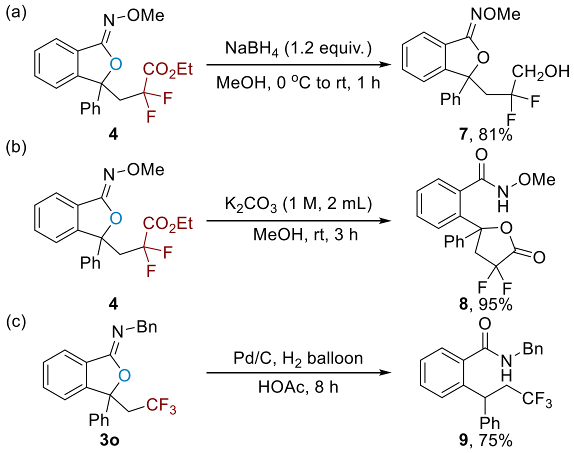
1a **2b** **4**, 83%

1a **2c** **5**, 72%

1a **2d** **6**, 73%

Scheme 2. Examination of other radical precursors.

With the ester group as a synthetically versatile handle, the product **4** could be readily transformed to alcohol **7** in 81% yield upon reduction with $NaBH_4$ (Scheme 3a). Interestingly, treatment of **4** with base resulted in a facile hydrolysis/intramolecular cyclization cascade, leading to formation of fluorinated γ-lactone **8** in 95% yield (Scheme 3b). Such a scaffold might be useful in the pharmaceutical and agrochemical fields.[18] Surprisingly, Pd/C-catalyzed hydrogenation of product **3o** in HOAc gave rise to trifluoromethylated benzamide **9** in 75% yield, which should be formed via an acid-promoted ring-opening/hydrogenation sequence (Scheme 3c).[15]



Scheme 3. Derivatization of products **4** and **3o**.

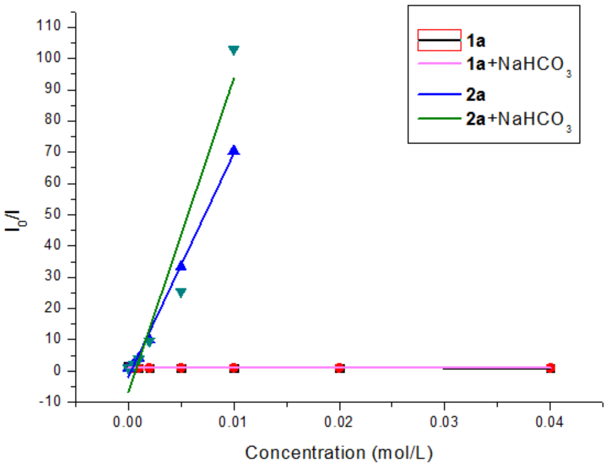
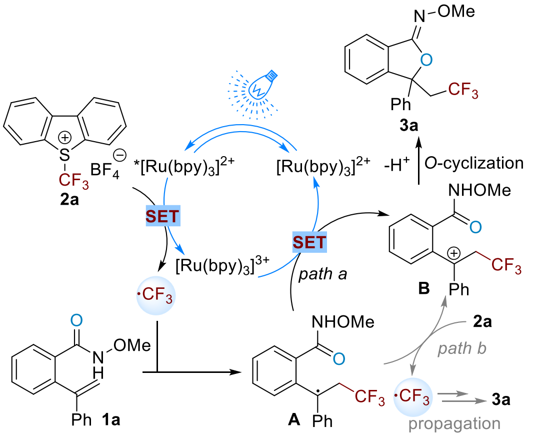


Figure 1. Fluorescence quenching of $Ru(bpy)_3(PF_6)_2$.

In principle, both *o*-vinyl-*N*-methoxyl-benzamide **1a** and **2a** are capable of quenching the excited state photocatalyst $*[Ru(bpy)_3]^{2+}$ via a reductive quenching[12] or oxidative quenching process,[1c,11] respectively. To assist the understanding of the mechanism, we conducted a series of luminescence quenching experiments with **1a** and **2a** (Figure 1).[15] No direct quenching of the excited state $*[Ru(bpy)_3]^{2+}$ by **1a** was observed at 350 nm in CH_3CN in the presence of or without base $NaHCO_3$. In sharp contrast, in the case of **2a**, significant decrease of luminescence emission intensity was obeved with or without $NaHCO_3$. These findings suggested that the reaction might proceed through a visible light-driven oxidative quenching cycle.

On the basis of these mechanistic studies and related literature,[11] we proposed a plausible redox-neutral process for the current photocatalytic radical addition/cyclization reaction (Scheme 4). First, a single electron transfer from the excited state photocatalyst $*[Ru(bpy)_3]^{2+}$, formed reversibly upon visible light irradiation, to the Umemoto reagent **2a** occurs to generate the highly reactive CF_3 radical and the oxdized form of the photocatalyst $[Ru(bpy)_3]^{3+}$. Next, the CF_3 radical undergoes a radical addition across the vinyl moiety to furnish benzyl radical intermediate **A**, which can be further converted to relatively stable benzylic cation **B** by the oxidizing state $[Ru(bpy)_3]^{3+}$, closing the photocatalytic cycle (path a). Finally, nucleophilic *O*-cyclization results in formation of the product **3a**. Another pathway involving transformation of **A** to **B** by radical chain propagation can not be ruled out at the current stage, but should not be the predomidant way, as continuous irradiation is critical to the reaction. Moreover, we determined the quantum yield of the reaction of **1a** to be 1.32, which suggests that the photocatalytic cycle should be the predominant pathway.[17]



Scheme 4. Proposed catalytic cycle.

In conclusion, we have developed a room temperature visible light-induced photocatalytic radical addition/cyclization reaction of *o*-vinyl-*N*-alkoxybenzamides, providing efficient access to diversely substituted iminoisobenzofurans. This external oxidant-free and mild protocol features ready availability of starting materials, excellent regioselectivity, good substrate scope and functional group tolerance. Further studies to modulate the regioselectivity are currently underway in our group.

Experimental Section

General Procedure for the Radical Addition/Cyclization Reaction of *o*-Vinyl-*N*-alkoxybenzamides: To a 10 mL Schlenk tube equipped with a magnetic stirring bar was charged with **1a** (0.30 mmol, 76 mg), **2a** (0.33 mmol, 113 mg) and $NaHCO_3$ (0.60 mmol, 51 mg) in 6 mL of CH_3CN. The mixture was degassed using the "freeze–pump–thaw" technique (3 times) and then irradiated with 3 W blue LEDs at room temperature under Ar. Upon completion of the reaction as monitored by TLC, the crude reaction mixture was concentrated and directly subjected to column chromatography, and eluted with petroleum ether and ethyl acetate to afford the product **3a** as a white solid in 80% yield.

Acknowledgements

We are grateful to the NNSFC (Nos. 21622201, 21472058, 21472057, and 21772053), the Distinguished Youth Foundation of Hubei Province (No. 2016CFA050), the Science and Technology Department of Hubei Province (2017AHB047), and CCNU (Nos. CCNU17TS0011 and CCNU16JCZX02) for support of this research. The Program of Introducing Talents of Discipline to Universities of China (111 Program, B17019) is also appreciated.

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[15] Please see the Supporting Information for more details.

[16] CCDC 1814259 (**3a**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/daa_request/cif.

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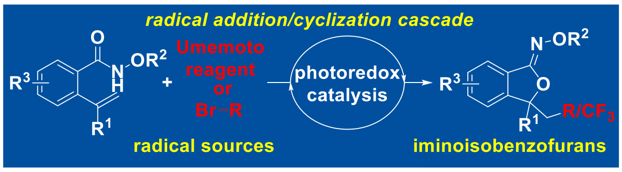
Visible Light Photocatalytic Radical Addition/Cyclization Reaction of *o*-Vinyl-*N*-alkoxybenzamides for Synthesis of CF_3-Containing Iminoisobenzofurans

Adv. Synth. Catal. **Year**, *Volume*, Page – Page



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