# Visible Light Photoredox Catalyzed Cascade Cyclizations of α-Bromochalcones or α-Bromocinnamates with Heteroarenes

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**Abstract:** Vinyl radicals were generated from  $\alpha$ -bromochalcones or  $\alpha$ -bromocinnamate ethyl ester under visible light photoredox catalyzed conditions *via* an oxidative quenching cycle of the iridium complex [Ir{dF(CF<sub>3</sub>)ppy}<sub>2</sub>(dtbbpy)]PF<sub>6</sub> and subjected to cascade cyclizations with heteroarenes entailing two consecutive C–C bond formations and three C–H activations. The process is amenable to furans, ben-

zofurans, pyrroles, and indoles, giving rise to a broad variety of novel polycyclic frameworks in high yields under mild and environmentally benign reaction conditions.

**Keywords:** cascade cyclization; heteroarenes; iridium; vinyl radicals; visible-light photocatalysis

## Introduction

Cascade cyclizations<sup>[1,2]</sup> are a powerful tool in organic chemistry for the synthesis of polycyclic compounds, being characterized by high efficiency and operational simplicity. A particularly well-explored strategy is the cyclization of 1,6-enynes, and only recently, an elegant example for the coupling of this structural element with aryl sulfonyl chlorides by a visible-light driven process to arrive at polycyclic aromatic compounds was demonstrated.<sup>[3]</sup> We report here an alternative strategy by coupling photochemically generated vinyl radicals with heteroarenes in an intermolecular process involving a threefold C–H activation to give rise to novel scaffolds such as naphtho[2,1-*b*]furans, 3*H*benzo[*e*]indoles and related heterocycles (Scheme 1).

Despite an astonishing resurrection<sup>[4]</sup> of visible light photocatalysis<sup>[5]</sup> demonstrating impressively the synthetic potential of such processes, there are only few examples for the formation of vinyl radicals by photoredox activation of  $C(sp^2)$ –X (halogen) bonds. Very recently Stephenson et al. reported vinyl radicals obtained by photoredox catalysis from vinyl iodides, engaging them in reductions or cyclizations.<sup>[6]</sup> In our previous report<sup>[7]</sup> of visible-light mediated dehalogenations<sup>[8]</sup> we showed that vicinal dibromo carbonyl compounds can be used as a source for  $\alpha$ -keto vinyl radicals, giving rise to the formation of alkynes. Given the high reactivity of such radicals,<sup>[9]</sup> we questioned whether those could engage in C–C coupling reactions if the elimination pathway to alkynes is not possible. Indeed, we found that a highly efficient photoredox catalyzed tandem cyclization between a broad variety of heteroarenes<sup>[10]</sup> and  $\alpha$ -bromochalcones or  $\alpha$ -bromocinnamates (employed as an *E/Z*-mixture, see the Supporting Information for details) can be achieved, in which the latter both serve as precursors





**Scheme 1.** Photoredox catalyzed cascade cyclization between  $\alpha$ -bromochalcones or  $\alpha$ -bromocinnamates.

for vinyl radicals and provide *ortho*-C<sub>aryl</sub>-H bonds for the cyclization (Scheme 1).

### **Results and Discussion**

We began our investigation with the reaction between  $\alpha$ -bromochalcone **1a** and furan **4a** (Table 1). Employing  $Ru(bpy)_3Cl_2$  (bpy=bipyridine) (1 mol%) as the photocatalyst in the presence of an amine, conditions typical for a reductive quenching cycle (Table 1, entries 1 and 2), gave rise to dehalogenation of 1a without formation of a coupling product with 4a. In contrast, on attempting to utilize the oxidative quenching cycle of Ru(bpy)<sub>3</sub>Cl<sub>2</sub>, being operationally and economically advantageous since there is no need for the addition of a sacrificial electron donor, indeed a coupling between the chalcone 1a and furan (4a) took place (Table 1, entry 3) to give rise to 5aa. Product **5aa** was formed in a clean reaction and especially no competing dehalogenation of the starting material took place, nevertheless, the low conversion of 1a resulting in a yield of  $\leq 5\%$  made optimization of the process necessary.

Turning to  $Cu(dap)_2Cl$  [dap=2,9-bis(*para*-anisyl)-1,10-phenanthroline], Eosin Y or  $Ir[(ppy)_2$ (dtbbpy)]PF<sub>6</sub> (ppy=2-phenylpyridine, dtbbpy=4,4'di-*tert*-butyl-2,2'-dipyridyl), which all have been successfully utilized in coupling reactions *via* an oxidative quenching cycle,<sup>[11]</sup> did not result in any conversion of **1a** (Table 1, entries 4–6). Gratifyingly, when using [Ir{dF(CF<sub>3</sub>)ppy}<sub>2</sub>(dtbbpy)]PF<sub>6</sub> [**A**, dF(CF<sub>3</sub>)ppy=2-(2,4-difluorophenyl)-5-trifluoromethylpyridine] at a catalyst concentration of only 1 mol%, **1a** was fully consumed after 12 h, giving rise to **5aa** in high yield

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[91% (NMR), 85% isolated; Table 1, entry 7 and Table 2, entry 1]. DMF proved to be essential as solvent, for example, when acetonitrile (Table 1, entry 8) was used no conversion of **1a** was observed. Likewise, both light (Table 1, entry 9) and catalyst (Table 1, entry 10) were essential for the reaction to take place.

Having found suitable reaction conditions we examined the scope of the process. The chalcone 1 can be varied with electron-donating and electron-accepting substituents in either ring (Table 2). Especially, halides in the arene rings did not show any cross-reactivity with the vinyl bromide that is activated in the photochemical key step. Limitations were observed with substrates having an *ortho*-substituent as  $R^2$ (Table 2, entries 6 and 10) thus blocking one possible reaction site for cyclization. Products 5fa and 5ja were still formed in a clean reaction, but conversion of the starting material was incomplete. Substrates with nitro groups either as  $R^1$  (Table 2, entry 12) or  $\mathbf{R}^2$  (Table 2, entry 13) did not give any conversion of the starting materials, which is surprising since the initial photoreduction should be facile ( $E_0 = -1.0 \text{ V}$  for 11 and 1m, see the Supporting Information) as was, for example, proven in ATRA reactions with nitrobenzyl bromides.<sup>[11h]</sup> Examination of the UV spectra of 11 and 1m also proved that there is no absorption of these substrates at 420 nm that was used for irradiation. Other furans such as 2-methylfuran (Table 2, entries 14 and 15) and benzofuran (Table 2, entry 16) were also found to be excellent reaction partners for chalcones 1.

*N*-Heteroaromatic systems such as pyrroles and indoles, either in *N*-protected or *N*-unprotected form, proved to be even better coupling partners for chalcones 1 (Table 3). Functional group tolerance of

Table 1. Optimization of the reaction conditions - screening of different photocatalysts and solvents.<sup>[a]</sup>

Br	+	LED, 12 h	
<b>1a</b> ( <i>E</i> /Z = 12:88)	4a		5aa

Entry	Photocatalyst	Solvent	Yield [%] <sup>[b]</sup>
1	$Ru(bpy)_3Cl_2$ , NEt <sub>3</sub> , 455 nm	DMF	dehalogenation, >95
2	$Ru(bpy)_3Cl_2$ , NEt <sub>3</sub> , 455 nm	MeCN	dehalogenation, 70
3	$Ru(bpy)_3Cl_2$ , 455 nm	DMF	$\leq 5$
4	$Cu(dap)_2Cl$ , 530 nm	DMF	no reaction
5	Eosin Y, 530 nm	DMF	no reaction
6	$Ir[(ppy)_2(dtbbpy)]PF_6, 455 nm$	DMF	no reaction
7	$[Ir{dF(CF_3)ppy}_2(dtbbpy)]PF_6$ ( <b>A</b> ), 420 nm	DMF	91
8	$[Ir{dF(CF_3)ppy}_2(dtbbpy)]PF_6(\mathbf{A}), 420 nm$	MeCN	no reaction
9 <sup>[c]</sup>	$[Ir{dF(CF_3)ppy}_2(dtbbpy)]PF_6(\mathbf{A})$	DMF	no reaction
10	no photocatalyst, 420 nm	DMF	no reaction

<sup>[a]</sup> Reaction conditions: 1a (1 equiv.), furan 4a (5 equiv.), photocatalyst (1 mol%).

<sup>[b]</sup> Yields were determined by <sup>1</sup>H NMR analysis.

<sup>[c]</sup> Without light irradiation

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Entry	$\mathbf{R}^1$	$\mathbb{R}^2$	1	Furan (4)	Product (5)	Yield [%] <sup>[b]</sup>
1	Н	Н	<b>1</b> a	furan ( <b>4a</b> )	5aa	85
2	Н	4-Cl	1b	furan ( <b>4a</b> )	5ba	82
3	Cl	Н	1c	furan ( <b>4a</b> )	5ca	91
4	Cl	4-Br	1d	furan ( <b>4a</b> )	5da	80
5	Cl	4-Me	1e	furan ( <b>4a</b> )	5ea	80
6	Cl	2-Me	1f	furan ( <b>4a</b> )	5fa	32
7	Me	4-Me	1g	furan ( <b>4a</b> )	5ga	83
8	OMe	Н	1ĥ	furan ( <b>4a</b> )	5ha	60
9	Н	4-F	<b>1i</b>	furan ( <b>4a</b> )	5ia	82
10	Н	2-F	1j	furan ( <b>4a</b> )	5ja	42
11	F	Н	1k	furan ( <b>4a</b> )	5ka	78
12	$NO_2$	Н	11	furan ( <b>4a</b> )	_	no reaction
13	Н	$4-NO_2$	1m	furan ( <b>4a</b> )	_	no reaction
14	Cl	4-Br	1d	2-methylfuran (4b)	5db	65
15	Н	4-Cl	1b	2-methylfuran (4b)	5bb	78
16	Cl	4-Br	1d	benzofuran (4c)	5dc	85

<sup>[a]</sup> *Reaction conditions:* **1** (0.5 mmol), **4** (5 equiv.) and photocatalyst (1 mol%) in dry DMF (2.0 mL) were irradiated for 12 h with an LED light source (420 nm).

<sup>[b]</sup> Yield of isolated product.

Table 3. Reaction of  $\alpha$ -bromochalcones with other heteroarenes.<sup>[a]</sup>

$R^1$ $R^2$ +	R = H, Boc, Me	A (1 mol%) ► DMF, LED <sub>420</sub> , 12 h	
			7

Entry	$\mathbb{R}^1$	$\mathbb{R}^2$	1	Heteroarene (6)	Product (7)	Yield [%] <sup>[b]</sup>
1	Н	Н	<b>1</b> a	pyrrole ( <b>6a</b> )	<b>7</b> aa	89
2	Н	4-Cl	1b	pyrrole (6a)	7ba	95
3	Cl	4-Me	1e	pyrrole (6a)	7ea	91
4	Cl	2-Me	1f	pyrrole (6a)	7fa	78
5	OMe	Н	1h	pyrrole (6a)	7ha	80
6	Н	4-F	1i	pyrrole (6a)	7ia	87
7	Н	2-F	1j	pyrrole (6a)	7ja	83
8	F	Н	1k	pyrrole (6a)	7ka	84
9	$NO_2$	Н	11	pyrrole (6a)	-	no reaction
10	Н	$NO_2$	1m	pyrrole (6a)	-	no reaction
11	Cl	Н	1c	<i>N</i> -Boc-pyrrole ( <b>6b</b> )	7cb	92
12	Н	Н	<b>1</b> a	<i>N</i> -Boc-pyrrole ( <b>6b</b> )	7ab	85
13	Cl	Н	1c	indole (6c)	<b>7cc</b>	87
14	Н	4-Me	1n	indole (6c)	7nc	72
15	Cl	Н	1c	5-methoxyindole (6d)	7cd	70
16	Н	Н	<b>1</b> a	<i>N</i> -methylindole ( <b>6e</b> )	7ae	70

<sup>[a]</sup> Reaction conditions: **1** (0.5 mmol), **6** (5 equiv,) and photocatalyst (1 mol%) in dry DMF (2 mL) were irradiated for 12 h with an LED light source (420 nm).

<sup>[b]</sup> Yield of isolated product.



Figure 1. X- ray crystal structures of 5ga and 7ba.

**1** was similar as found in coupling with furans, but noteworthy, an *ortho*-substituent in the arene ring of **1** that is involved in the cyclization process, although somewhat lower than the *para*-substituted analogues, gives rise to **7** in much higher yields compared to the coupling with furans (Table 3, entries 4–7; Table 1, entries 5, 6 and 9,10). Again, nitro substituents in either arene ring of **1** did not lead to any conversion of the starting materials (Table 3, entries 9 and 10).

The structural assignments of products 5 and 7 were confirmed unambiguously by single-crystal X-ray analyses of 5ga and 7ba (Figure 1).<sup>[12]</sup>

Replacement of the arene ring in 1 being not involved in the cyclization process was also possible (Scheme 2). Besides the thiophene derivative 8, especially useful from a preparative point of view appears to be cinnamate 10 as coupling partner, leading to benzoanellated 1*H*-indole-7-carboxylates 11. Such 1*H*-indole-7-carboxylates have been recognized to display manifold biological activities and have been identified as EP4 receptor antagonists and PPAR active compounds.<sup>[13]</sup>



Scheme 2. Photocyclization of chalcone 8 or ethyl  $\alpha$ -bromocinnamate (10) with pyrrole (6a).



Scheme 3. Allylation and reduction of  $\alpha$ -bromochalcone 1a.

To further prove the formation of vinyl radical **14** in the photochemical key step of the anellation process, the coupling of **1a** was carried out with allylstannane **13**, which is a known radical allylating agent.<sup>[14]</sup> Indeed, the expected allylated compound **15** was isolated in high yield.

Furthermore, as already observed for  $\text{Ru}(\text{bpy})_3\text{Cl}_2$  (Table 1, entries 1 and 2), by switching to the reductive quenching cycle by adding triethylamine as sacrificial electron donor a clean reduction of **1a** to **16** is observed with the iridium catalyst in high yields, being also consistent with the formation of a vinyl radical **14** (Scheme 3).

A plausible reaction mechanism (Scheme 4) for the above anellation reaction should therefore involve the initial photoredox catalyzed formation of vinyl radical 14 with concurrent oxidation of excited  $*Ir^{3+}$ . The radical 14 then adds to the heteroarene 2 to form the radical 17, which subsequently adds chemoselectively to the arene ring of chalcone bearing the vinyl, but not the carbonyl group. The observed chemoselectivity might be a consequence of the known preference of a-bromochalcones to reside in the s-cis-conformation.<sup>[15]</sup> The resulting 18 undergoes back electron transfer to Ir4+, thus regenerating the catalyst with formation of the cation 20. Alternatively, intermediate 17 could be oxidized with concurrent reduction of Ir<sup>4+</sup>, followed by electrophilic ring closure to 20. We assume that the back electron transfer step (17 to 19 or 18 to 20) to the iridium catalyst is responsible for the fact that other catalysts such as Cu(dap)<sub>2</sub>Cl (cf. Table 1, entry 4) are not active in the process: While the initial vinyl radical formation (reduction potentials of 1a-1j, 8 and 10 are in the range of -0.59 to -0.97 V, see the Supporting Information) should easily proceed also with the copper catalyst  $\{Cu(dap)_2Cl:$ \*Cu(I)/(II) = -1.43 Vvs  $[Ir{dF(CF_3)ppy}_2(dtbbpy)]PF_6$ \*Ir(III)/Ir(IV) =-0.89 V}, the oxidation potential of Cu(dap)<sub>2</sub>Cl<sup>2+</sup>



**Scheme 4.** Proposed reaction mechanism for the photoredox catalyzed cascade cyclization between chalcones and heteroarenes.

[Cu(II)/Cu(I) = +0.62 V vs. Ir(IV)/Ir(III) = +1.69 V]appears to be not sufficient to close the catalytic cycle.

Carbocation 20 then finally forms product 3, in which overall one molecule of hydrogen is lost, driven by the aromatization of the final product. The mechanism for this dehydrogenation is still elusive but has been reported in the literature before in different processes.<sup>[11g,16]</sup> We have performed the reaction of  $\alpha$ bromochalcone **1a** with pyrrole **6a** in DMF- $d_7$  under deaerated conditions: NMR analysis showed that the dehydrogenation giving rise to 7aa indeed takes place during the reaction and is not a consequence of oxidation during the work-up procedure (see the Supporting Information for details). Iridium catalysts are well known for their power to catalyze hydrogenation/dehydrogenation processes, and we therefore assume that also here the iridium photocatalyst employed can take on such a role.

#### Conclusions

In conclusion, we have developed an intermolecular tandem cyclization methodology involving  $\alpha$ -bromochalcones and heteroarenes under visible light irradiation, involving a threefold activation of aromatic C–H bonds. The process is characterized by low catalyst loading, excellent chemoselectivity, broad scope and functional group tolerance, and proceeds in high yields, giving a rapid access to polycyclic heteroarenes with novel connection patterns.

# **Experimental Section**

# Typical Procedure for the Photoredox Catalyzed Cascade Cyclization

An oven-dried 10-mL vial equipped with a plastic septum and magnetic stir bar was charged with  $[Ir{dF(CF_3)ppy}]_2$ (dtbbpy)]PF<sub>6</sub> (1 mol%) and the  $\alpha$ -bromochalcone **1a** (143 mg, 0.5 mmol, 1 equiv.). The flask was purged with a stream of nitrogen and 2.0 mL of dry dimethylformamide were added. The resultant mixture was degassed for 5 min by nitrogen sparging and furan (4a) (5 equiv.) was added to the vial. The vial was placed at a distance of  $\sim 0.5-1.0$  cm from a blue LED lamp (420 nm) and irradiated for 12 h at room temperature. After completion of the reaction (as judged by TLC analysis), the mixture was transferred to a separating funnel, diluted with ethyl acetate (15 mL) and washed with water. The aqueous layer was extracted 3 times with ethyl acetate  $(3 \times 10 \text{ mL})$ , and the combined organic layers were dried (anhydrous sodium sulfate) and concentrated under vacuum. The residue was purified on silica, using hexane/ethyl acetate as solvent system to afford 5aa as a yellow solid; yield: 116 mg (85%);  $R_{\rm f}$  (EtOAc/hexane 1:9): 0.38; mp 147–149 °C; IR (neat): v=3057, 1658, 1598, 1293, 1265,734, 632 cm<sup>-1</sup>; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):  $\delta = 8.19$  (d, J=8.3 Hz, 1 H), 8.01 (d, J=10.2 Hz, 2 H), 7.95–7.89 (m, 2H), 7.82 (d, J=2.1 Hz, 1H), 7.70 (m, 1H), 7.67-7.61 (m, 1 H), 7.59–7.47 (m, 3 H), 7.33 (d, J=2.1 Hz, 1 H); <sup>13</sup>C NMR  $(75 \text{ MHz}, \text{ CDCl}_3): \delta = 193.95, 145.32, 137.95, 133.02, 130.23,$ 129.95, 129.43, 129.37, 128.61, 128.41, 125.39, 124.25, 123.77, 123.48, 105.40; HR-MS (ESI): m/z = 272.0837, calcd. for  $C_{19}H_{12}O_2 [M +]^+: 272.0837.$ 

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