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Allenamides Playing Domino: A Redox-Neutral Photocatalytic Synthesis of Functionalized 2-Aminofurans

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Abstract: A photoredox catalytic synthesis of functionalized 2-aminofurans is proposed starting from α-halo carbonyl substrates and *N*-allenamides. The protocol proves to be efficient and sustainable thanks to: *i*) the use of visible light as green energy source, *ii*) the redox-neutral nature of the transformation, allowing to avoid additives and strong oxidants, *iii*) the mild reaction conditions and the functional groups tolerance, *iv*) the low photocatalyst loading and the absence of excess reagents, *v*) the one-pot formation of three new bonds in a domino sequence. According to our mechanistic hypothesis, the transformation is configured as a *double radical-polar crossover* reaction, in which the photocatalyst is excited, oxidized and reduced twice for each molecule of 2-aminofuran produced. The novelty of the designed synthetic approach also lies in the use of *N*-allenamides as substrates, which, after the addition of the first electrophilic radical, preserve a further reactive π-system, making possible the addition of a second α-keto radical and enabling the installation of a keto functionality at a remote position. The good yields, the broad scope, and the possibility to further synthetically elaborate the obtained furans make this protocol particularly promising for the construction of useful products.

Keywords: allenamides; 2-aminofurans; heterocycles; iridium; photocatalysis; radical-polar pathway; radicals; redox-neutral; visible light

Introduction

2-Aminofurans are versatile scaffolds that have been extensively exploited as starting materials or synthetic intermediates for the construction of useful products,[1] in some cases showing interesting pharmacological properties (Figure 1).[2]

Considering their remarkable role, significant efforts have been devoted in developing efficient transformations able to provide variably substituted 2-aminofurans (Scheme 1).

Besides traditional protocols often employing stoichiometric or more than stoichiometric mediators,[3] more sustainable catalytic processes have been recently developed.[4] Among them, the most noteworthy processes employ α,β-unsaturated nitriles,[4a–b,s–t] ynamides,[4d,k,m] α-diazo carbonyl compounds,[4j–k] the

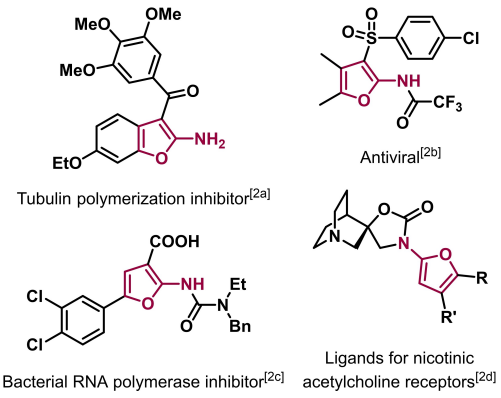
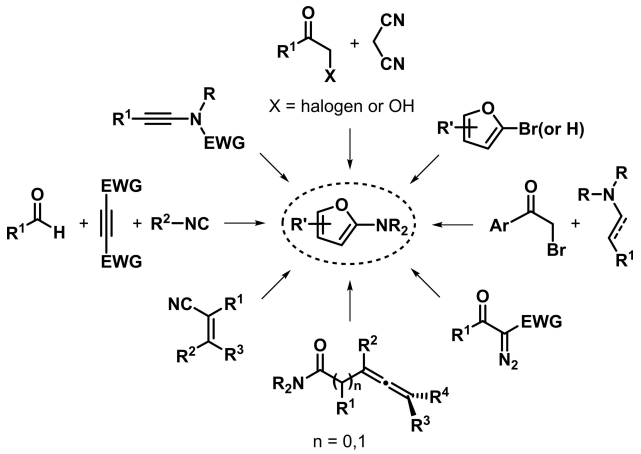


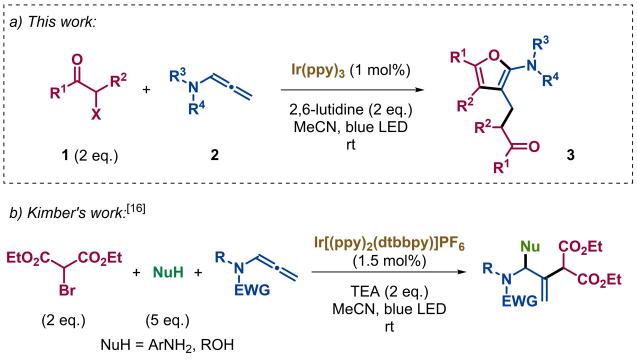
Figure 1. Examples of bioactive 2-aminofurans.



Scheme 1. Previously reported synthetic approaches to 2-aminofurans.

tricomponent mixture aldehyde/isocyanide/electron-poor alkyne,[4n–p] furans,[4r] α-haloketones with tertiary amines or enamines,[4q] allenylamides[4l] or homoallenyl amides[4e–i] (Scheme 1). All the reported protocols generally require properly functionalized and not commonly available substrates, noble metal catalysts in high loadings, excess reagents, high temperatures or environmentally unfriendly solvents, resulting in cost and toxicity concerns, poor functional group compatibility and narrow applicability. Therefore, sustainable and flexible transformations enabling the efficient construction of variably functionalized 2-aminofurans are still highly desirable.

As part of our ten years research interests in the synthesis of heterocyclic molecules[5] and based on our recent results on the photocatalyzed construction of 2,3-dihydrofurans,[6] herein we report a synthetic approach to substituted 2-aminofurans **3** starting from α-halo carbonyl substrates **1** and allenamides **2** (Scheme 2a). This protocol represents the first example



Scheme 2. a) The proposed visible light-promoted photoredox catalytic synthesis of functionalized 2-aminofurans; b) the photoredox catalytic intermolecular radical addition to allenamides proposed by Kimber in 2020.

of visible light-promoted photoredox catalytic synthesis of functionalized 2-aminofurans.

Domino transformations offer an ideal solution to sustainability problems, enabling the efficient construction of complex architectures in one sequence, without isolating any intermediate and minimizing the waste production.[7] Our approach allows to achieve 2-aminofurans with an uncommon substitution pattern through the one-pot formation of three new bonds and involving two molecules of α-halo compound **1** in the product **3** skeleton (Scheme 2a). The sustainability of our protocol also derives from the use of visible light as a green energy source, able to provide mild and selective activation of photocatalysts or substrate-catalyst complexes.[8] Moreover, the redox-neutral nature of the proposed transformation allows to work in the absence of additives or additional strong oxidants, leading to an economical and environmentally benign process occurring under mild conditions.

The novelty of the designed synthetic approach also lies in the use of *N*-substituted allenamides **2** as substrates, which have never been used in the construction of 2-aminofurans. Conversely, the already reported procedures invariably exploit *C*-substituted allenes as starting materials.[3e,4e–i,l] Heteroatom-substituted allenes,[9] in particular nitrogen-substituted[10] ones, are characterized by a peculiar reactivity. Not only they are more electron-rich than simple allenes, but the nitrogen lone pair enables regioselective consecutive additions of both electrophiles and nucleophiles. However, allenamines are highly sensitive toward hydrolysis and they tend to polymerize, becoming difficult to prepare and to handle. Allenamides, characterized by a lower donating ability on the allene system, could thus represent the perfect balance between stability and reactivity.[11] Based on the easy handling of allenamides and their electron-rich π-system, we selected these substrates (**2**) to be reacted with electrophilic radical species[12] generated from α-halo carbonyl substrates **1** (Scheme 2a).

In the last decades several radical reactions involving allenes have been proposed,[13] but only a few recent examples explore the reactivity between allenes and radical species generated by photocatalysts excited by visible-light.[14] The use of allenamides in radical transformations is extremely rare[15] and there is only a very recent example in the literature reporting on the application of these substrates in a photoredox catalytic process (Scheme 2b).[16] In this paper Kimber *et al.* presented the intermolecular addition of a photocatalytically generated radical to some allenamides. The obtained radical intermediate was oxidized to conjugated *N*-acyliminium which underwent an intermolecular nucleophilic addition. Despite the moderate yields and the need for large excesses of reagents and additives, this protocol demonstrated the promising reactivity between allenamides and photocatalytically

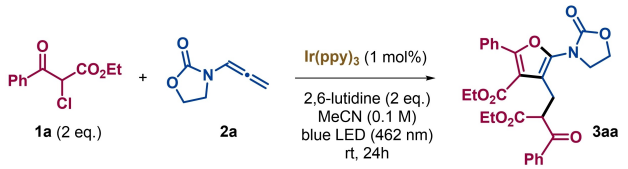
generated electrophilic radicals. On this basis, we decided to exploit the advantages of visible light photocatalysis to develop a novel, efficient and sustainable radical synthetic approach to substituted 2-aminofurans **3** (Scheme 2a).

Results and Discussion

We accomplished our first investigations on the model system involving ethyl 2-chloro-3-oxo-3-phenylpropanoate **1a** and 3-(propa-1,2-dien-1-yl)oxazolidin-2-one **2a**. Employing these two substrates in a stoichiometric ratio (**1a**:**2a** = 2:1), in the presence of a stoichiometric amount (2 equivalents) of 2,6-lutidine as base, *fac*-Ir(ppy)$_3$ (1 mol%) as photoredox catalyst, MeCN as reaction medium (0.1 M), being the vessel irradiated with blue LEDs at 462 nm for 24 hours and maintained at room temperature by a fan, we were gratified by obtaining our best result: the formation of the desired 2-aminofuran **3aa** in 80% yield (Table 1, Entry 1).

The variation of the substrates ratio did not lead to the observation of different products or intermediates and it only resulted in lower conversion (Entries 2–3). The base has a crucial role in this transformation, as it did not proceed in its absence (see Supporting Information for a detailed study on the base nature and amount). We supposed that the base acts as scavenger for the acid formed during the reaction and the best performance was obtained using it in stoichiometric amount (2 equivalents; Entry 1). Some organic and inorganic bases were tested, but the results were significantly worse than those achieved with 2,6-lutidine. The solvent screening (see Supporting Information) proved that MeCN was the best choice, with slightly different yields of **3aa** obtained using anhydrous or HPLC-grade wet MeCN. We proceeded with dry MeCN to ensure greater reproducibility. Halving the reactants concentration marginally affected the product yield (Entry 4), conversely a doubled concentration significantly decreased the yield (Entry 5), probably due to a lower catalyst solubility and to a smaller irradiated surface area. The reaction time was also evaluated (see Supporting Information). Despite the maximum product yield with the model substrates was recorded after 24 hours (80%), it is noteworthy that a high yield (76%) was obtained in only 4 hours, therefore 2-aminofuran **3aa** proved to be stable under the reaction conditions. Pleasingly, a very efficient reaction between **1a** and **2a** resulted even halving the photocatalyst loading (0.5 mol%) (Entry 6). Finally, a brief catalysts screening showed that Ir[dF(CF$_3$)ppy]$_2$(dtbbpy)PF$_6$ provided **3aa** with significantly lower yield (Entry 7) and in the presence of Ru(bpy)$_3$Cl$_2$ the reaction did not proceed at all (Entry 8). Two organic photoredox catalysts, possessing possibly suitable reduction potentials, were also tested: Eosin Y was not able to promote the reaction (Entry 9), whereas 3DPA2FBN furnished a poor result (Entry 10). Taking into account the oxidation and reduction potentials of the employed photocatalysts (*fac*-Ir(ppy)$_3$,[17] Ir[dF(CF$_3$)ppy]$_2$(dtbbpy)PF$_6$,[17] Ru(bpy)$_3$Cl$_2$,[17] Eosin Y,[18] and 3DPA2FBN[19]), we supposed that some species might be unable to reduce the chloro-compound **1**, whereas for other catalysts the initial active state probably could not be restored.

Table 1. Reaction conditions optimization study.



Entry	Reaction conditions modification	**3aa** Yield [%][a]
1	–[b]	80
2	**1a**:**2a** = 1:1 Base (1 eq.)	48
3	**1a**:**2a** = 1:2 Base (1 eq.)	49
4	MeCN (2 mL)	72
5	MeCN (0.5 mL)	50
6	*fac*-Ir(ppy)$_3$ (0.5 mol%)	72
7	Ir[dF(CF$_3$)ppy]$_2$(dtbbpy)PF$_6$	46
8	Ru(bpy)$_3$Cl$_2$ · 6H$_2$O	nr
9	Eosin Y[c]	nr
10	3DPA2FBN[d]	37

[a] Determined by ^{1}H NMR spectroscopic analysis of the crude mixture using triphenylmethane as internal standard.

[b] Optimized reaction conditions: **2a** (0.1 mmol), **1a** (0.2 mmol), *fac*-Ir(ppy)$_3$ (1 mol%), 2,6-lutidine (2 eq.), dry MeCN (1 mL), blue LEDs (462 nm), freeze pump thaw (3 cycles), rt, 24 h.

[c] Irradiated at 517 nm; $E_{1/2}$ ($EY^{\bullet+}$/EY*) = −1.11 V *vs.* SCE, CH_3CN/H_2O 1:1.

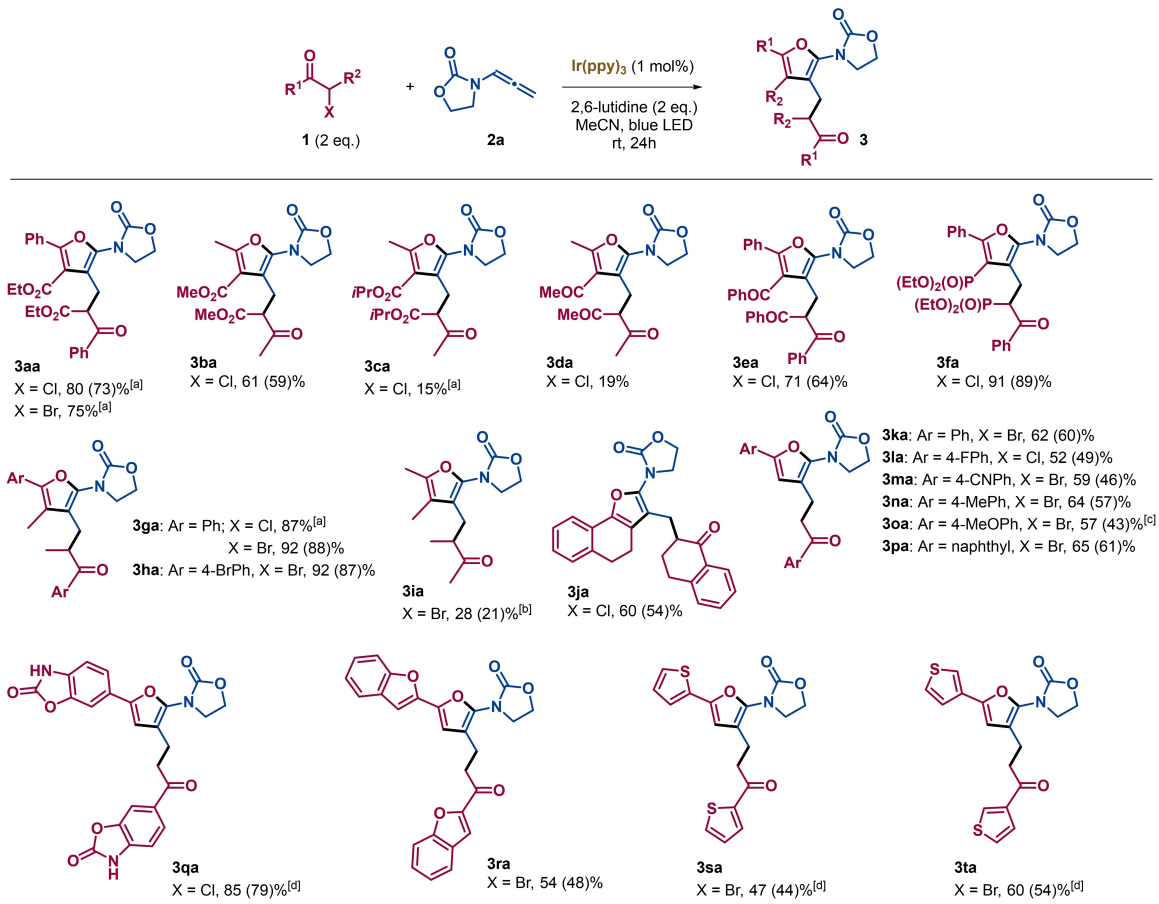
[d] 2,4,6-Tris(diphenylamino)-3,5-difluorobenzonitrile; $E_{1/2}$ ($PC^{\bullet+}$/PC*) = −1.60 V *vs.* SCE, CH_3CN.

ppy = 2-phenylpyridinato; rt = room temperature; dtbbpy = 4,4'-di-*tert*-butyl-2,2'-dipyridyl; bpy = 2,2'-bipyridine; nr = no reaction.

Aiming to explore the impact of the light source (wavelength and power) on the reaction outcome, we irradiated our model system with a 45 W Kessil© lamp at 427 nm, a 50 W Kessil© lamp at 456 nm, a home-assembled 50 W lamp at 462 nm, or a 100 W blue LED system at 448 nm. We did not observe significant variations working on the model substrates **1a** and **2a**.

Once the best reaction conditions were identified, we focused our attention on the application of the developed photoredox catalytic protocol to different substrates. At first, the α-halo ketones **1** scope was evaluated (Scheme 3).

Although the light source did not affect the performance of the model substrate **1a**, many less



Scheme 3. α-Halo ketones **1** scope. Optimized reaction conditions: **1** (2 eq.), **2a** (0.1 mmol), *fac*-Ir(ppy)$_3$ (1 mol%), 2,6-lutidine (2 eq.), dry MeCN (1 mL), blue LED (448 nm, 100 W), freeze pump thaw (3 cycles), rt, 24 h. All the products were obtained as racemates. NMR yields determined by ^{1}H NMR spectroscopic analysis of the crude mixture using triphenylmethane as internal standard. Yields after purification reported in brackets. [a] Blue LED: 462 nm. [b] **1i** (5 eq.). [c] Reaction time: 72 h. [d] *fac*-Ir(ppy)$_3$ (2 mol%).

reactive α-halo ketones benefited from using the most powerful lamp (100 W, 448 nm) for 24 hours. For this reason, the following investigations were generally performed under these conditions.

Starting from the good result obtained with α-chloro β-ketoester **1a** (product **3aa**, 80% yield), we tested some other haloketones bearing an electron-withdrawing group (EWG) at α-position. Alkyl β-ketoester **1b** provided slightly worse results (**3ba**, 61% yield), whereas the increased steric hindrance on the ester moiety (**1c**) strongly decreased the reaction conversion (**3ca**, 15% yield). Aryl β-diketone **1e** proved to be a good substrate for this transformation (**3ea**, 71% yield), whereas alkyl β-diketone **1d** showed a high reactivity but was not selective towards the formation of the desired product (**3da**, 19% yield). 2-Chloro-3-oxo-3-phenylpropanenitrile provided a complex reaction mixture (data not shown). Diethyl (1-chloro-2-oxo-2-phenylethyl)phosphonate **1f** was also tested, characterized by a less conventional EWG at α-position, and an excellent performance was observed (**3fa**, 91% yield). Phosphorylated furans have been the subject of recently developed syntheses and some of these compounds show pharmacological properties.[20]

Afterwards, we turned our attention to haloketones with an alkyl substituent at α-position, aiming to establish if an EWG was a crucial requirement. We demonstrated that the developed photoredox protocol works well on 2-halopropiophenones (**1g** and **1h**) furnishing the corresponding 2-aminofurans in excellent yields (**3ga**, 92% yield; **3ha**, 92% yield). Conversely, the poor result (**3ia**, 28% yield) obtained starting from 3-bromo-2-butanone **1i** confirmed that this transformation proceeds with better performance on α-halo aryl ketones (R^1 = aryl, Scheme 3; see **3aa** *vs* **3ba**, **3da** *vs* **3ea**, **3ga** *vs* **3ia**). Among the α-alkyl-substituted haloketones we also tested 2-chloro-1-tetralone **1j** showing a cyclic scaffold. The corresponding 2-aminofuran **3ja** characterized by a tricyclic fused system was achieved in good yield (60%). Our investigation on the reactivity of the α-halo ketones proceeded by applying the protocol to a series of

acetophenone-derivatives (**1 k**–**1 p**) lacking the α-substituent. These substrates are known to provide less efficient processes,[21] probably due to the formation of a relatively unstable primary alkyl radical intermediate. However, under our reaction conditions, they furnished the expected 4-unsubstituted 2-aminofurans in acceptable to good yields, regardless of the presence of electron-withdrawing or electron-donating groups (**3 ka**–**3 pa**, yields range = 52–65%), but providing a slower reaction with the strongly electron-donating group -OMe. 6-Chloroacetyl-2-benzoxazolinone **1 q** was evaluated and it provided the corresponding product **3 qa** in excellent yield (85%). However, due to the low reactivity of this substrate, 2 mol% of photocatalyst were required to achieve high conversion in 24 hours. The good result obtained with this α-chloro ketone bearing an unprotected amide group showed the significant functional group tolerance of the developed synthetic approach. Moreover, it is noteworthy that the 6-(furan-2-yl)benzo[*d*]oxazol-2(*3H*)-one moiety is present in medicinally relevant compounds.[22]

Lastly, some heteroaryl α-halo ketones were used as radical precursors. 3-(Bromoacetyl)pyridine hydrobromide generated a complex reaction mixture regardless of the employed amount of base (data not shown). Conversely, 2-(bromoacetyl)benzofuran **1 r** furnished the desired product **3 ra** in good yield (54%). 2-(2-Bromoacetyl)thiophene **1 s** and 3-(bromoacetyl) thiophene **1 t** both provided the corresponding 5-thiophen-2-aminofurans **3 sa** and **3 ta** in acceptable and good yield, respectively. Also in these cases, the low reactivity of the bromoketones led us to employ 2 mol% of photocatalyst to reach good conversions. The 5-thiophen-2-aminofuran is a remarkable structural moiety, being present in the scaffolds of beta-hydrolase inhibitors for cancer treatment,[23a] cannabinoid receptor CB_1 modifiers,[23b] thienopyranones as kinase, bromodomain and checkpoint inhibitors,[23c] ligands for alpha7 nicotinic acetylcholine receptor,[23d] furopyridinyl and furopyrimidinyl derivatives with promising fluorescence performance[23e] (Figure 2).

Analyzing the results obtained during the investigation of the α-halo ketones reactivity, it should be mentioned that α-chloro and α-bromo ketones can be both used in our transformation, thanks to the high reducing ability of the excited photocatalyst *fac*-$Ir(ppy)_3$.[17]

Subsequently, the nature of the allene partner (**2**) was changed (Scheme 4), aiming to explore the potential and the limitations of the developed process.

At first, we moved from the model oxazolidinone allene **2 a** to some substrates characterized by an amide group, cyclic (**2 b** and **2 c**) or acyclic (**2 d**). In all cases we achieved good results (**3 ab**–**3 ad**, yields range = 68–86%). However, it should be mentioned that the reaction performance significantly depends on the purity of allenamides **2**, which, therefore, were usually

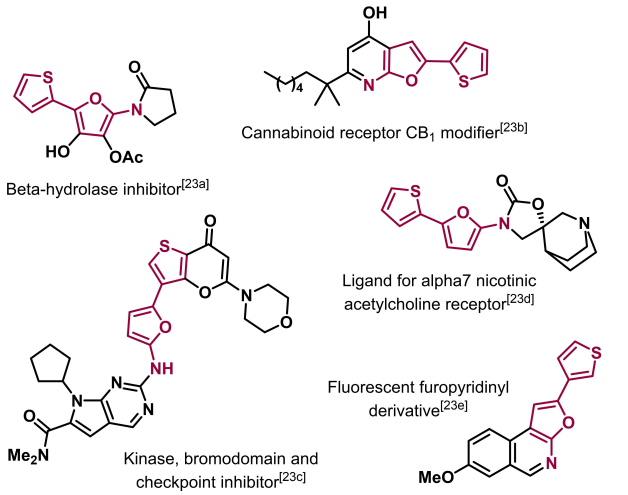
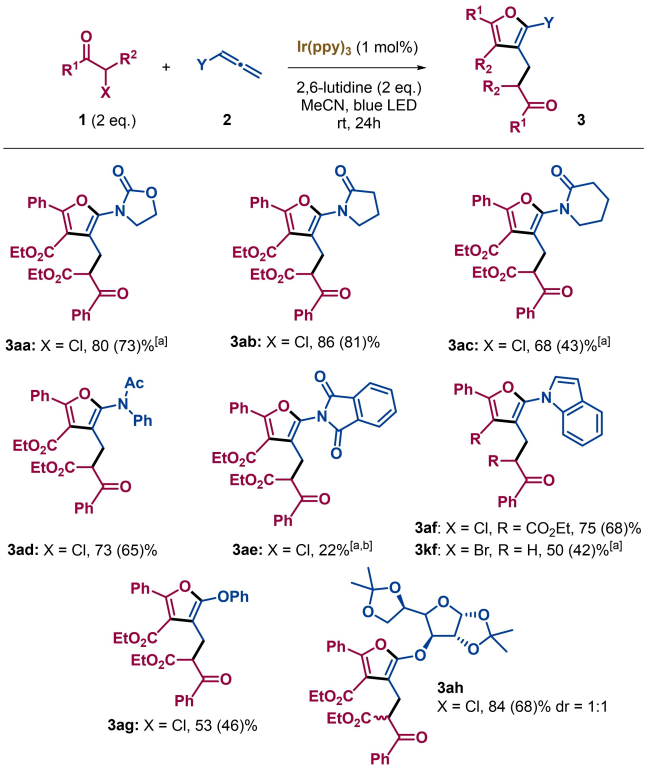


Figure 2. Examples of remarkable compounds containing the 5-thiophen-2-aminofuran moiety.

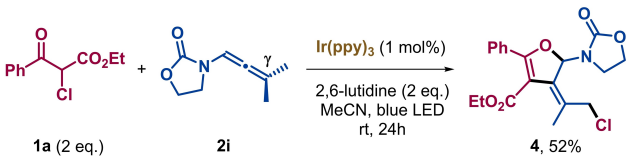


Scheme 4. Allenes **2** scope. Optimized reaction conditions: **1** (2 eq.), **2** (0.1 mmol), *fac*-$Ir(ppy)_3$ (1 mol%), 2,6-lutidine (2 eq.), dry MeCN (1 mL), blue LED (448 nm, 100 W), freeze pump thaw (3 cycles), rt, 24 h. Unless noted otherwise, the products were obtained as racemates. NMR yields determined by ^1H NMR spectroscopic analysis of the crude mixture using triphenylmethane as internal standard. Yields after purification reported in brackets. [a] Blue LED: 462 nm. [b] Reaction time: 48 h.

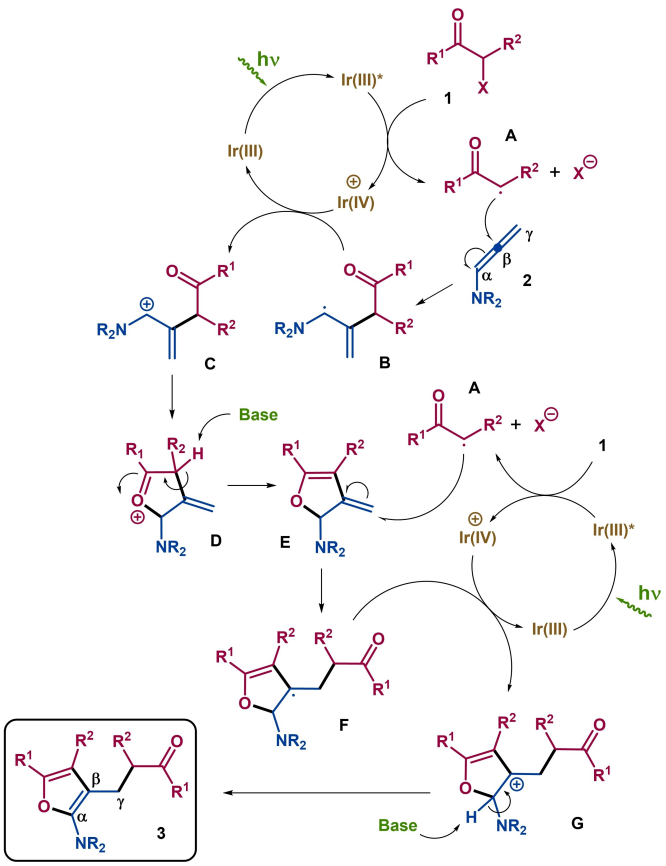
used as recently purified. The phthalimido-allene **2e** provided much worse results, probably due to the two EWGs on the nitrogen which reduce the electron density and the reactivity of the allene in this process. The *N*-allenyl acridinone proved to be unreactive probably for the same reason (data not shown). Conversely, good yields were obtained employing indolyl-allene **2f** with both α-chloro-β-ketoester **1a** (product **3af**, 75%) and α-bromo-acetophenone **1k** (product **3kf**, 50%). It is noteworthy that the *N*-furan indole core can be found in $sPLA_2$ inhibitors for atherosclerosis treatment,[24a] bis-heterocycles with antiproliferative activity in melanoma cells,[24b] EP_1 receptor antagonists[24c] and antimitotic agents.[24d]

Once demonstrated that different kinds of *N*-substituted allenes worked well under our reaction conditions (provided they were sufficiently electron-rich), we applied our protocol to oxygenated allenes (**2g** and **2h**). We were delighted to obtain the corresponding 2-oxyfurans in good (**3ag**, 53%) to excellent (**3ah**, 84%) yields, in particular for product **3ah** characterized by a structurally complex sugar moiety. As last remark, we tested the behavior of allenamide **2i** bearing two methyl groups at Cγ (Scheme 5). Under the previously established reaction conditions the allene was fully consumed providing a main product (52% yield), for which we proposed a tentative structure (**4**) (see Supporting Information for a mechanistic hypothesis). The spectroscopic analyses demonstrated that, as expected, the increased steric hindrance at Cγ prevents the addition of the second molecule of α-keto radical.

After evaluating the applicability of the process to various substrates **1** and **2**, we focused our attention on the reaction mechanism. Based on our experimental findings and the previous literature reports, we proposed a reasonable mechanistic hypothesis for our photoredox Ir-catalyzed transformation, depicted in Scheme 6. According to our hypothesis, the catalyst $Ir^{III}(ppy)_3$ is photoexcited by visible light to $[Ir^{III}(ppy)_3]^*$ ($E_{1/2}^{IV/III*} = -1.73$ V),[17] which undergoes a single electron transfer (SET) process in the presence



Scheme 5. Reactivity of γ-disubstituted allenamide **2i**. Reaction conditions: **1a** (2 eq.), **2i** (0.1 mmol), *fac*-$Ir(ppy)_3$ (1 mol%), 2,6-lutidine (2 eq.), dry MeCN (1 mL), blue LED (448 nm, 100 W), freeze pump thaw (3 cycles), rt, 24 h. Product obtained as racemate. NMR yield determined by ^1H NMR spectroscopic analysis of the crude mixture using triphenylmethane as internal standard.



Scheme 6. Double radical-polar crossover reaction pathway.

of α-halo ketone **1** (*ie* **1k** $E_{1/2}$ RX/R·+X⁻ = −1.46 V),[25] generating $Ir(IV)^+X^-$ species and the electrophilic radical **A**. This intermediate regioselectively adds to the most electron-rich carbon of allenamide **2** (Cβ), providing the α-amino radical **B**, that is readily oxidized ($E_{1/2} = -1.03$ V *vs.* SCE)[26] by Ir(IV) species ($E_{1/2}^{IV/III} = +0.77$ V *vs.* SCE),[17] restoring the Ir(III)-complex and generating the allylic carbocation **C**, further stabilized by the adjacent nitrogen atom. Unlike what was reported by Kimber,[16] that is an intermolecular nucleophilic addition (Scheme 2b), in our case a nucleophilic carbonyl function is already present in the molecule. Therefore, the intermediate carbocation **C** undergoes a polar cyclization providing the cyclic cation **D**, which stabilizes by losing a proton and generating the dihydrofuran **E**. This species is characterized by a conjugated electron-rich exocyclic double bond, prone to be attacked by a second molecule of the electrophilic radical **A**. The intermediate unsubstituted dihydrofuran **E** has never been isolated or observed, even by varying the reaction conditions, suggesting that its reactivity in this process is higher than that of the corresponding allenamide **2**. The addition of radical **A** to the dihydrofuran **E** provides the radical **F**, which is first oxidized by the

Ir(IV)-complex to the tertiary allylic carbocation **G**, and then undergoes aromatization by losing a second proton.

It is noteworthy that, according to the hypothesized mechanism, the transformation is configured as a *double radical-polar crossover* reaction, in which the photocatalyst is excited, oxidized and reduced twice for each molecule of product **3**. The good yields obtained with low catalyst loading (1 mol%) demonstrate the high efficiency of the process. The possibility to achieve a double radical-polar transformation directly derives from the use of an allenamide as substrate, which, after the addition of the first radical **A**, preserves a further reactive π-system, enabling the installation of a keto functionality at a remote position. The developed transformation is *fully redox-neutral* and, therefore, particularly sustainable, avoiding the use of sacrificial reactants and/or stoichiometric strong oxidants, sometimes expensive, environmentally unfriendly and/or source of side-reactions. Finally, it is interesting to note that the functionalization of all the allenyl carbons (Cα, Cβ and Cγ) is achieved one-pot according to a domino sequence.

Transformations involving oxidation states modifications proceed through the formation of very reactive intermediates characterized by short life-times. For this reason a thorough study of these mechanisms is quite challenging.[27] Aiming to support our mechanistic hypothesis, we accomplished a series of properly designed experiments and investigations (Table 2).

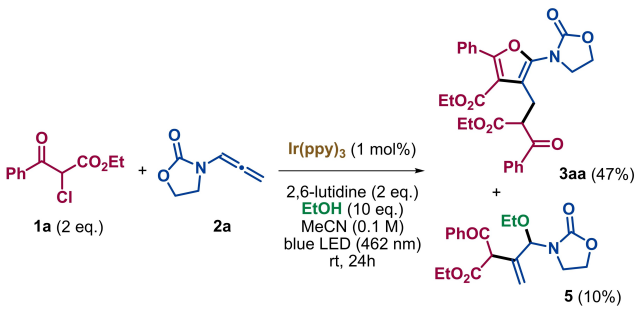
Photocatalyst and light played both a crucial role, being the reactants completely unreactive in their absence (Table 2, Entries 2–3), thus demonstrating the visible light-promoted pathway of our reaction. A significant behavior of the excited catalyst *fac*-Ir(ppy)$_3$ as initiator of a radical chain propagation mechanism was excluded, being the product amount obtained after two hours of irradiation (Entry 4) comparable to that observed after 22 hours of further stirring in the dark (Entry 5). Moreover, the measured photoreaction quantum yield was 0.24, reasonably confirming a closed catalytic cycle ($\Phi < 1$) (see Supporting Information for details).[28] The radical inhibitor TEMPO completely stopped the reaction (Entry 6), thus suggesting an electron transfer-triggered radical pathway. Lastly, the presence of oxygen, a known quencher of the excited state of many transition-metal polypyridyl compounds,[29] significantly decreased the reaction efficiency, providing 2-aminofuran **3aa** in lower yield (45%, entry 7). The Stern-Volmer luminescence quenching experiments (see Supporting Information) demonstrated that the quenching of excited *fac*-Ir(ppy)$_3$ was basically fulfilled by α-chloro substrate **1a** and not by allenamide **2a** or 2,6-lutidine, supporting the postulated SET in generating the first α-keto radical intermediate **A** (Scheme 6). The analysis of the crude reaction mixture containing TEMPO as radical inhibitor, carried out by high resolution mass spectrometry (HRMS), allowed us to observe the adducts between TEMPO and both the radical intermediates **A** and **B**, strongly suggesting their formation in the reaction course (see Supporting Information for details). We also tried to trap the conjugated *N*-acyliminium ion **C**, a key intermediate in allenamide chemistry, usually generated via electrophilic activation.[30] Conversely, in our case, it results from a radical addition and a subsequent oxidation. To this purpose, we carried out a reaction in the presence of 10 equivalents of EtOH (Scheme 7).

Although the main reaction product remained 2-aminofuran **3aa**, it was evident in the crude mixture the presence of some species characterized by double bonds and involving only one β-ketoester unit (see Supporting Information), probably deriving from the ethanol addition to the intermediate iminium ion **C**. At last, we confirmed that, according to our mechanistic hypothesis, the base plays a key role in our process as

Table 2. Investigations on the reaction mechanism.

Entry	Reaction conditions modification	**3aa** Yield [%][a]
1	–[b]	80
2	No light	nr
3	No photocatalyst	nr
4	2 h (light)	57
5	2 h (light) + 22 h (dark)	51
6	TEMPO (2 eq.)	np
7	Air atmosphere[c]	45

[a] Determined by ^{1}H NMR spectroscopic analysis of the crude mixture using triphenylmethane as internal standard.
[b] Optimized reaction conditions: **2a** (0.1 mmol), **1a** (0.2 mmol), *fac*-Ir(ppy)$_3$ (1 mol%), 2,6-lutidine (2 eq.), dry MeCN (1 mL), blue LEDs (462 nm), freeze pump thaw (3 cycles), rt, 24 h.
[c] Carried out without freeze pump thaw and in a closed vessel under air atmosphere.
nr = no reaction; np = no product; TEMPO = 2,2,6,6-tetramethylpiperidine-1-oxyl.



Scheme 7. Attempted interception of intermediate *N*-acyliminium **C** by ethanol.

two protons are removed along the reaction path. In fact, significantly worse results were obtained using less than two equivalents of base (see Supporting Information).

Conclusion

In summary, we developed a photoredox catalytic synthetic approach to functionalized 2-aminofurans (**3**) starting from α-halo carbonyl substrates (**1**) and allenamides (**2**). Some features of this protocol make it particularly efficient and sustainable: *i*) the use of visible light as a green energy source, *ii*) the redox-neutral nature of the transformation, allowing to avoid additives and strong oxidants, *iii*) the mild reaction conditions and the functional groups tolerance, *iv*) the low photocatalyst loading and the absence of excess reagents, *v*) the one-pot formation of three new bonds in a domino sequence, involving two molecules of α-halo ketone (**1**) in the architecture of the final product (**3**). Concerning the hypothesized mechanism, it deserves to be emphasized that the transformation is configured as a *double radical-polar crossover* reaction, in which the photocatalyst is excited, oxidized and reduced twice for each molecule of 2-aminofuran **3** produced. The good yields obtained with low catalyst loading demonstrate the high process efficiency. The novelty of the designed approach lies not only in the photoredox catalytic radical strategy, but also in the use of *N*-allenamides (**2**) as substrates, proving to act as a good balance between stability and reactivity. After the addition of the first electrophilic radical (**A**), these compounds preserve a further reactive π-system, making possible the addition of a second α-keto radical and enabling the installation of a keto functionality at a remote position. The wide applicability of the protocol allows to synthesize different variably decorated furans, some of which containing medicinally remarkable bis-heterocyclic moieties. Moreover, the functional groups installed on the furan skeleton can be usefully exploited in further synthetic elaborations.[4j–k,31]

Experimental Section

General Information. All the commercial chemicals were purchased from Sigma-Aldrich, VWR, Alfa Aesar, or TCI-Chemicals and used without additional purifications. The ^{1}H and ^{13}C NMR spectra were recorded on a Varian INOVA 400 NMR instrument with a 5 mm probe. All chemical shifts have been quoted relative to residue solvent signal; chemical shifts (δ) are reported in ppm and coupling constants (*J*) are reported in hertz (Hz). HPLC analyses were performed on an Agilent Technologies HP1100 instrument. A Phenomenex Gemini C18 3 µm (100×3 mm) column was employed for the chromatographic separation: mobile phase H_2O/CH_3CN, gradient from 30% to 80% of CH_3CN in 8 min, 80% of CH_3CN until 22 min, then up to 90% of CH_3CN in 2 min, flow rate 0.4 mL min^{-1}. Low-resolution MS (LRMS) ESI analyses were performed on an Agilent Technologies MSD1100 single-quadrupole mass spectrometer. Mass spectrometric detection was performed in the full-scan mode from *m/z* 50 to 2500, with a scan time of 0.1 s in the positive ion mode, ESI spray voltage of 4500 V, nitrogen gas pressure of 35 psi, drying gas flow rate of 11.5 mL min^{-1} and fragmentor voltage of 30 V. High-resolution MS (HRMS) ESI analyses were performed on a Xevo G2-XS QTof (Waters) mass spectrometer. Mass spectrometric detection was performed in the full-scan mode from *m/z* 50 to 1200, with a scan time of 0.15 s in the positive ion mode, cone voltage: 40 V, collision energy: 6.00 eV. ESI: capillary: 3 kV, cone: 40 V, source temperature: 120 °C, desolvation temperature: 600 °C, cone gas flow: 50 L h^{-1}, desolvation gas flow: 1000 L h^{-1}. Melting point (m.p.) measurements were performed on Bibby Stuart Scientific SMP3 apparatus. Flash chromatography purifications were carried out using VWR silica gel (40–63 µm particle size). Thin-layer chromatography was performed on Merck 60 F254 plates.

Typical Procedure for the Photocatalytic Synthesis of Furans 3 and Dihydrofuran 4. All reactions were performed on 0.1 mmol scale of allene **2**. A 4 mL screw cap septum vial equipped with a magnetic stirring bar was charged with the allene **2** (0.1 mmol), dry MeCN (1 mL), the halogenated compound **1** (2 equivalents), 2,6-lutidine (2 equivalent) and *fac*-$Ir(ppy)_3$ (1 mol%). The vial was closed and the oxygen was removed by three cycles of the freeze-pump-thaw procedure, then the vial was filled with argon. The reaction mixture was irradiated under strong stirring using blue LED (stripes at 462 nm or 100 W at 448 nm) for 24 h at room temperature unless otherwise stated. Eventually, the solvent was removed under reduced pressure at room temperature. The crude mixture was analyzed by ^{1}H NMR spectroscopy using triphenylmethane (0.1 mmol) as internal standard. The product was then purified by flash chromatography on silica gel.

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