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Photoredox Initiated α -Alkylation of Imines *via* a Three-Component Radical/Cationic Reaction

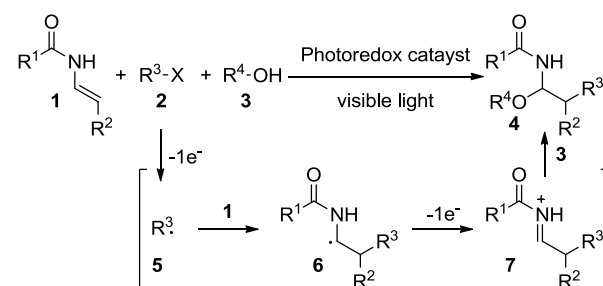
Thibaut Courant and Géraldine Masson*^[a]

Dedication ((optional))

The α -alkylation of imines is a valuable carbon–carbon bond-forming strategy which is still an underdeveloped area,^[1–3] despite the synthetic potential of its α -branched imine products.⁴ The direct C–H bond functionalization of imines with alkyl halides has proven challenging due to competing side reactions, such as Mannich condensation, *N*-alkylation and hydrolysis.^[1,5] The indirect approach based on the intermolecular nucleophilic alkylation reaction of enamine^[6] or enamide^[7] derivatives was not found more efficient. Moreover, the only corresponding products reported were α -alkylated carbonyl compounds.^[8] To the best of our knowledge, there is no efficient method for the preparation of α -alkylated imines. In this communication, we disclose a novel α -alkylation reaction of imines which can be achieved by photoredox-mediated direct intermolecular C–H functionalization of enamide derivatives, involving a radical-cationic domino process.

Recently, Friestad *et al.*^[9] reported an interesting tin-mediated non-reductive radical alkylation of tertiary enamides, forming two carbon-elongated homologs *via* oxidation and proton-transfer through *N*-amidoradical intermediates.^[10–12] Based on this, we envisaged that the same radical/cationic process in the presence of a nucleophile might provide an expedient synthesis of α -alkylated imines. The principle of this multicomponent domino process is depicted in Scheme 1.^[13,14] After radical reduction of alkyl halide **2**, the resulting alkyl radical **5** would react with enamide **1** to produce α -amidoalkyl radical **6**. The oxidative radical-polar crossover^[15] could then furnish an *N*-acyliminium cation **7**, which should be trapped by a suitable nucleophile. Alcohol **3** was chosen as a nucleophile of choice to generate β -alkylated α -amidoether **4**, which is a stable precursor of α -alkylated imine^[16, 14f] and can be found in a number of biologically important natural

products.^[17,18] To initiate this radical/cationic domino process, a free radical redox initiator, which was compatible with the nucleophile was selected. As visible light photoredox catalysis^[19] has emerged as an efficient tool to promote single-electron transfer (SET) redox transformations since the success of MacMillan *et al.*,^[20] Yoon *et al.*,^[21] Stephenson *et al.*^[22] and others,^[23] suitable environmentally friendly photoredox catalysts were chosen.^[24]



Scheme 1. Rational design for a three-component radical/cationic reaction of enamide, alkyl halide and alcohol.

Initial studies centred on examining the reaction of (*E*)-benzyl prop-1-enylcarbamate (**1a**), diethyl bromomalonate (**2a**) and ethanol (**3a**), in the presence of Et₃N (2 eq), [Ru(bpy)₂Cl₂] (**8**, 1.5 mol%), and light from a 25 W compact fluorescent lamp. As described in Table 1, we were able to obtain the desired three-component adduct **4a** as a 3:2 mixture of diastereomers, although the reaction was not clean. In order to optimize the reaction, photoredox catalysts, alcohols and solvents were screened. To our delight, a change from Ru-containing photocatalyst to Ir(ppy)₂(dtbbpy)PF₆ (**9**) furnished the product in higher yield (79%, Table 1, entries 1 vs. 2). The change in the nature of the base (DIPEA in the place of Et₃N) lowered the yields (entry 3). The reaction proceeds in various solvents, except DMF. Dichloromethane was found to be the solvent of choice in both yield and reaction rate to give product **4a** in almost quantitative yield, within 3 hours (entry 7). Reduced reaction time to less than one hour was observed under same conditions but in sunlight (entries 7 vs. 8). Additional alcohols, namely MeOH and *i*PrOH, were also found to be suitable nucleophiles, albeit slightly lower

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in yield, to give corresponding β -alkylated α -carbamidoethers **4b** and **4c** respectively (entries 11 and 12).

Table 1. Survey of reaction conditions for the photoredox-initiated three-component radical/cationic reaction.

Entry	3	Cat.	Solvent	Et ₃ N	4	<i>t</i> [h]	Yield [%] ^[a,b]
1	3a	8	MeCN	2 eq	4a	24	60
2	3a	9	MeCN	2 eq	4a	12	79
3	3a	9	MeCN	2 eq	4a	12	65 ^[c]
4	3a	9	toluene	2 eq	4a	12	79
5	3a	9	EtOH	2 eq	4a	12	78
6	3a	9	DMF	2 eq	4a	12	0 ^[d]
7	3a	9	CH ₂ Cl ₂	2 eq	4a	3	>99
8	3a	9	CH ₂ Cl ₂	2 eq	4a	1	>99 ^[e]
9	3b	9	CH ₂ Cl ₂	–	4b	1	–
10	3b	9	CH ₂ Cl ₂	1 eq	4b	1	–
11	3b	9	CH ₂ Cl ₂	2 eq	4b	1	88
12	3c	9	CH ₂ Cl ₂	2 eq	4c	1	62

[a] Reaction conditions: enecarbamate (**1a**) (0.1 mmol), diethyl-2-bromomalonate (**2a**) (0.2 mmol), **3** (1.0 mmol), **8** or **9** (0.001 mmol), *c* = 0.10 M at RT. [b] Isolated yield after column chromatography. [c] Et₃N was replaced by DIPEA. [d] Non-reductive radical alkylated enecarbamate was isolated. [e] Sunlight was used.

After having identified the optimal conditions of the three-component radical/cationic process, the scope of the enamide substrates **1** was investigated (Table 2). We were pleased to find that the reaction conditions developed were applicable to a range of enamides to provide good to excellent yields of α -alkylated imines adducts **4**, in short reaction time (1 to 3h). It is noteworthy that no side products, such as homocoupling products or those deriving from reduction of the malonyl radical or the α -amidoalkyl radical, were detected.^[22] Several protecting groups at the nitrogen of **1** such as Boc (entry 3), alloc (entry 6), methylcarbonate (entry 9) and acetate (entry 8) were tolerated. However, a slightly lower yield was noted with a triple bond bearing carbamate protecting group, even when an excess of enecarbamate was used (entry 7). This method was also compatible with silylated alcohols (entries 2 and 3). In addition, a β -branched cyclopropyl enecarbamate participated successfully in the reaction to afford **4g** in 92% yield (entry 4). Most remarkably, the radical-polar crossover process worked well with aliphatic ketone-derived enamides. This was demonstrated as the *N*-acyl enamide from cyclohexanone being converted into the quaternary carbon-containing β -alkylated α -amidoether **4k** which is a corresponding α -alkylated ketamine (entry 8). Interestingly, the endocyclic enecarbamate worked well to afford a suitable framework **4m** for the construction of a number of nitrogen containing heterocycles (entry 10).

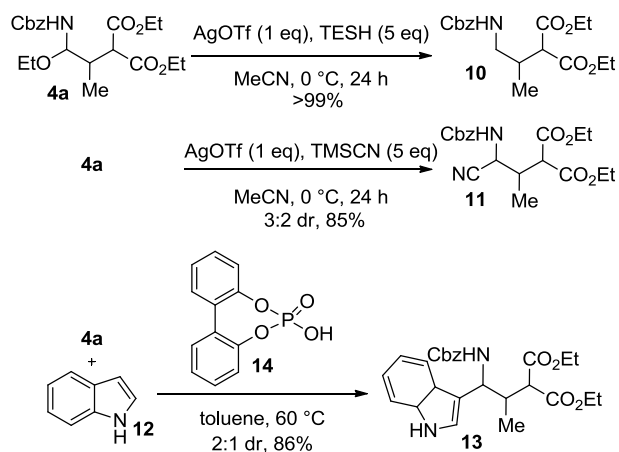
Table 2. Photoredox-Initiated Alkylation of enamide derivatives.

Entry	Product	4	Yield [%]/(dr) ^[a,b,c]
1		4d	>99 (1:1)
2		4e	95 (3:2)
3		4f	84 (1:1)
4		4g	92 (1:1)
5		4h	62
6		4i	60 (1:1)
7		4j	45 (1:1)
8		4k	74 (1:1)
9		4l	62
10		4m	48 (1:1)

[a] Reaction conditions: enecarbamate (**1a**) (0.1 mmol), diethyl-2-bromomalonate (**2a**) (0.2 mmol), Et₃N (0.2 mmol), **3** (1.3 mmol), **9** (0.001 mmol), *c* = 0.10 M at RT. [b] Isolated yield after column chromatography. [c] dr determined by ¹H-NMR analysis of crude mixtures.

The photoredox-initiated α -alkylation of enamides provided a convenient synthesis to highly functionalized precursor of α -alkylated imines **4**, which are important synthetic intermediates for several transformations.^[15] To illustrate this, **4a** was easily

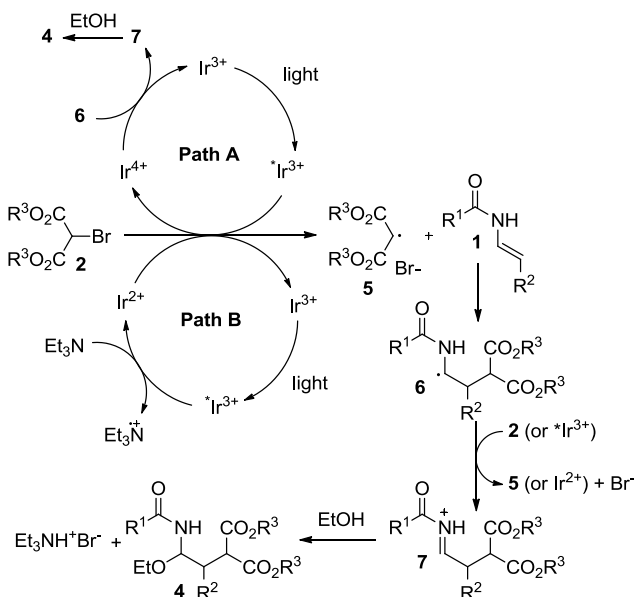
prepared on a 5-mmol scale using 0.5 mol% of iridium(III) catalyst (4 mg). Its reduction using triethylsilane (TESH) and AgOTf proceeded smoothly to afford amine **10** in quantitative yield (Scheme 2). The cyanation of **4a** was also carried out, using AgOTf and TMSCN to give easy access to a highly functionalized precursor of amino acid **11**.^[25] Finally, a Friedel-Crafts alkylation^[26] of indole **12** was performed with 10 mol% of phosphoric acid catalyst **14** in toluene at 60 °C. The desired product **13** was isolated as a mixture of diastereomers in a ratio of 2 : 1, with 86% yield over two steps. Additionally, no undesirable bisindolyl by-product was isolated.^[27]



Scheme 2. Synthetic application of β -alkylated α -carbamidoethers **4**.

Control experiments were carried out to investigate whether an ionic pathway was involved in this three-component reaction. It was found that no reaction proceeded in the absence of any of the reaction partners, including $[\text{Ir}(\text{ppy})_2(\text{dtbbpy})]\text{PF}_6$ (**9**) and light. One equivalent of TEMPO totally suppressed the reaction. These control experiments confirm that the alkylation of enamides occurs through a radical/cationic pathway and two possible mechanisms are proposed in Scheme 3. In the first mechanism (Path A), a strong reductant $^*\text{Ir}^{3+}$ is formed from the photoredox initiator after its excitation with weak fluorescent light.^[20b,22c] Then, the reduced iridium species carry out a single electron transfer (SET) to activate the carbon-bromine bond, forming the electron-deficient alkyl radical **5** and a bromide anion, and regenerating the Ir^{4+} catalyst. Enamide **1** then reacts with the electrophilic radical generated to give nucleophilic α -amido radical intermediate **6**,^[28] which could be rapidly oxidized into *N*-acyliminium cation **7**, either by SET from Ir^{4+} , or by bromine atom transfer and subsequently trapped by the ethanol component.^[29] On the basis of previous proposed mechanism, the radical propagation probably occurs through an atom transfer mechanism.^[30] However, this mechanism does not explain the role of Et_3N which does not seem to be limited solely to trapping HBr .^[30] Indeed, only a complex mixture could be observed when the reaction was conducted with one equivalent or without a tertiary amine (Table 1, entry 9-10). Similar results were also obtained with bases other than Et_3N such as NaHCO_3 , K_2CO_3 , lutidine. To investigate these issues, we hypothesized that, since the oxidation potential of iridium(III) is high (1.60 V vs. NHE in CH_3CN),^[31] it might oxidize enamide derivatives **1** in the absence of Et_3N .^[32-34] On this basis, a second mechanism, which involves the reductive quenching of the excited state of $^*\text{Ir}^{3+}$ by Et_3N to

produce the reducing Ir^{2+} species (-1.51 V vs. SCE in CH_3CN)^[24b,35] and the ammonium radical cation,^[20c,22i] is postulated (Path B). Then, alkyl radical **5**, formed by the Ir^{2+} -mediated reduction of **2**, reacts with **1** to provide α -amidoradical **6**. Reduction of $^*\text{Ir}^{3+}$ or radical propagation, and subsequent addition of alcohol, afford the desired product **4**. In this case, only a catalytic amount of tertiary amine is, therefore, required; and the excess of the base neutralizes HBr , formed in the reaction media.



Scheme 3. Proposed mechanism.

In summary, we have described a photoredox-initiated three-component domino synthesis of *N*-carbamoyl α -alkylated imines from easily accessible starting materials. Key features of this approach are its operational simplicity, high atom-economy, wide substrate scope and good to excellent chemical yields. The ready accessibility to α -alkylated imines, which are stable precursors in many useful synthetic transformations, makes the methodology particularly attractive in organic synthesis. Synthetic potentials have also been illustrated in various transformations into functionalized amines.

Experimental Section

General protocol: A flame-dried tube under argon atmosphere (1 atm) is charged with $[\text{Ir}(\text{ppy})_2(\text{dtbbpy})]\text{PF}_6$ catalyst **9** (1.3 mg, 1.5 μmol) in 1 mL of dry dichloromethane or dry acetonitrile. Enecarbamate **1** (0.1 mmol), diethyl bromomalonate **2a** (37 μL , 0.2 mmol), Et_3N (28 μL , 0.2 mmol) and alcohol **3** (1 mmol) were added in this order. The tube heterogeneous solution was degassed by three freeze-pump-throw cycles and the tube was irradiated with 25W fluorescent lamp. After reaction completed (judged by TLC monitoring), the solvent is removed *in vacuo* and the residue was purified by flash chromatography on silica gel [Heptane/EtOAc : 7/3] to afford the corresponding product **4**.

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Keywords: alkylation • multicomponent • domino • photoredox catalysis • enamides

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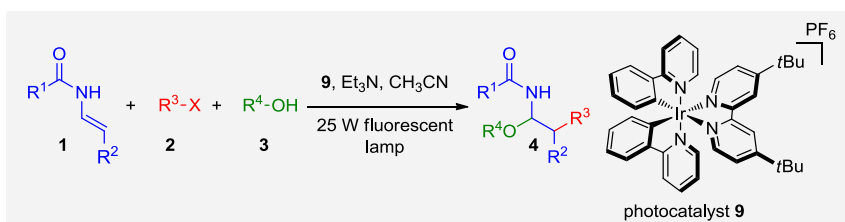
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The photoredox-mediated alkylation of enamides with diethyl bromomalonate in the presence of alcohols has been developed. This multicomponent domino process affords β -alkylated α -carbamidoethers as stable imines surrogates in good to excellent yields under mild conditions.