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Exploiting photoredox catalysis for the synthesis of tetra- and di-hydrofurans

Gabriele Fumagalli^a, Scott Boyd^b, Michael F. Greaney^{a,*}^a School of Chemistry, The University of Manchester, Oxford Road, Manchester M13 9PL, UK^b Oncology Department, AstraZeneca, Alderley Park, Macclesfield SK10 4TG, UK

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ABSTRACT

Tetra- and di-hydrofuran heterocycles can be synthesised in a single step through the addition of functionalised alkyl bromides to styrene derivatives under photoredox catalysis.

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Photoredox catalysis (PRC) is receiving renewed attention as a vehicle for reaction discovery. Irradiation of commercially available catalysts with visible light creates a long-lived triplet excited state, which may undergo facile single electron transfer (SET) reactions with suitable substrates. The mild conditions contrast favourably with classical UV photochemistry or metal hydride radical reactions, and are readily adaptable to a wealth of compound and reaction classes.¹

A number of recent PRC systems concern the double functionalisation of olefins. Feedstock alkenes, especially the more reactive styrenes, can undergo a range of C–C and C–X bond formations to produce value-added building blocks in a single step.² We have recently described a photoredox catalysed oxyarylation and aminoarylation of styrenes, using diaryliodonium and diazonium salts as aryl radical precursors, and a variety of *O*- and *N*-based solvents as nucleophiles.³

We envisioned that this pattern of reactivity could be used to create interesting heterocycles, if the chemistry could be extended to alkyl bromides containing a suitable nucleophilic site. The planned transformation is set out in Scheme 1. The excited state of a photoredox catalyst (e.g. Ir(ppy)₃) could initially reduce a suitably activated alkyl bromide **2**,⁴ generating radical intermediate **2'**. Reaction with the styrene double bond would yield benzylic

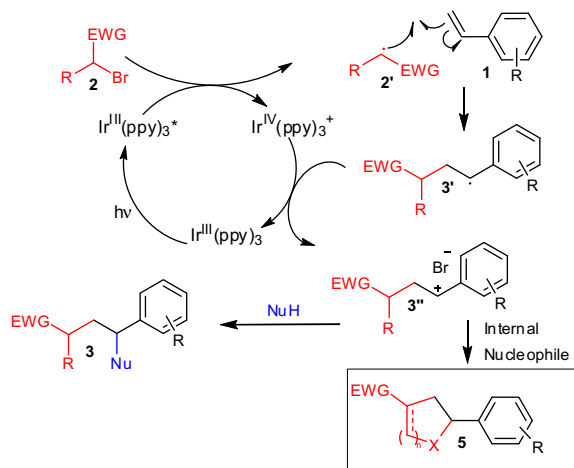
radical intermediate **3'**, which is readily oxidised to the corresponding cationic species **3''**. Capture by an internal nucleophile would then yield the heterocyclic product **5**.

We began our investigation by trialling methyl bromoacetate **2a**, in a three-component coupling reaction with styrene as the acceptor and methanol as the nucleophilic solvent. Initial results were encouraging; using Ir(ppy)₃ (1 mol %) as the photoredox catalyst gave the desired product **3a** in 35% yield (Table 1, entry 2). Based on our previous experience in the field, we decided to screen different metal salts as additives and found that Zn(OAc)₂ was optimal, increasing the yield to 68% (entry 3). Control experiments established that the photoredox catalyst, light source and absence of oxygen were all required for successful reaction (entries 6, 7 and 8).

A brief screen of other activated alkyl bromides identified bromoacetonitrile **2b** as being particularly effective under the optimised conditions, giving the methoxymethylnitrilated product in 99% yield (Scheme 2, **3b**). Further substrate scope around the nitrile structure established a versatile reaction, with a variety of electron-donating groups being tolerated on the styrene (**3c–3p**). Aryl halogen substituents were not reduced under the reaction conditions, demonstrating orthogonality to classic transition-metal catalysed reactions and ensuring the presence of useful handles for later stage functionalisation (**3m** and **3n**). In the course of this work the Lei group reported a similar alkoxycyanomethylation protocol, using Ir(ppy)₃ in the presence of NaHCO₃,⁵ with a substrate scope that encompassed simple styrenes and 1,1-diphenyl

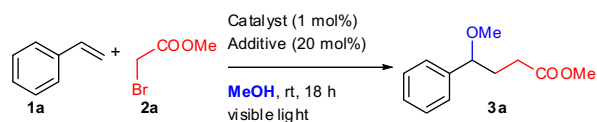
* Corresponding author.

E-mail address: michaelgreaney@manchester.ac.uk (M.F. Greaney).



Scheme 1. Reaction plan.

Table 1
Optimisation of reaction conditions and control experiments



Entry	Catalyst	Additive	1a:2a (equiv)	Yield ^a
1	Ru(bpy) ₃ Cl ₂	—	5:1	<5%
2	Ir(ppy) ₃	—	5:1	35%
3	Ir(ppy) ₃	Zn(OAc) ₂	5:1	68%
4	Ir(ppy) ₃	Zn(OAc) ₂	2:1	51%
5	Ir(ppy) ₃	Zn(OAc) ₂	1:1	40%
6	—	Zn(OAc) ₂	5:1	n.r.
7 ^b	Ir(ppy) ₃	Zn(OAc) ₂	5:1	n.r.
8 ^c	Ir(ppy) ₃	Zn(OAc) ₂	5:1	<5%

Conditions: 2.5 mmol of styrene, 0.5 mmol of bromoalkane, 0.005 mmol of photoredox catalyst, 0.1 mmol of additive and 3 mL of methanol.

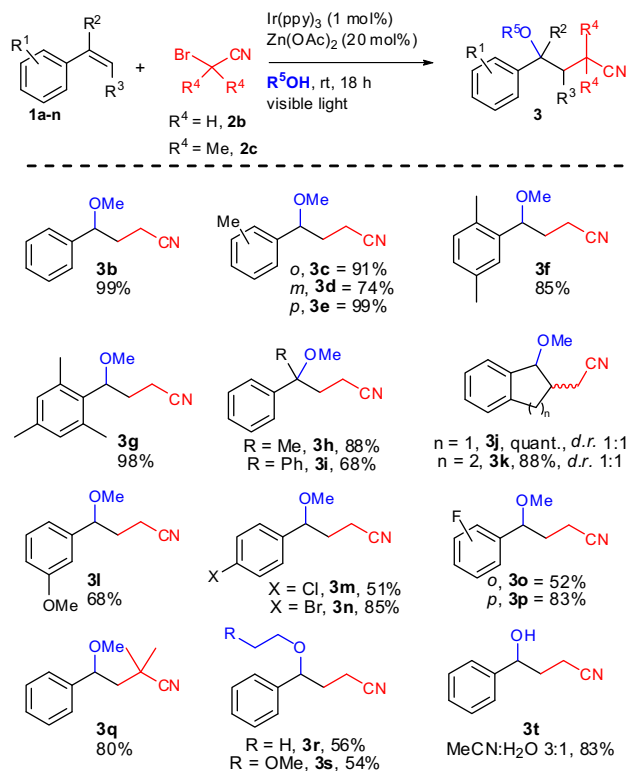
^a Isolated yields.

^b Reaction performed without irradiation.

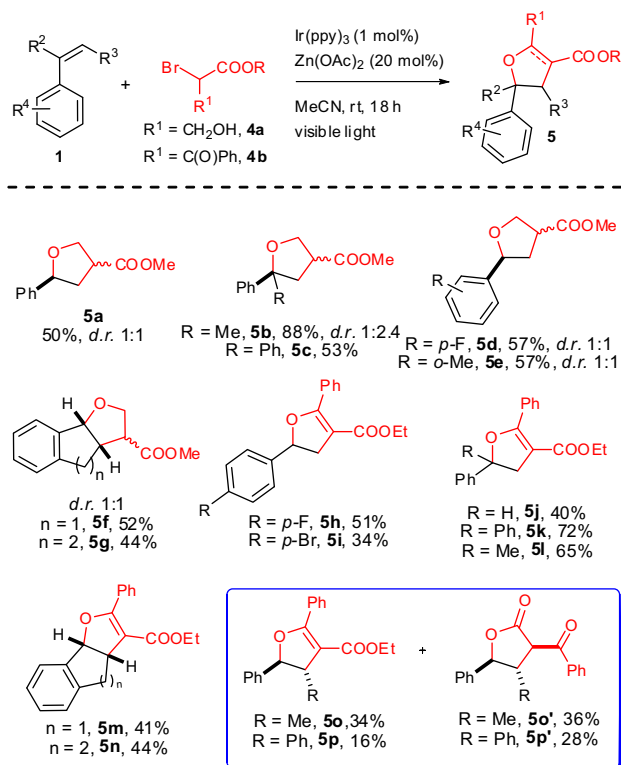
^c Reaction performed using non-degassed methanol.

alkenes (2 examples). In contrast to their work, we were pleased to find that the Zn(OAc)₂ additive enabled us to extend the process to α - and β -substitution on the alkene, encompassing indene and 1,2-dihydronaphthalene as substrates to give compounds **3j** and **3k** in excellent yields. Additional steric demand on the bromide was likewise tolerated, with 2-bromo-2,2-dimethylacetonitrile undergoing smooth conversion to yield **3q** in 80% yield. Finally, we could incorporate different *O*-nucleophiles using alternative alcohols (**3r** and **3s**) and water (**3t**) as the reaction solvent (the latter as a 3:1 mixture with MeCN).

In terms of limitations, the reaction was not successful for vinyl pyridines, nor for electron-poor styrenes, which tended to give the bromo-alkylated atom-transfer products in low yield. We were also unable to replicate the Ritter-type addition of nitrile solvents that we observed in our previous styrene arylation system. With the styrene functionalisation established, we moved on to address heterocycle synthesis using bromides bearing an internal oxygen nucleophile. We were pleased to find that bromide **4a**, readily prepared from serine,⁶ underwent smooth reaction with styrene to give the tetrahydrofuran derivative **5a** in 50% yield (1:1 mixture of diastereoisomers). The Zn(OAc)₂ additive was crucial here, as only trace amounts of product were observed in its absence.



Scheme 2. Scope of the oxymethylnitration reaction. Reagents and conditions: 2.5 mmol of styrene, 0.5 mmol of bromoalkane, 0.005 mmol of photoredox catalyst, 0.1 mmol of additive and 3 mL of solvent. All yields are isolated. Diastereomeric ratios determined by ¹H NMR from crude reaction mixtures.



Scheme 3. Scope of THF and DHF synthesis. Reagents and conditions: 2.5 mmol of styrene, 0.5 mmol of bromoacetone nitrile, 0.005 mmol of photoredox catalyst, 0.1 mmol of additive and 3 mL of solvent. All yields are isolated. Diastereomeric ratios determined by ¹H NMR from crude reaction mixtures.

The reaction was readily extended to α -substituted styrenes (**5b** and **5c**), indenes and dihydronaphthalenes, with the latter two substrates providing a one-step entry into the tricyclic compounds **5f** and **5g**. *Ortho*- and *para*-substitution on the aryl ring was tolerated with mild electron-donating and mild electron-withdrawing groups, such as methyl and fluoro substituents (**5d** and **5e**).

The use of α -bromo- β -ketoesters in the reaction gave dihydrofurans, *via* trapping of the benzyl carbocation with the enolic tautomer.⁷ Yields were moderate for simple styrene addition (**5h**, **5i** and **5j**), but α -substitution enhanced the reactivity, generating the desired products **5k** and **5l** in good yields. Indene and dihydronaphthalene were again successful, affording tricycles **5m** and **5n** in a single step. β -Methyl styrene and stilbene, however, each gave two products in the reaction. The expected dihydrofurans **5o** and **5p** were accompanied by the corresponding butyrolactone structures **5o'** and **5p'** (**5o** + **5o'** = 70% total yield, 1:1. **5p** + **5p'** = 44% total yield, 4:7), as single stereoisomers (*trans*), arising from carbocation trapping with the ester group (Scheme 3).

To conclude, we have developed a mild and high yielding methodology for concomitant C–C and C–O bond formation across activated alkenes. The reaction provides access to saturated and unsaturated furan heterocycles, including tricyclic derivatives, in a single step starting from cheap and readily available starting materials. Further applications of this chemistry are currently being explored in our laboratory.

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Supplementary data

Supplementary data (synthesis and characterisation data for all new compounds) associated with this article can be found, in the online version, at <http://dx.doi.org/10.1016/j.tetlet.2015.03.124>.

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