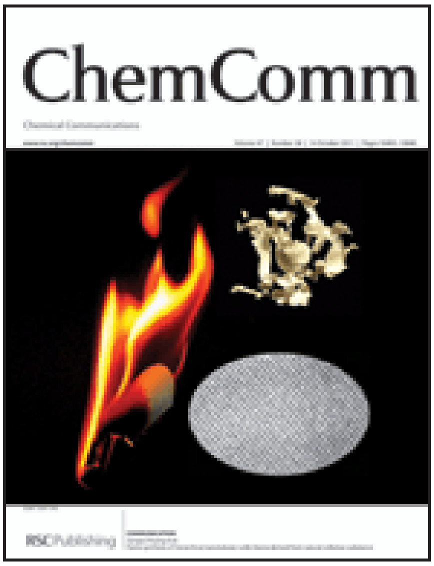

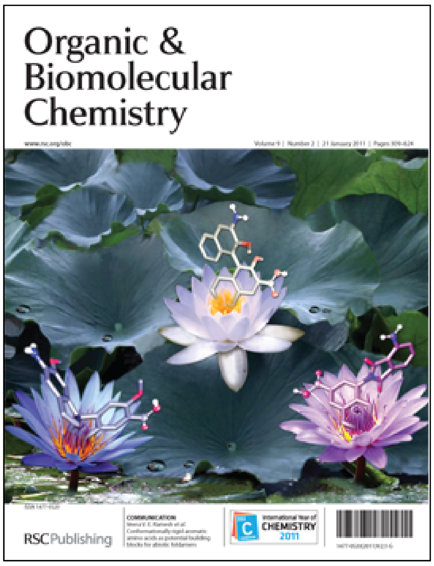

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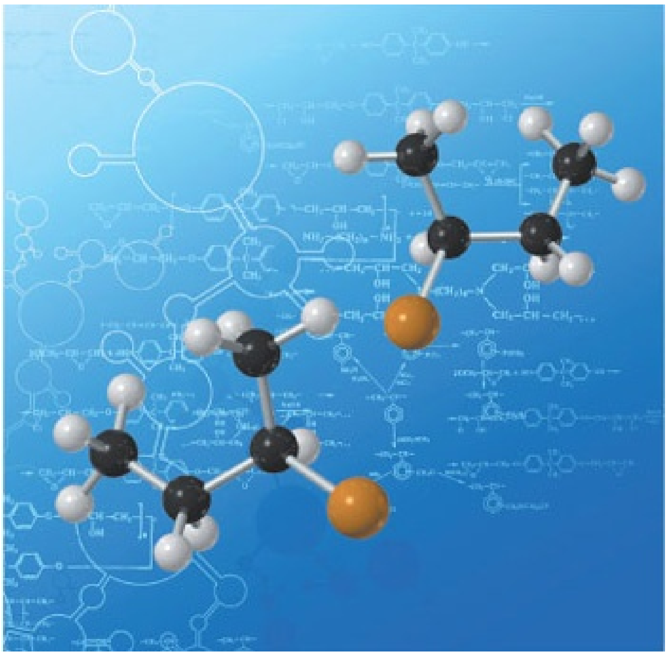

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COMMUNICATION

Synthesis of symmetric anhydrides using visible light-mediated photoredox catalysis†‡

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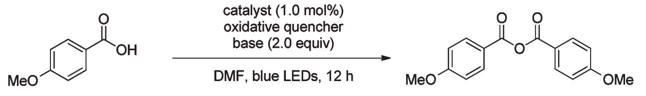
A new approach to anhydride formation is reported *via* activation of C–O bonds by the Vilsmeier–Haack reagent formed by $Ru(bpy)_3Cl_2$ and CBr_4 in DMF. Various aryl and alkyl carboxylic acids are converted to the corresponding anhydrides in excellent yields.

The development of methods for the preparation of anhydrides remains a significant goal since these structural motifs serve as precursors for amides and esters,[1] and have applications in peptide synthesis.[2] Various strategies for the synthesis of carboxylic anhydrides have been reported. The majority of methods currently available utilize carboxylic acids with dehydrative coupling agents, including phosgene,[3] thionyl and sulfonyl chlorides,[4,5] phosphoranes,[6] isocyanates,[7] pyridazin-3(2*H*)-ones,[8] 1,3,5-triazines,[9] and carbodiimides.[10] Other approaches have centered around reactions of carboxylate salts with strong acylating agents such as acid chlorides or acid anhydrides,[11] or more recently, polymer-supported cobalt phosphine complexes.[12] Due to anhydride instability, finding a mild and practical method is crucial. Based on our recent study into visible light-mediated halogenation of alcohols to the corresponding bromides and iodides, we sought to expand this methodology to the use of the *in situ* formed Vilsmeier–Haack reagent[13] for the synthesis of anhydrides. Herein we report a conversion of carboxylic acids into symmetrical anhydrides *via* visible light photoredox catalysis.[14]

Previously, we have shown that the catalytic generation of a Vilsmeier–Haack reagent can be accomplished under mild conditions *via* the oxidative quenching[15] of $^*Ru(bpy)_3^{2+}$ by polyhalomethanes CBr_4 (E_{red} = −0.30 V *vs.* standard calomel electrode [SCE])[16] or CHI_3 (E_{red} = −0.49 V *vs.* SCE)[16] in DMF. The Vilsmeier–Haack reagent activates the alcohol and allows for nucleophilic substitution by the halide. Hence, we anticipated that this protocol could be applied to the activation of carboxylic acid C–O bonds for nucleophilic addition reactions to form anhydrides.

We began our study by subjecting *para*-methoxybenzoic acid, CBr_4 and 2,6-lutidine in DMF to visible light irradiation (blue LEDs, λ_{max} = 435 nm) in the presence of $Ru(bpy)_3Cl_2$ (1.0 mol %) at 25 °C for 12 h, which led to the formation of the corresponding anhydride in 85% isolated yield (Table 1, entry 1). Increasing the temperature to 35 °C furnished the product in a slightly decreased yield (entry 2). In both cases, we observed a significant decomposition of the anhydride to the starting acid upon purification on silica gel. Therefore, we reasoned that lowering the amount of CBr_4 from 2.0 equiv to 1.0 equiv and performing an alkaline aqueous work-up would allow for the isolation of analytically pure product without the need for further purification. Indeed, this new protocol led to the formation of the anhydride in 90% yield (entry 3). Additional control experiments were performed in the absence of the catalyst and careful exclusion of light, in which no reaction was observed, supporting the necessity of the photoredox catalyst and a light source (entries 4 and 5). Excluding the oxidative quencher (CBr_4) gave no desired product (entry 6). Furthermore, the reaction was run in the absence of a base, providing a mixture of product and starting material in a 3 : 1 ratio (entry 7).

Table 1 Optimization of reaction parameters[a]



Entry	Catalyst	Oxidative quencher (equiv)	Base	Yield (%)
1[b]	$Ru(bpy)_3Cl_2$	CBr_4 (2.0)	2,6-lutidine	85
2[b,e]	$Ru(bpy)_3Cl_2$	CBr_4 (2.0)	2,6-lutidine	79
3	$Ru(bpy)_3Cl_2$	CBr_4 (1.0)	2,6-lutidine	90
4	None	CBr_4 (2.0)	2,6-lutidine	NR
5[d]	$Ru(bpy)_3Cl_2$	CBr_4 (1.0)	2,6-lutidine	NR
6[c]	$Ru(bpy)_3Cl_2$	None	2,6-lutidine	NR
7[c]	$Ru(bpy)_3Cl_2$	CBr_4 (1.0)	None	77

[a] All reactions were performed on a 0.5 mmol scale and were degassed (freeze-pump-thaw). Yields (%) were obtained after aqueous work-up unless otherwise noted. [b] Isolated yield (%) after purification by chromatography on SiO_2. [c] Conversion (%) determined by crude ^1H NMR. [d] Experiment was conducted in absence of light. [e] Experiment was run at 35 °C.

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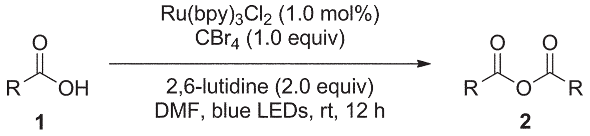
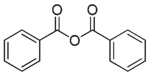
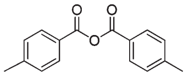
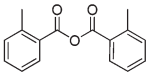
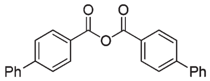
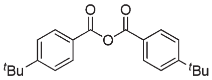
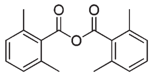
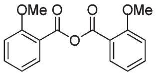
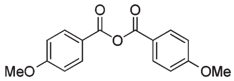
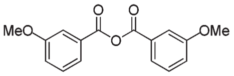
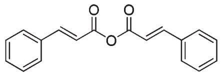
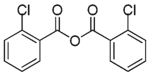
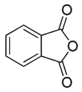
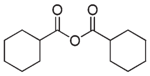
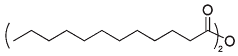
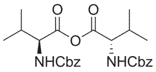
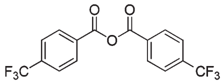
Table 2 Substrate scope



Entry	Product	Yield (%)	Entry	Product	Yield (%)
1		99	2		98
3		97	4		95
5		99	6		96
7		91	8		90
9		92	10		90
11		61	12		99
13		98	14		97
15		<5%	16		<5%

Reactions were performed on a 0.5 mmol scale and were degassed (freeze-pump-thaw). Yields (%) were obtained after aqueous work-up.

In this case, lower conversion could be the result of an acid-mediated decomposition of the anhydride.

With the optimized reaction conditions in hand, a series of electronically diverse carboxylic acids were evaluated (Table 2). Aryl carboxylic acids bearing electron-rich substituents were readily accommodated and provided the corresponding anhydrides in greater than 90% yield (entries 2–9). The use of electron-withdrawing *ortho*-chlorobenzoic acid (entry 11) gave rise to the desired product in lower yield, presumably due to the decreased nucleophilicity of the acid or instability of the product. *trans*-Cinnamic acid provided the anhydride in excellent yield (entry 10). Phthalic acid was also a viable substrate in this reaction, furnishing the intramolecular cyclization product in 99% yield (entry 12). Aliphatic carboxylic acids were also subjected to the reaction conditions and afforded the corresponding products in outstanding yields (entries 13 and 14). However, when α-amino acids or aryl carboxylic acids bearing strongly electron-withdrawing groups were utilized, less than 5% of the anhydrides were obtained (entries 15 and 16).

As proposed for the conversion of alcohols to halides, a mechanistic hypothesis for the anhydride formation involves trapping of the electron-deficient ·CBr_3 by DMF to form the Vilsmeier–Haack reagent **A**. Subsequently, an attack by the carboxylic acid to furnish the iminium intermediate **B**, followed by displacement by another carboxylic acid to provide the anhydride and liberate DMF (Fig. 1).

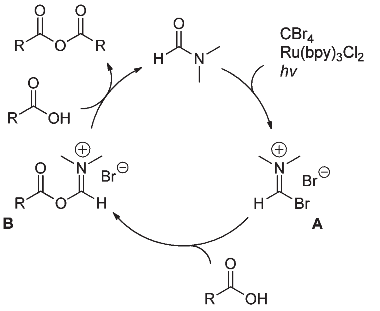


Fig. 1 Proposed mechanism.

To demonstrate the efficiency of the anhydride protocol on a preparative scale, the reaction of 4-*tert*-butylbenzoic acid (2.5 g) was performed with a lower catalyst loading (0.2 mol%). Gratifyingly, no significant loss of efficacy was observed and the desired anhydride was obtained in 85% yield after work-up (Fig. 2A). Additionally, when the reaction of 4-*tert*-butylbenzoic acid was conducted in a flow reactor, the reaction time was significantly shortened, providing the anhydride in 97% yield (Fig. 2B).

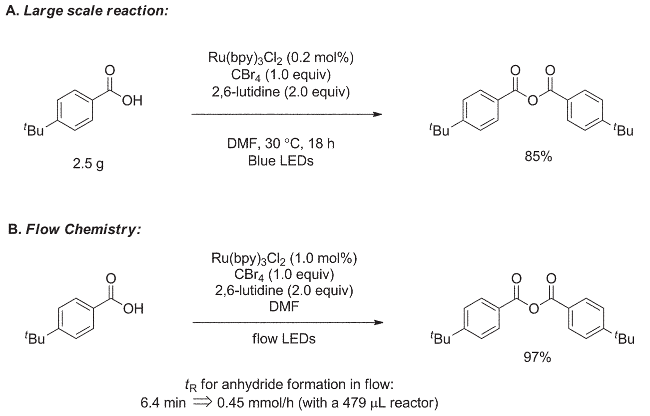


Fig. 2 Scale-up and flow reactions.

In summary, we have demonstrated the application of visible light-mediated photoredox catalysis for the synthesis of symmetric anhydrides. This method is highlighted by the use of mild reaction conditions and isolation of analytically pure products after simple aqueous work-up. Furthermore, the efficacy of the protocol is exemplified by performing scale-up and flow reactions, in which high yields of the anhydrides were obtained. The exploration of different nucleophiles, other than the carboxylates, to give access to a wider range of products is currently underway.

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