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Synthesis, Characterization and Diverse Reactivity of a Hypervalent Iodine-Based Nitrooxylating Reagent

Roxan Calvo,[a] Antoine Le Tellier,[b] Thomas Nauser, [a] David Rombach, [a] Darryl Nater, [a] Dmitry Katayev*[a]

Dedicated to Professor Antonio Togni on the occasion of his 65th birthday.

[a] R. Calvo, Dr. T. Nauser, Dr. D. Rombach, D. Nater, Dr. D. Katayev
Department of Chemistry and Applied Biosciences
Swiss Federal Institute of Technology ETH Zürich
Vladimir-Prelog-Weg 2, 8093 Zürich (Switzerland)
E-mail: katayev@inorg.chem.ethz.ch
[b] A. Le Tellier
Department of Organic Chemistry
University of Geneva
Quai Ernest Ansermet 30, 1211 Geneva 4 (Switzerland)

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Abstract: Herein, the synthesis and characterization of a hypervalent iodine-based reagent that enables a direct and selective nitrooxylation of enolizable C-H bonds to access a broad array of organic nitrate esters is reported. This compound is bench stable, easy-to-handle, and delivers the nitrooxy (-ONO_2) group under mild reaction conditions. Activation of the reagent by Brønsted and Lewis acids was demonstrated in the synthesis of nitrooxylated β-keto esters, 1,3-diketones and malonates, while its activity under photoredox catalysis was shown in the synthesis of nitrooxylated oxindoles. Detailed mechanistic studies including pulse radiolysis, Stern-Volmer quenching studies, and UV-Vis spectroelectrochemistry reveal a unique single electron transfer (SET)-induced concerted mechanistic pathway, not reliant upon generation of the nitrate radical.

Organic nitrates are among the oldest class of compounds employed in the treatment of general coronary heart disease, with the earliest accounts on the use of glyceryl trinitrate as treatment for angina pectoris dating back to 1879.[1] Since then, the activity of organic nitrates as nitric oxide (NO) donors has been well established, and over the past century the diverse biological role of NO as a key signaling molecule involved in a variety of physiological and pathological processes, including vasodilation, platelet aggregation, neurotransmission and immune regulation, has been elucidated.[1] Consequently, a manifold of novel classes of organic nitrates have been developed in recent decades, generally through coupling of known pharmacophores with the nitrooxy (-ONO_2) group. These "hybrid drugs" demonstrate enhanced activity and a reduced number of side effects as non-steroidal anti-inflammatory,[2] anti-diabetic,[3] anti-malarial,[4] anti–glaucoma[5] and anti-Alzheimer's agents,[6] while their application as COX-2 inhibitors in cancer treatments has also been implicated with a reduced risk of drug resistance in tumor cells.[7] In addition, the nitrooxy group can behave as a versatile handle in organic synthesis for the introduction of functionality by nucleophilic displacement, or cleavage of the weak O-NO_2 bond.[8]

Despite the sustained interest in the development of new organic nitrates, synthetic methods to access these compounds remain remarkably underdeveloped. Classical approaches include esterification of alcohols using either mixed acid (HNO_3/H_2SO_4), acetyl nitrate, nitronium tetrafluoroborate[9] or thionyl nitrate,[10] nucleophilic displacement of alkyl (pseudo)halides with various nitrate salts,[8,11] and ring opening of epoxides using mixed acid,[8] Bi(III)nitrate salts,[12] tetranitromethane,[13] ceric ammonium nitrate (CAN),[14] NO gas[15] or dinitrogen pentoxide[16] (Scheme 1a-b). The requirement for prefunctionalized starting materials presents a synthetic limitation in all cases, while further drawbacks include the moisture sensitivity and thermal instability of reagents, the use of strong oxidants, as well as harsh reaction conditions and poor functional group tolerance. Alternative strategies include the oxidative nitration of alkenes using *tert*-butyl nitrite/O_2,[17] CAN in the presence and absence of nucleophilic partners,[18] or Hg(II) salts with halogens,[19] but a drawback to these examples remains the need for hazardous reagents, as well as the formation of product mixtures or dinitrooxylated products. Further methodologies include a CAN-mediated radical alkylation, which although interesting from a mechanistic stand point, presents limited synthetic applicability and scope.[20] More recently, a CAN-mediated benzylic nitrooxylation,[21] and the formal insertion of HNO_3 into aryldiazoacetates[22] have been described.

Evidently, a bench stable reagent that behaves as a convenient source of the NO_3 group and is amenable to direct C-H nitrooxylation of a broad range of substrates under mild conditions, while avoiding the use of prefunctionalized starting materials or strong oxidants, remains synthetically desirable, and essential to facilitate the development of new classes of organic nitrates with unexplored properties. In view of our group's interest in C-H nitration[23] and hypervalent iodine chemistry,[24] we envisaged that the merger of the nitrooxy functional group with a hypervalent iodine scaffold would provide a platform for the development of such a reagent. Hypervalent iodine benziodoxole and benziodoxolone reagents have emerged as powerful tools for oxidative functional group installation, and are generally considered as environmentally benign and widely available

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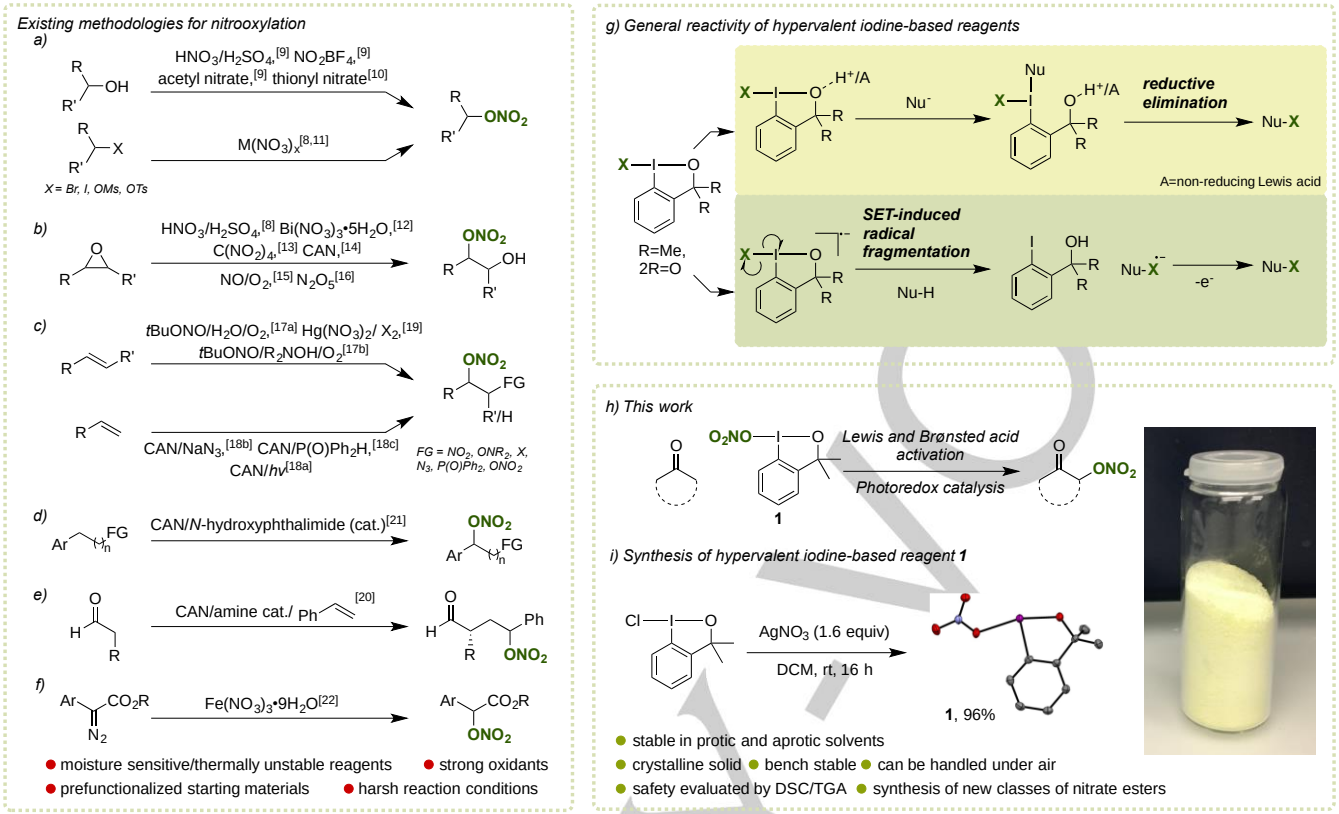

Scheme 1. Existing methods for synthesis of organic nitrates through: [a] esterification of alcohols and nucleophilic displacement of (pseudo)halides; [b] ring opening of epoxides; [c] difunctionalization of alkenes; [d] oxidation at benzylic positions; [e] radical alkylation; [f] formal insertion of HNO_3 into aryldiazoacetates. [g] Generally accepted mechanisms of functional group transfer from benziodoxole and benziodoxolone reagents to nucleophilic substrates. [h] This work; synthesis of new classes of nitrate esters. [i] Synthesis of reagent **1**.

alternatives to traditional transition metal-based reagents.[25] The reactivity of these reagents is dependent upon suitable activation, which has been shown to occur by two distinct pathways; coordination of a Brønsted or Lewis acid to the O atom results in elongation of the I-O bond, facilitating a 2-electron reductive elimination from iodine (Scheme 1g).[26] Alternatively, a SET-induced radical fragmentation involves reduction of the reagent, followed by homolytic cleavage of the I-ligand bond. This latter pathway has been proposed in the presence of single-electron reductants, particular organic substrates, and under photoredox catalysis.[26a] Herein, we demonstrate the reactivity of hypervalent iodine-based reagent **1** towards the synthesis of new classes of organic nitrate esters through both reductive elimination and outer sphere photoredox mechanistic pathways.

We commenced by preparing **1** through a ligand exchange of the readily available chloroiodane with $AgNO_3$, affording the reagent as a crystalline yellow solid in excellent yield (Scheme 1i). Although the synthesis of **1** has been noted in the literature by Kita and co-workers in 1996,[27] it has, to the best of our knowledge, never been exploited in organic synthesis to date. Optimization of the reagent synthesis revealed that chloroiodane reacts smoothly with 1.6 equivalents of $AgNO_3$ to yield **1** in 96% yield, however further attempts to identify suitable cheaper nitrate sources were unsuccessful (see SI). Studies toward the synthesis of the corresponding benziodoxolone reagent unfortunately were also unsuccessful. Single crystal X-ray structure analysis confirmed the "closed-form" benziodoxole structure, which displays a typical distorted T-shaped geometry. Further characterization by differential scanning calorimetry and thermal gravimetric analysis revealed **1** to be stable until 155 °C, whereby exothermal decomposition was observed. In our hands **1** was found to be shock insensitive, and could be stored under ambient conditions for up to one year with no observed decomposition. A reduction potential of –1.03 V versus $Fc^{0/+}$ in MeCN was determined by cyclic voltammetry (see SI). To gain some preliminary insights into suitable activators, ^{1}H NMR analyses of 1:1 mixtures of **1** with various additives were performed. Indeed, a clear downfield shift was observed in the presence of select Brønsted and Lewis acids including TfOH, $Zn(NTf_2)_2$ and AgOTf (see SI). Motivated by these preliminary indications of reactivity, we explored the nitrooxylation of carbonyl compounds and commenced with β-keto esters, which are valuable building blocks in the synthesis of natural products and bioactive compounds.[28] We chose the easily enolizable indanone carboxylate **2f** as a model substrate, and after screening reaction conditions (see SI) were pleased to observe that the reaction with **1** proceeds readily at room temperature in the absence of catalyst or exogenous base, delivering the desired product in excellent yield (Scheme 2). Incorporation of the nitrooxy group at the α-position was unambiguously confirmed through single crystal X-ray structure analysis of **3f**. Under these conditions, a broad range of previously unreported indanone-derived β-keto esters could be nitrooxylated under exceedingly mild conditions and in good to excellent yields. In addition to the *t*-butyl ester (**3a**), the reaction

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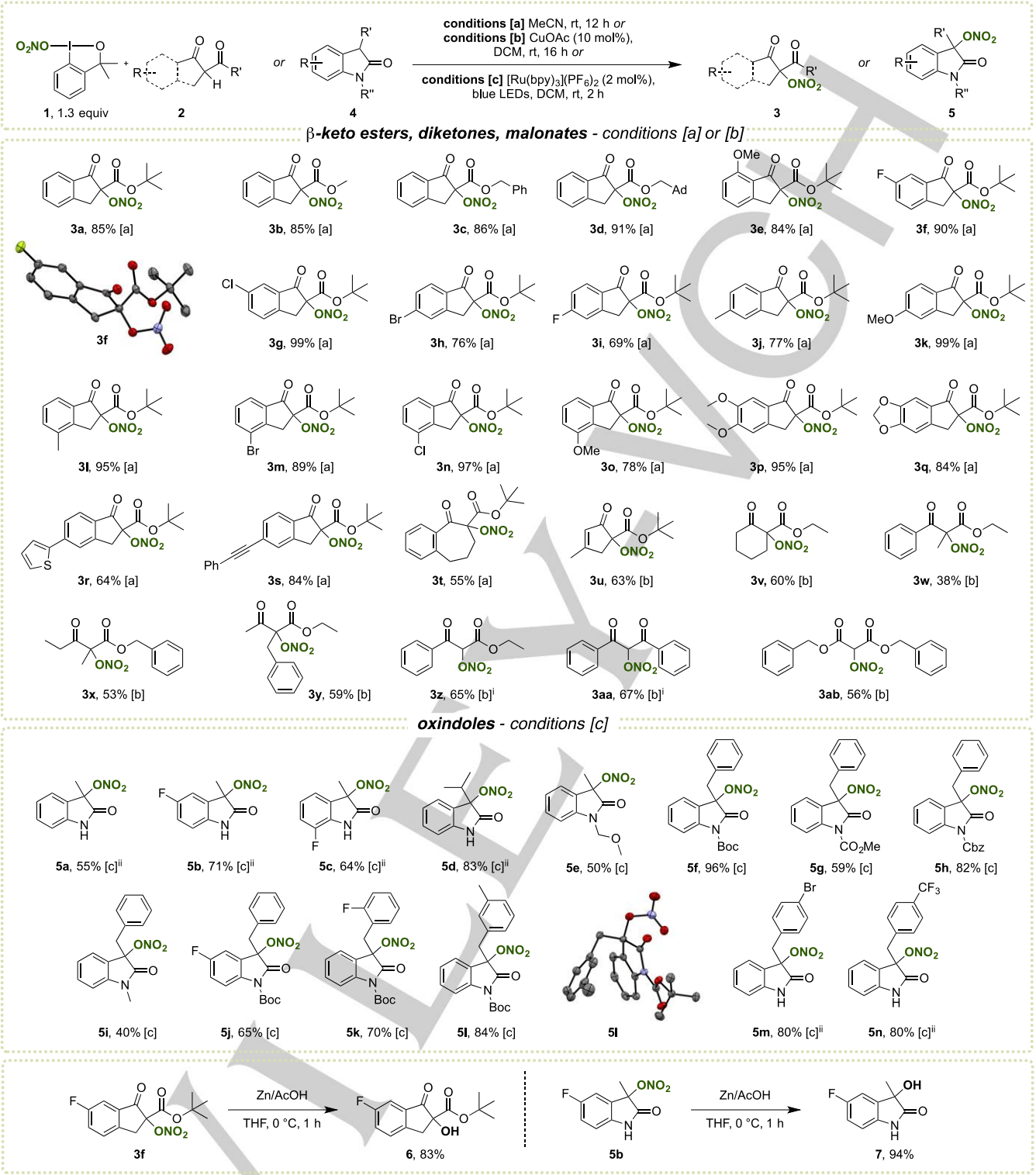

Scheme 2. Substrate scope for nitrooxylation of carbonyl compounds using **1**. [i] 3 equivalents of substrate employed. [ii] Treatment of crude reaction mixture with TFA, 0 °C, 1 h. Isolated yields reported.

proceeded smoothly in the presence of methyl (**3b**), benzyl (**3c**) and methyl adamantyl esters (**3d**), with no decrease in yield. Various deactivating and activating substituents were tolerated at the C4 (**3l**-**o**), C5 (**3h**-**k**), C6 (**3g**) and C7 (**3e**) positions, and we were pleased to observe that the reaction also proceeded in good yield in the presence of thiophene (**3r**) and phenylacetylene (**3s**) substituents. Interestingly, the reaction with a 6-membered tetralone-derived β-keto ester resulted in formation of the 1-hydroxy-3-nitro-napthoate derivative, presumably following reduction of the reagent by the substrate (see SI). Fortunately, the reaction with a 7-membered fused ring system provided the desired product **3t** in acceptable yield. However, upon attempting

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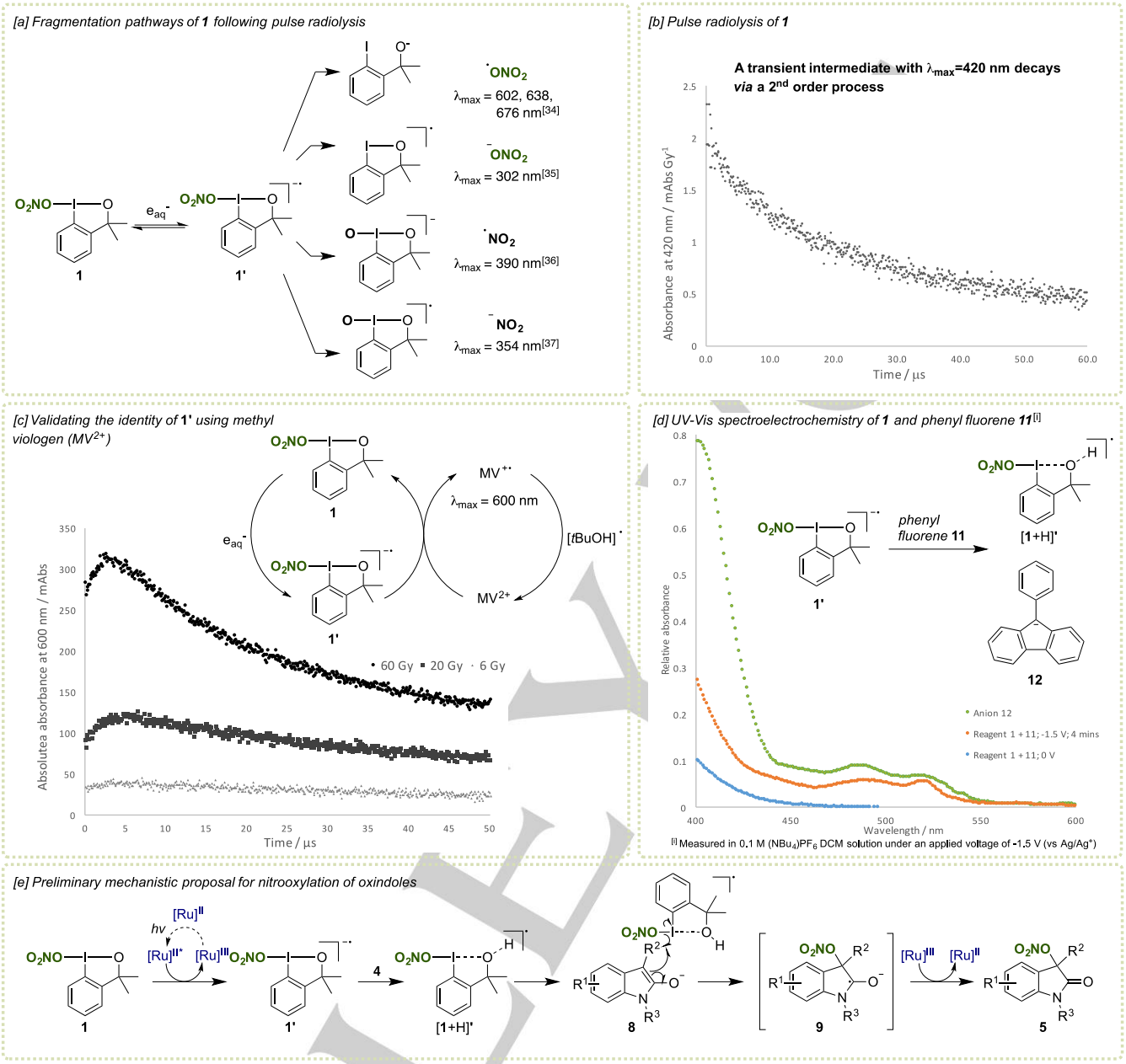

Scheme 3. Mechanistic proposal for synthesis of nitrooxylated oxindoles **5**.

the nitrooxylation of acyclic β-keto ester **2w** of lower acidity, no reaction was observed. After screening various Lewis acids (see SI), it was found that the reaction proceeds in acceptable yield in the presence of 10 mol% CuOAc in DCM. Under these conditions, β-keto esters **2w-y** were successfully nitrooxylated, as well as ester derivatives of cyclopentenone (**2u**) and cyclohexanone (**2v**). In addition, these reaction conditions also proved amenable to the mono-nitrooxylation of unsubstituted β-keto ester **2z.** We were pleased to observe that the protocol could further be extended to the nitrooxylation of 1,3-diketones (**3aa**), as well as malonates (**3ab**), whereby the mono-substituted products were obtained in acceptable yields.

In order to elucidate mechanistic details, nitrooxylation of **2f** in the presence of various additives was conducted (see SI). A lack of inhibition in the presence of radical scavengers styrene, 1,4-dinitrobenzene, *p*-benzoquinone and allyl benzyl ether was observed, while the complete suppression of reactivity after addition of various bases including K_2CO_3, DIPEA and DBU suggests that protonation of **1** may be critical to its activity. The reaction was furthermore found to exhibit a first order dependence on substrate **2f** and reagent **1** under pseudo-order conditions (see SI). From these findings, a preliminary mechanistic proposal involving protonation of the reagent by a substrate molecule, followed by reductive elimination from the iodine center is plausible (Scheme 1g). However, an S_N2 pathway cannot completely be excluded at this stage, nor can a “metathesis” type reaction occurring through concomitant protonation of **1** and I–C bond formation through a 4-membered TS.[26d, 29] While in the Lewis acid catalyzed nitrooxylation of acylic β-keto esters, chelation of Cu to the dicarbonyl moiety could facilitate

protonation of **1**, a dual activation by Cu involving coordination to both substrate and reagent is also plausible.

Encouraged by our results with β-keto esters, we turned towards the nitrooxylation of oxindoles which form the core of a large number of natural products and bioactive compounds, many of which have been studied as potential therapeutic agents.[30] Using *N*-boc-protected **4b** as a model substrate, various reaction conditions and Lewis and Brønsted acids were screened, but did not lead to formation of the desired product. Motivated by voltammetric measurements, we speculated that in the presence of a photocatalyst operating under oxidative quenching conditions, **1** should undergo a reductive single electron transfer to afford the radical anion **1'** (Scheme 3a), which in turn should fragment to the NO_3 radical. Indeed, we were pleased to observe formation of the desired product upon irradiation of a solution of **1**, **4b** and a catalytic amount of $[Ru(bpy)_3](PF_6)_2$ in DCM with high intensity blue LEDs (see SI for optimization of reaction conditions). To our surprise, no exogenous base was required. While almost complete conversion to the *N*-Boc protected nitrooxylated product was observed by NMR spectroscopy, partial *N*-deprotection occurred during purification on silica gel. The free amine **5b** was instead isolated following treatment of the intermediate with TFA (Scheme 2). Substitution of the methyl group at the C3 position for a more sterically demanding isopropyl group was well tolerated (**5d**), and the reaction also proved amenable to the dimethyl ether (**5e**) *N*-protecting group. Upon introduction of a benzyl group at the C3 position the *N*-protected products could be isolated in most cases, with **5f** isolated in excellent yield. The acetoxy (**5g**) and Cbz (**5h**) *N*-protecting groups were well tolerated, while introduction of a *N*-methyl group (**5i**) resulted in a slightly lower yield. The reaction tolerated activating and deactivating substituents at various positions on both the oxindole core (**5b**-**c**, **j**) and the benzyl group (**5k**-**n**). To demonstrate the synthetic utility of the nitrooxy group as a tentative protecting group, **3f** and **5b** were reduced to the corresponding alcohols using zinc in acetic acid (Scheme 2, bottom).

To acquire a preliminary mechanistic understanding, control experiments were performed which validated the requirement of both photocatalyst and light, and Stern-Volmer analysis confirmed quenching of the excited state $[Ru(bpy)_3]^{2+*}$ by **1** (see SI). Curious about the identity of the radical intermediates involved in the transformation, we turned to pulse radiolysis, which is a powerful tool for probing the nature and studying the kinetics of highly oxidizing and reducing species and radicals.[31] This technique involves exposure of water to a single pulse of ionizing radiation, resulting in formation of $OH^{\bullet}$, $H^{\bullet}$, H^+ and the solvated electron e_{aq}^- in linear dose dependent concentrations. These species in turn react with a sample of interest to generate transient reactive intermediates, which can be observed by fast time-resolved spectroscopic measurements. As such, pulse radiolysis provides a means of characterizing reactive intermediates, and can further be used to predict reactivity.[32] Motivated by a recent study determining the rate of single electron reduction of the analogous hypervalent iodine-based CF_3 reagent by pulse radiolysis,[33] we were interested in using this technique to observe the fragmentation products following single electron reduction of **1**. Alternative fragmentation pathways and the corresponding absorption maxima are presented in Scheme 3a. Argon saturated sample solutions were prepared in MilliQ water containing 10 vol% *t*-BuOH, which was used to scavenge oxidizing $OH^{\bullet}$ radicals. Following the irradiation of a 1 mM solution of **1** with a 60 Gy dose, the build-up of a transient species with an absorbance maximum at 420 nm was observed, which subsequently decayed by a second-order process (Scheme 3b). These findings indicate that homolytic fragmentation of **1'** is highly improbable, and the observed decay of **1'** is likely due to oxidation by *t*-BuOH radicals present in a comparable concentration. To validate the identity of the reducing radical **1'** as the absorbing species at 420 nm,[38] the measurement was repeated in the presence of 40 μM methyl viologen (MV^{2+}), which is a probe for single electron reductants. MV^{2+} should be readily reduced by **1'** to produce the radical cation $MV^{+\bullet}$ with a known λ_{max} of 600 nm (Scheme 3c).[39] Indeed, a strong absorption at 600 nm was observed, and the gradual build-up in absorption over 6 μs after initial irradiation confirms that $MV^{+\bullet}$ is formed exclusively through a reaction with **1'** and not through direct reaction with e_{aq}^-.[40]

Nevertheless, we remained curious about the deprotonation of oxindole substrates, as their relatively high p*K*a values[41] make deprotonation by **1** improbable in the absence of additional, non-specific interactions. We turned to UV-Vis absorption spectroscopy to determine whether such interactions between **4b** and **1** exist in solution, however, a titration of **4b** with **1** did not result in observation of a new species, and a mixture of both species matched the linear combination of their individual signatures (see SI). We speculated that the p*K*a of radical anion **1'** may be sufficiently high to deprotonate the oxindole substrates, and we sought to observe this deprotonation using UV-Vis spectroelectrochemistry (Scheme 3d). As the enolate of **4b** was not expected to exhibit a characteristic UV-Vis signature, phenyl fluorene **11** was instead used as an indicator (p*K*a of 17.9 in DMSO).[42] Indeed, subjecting a mixture of **11** and reagent **1** to an applied voltage of -1.5 V *vs*. $Ag^{0/+}$ resulted in irreversible reduction of **1**, and observation of the UV-Vis absorption signature corresponding to anion **12** (Scheme 3d). In correspondence with pulse radiolysis, the UV-Vis signature of the reduced **1'** species was found to have an absorption maximum at 420 nm. A preliminary mechanism for the synthesis of nitrooxylated oxindoles **5** is proposed in Scheme 3e; oxidative quenching of $[Ru(bpy)_3]^{2+*}$ by **1** results in formation of radical anion **1'**, which deprotonates the oxindole substrate to form [**1**+H]'. This in turn reacts with enolate **8** in a concerted fashion. Subsequent oxidation of **9** completes the catalytic cycle. Although the reactive intermediates involved in the transformation have been probed, the intimate mechanism of addition of the nitrooxy group to **8** remains speculative. At this stage, a reaction sequence involving radical addition of [**1**+H]**'** to enolate **8**, followed by single-electron oxidation and reductive elimination from iodine, as proposed in Zhu's decarboxylative trifluoromethylation of α- β-unsaturated carboxylic acids, cannot totally be excluded.[43] Nevertheless, this work not only constitutes the first examples of a nitrooxylation under photoredox catalysis, but is one of the exceedingly rare examples whereby reduction of such hypervalent iodine-based reagents does not result in fragmentation and liberation of a free radical.

In conclusion we have described the development of a hypervalent iodine-based reagent **1** and its application as a mild and convenient source of the nitrooxy functional group through the synthesis of new classes of organic nitrate esters with unexplored properties. The reagent was furthermore revealed to act as an internal base during the reactions, while transfer of the nitrooxy group through two distinct pathways, namely reductive

elimination and an outer sphere photoredox mechanism, was also demonstrated. We anticipate that the mechanistic insights in combination with physical properties of **1** elucidated herein will guide future reaction development towards a more facile introduction of the NO_3 group onto various organic scaffolds, thereby facilitating further investigations into the biological effects imparted by this unique functional group.

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Keywords: nitrate esters • photoredox catalysis • hypervalent iodine • pulse radiolysis • spectroelectrochemistry

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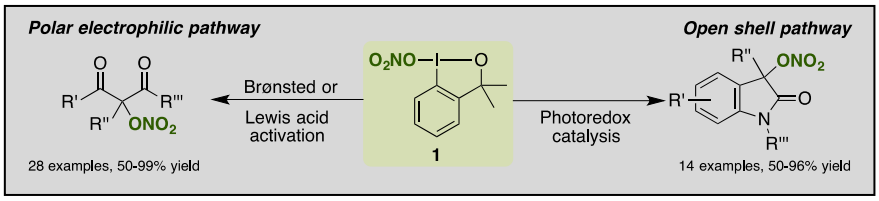

A hypervalent iodine-based nitrooxylating reagent behaves as a convenient source of the ONO_2 group for the synthesis of new classes of organic nitrate esters. Its versatile reactivity under various forms of catalysis is demonstrated in the selective and direct functionalization of enolizable C-H bonds *via* polar electrophilic and open shell pathways, enabling the synthesis of nitrooxylated β-keto esters, 1,3-diketones, malonates and oxindoles under mild conditions.