Visible Light-Enhanced C–H Amination of Cyclic Ethers with Iminoiodinanes

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Manuscript received: October 6, 2022; Revised manuscript received: October 31, 2022; Version of record online: November 23, 2022

Supporting information for this article is available on the WWW under https://doi.org/10.1002/adsc.202201095

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Abstract: A two-step protocol allowing the C–H amination of cyclic ethers with iminoiodinanes, followed by the reduction of the resulting intermediates has been developed for the preparation of amino alcohols. The initial C–H functionalization is accelerated by visible light, improving the reactivity compared to the thermal process performed in the dark. The effect of different substituents on the photochemical reactivity of iminoiodinanes has been studied both experimentally and computationally. Photophysical measurements and DFT calculations were performed to better understand the observed reactivities and corroborate the proposed mechanistic proposal.

Keywords: Iminoiodinanes; Cyclic Ethers; C–H functionalization; Amino Alcohols; Visible Light; Photochemistry

C–H functionalization strategies have evolved over the past decades into an important research area driven by the ubiquity of C–H bonds in organic molecules and the power of such approaches to streamline the preparation of sophisticated synthetic targets with good selectivity and efficiency.

Among these strategies, C–H aminations are particularly important,1–3 as they give access to high-value chemicals from readily available hydrocarbons. Historically, metal-catalyzed nitrene transfer approaches were the typical choices for such chemical transformations. Remarkable examples involve the Rh-catalyzed preparation of unadorned aziridines from olefins by Ess, Kürti, Falck and co-workers;2a the C–H amination of different arenes, as reported by Falck and co-workers;2b and the C–H amination of numerous complex natural products, as reported by Du Bois and co-workers;2c among many others, including also the use of other metal catalysts2d–f or metal-free conditions.5

In the past decade, the promotion of chemical reactions by visible light irradiation has been established as a powerful technique. Because most organic molecules do not absorb in the visible region, photocatalysts are generally required for initiating electron4 or energy transfer events,5 which can trigger radical reactions. In contrast to these reaction manifolds, it has been recently reported that some diazo compounds can absorb in the visible region, thus undergoing photolysis to generate free nitrenes.6 Remarkably, in this same context, iminoiodinanes were also reported to absorb in or close to the visible light region and undergo photolysis to generate highly reactive free nitrene intermediates.7 Indeed, Takemoto and co-workers have shown that such ortho-stabilized hypervalent iodine compounds can be irradiated under low-energy UV light (black light, 370 nm) to promote the aziridination of olefins (Scheme 1a)7a and the α-amination of silyl enol ethers (Scheme 1b).7b Könenigs and co-workers demonstrated that iminoiodinanes can...
be irradiated by blue light (470 nm) to enhance the generation of free nitrene intermediates, which were successfully trapped with olefins to afford aziridines (Scheme 1c), or with sulfides to generate sulfilimines (Scheme 1d).

Building on our own work in visible light-mediated transformations, we became interested in developing visible light-mediated C–H amination reactions using iminoiodinanes 1. In this context, we started our investigations by studying the reaction between iminoiodinane PhINTs 1a and THF 2a under blue light irradiation, aiming at synthesizing the corresponding N,O-acetal 3a as our model reaction.

The desired compound 3a was successfully observed in the $^1$H NMR of the crude reaction mixture, but our attempts to isolate it failed. This compound proved to be unstable, leading to the elimination of TsNH$_2$ under different purification conditions. Consequently, we decided to reduce it in situ using NaBH$_4$ to afford the corresponding amino alcohol 4a (Table 1). When the reaction was performed using THF 2a as the solvent under blue light irradiation (blue LEDs, 455 nm) at room temperature, we observed the rapid consumption of the iminoiodinane 1a to afford the N,O-acetal 3a in only 20 min, which upon subsequent addition of NaBH$_4$ and MeOH led to the formation of amino alcohol 4a in overall 71% yield (Entry 1, Table 1). Then, we became interested on the possibility of observing a positive effect on the reaction yield of 4a due to simultaneous blue light irradiation and heating (60°C) during the first step. However, we only observed a slightly reduced yield of 4a of 60% (Entry 2, Table 1). Attempts to promote the reaction in the presence of a photoredox catalyst, such as Ru(bpy)$_3$Cl$_2$ in different loadings (Entries 3 and 4, Table 1) or 4CzIPN (Entry 5, Table 1) did not afford improved yields for the amino alcohol 4a. The control experiment of this model reaction under air and ambient light, at 20°C revealed that this reaction could be also performed with the same high efficiency as previously found under blue light irradiation, (i.e. producing 4a in 71%), but the reaction required a longer reaction time for completion, 1 h (Entry 6, Table 1). When the reaction is only thermally promoted (heating at 60°C), a 60% yield for 4a is again obtained (Entry 7, Table 1).

Based on these optimization studies, we noted the beneficial effect of the blue light irradiation, which

### Table 1. Optimization studies for the C–H amination of THF 2a using iminoiodinane 1a under blue light irradiation.

<table>
<thead>
<tr>
<th>Entry</th>
<th>deviation from optimal conditions</th>
<th>yield (%)$^{[a]}$ 4a</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>none</td>
<td>71/70$^{[b]}$</td>
</tr>
<tr>
<td>2</td>
<td>60°C</td>
<td>60</td>
</tr>
<tr>
<td>3</td>
<td>Ru(bpy)$_3$Cl$_2$ (1 mol%), 4 h</td>
<td>70</td>
</tr>
<tr>
<td>4</td>
<td>Ru(bpy)$_3$Cl$_2$ (3 mol%), 4 h</td>
<td>70</td>
</tr>
<tr>
<td>5</td>
<td>4-CzIPN (1 mol%), 4 h</td>
<td>67</td>
</tr>
<tr>
<td>6</td>
<td>ambient light, under air, 20°C, 1 h</td>
<td>71</td>
</tr>
<tr>
<td>7</td>
<td>ambient light, under air, 60°C, 1 h</td>
<td>60</td>
</tr>
</tbody>
</table>

$^{[a]}$ Estimated by $^1$H NMR of the crude reaction mixture using 1,3,5-trimethoxybenzene as internal reference.  
$^{[b]}$ Isolated yield.

Scheme 1. Representative low-energy light-mediated nitrene transfer reactions using iminoiodinanes. (CG: coordinating group, PG: protecting group)
accelerated the first step of our reaction sequence, even if the final yield of the photochemical sequence was found to be the same as the one from the thermal, dark reaction.

At this moment, we hypothesized that no significant alteration in reaction efficiency (i.e., chemical yield) was noted because THF 2a was employed as solvent. However, more important differences in reaction performance could possibly emerge if more valuable cyclic ethers were to be reacted in lower relative amounts with different iminoiodinanes 1.

With this in mind, we moved forward to evaluate the substrate scope of this transformation under blue light irradiation, while comparing the observed performance with the same reactions under the thermal condition. For this study, the first photochemical (or thermal) step was allowed to run overnight (typically 12 h) for convenience and to ensure full conversion, regardless of the substitution pattern of the reacting partners. Indeed, no negative effects on the obtained yields for the target compounds 4 were noted when comparing longer reaction times with shorter reaction durations showing full conversion (Scheme 2).

Initial investigations using THF 2a as solvent and different iminoiodinanes PhINSO4Ar 1 as limiting reagent showed a good general reactivity in most cases, allowing the preparation of amino alcohols 4b (46%), 4c (50%), 4d (70%) and 4e (71%) in synthetically useful yields. Among these examples, only 4e could be also prepared with the same efficiency under thermal conditions, 71%. All other amino alcohols 4b, 4c and 4d exhibited significantly lower conversions under ambient light and under air, 30%, 27% and 12%, respectively. In this context, 4d could be also photochemically accessed in a preparative 1 mmol-scale in a slightly lower 58% yield (see the SI for details). On the other hand, amino alcohol 4f could not be prepared, presumably due to the very poor solubility of the required iminoiodinane 1f (Scheme 2). Furthermore, the reaction of 2-methyltetrahydrofuran 2b used as solvent with PhINTs 1a afforded a 1:2 mixture of regioisomers 4g:4g' in a combined 66% yield, which was the same outcome produced when the reaction was performed under thermal condition (Scheme 2).

The ring-opening of other common cyclic ethers, such as 1,4-dioxane 2c or tetrahydropyran (THP) 2d, both employed as solvents, was more efficient when light irradiation was performed simultaneously with heating to 60°C, thus affording the corresponding products, 4h and 4i, in 23% and 46% isolated yields, respectively. Notably, again, no changes in reaction performance were observed when these transformations were conducted in the presence of photoredox catalysts Ru(bpy)3Cl2 and 4-CzIPN; and both products could not be accessed in any extension when the reactions were performed under thermal conditions (Scheme 2). Finally, investigations under photochemical conditions aiming at the ring-opening of phthalan 2j, xanthene 2k and (−)-ambroxide 2l as limiting reagents, in the presence of an excess of iminoiodinane PhINTs 1a (3 equiv.) allowed synthetically useful yields for the corresponding products 4j (62%), 4k (72%) and 4l (34%)[13] respectively; while significantly lower yields were obtained for the same reactions performed under thermal conditions (Scheme 2). Remarkably, during our attempts to synthesize 4k, we observed the possibility of accessing imine derivative 4k' as the major compound derived from the first step of this reaction sequence, albeit it could be isolated only in a modest yield of 34% (Scheme 2). In this case, this finding suggests that 4k' is the intermediate that is reduced by NaBH4 to afford 4k.

Additionally, attempts aiming at the C–H amination of more functionalized cyclic ethers or containing less reactive α-C–H bonds (i.e., more hindered, more geometrically constrained or not benzylic) were unsuccessful (Figure 1).

Based on the observed reactivity of the previously investigated iminoiodinanes 1a–1e, we became interested in evaluating their photophysical properties and measured UV-Vis absorbance spectra (Figure 2).

Although all iminoiodinanes were initially poorly soluble in DCM or THF (thus typically producing suspensions at 0.05 M concentrations); when the transformations progressed, all productive reaction mixtures became homogeneous, thus showcasing the full chemical utility of these reagents.

![Figure 1](https://asc.wiley-vch.de)

**Figure 1.** Cyclic ethers that were not successfully C–H aminated under our photochemical conditions.

![Figure 2](https://asc.wiley-vch.de)

**Figure 2.** UV-Vis absorbance spectra of iminoiodinanes 1a–1e, 0.001 M in DCM.
Scheme 2. Substrate scope evaluated for the C–H amination/reduction sequence using different reaction conditions. Reactions were performed at 0.1 mmol-scale of the limiting reagent. **Condition A:** Under N\textsubscript{2}, photoirradiated at 455 nm (blue light). **Condition B:** Under air and ambient light, thermally promoted. (In this case, the reaction is not irradiated under blue light). *Estimated yield based on 1H NMR of the crude reaction mixture using 1,3,5-trimethoxybenzene as internal standard. *Isolated yield.\n
**Condition A:**

- A, no additive, 20 °C: 46%\textsuperscript{b}/ 50%\textsuperscript{a}
- A, no additive, 60 °C: 46%\textsuperscript{b}/ 50%\textsuperscript{a}
- A, Ru(bpy)\textsubscript{3}Cl\textsubscript{2} (1 mol%), 20 °C: 15%\textsuperscript{a}
- A, 4-CzIPN (1 mol%), 20 °C: 15%\textsuperscript{a}
- B, 20 °C: 0%\textsuperscript{a}
- B, 60 °C: 0%\textsuperscript{a}

**Condition B:**

- A, no additive, 20 °C: 66%\textsuperscript{b}/ 70%\textsuperscript{a} combined, 1:2
- B, 20 °C: 66%\textsuperscript{b}/ 70%\textsuperscript{a} combined, 1:2
sumption of the starting iminoiodinane. In order to prepare homogeneous solutions upon immediate mixing within DCM for the appropriate UV-Vis measurements, diluted mixtures (0.001 M) were prepared. All iminoiodinanes were soluble in DCM in this concentration, except for 1b (i.e., 1a, 1c–1e). Among these substrates, iminoiodinane 1d showed the strongest bathochromic shift (Figure 2).

Remarkably, in agreement with this observation, iminoiodinane 1d exhibited the greatest difference in reaction efficiency between the photochemical and the thermal C–H amination reactions leading to amino alcohol 4d.

Additional investigation of the reaction mechanism involving the blue light irradiation of iminoiodinane 1a within a 1:1 mixture of THF:d8-THF afforded a 4:1 mixture of 4a:d7–4a in 66% combined yield, thus revealing a rough estimation of a KIE ≈ 4 (Scheme 3).

This outcome indicates that the C–H breaking event is the rate-determining step (rds) of this transformation.

Then, we became interested in investigating the reactivity of the iminoiodinane 1a using spectroscopic techniques (see also the SI for additional details). We initially focused our attention on the analysis of UV-Vis spectra of 1a in DCM as a function of its concentration. From this data, we calculated the molar extinction coefficient as a function of wavelength (Figure 3, black curve). Overall, from the concentration-dependent absorption spectra, the experimental values of the molar extinction coefficient at 350 nm and 450 nm were in good agreement with the quantum chemical calculations for iminoiodinanes 1a–1e (see DFT calculations below). In particular, the weak absorption at 450 nm is consistent with a S0→T1 transition and spin-orbit coupling (SOC), which is enhanced by the presence of a heavy-atom (iodine) in the molecular structure of iminoiodinanes.[14,15] Then, we measured the emission spectra (λexc = 440 nm) of 1a in the solid state at T = 294 K and 11 K (Figure 3, blue and green curves, respectively). At 294 K, an emission band with broad, structureless and low intensity is centred at 546 nm; whereas at 11 K, an emission band is centred at 633 nm. Furthermore, the measured time-resolved emission decays were approximately 20 ns at 546 nm, at T = 294 K; and 60 μs at 633 nm, at T = 11 K (See also Figures S3 and S4 in the SI). Thus, we tentatively assign these two emission bands to the decays from the singlet S1 and triplet T1 states, respectively.[16]

To characterize the effect of the irradiation (using a laser with a similar wavelength of 440 nm) of 1a in DCM and THF, we measured emission spectra as a function of time over the course of the reaction (approximately for 40 minutes). Figure 4 shows the area-normalized emission spectra as a function of irradiation time. The arrows indicate increasing emission intensity around 503 nm, concomitant with decreasing intensity around 550 nm, and an isosbestic point around 520 nm that is indicative of interconversion between singlet and triplet nitrenes (see Figures S6 and S7 in the SI for a correlation analysis of the data shown in Figure 4). The opposite trend is observed upon irradiation of 1a in THF, that is, decreasing emission intensity at 503 nm and increasing intensity in the shoulder near 550 nm. We also note that the emission signal registered at 503 nm is coupled to a vibrational transition at 2890 cm−1, which can be presumably assigned to a C–H stretching transition. The lifetime of the nitrene species (major form as

![Scheme 3. Investigation of reaction mechanism, KIE.](image)

**Figure 3.** Steady-state electronic spectroscopy. Molar extinction coefficient (black curve) as a function of wavelength for iminoiodinane 1a in DCM ([1a] = 1 mmol·L⁻¹) at T = 294 K. Emission of 1a in the solid state at T = 294 K (blue curve) and T = 11 K (green curve). λexc = 450 nm.

![Figure 4.](image)

**Figure 4.** Time-resolved, area-normalized emission spectra of 1a upon irradiation, a) in DCM and b) in THF. In both cases, λexc = 440 nm and [1a] = 1 mmol·L⁻¹.
singlet) in THF, observed at 500 nm, can be estimated to be ca. 5 ns (Figure S5).

The difference in behaviour observed in these two solvents can be roughly and tentatively attributed to differences in kinetics between the events associated to the interconversion between singlet and triplet nitrenes. At this point, we performed computational analyses to optimize the structures of the substituted iminoiodiinanes 1a–1e, and to compare the effect of the substituents on the UV-Vis spectra and on the structure of the triplet states (See SI for details). Natural transition orbital analysis was used to better represent the nature of the first electronic transition. In all cases, the transition primarily involves the excitation from a lone pair on the nitrogen to the N–I σ* orbital, making this an n-σ* excitation, in accordance with the previous report from Koenigs and co-workers.[5] The oscillator strengths (f) are compatible with a non-allowed electronic transition (Table 2). The substituents on the iminoiodinanes 1a–1e minimally affect the energy of the transition, with the larger effect attributable to the 2-NO₂ group in 1c. As observed experimentally, more electron-donating groups shift the first electronic transition bathochromically (Table 2). In addition, more electron-donating groups display longer N–I bond lengths and lower Mulliken spin densities on the iodine, with the notable exception of Br in 1b, that in the triplet state shows a geometry and spin distribution similar to the tosyl derivative 1a (Table 2).

The limited effect of the substituents can be attributed to the fact that the orbitals involved in the excitation are not directly conjugated with the aromatic ring. Nevertheless, in the natural transition orbitals (NTO), it is possible to appreciate the contribution of the substituents, which possibly lower (electron-withdrawing groups) or raise (electron donating) the energy of the n filled orbital, varying as a consequence the S₀–S₁ energy gap (Figure 5a). Interestingly, similar effects can be seen in the structure of the triplet states (optimized at the rSCAN-3c level), where the N–I elongates, forming iodobenzene interacting with the triplet nitrene (Figure 5b).

Based on the experimental evidence collected, our mechanistic proposal for this reaction sequence leading to amino alcohols 4 starts with the blue light-accelerated extrusion of Ph from iminoiodiane 1 to afford a nitrene intermediate 5. Irradiation of 1 may either lead to a singlet nitrene (5¹, via S₀→S₁) or a triplet nitrene (5³, via S₀→T₁). This second hypothesis was confirmed by computing the SOC corrected absorption spectra of the compounds using zero-order regular approximation (ZORA)[17] and its required basis set (see SI): in all cases, the direct excitation S₀→T₁ has oscillator strengths in the same order of magnitude as S₀→S₁, albeit slightly lower in intensity (see Table S1). Moreover, both species can possibly interconvert via inter-system-crossing (ISC, S₁→T₁) and via reverse intersystem-crossing (RISC, possibly T₁→S₀).[18] The SOC values for the S₁→T₁ conversion at the ground state geometry are: 4-NO₂, 1f (23 cm⁻¹) > 2,2'-F₂, 1e (22.7 cm⁻¹) > 4-Br, 1b (18 cm⁻¹) > 4-Me, 1a (15 cm⁻¹) > 4-MeO, 1d (14 cm⁻¹).

Singlet nitrenes 5¹ can presumably undergo direct C–H insertion to provide the N,O-acetal intermediate 3, while triplet nitrenes 5³ can undergo hydrogen atom transfer (HAT) with the cyclic ether 2, followed by radical combination to afford the corresponding N,O-acetal 3. Upon addition of NaBH₄, this intermediate is reduced to the observed amino alcohol 4 (Scheme 4).

In summary, we have studied a blue light-enhanced C–H amination strategy of cyclic ethers employing iminoiodinanes, followed by a NaBH₄-reduction event leading to the corresponding amino alcohols. Yields in the range 23–72% were obtained for activated cyclic ethers reacting with different iminoiodinanes, while other cyclic ethers showed to be less reactive. Key elements of the reaction mechanism were proposed based on experimental evidence, spectroscopic analyses and DFT calculations. Of note, we showed that the

Table 2. Simulated properties of the S₀→S₁ transition and of the excited triplet states of different iminoiodinanes 1a–1e at the CPCM(DCM)-TD-M06-2X-D3/def2-TZVPD/rSCAN-3c level.

<table>
<thead>
<tr>
<th></th>
<th>Ground state (S₀)</th>
<th>Triplet state (T₁)</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>λ (nm)</td>
<td>f</td>
</tr>
<tr>
<td>1a</td>
<td>4-Me</td>
<td>362.1</td>
</tr>
<tr>
<td>1b</td>
<td>4-Br</td>
<td>369.9</td>
</tr>
<tr>
<td>1c</td>
<td>2-NO₂</td>
<td>279.4</td>
</tr>
<tr>
<td>1d</td>
<td>4-MeO</td>
<td>365.3</td>
</tr>
<tr>
<td>1e</td>
<td>2,2'-F₂</td>
<td>369.0</td>
</tr>
</tbody>
</table>

Figure 5. a) Natural transition orbitals (NTO) associated with the predominant component found in the first singlet electronic transition of (4-MeO)C₆H₄SO₂NIpH. b) Structures of (2-NO₂)C₆H₄SO₂NIpH and (4-MeO)C₆H₄SO₂NIpH in their triplet states.
General Experimental Procedure for the Preparation of Amino Alcohols 4 Using the Cyclic Ether 2 as Limiting Reagent

Under air, at rt, a 5-mL crimp cap vial containing a stirring bar is charged with the cyclic ether 2 (1 equiv.), DCM (2 mL) and the iminoiodinane 1 (3 equiv.). Then, the vial is closed, and the reaction mixture is degassed via freeze-pump-thaw (3x), being back-filled with N₂ and irradiated under blue light (455 nm) overnight, while the temperature is controlled at 20°C using a thermostatic bath. Then, the reaction vial is opened to air, NaBH₄ (2 equiv.) and MeOH (1 mL) are sequentially added, and the reaction mixture is allowed to stir under air at rt for additional 2 h. Then, water is added, and the resulting mixture is extracted with AcOEt (3x). The combined organic phases are dried (MgSO₄), filtered and concentrated under reduced pressure. The resulting residue is purified by flash column chromatography to afford the corresponding amino alcohol 4 in the stated yield.

Acknowledgements

IDJ greatly acknowledges a Visiting Scholar Fellowship from CAPES (88881.312988/2020-01) – Alexander von Humboldt Foundation (1144417-BRA-HFSTCAPES-E). Fapesp is also greatly acknowledged for Regular Research Grants to IDJ (2019/01235-8), RAN (2020/10541-2) and TDZA (2009/14135-8). SC thanks the Swedish Vetenskapsrådet for a Starting Grant (2021-05414). The project was partially funded by the Deutsche Forschungsgemeinschaft (DFG, German Research Foundation) TRR 325 444632635. The authors thank Sérgio Coelho and Milene Martins (both from Unicamp, Brazil) for the measurements shown in Figures 3 and S3.

References


CCDC 2206335 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/structures.


The involvement of singlet and triplet nitrenes derived from Ar′INAr2 has been previously discussed based on DFT calculations. See: B. A. Shainy, A. V. Kuzmin, *J. Phys. Org. Chem.* 2014, 27, 156–162.

The observed lifetimes for singlet and triplet nitrenes are in good agreement in terms of magnitude with previously reported values. See for instance: J. Kubicki, H. L. Luk, Y. Zhang, S. Vyas, H.-L. Peng, C. M. Hadad, M. S. Platz, *J. Am. Chem. Soc.* 2012, 134, 7036–7044.


The involvement of singlet and triplet nitrenes derived from Ar′INAr2 has been previously discussed based on DFT calculations. See: B. A. Shainy, A. V. Kuzmin, *J. Phys. Org. Chem.* 2014, 27, 156–162.