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# Catalyst-Free Visible-Light-Mediated Iodoamination of Olefins and Synthetic Applications

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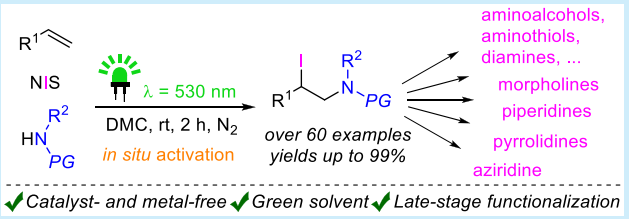
**ABSTRACT:** Herein we report a catalyst- and metal-free visible-light-mediated protocol enabling the iodoamination of miscellaneous olefins. This protocol is characterized by high yields under environmentally benign reaction conditions utilizing commercially available substrates and a green and biodegradable solvent. Furthermore, the protocol allows for late-stage functionalization of bioactive molecules and can be scaled to gram quantities of product, which offers manifold possibilities for further transformations, including morpholine, piperidine, pyrrolidine, and aziridine synthesis.

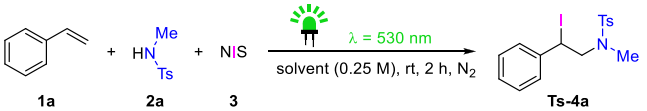





Pioneered in the mid-1900s, aminohalogenation has developed into a powerful tool in organic synthesis to incorporate an amine as well as a halogen group into unsaturated C−C bonds in a single step. The resulting vicinal haloamine moiety represents a key motif in many bioactive metabolites and can serve as a versatile intermediate in organic synthesis.[1] Consequently, a broad range of protocols for chloroamination[2,3] and bromoamination[4] of unfunctionalized double bonds have been disclosed. However, while impressive work has been published on intramolecular iodoamination[5] yielding various heterocyclic products, the analogous intermolecular ATRA-type iodoamination seems to be far less explored. Recent seminal work describes this basic idea in only limited examples[6] and with difficulties in product isolation.[7] It is noteworthy that Li and co-workers[8] described a thermal iodoamination under mild conditions that gives the corresponding products with different regioselectivity compared to the present report via a closed-shell mechanism. Nonetheless, especially when further synthetic transformations of the corresponding halogen moieties are envisioned in order to rapidly build up complex amine-containing molecules, the highly reactive C−I bond might offer distinct advantages against its lighter homologues. This fact is reflected by the lack of further transformations for chloroamination of styrenes[2] and by the limited number of applications in bromoamination studies.[4e,g] Motivated by this literature void, we aimed to develop a broadly applicable protocol for the iodoamination of various alkenes, which further can serve as versatile building blocks for subsequent diversification and construction of molecular complexity through simple operations.

On the basis of our experience in the field of photocatalyzed ATRA reactions,[9] we started our investigations using styrene (**1a**), *N*,4-dimethylbenzenesulfonamide (**2a**), NIS (**3**), and various metal-based photocatalysts (Table 1, entries 1−3). The desired iodoamination product **Ts-4a** was observed in up to

**Table 1. Reaction Optimization**[a]




| entry | solvent | 1:2:3 ratio | catalyst/condition | yield (%)[b] |
|---|---|---|---|---|
| 1[c] | DCM | 2:1:1 | $[Cu(dap)_2]Cl$ (1 mol %) | 46 |
| 2[c,d] | DCM | 2:1:1 | $[Ru(bpy)_3]Cl_2$ (1 mol %) | 34 |
| 3[c,d] | DCM | 2:1:1 | *fac*-$[Ir(ppy)_3]$ (1 mol %) | 33 |
| 4 | DCM | 2:1:1 | – | 98 |
| 5 | DCM | 1:1:1 | – | 98 |
| 6 | DMC | 1:1:1 | – | 98[e] |
| 7[c] | DMC | 1:1:1 | dark reaction | 19 |
| 8[c] | DMC | 1:1:1 | dark reaction, $T$ = 50 °C | 3 |
| 9 | DMC | 1:1:1 | under air | 93 |

[a]Reaction conditions: 0.5 mmol scale in the solvent (degassed, 0.25 M); irradiation at 530 nm under an atmosphere of $N_2$ for 2 h at 25 °C. [b]NMR yields. [c]the reaction time was 24 h. [d]Irradiation at 455 nm. [e]Isolated yield.

46% yield when $[Cu(dap)_2]Cl$ was used as the catalyst under green LED irradiation (entry 1). Surprisingly, omitting the photocatalyst in the reaction increased the yield of **Ts-4a** to 98%, providing a catalyst- and metal-free protocol (entry 4). In accordance with our previous study,[9] we assume that traces of metal might inhibit free radical chain pathways of such processes. Following the principles of green chemistry, it is

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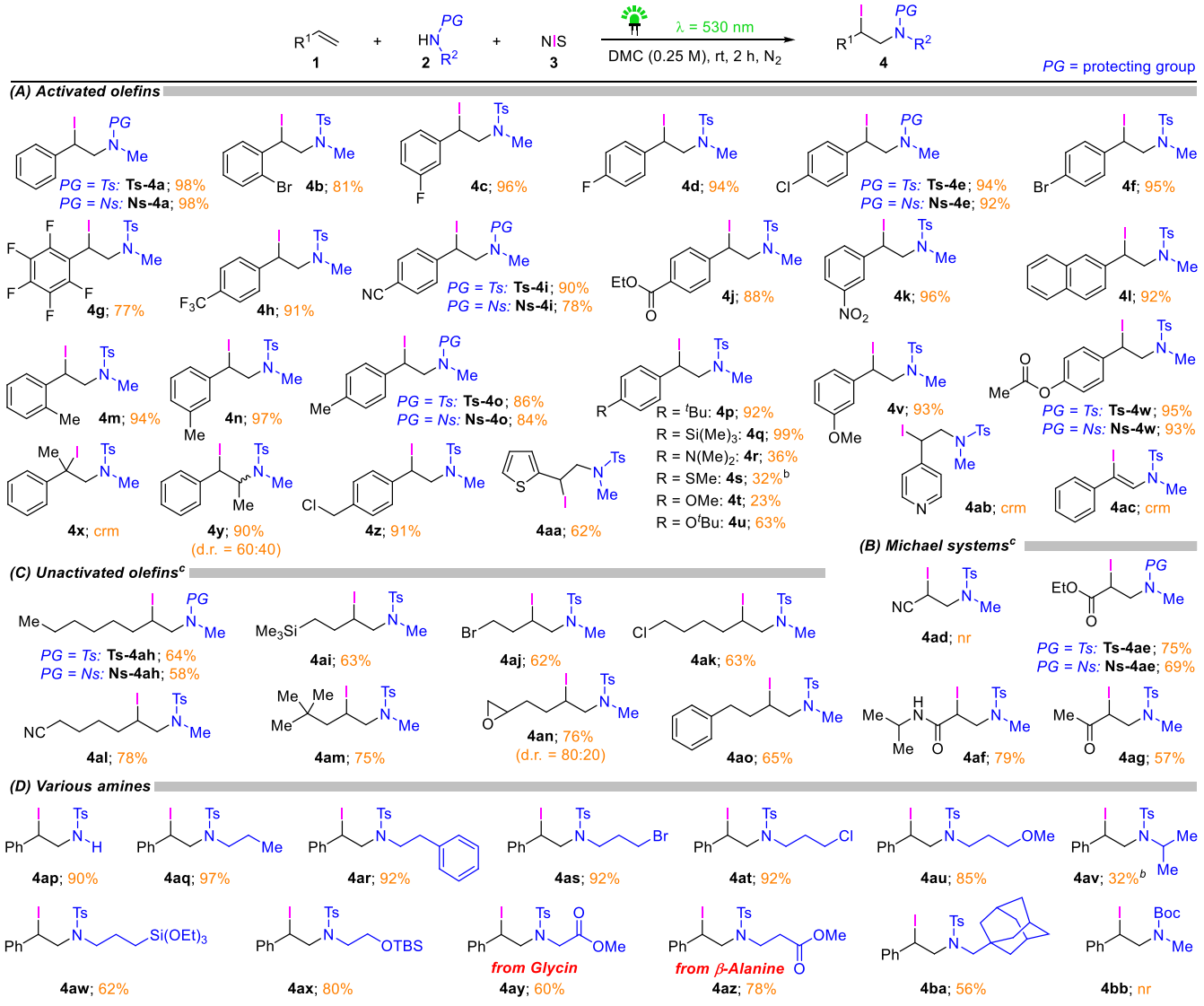
**Scheme 1. Substrate Scope**[a]




[a]Reaction conditions: 0.5 mmol scale in DMC (degassed); irradiation at 530 nm under an atmosphere of $N_2$ for 2 h at 25 °C. Abbreviations: crm = complex reaction mixture; nr = no reaction. [b]The product could not be isolated. The NMR yield of the crude product is shown. [c]4.0 equiv of alkene **1**.

desirable to achieve high atom economy and replace chlorinated solvents by more environmentally friendly and preferable alternatives. Thus, we were pleased that also an almost quantitative yield was also observed when the **1**:**2**:**3** molar ratio was changed to 1:1:1 and dimethyl carbonate (DMC) was used as a green and biodegradable solvent (entries 5 and 6). Control experiments omitting light (entry 7) or promoting the reaction under thermal activation (entry 8) significantly decreased the yield of **Ts-4a** even after 24 h of reaction time.

Next, we set out to explore the scope of the title reaction (Scheme 1). Starting with activated alkenes (Scheme 1A), electron-withdrawing halogen substitution was well-tolerated at various positions, giving rise to the corresponding products **4b**−**f** in high yields. Further increasing the electron-withdrawing character of the styrene did not alter the reactivity and the iodoamination products **4g**−**k** were obtained in 77−96% yield. Electron-donating alkyl substitution at the *ortho*, *meta*, or *para* position still provided the desired products **4m**−**p** in very high yields. However, further increasing in the electron-donating character by installing *p*-$N(Me)_2$, *p*-SMe, or *p*-OMe decreased the yield of the corresponding products **4r**−**t** to 23−36%. In line with this, when the OMe group was placed at the *meta* position, thus acting as an acceptor, the desired iodoamination product **4v** was obtained in 93% yield. In the same way, protection of the electron-donating alkoxy substituent with an electron-withdrawing acetyl group at the *para* position increased the yield of the corresponding product **4w** to 95%. While $\alpha$-substitution aiming at the synthesis of **4x** led to a complex reaction mixture, $\beta$-substitution proved to be compatible, allowing the isolation of **4y** in 90% yield. Remarkably, a benzylic chloride-containing substrate, presenting a highly reactive benzylic C−H or C−Cl bond, nevertheless showed no cross-reactivity and yielded **4z** in 91% yield. We were pleased to see that vinylthiophene was also an amenable substrate, thus giving access to **4aa** in 62% yield. Remarkably, the protocol was also capable of converting $\alpha,\beta$-unsaturated Michael systems to afford **4ae**−**ag** in good yields



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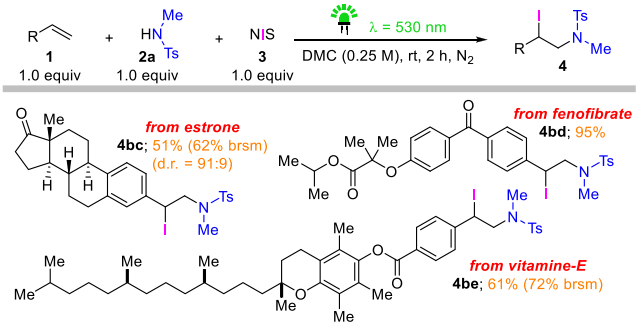
(Scheme 1B), even though the addition of electrophilic radicals to such substrates is usually challenging. Besides activated olefins, unactivated alkenes were also accessible in this transformation by adjustment of the reaction stoichiometry (Scheme 1C). In this case, a large variety of different functional groups were well-tolerated, giving rise to the desired products **4ai**–**an** in synthetically useful yields. Next, we explored the scope of different amines in the iodoamination of **1a** (Scheme 1D). A broad range of functional groups were tolerated, allowing rapid access to highly functionalized molecules. The latter offer manifold possibilities to further build up molecular complexity through simple operations, which is demonstrated later on (see Scheme 3). Notably, a primary tosylamide also leads to the desired ATRA product **4ap** in excellent yield, enabling easy access to aziridines (see Scheme 3E). Amino acid derivatives are suitable starting materials in the same way, providing the desired products **4ay** and **4az** in good yields. Sterically demanding adamantyl substitution did not alter the reactivity, and iodoamination product **4ba** was obtained in 56% yield. A limitation was found when the tosyl group was replaced by a Boc group, leading to no conversion of the starting materials to **4bb**. However, considering that the nosyl group is a much milder removable sulfonyl protecting group compared with the tosyl group,[10] we were very pleased to observe that the nosyl group was tolerated in the same way, as demonstrated by selected representative examples (**Ns-4a**, **Ns-4e**, **Ns-4i**, **Ns-4o**, **Ns-4w**, **Ns-4ae**, **Ns-4ah**) in comparable yields.

We next investigated the late-stage functionalization of more complex, biologically active molecules (Scheme 2). Estrone-,

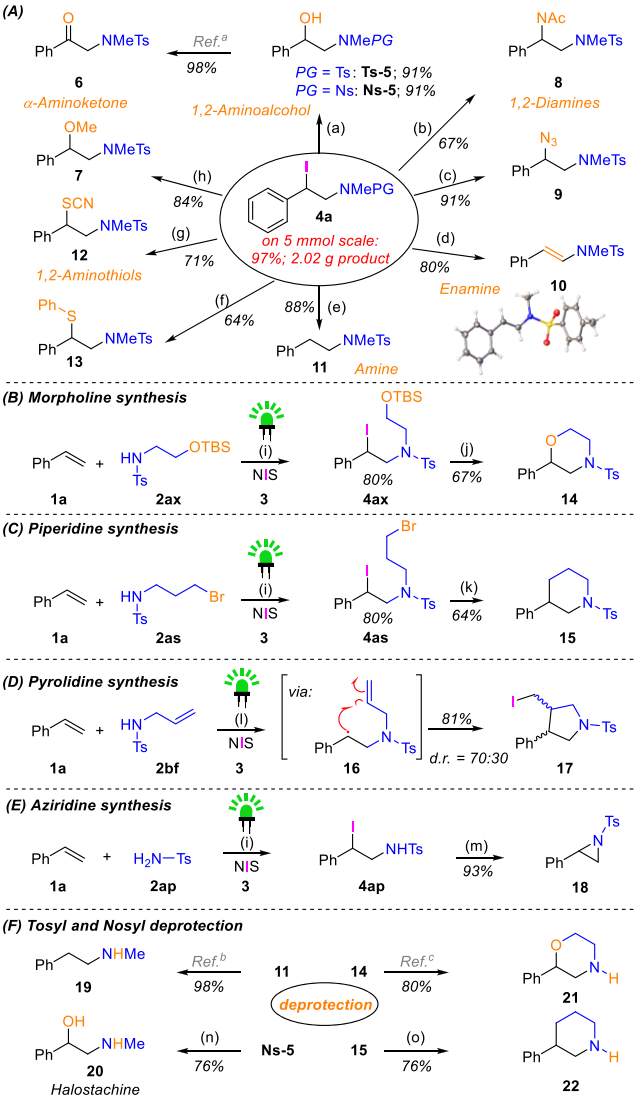
**Scheme 2. Late-Stage Functionalizations**[a]




[a]Reaction conditions: 0.5 mmol scale in DMC (degassed); irradiation at 530 nm under an atmosphere of $N_2$ for 2 h at 25 °C.

fenofibrate-, and vitamin E-derived substrates were successfully transformed to the desired iodoamination products **4bc**–**be** in good to excellent yields, showcasing the capacity of the protocol in multistep synthesis of complex molecules. Next, we established the viability of the protocol for preparative purposes. When the scale was increased by a factor of 10, the iodoamination product **Ts-4a** was obtained in multigram amounts in an almost quantitative yield of 97% in a simple batch setup without the necessity to prolong the reaction time (Scheme 3). Given the scarcity of synthetic utility of the corresponding benzylic 1,2-chloro-[2] and 1,2-bromoamination compounds,[4e,g] we were pleased to find that the benzylic iodides offer manifold possibilities for further transformations. Various nucleophiles can smoothly be introduced, leading to a whole family of 1,2-functionalized amines. For example, substitution with oxygen nucleophiles delivers not only methyl

**Scheme 3. Synthetic Utility**[a]




[a]Reaction conditions: reactions were conducted on a 0.3 mmol scale. (a) **4a** in acetone/water (1:1) for 12 h at 100 °C. (b) **4a** and $FeCl_3 \cdot 6H_2O$ (4.0 equiv) in MeCN for 2 h at 80 °C. (c) **4a** and $NaN_3$ (5.0 equiv) in DMF for 5 h at 25 °C. (d) **4a** and NaOAc (10.0 equiv) in DMF for 5 h at 25 °C. (e) **4a**, $Bu_3SnH$ (3.0 equiv), and AIBN (10 mol %) in benzene for 12 h at 80 °C. (f) **4a**, thiophenol (2.5 equiv), and $Na_2CO_3$ (2.5 equiv) in MeCN for 24 h at 25 °C. (g) **4a** and NaSCN (5.0 equiv) in DMF for 24 h at 70 °C. (h) **4a** in MeOH for 12 h at 65 °C. (i) See Scheme 1. (j) **4ax** and TBAF (1.2 equiv) in THF for 1 h at 25 °C. (k) **4as**, $NiI_2$ (10 mol %), 2,2′-bipyridine (10 mol %), and Zn (3.0 equiv) in DMA for 16 h at 25 °C. (l) **1a** (0.5 mmol, 1.0 equiv), **2bf** (1.0 equiv), and **3** (1.0 equiv) in DMC (degassed); irradiation at 530 nm under $N_2$ for 2 h at 25 °C. (m) **4ap** and $NEt_3$ (3.0 equiv) in DCM for 3 h at 25 °C. (n) **Ns-5** (0.2 mmol), 2-mercaptoacetic acid (6.0 equiv), and DBU (6.0 equiv) in DMF for 12 h at 25 °C. (o) **21** and Mg (10 equiv) in MeOH for 3 h at 25 °C. Ref [a].[12] Ref [b].[13] Ref [c].[14]

ether **7** from **Ts-4a** but also 1,2-amino alcohols **Ts-5** and **Ns-5** from the tosyl- and nosyl-protected amines, respectively, representing a key structural motif in biologically active compounds as well as being important in coordination chemistry.[11] In the same way, sulfur nucleophiles can be applied to access 1,2-amino thiols **12** and **13**, while nitrogen nucleophiles give rise to 1,2-diamines **8** and **9**. Elimination of



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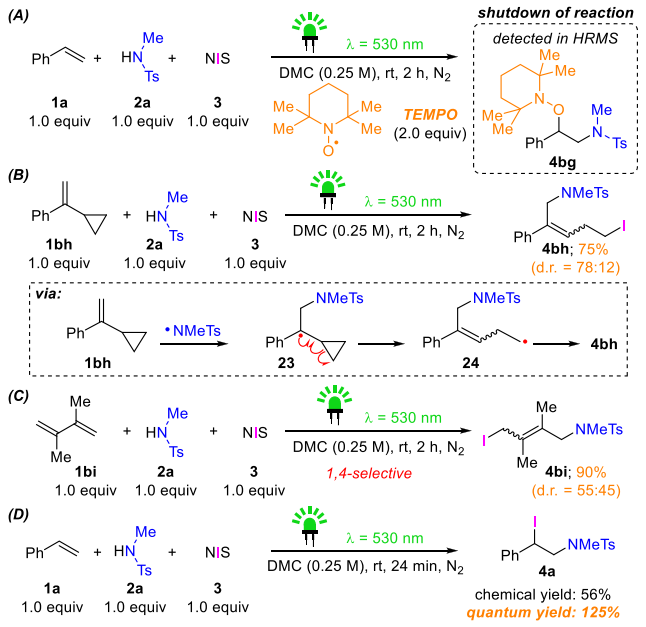
**Ts-4a** smoothly provides access to the corresponding enamine **10** in high yields, whereas dehalogenation provides the analogous amine **11**.

Simple deprotection of substrate **4ax** bearing a protected alcohol moiety gives rise to the substrate class of morpholines **14**, which possess great importance in bioorganic chemistry.[15] Transition metal catalysis offers the opportunity to insert Ni into the C−I bond, thus triggering intramolecular cyclization in compound **4as** to rapidly form 3-aryl-substituted piperidines, which have been investigated since the early 1980s in view of their dopaminergic activities and usually require harsh reaction conditions for their synthesis.[16] Subjecting allylamine **2bf** to the reaction conditions provided the opportunity for in situ radical 5-exo-trig cyclization to access pyrrolidine derivative **17** in a single step from commercially available bulk chemicals. Notably, analogous chloroamination protocols require either harsh radical conditions[17] or expensive Ir-based photocatalysis.[18] Treatment of photoproduct **4ap** with base smoothly leads to the substrate class of aziridines **18**, representing privileged structural motifs in organic chemistry.[19] We next investigated the tosyl and nosyl deprotection for representative examples (Scheme 3F). While morpholine derivative **14** and piperidine **15** can smoothly be tosyl-deprotected under mild reductive conditions, the introduced nosyl goup offers the possibility to deprotect more functionalized molecules like **Ns-5** under much milder redox-neutral conditions, giving halostachine (**20**) in good yields.

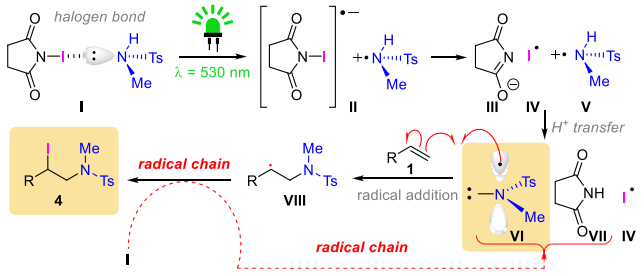
In line with a mechanistic pathway calling for radical intermediates, the addition of TEMPO to the standard reaction conditions resulted in complete shutdown of the reaction, while the TEMPO trapping adduct **4bg** was detected by HRMS (Scheme 4A). A radical clock experiment subjecting **1bh** to the reaction conditions exclusively led to the formation of product **4bh**, in agreement with radical intermediate **23**, which undergoes radical-initiated ring opening to give **24** (Scheme 4B). The reaction of diene **1bi** and amine **2a** together with NIS gave rise to product **4bi** with exclusive 1,4-selectivity (Scheme 4C). The quantum yield of the reaction was determined to be 125%, clearly pointing toward a radical chain mechanism (Scheme 4D). Hence, in agreement with a very recent study on the halogen-bond-induced C−H amination initiated by 4-methylbenzenesulfonamide and NIS,[7] we propose the following mechanism (Scheme 5).

**Scheme 4. Mechanistic Investigations**[a]




[a]Reaction conditions: 0.5 mmol scale in DMC (degassed, 2.0 mL, 0.25 M); irradiation at 530 nm under an atmosphere of $N_2$ for 2 h at 25 °C.

**Scheme 5. Proposed Reaction Mechanism**




First, the halogen bond complex **I** absorbs visible light, leading to visible-light-induced homolysis and generation of complex **II**. Extensive mechanistic investigations of the aforementioned study revealed this activation mode of such substrates.[7] After charge- and proton transfer, the iodine radical **IV** and the nitrogen-centered radical **VI** get extruded. The latter adds to the alkene **1**, forming radical intermediate **VII**, which now can abstract iodide from the starting complex **I** to deliver the final product **4** with concurrent regeneration of nitrogen-centered radical **VI**. Notably, this principle of photochemical iodide activation can be also found with phosphines.[20]

In conclusion, we have developed a highly efficient protocol to directly furnish a broad scope of iodoamination of commercially available alkenes utilizing simple and abundant sulfonamides and NIS under visible-light irradiation. The protocol excels through high yields and environmentally benign reaction conditions, omitting any metal or catalyst species and being driven in a green and biodegradable solvent. The protocol is robust and insensitive to air and allows for late-stage functionalization of biologically active molecules. For preparative purposes it can be smoothly scaled to gram quantities of the products, which offer a plethora of further synthetic transformations. Nucleophilic substitution with manifold nucleophiles provides a library of 1,2-functionalized amines, including amino alcohols, amino thiols, and diamines. Furthermore, several classes of biologically important heterocycles can be rapidly accessed using the iodoamination products as starting points, including morpholines, piperidines, pyrrolidines, and aziridines.

## ■ ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.1c02035.

(Experimental details, further optimization, full characterization data, detailed calculation of the quantum yield, and copies of NMR spectra PDF)



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### Notes

The authors declare no competing financial interest.

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