

Exploiting Imine Photochemistry for Masked *N*-Centered Radical Reactivity

Daryl Staveness; James L. Collins III; Rory C. McAtee; Corey R.J. Stephenson*

Department of Chemistry, University of Michigan, Ann Arbor, MI 48109, USA.

Keywords

1-aminonorbormane; aminocyclopropane; *N*-centered radical; Schiff base; excited state diyl; cyclopropylimine; visible light; photoisomerization; radical cyclization

Abstract

This report details the development of a masked *N*-centered radical strategy that harvests the chemical potential of violet light to drive the conversion of cyclopropylimines to 1-aminonorbormanes. This process is initiated by the nitrogen-centered radical character of a photoexcited imine, facilitating the homolytic fragmentation of the cyclopropane ring followed by a radical cyclization sequence that forms two new C–C bonds en route to the norbornane core. Employing the excited state diyl of a Schiff base as a masked *N*-centered radical is a unique mode of reactivity, the utility of which is amplified by the bathochromic shift into the visible spectrum imparted by the 4-nitrobenzimine. In addition to the intramolecular reactivity that generates 1-aminonorbormanes, intermolecular formal [3+2] cycloadditions are also amenable to this strategy. This photochemical methodology operates in continuous flow, enhancing the potential to translate this approach beyond the academic sector.

Introduction

The unique reactivity of excited state species has been a major driving force for synthetic innovation, both in classical times and during the modern reinvigoration of photochemical methodology.^{1,2} Importantly, as the pharmaceutical industry continues to increase its investment in photochemistry,^{3,4} the field now has an unprecedented opportunity to translate academic discoveries into disruptive new technologies. The large-scale production of artemisinin illustrates this transformative potential,⁵ and state-of-the-art visible light-based methods are also beginning to directly impact drug development (e.g. elbasvir⁶). The revival of photoredox catalysis has played a leading role in the rise of visible light photochemistry,^{7,8} largely because the strategy offers exceedingly mild access to open-shell species (e.g. carbon-centered radicals,⁹ amine radical cations¹⁰) and can be paired with additional catalytic protocols (e.g. Ni-based cross-coupling,¹¹ enantioselective Lewis acid catalysis¹²). However, photoredox catalysis is not the only photochemical technique that is worth exploring. Decades of photochemistry and photophysics research have set the stage for synthetic chemists to create and invent the technologies of tomorrow while addressing the major challenges of today. One such challenge is the need for more efficient syntheses of saturated building blocks in drug discovery.^{4,13,14} Increased saturation not only offers access to more diverse chemical space¹⁵ but is

also correlated with improved developmental properties,¹⁶ including a decreased likelihood of CYP450 inhibition and the associated adverse metabolic events.¹⁷ This work contributes to this need while also expanding our repertoire of photochemical methodology, demonstrating the ability of a 4-nitrobenzimine to drive the homolysis of a strained ring and ultimately facilitate the production of 1-aminonorbornanes (1-aminoNBs; systems being evaluated as potential aniline bioisosteres) using nothing other than violet light.

Our initial strategy for the synthesis of 1-aminoNBs¹⁸ (see Figure 1) was informed by our prior efforts leveraging photoredox catalysis for amine oxidation.¹⁹⁻²² While the majority of amine oxidation methods lead to α -amino radicals through heterolytic decomposition of amine radical cation intermediates,^{10,23} our initial approach operated through strain-driven homolytic decomposition of oxidized aminocyclopropanes, generating a carbon-centered radical that proceeds to the norbornane core via serialized radical cyclizations. Unfortunately, this strategy only proved effective for *N,N*-dialkylaminocyclopropane starting materials, prohibiting our planned applications of C1-NH₂ 1-aminoNBs. Circumventing this limitation would require another means of accessing open-shell character at nitrogen. A number of possibilities exist,²⁴ such as reduction/homolysis of N-X bonds or PCET²⁵ with carbamate-protected aminocyclopropanes. Alternatively, it was hypothesized that a cyclopropylimine could serve as a masked *N*-centered radical, revealing the nitrogen-based radical character upon excitation in order to initiate the fragmentation-cyclization sequence seen in the prior system. Directing the focus to aryl aldehydes (many of which are commercially-available) provided the potential for selective excitation, as the conjugated imines were anticipated to absorb at longer wavelengths than common organic chromophores. As both the introduction and removal of the Schiff base were expected to be facile and high-yielding, this strategy appeared to offer an efficient solution to the need for C1-NH₂ 1-aminoNBs.

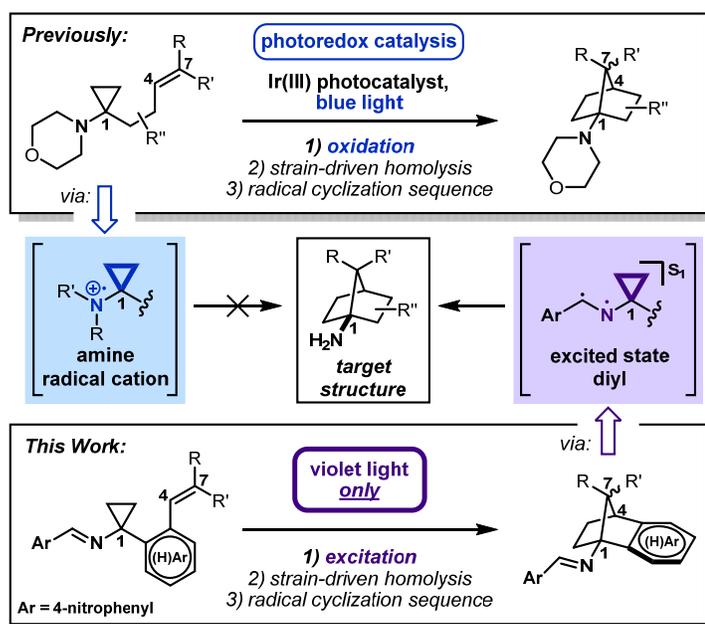


Figure 1: Photochemical strategies toward 1-aminonorbornanes

Top: Our prior methodology, employing photoredox catalysis and amine radical cation intermediates; Bottom: This strategy, employing an excited state diyl intermediate.

Interestingly, the *N*-centered radical character of excited state imines has yet to be harnessed as an initiator for radical cyclization chemistry. Most reports of photoexcited imines have been designed to follow closely to carbonyl or olefin photochemistry, but even early investigations appreciated that this translation is not necessarily a direct one.^{26,27} For instance, photoisomerizations of *N*-aryl benzimines are prone to thermal equilibration back to the *E*-isomer,²⁶ and *aza*-photocycloadditions tend to require specialized systems, specifically *N*-acyl imines.²⁶⁻²⁸ However, the mechanistic rules that govern excited state reactivity still hold, e.g. photochemical electrocyclic ring opening and ring closure reactions proceed through the $^1(\pi,\pi^*)$ state in concordance with Woodward-Hoffman rules.²⁶ One example of an imine-specific rearrangement is the photo-racemization of dihydropyrazine (-)-**3** (see Figure 2A),²⁹ facilitated by the non-classical bond structure available to [2.2.1] bicyclic systems with open-shell character adjacent to the bridgehead position. This work also represents a rare prior example of a 1-aminoNB in the literature; of note, the majority of prior 1-aminoNB preparations generate the bridgehead amine via a Hofmann or a Curtius rearrangement of terpene-based materials³⁰⁻³³ or from downstream products of cyclopentadiene-acrylate Diels-Alder reactions³⁴⁻³⁷ (only one radical closure existed before our work³⁸). The photochemical transformation most directly analogous to the strategy detailed herein is the rearrangement of *N*-cyclopropylimines to the corresponding pyrrolines.³⁹ While the thermal rearrangement was initially reported by Huisgen in 1974,⁴⁰ it was not until the efforts of Sampedro and co-workers in 2005^{41,42} that the light-driven process was revealed. Our approach, as designed to supply 1-aminoNBs (**2**; see Figure 2B) from the Schiff base of aminocyclopropanes (**1**), distinguishes itself from the decades of prior imine photochemistry by initiating a multi-step radical fragmentation/cyclization sequence (forming two new C–C bonds in the process) from the nitrogen-centered radical component of the excited state diyl. Initiating radical cascades from said diyls presents a major challenge: both radicals must be successfully terminated to generate a stable, closed-shell product. Our mechanistic design overcomes this factor by bringing the open-shell character back to the original atoms involved in the excitation event. While the carbon-based radical is simply a bystander, the nitrogen-based radical drives the multi-step formation of the norbornane core only to return to nitrogen, a unique attribute that is functionally-analogous to the round-trip radical probes introduced by Branchaud.^{43,44} Termination of both radicals is thus achieved simultaneously through simple restoration of the π_{CN} bond. The development of our masked *N*-centered radical strategy, performance in continuous flow, mechanistic proposal, and evaluation of scope (including intermolecular examples) is reported herein.

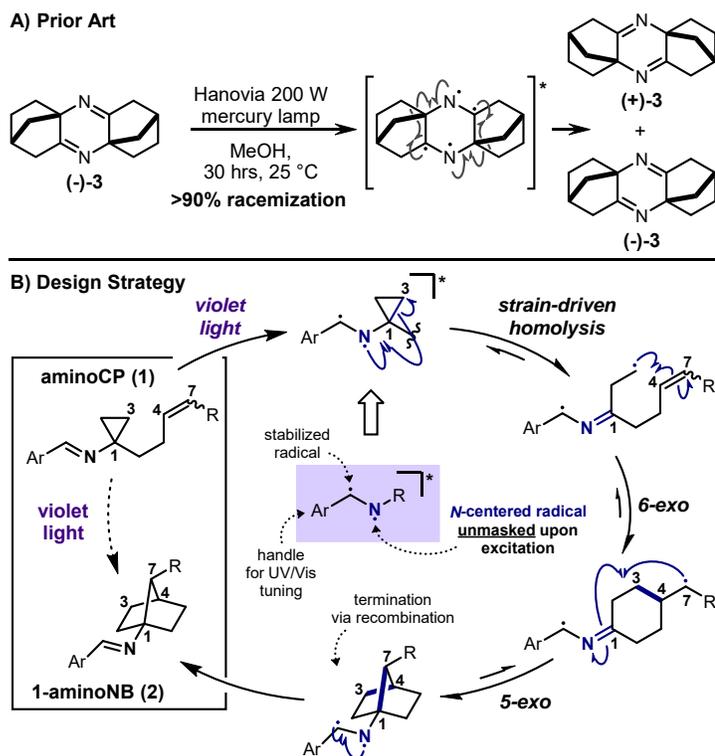


Figure 2: Imine-based photochemistry and the design of our masked *N*-centered radical strategy

A) Photo-racemization of dihydropyrazine (-)-**3** with UV light²⁹ (of note, all necessary electron-pushing arrows are depicted, but this is not expected to be a concerted rearrangement); B) Design principles behind our masked *N*-centered radical strategy for the synthesis of 1-aminoNBs.

Results

The initial assessment of our masked *N*-centered radical strategy began with UV/Vis spectroscopic analysis of benzo-fused cyclopropylimine starting material **1a** and model 4-nitrobenzidine **1b** (see Figure 3; 1-aminoNB **2a** included for completeness). All three Schiff base systems revealed a strong absorbance near 300 nm (see Figure 3A) and a second, much weaker absorbance around 380-385 nm (see Figure 3B); notably, the styrene functionality of cyclopropylimine **1a** is shown to absorb below 275 nm and is believed to be ineffectual in this work. These ~300 nm and ~385 nm maxima are assigned as the $\pi \rightarrow \pi^*$ and $n \rightarrow \pi^*$ transitions, respectively, consistent with the wealth of literature surrounding the photochemistry of carbonyl compounds and derivatives thereof (including imines^{26,27}). The discrepancy in molar absorptivities (see Figure 3C) is a function of orbital overlap, as the ground state species is optimally-aligned for a $\pi \rightarrow \pi^*$ transition but necessitates out-of-plane bending to overcome the perpendicularity of the n and π^* orbitals.⁴⁵ Importantly, the resolution between these maxima (as measured in acetonitrile) offers the potential for selective excitation of a given transition. It was anticipated that the desired cyclopropane fragmentation would operate via a mechanism analogous to C-H abstraction or α -cleavage reactions of excited state carbonyls (i.e. Norrish-type chemistry), as these modes of reactivity clearly rely on open-shell character at the heteroatom. The excited state species implicated in that chemistry is the $S_1(n, \pi^*)$ state, driving the reaction

forward through the in-plane association of a nucleophilic σ -bond with the electrophilic singly-occupied lone pair on oxygen.⁴⁵ Applying this logic to our system, the singly-occupied nitrogen lone pair (n_N) of the $S_1(n,\pi^*)$ state would serve as the electrophilic component, enabling the homolytic fragmentation of a nucleophilic, in-plane σ_{CC} bond of the adjacent cyclopropane (see Figure 3D). Significantly, the large bathochromic shift observed for the $n \rightarrow \pi^*$ transition for cyclopropylimine **1a** ($\Delta\lambda_{\max} \sim +100$ nm relative to acetaldehyde⁴⁶) allows for excitation near the visible range (violet light), suggesting a high degree of functional group tolerance relative to classical UVB/UVC-mediated carbonyl photochemistry.

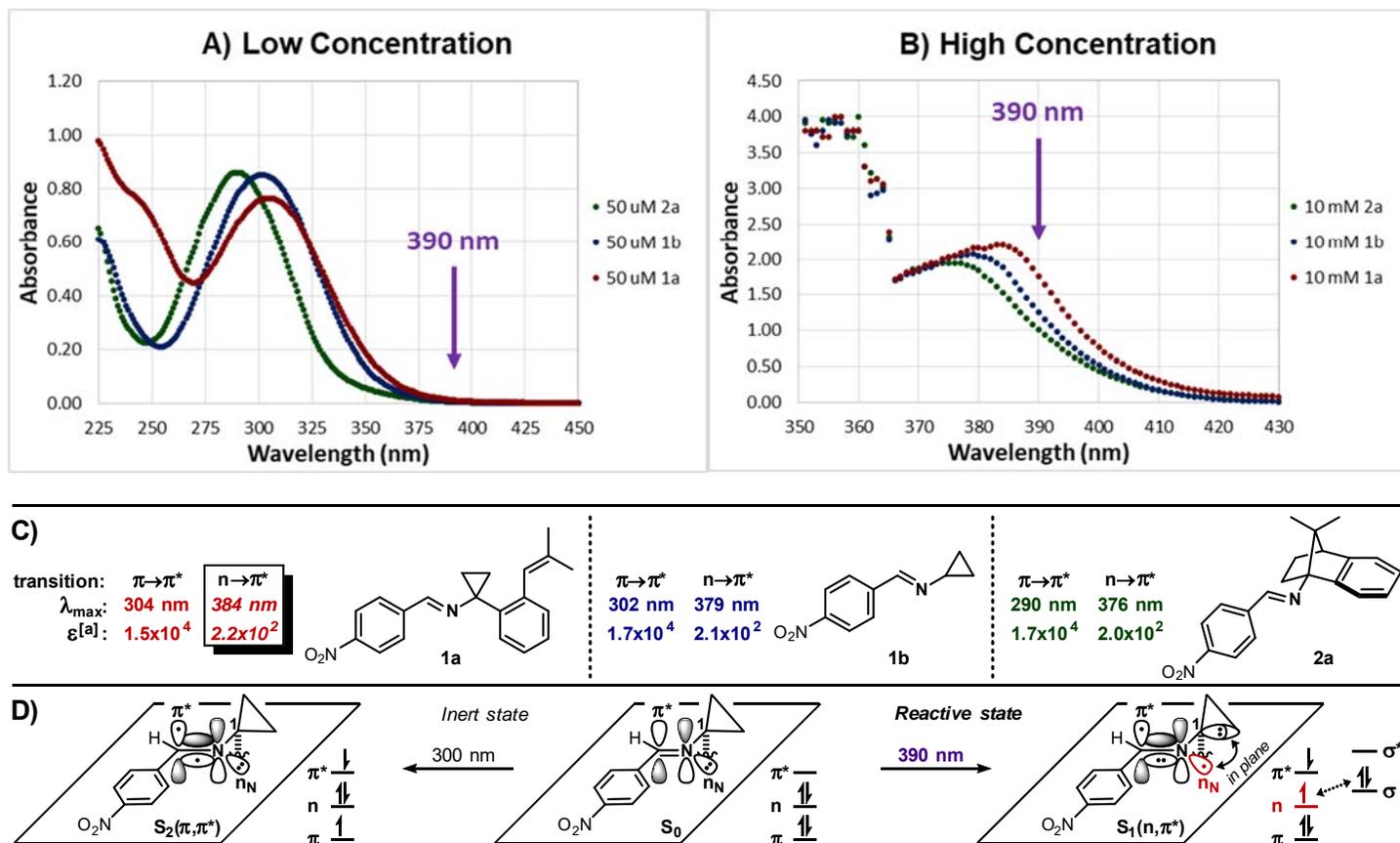
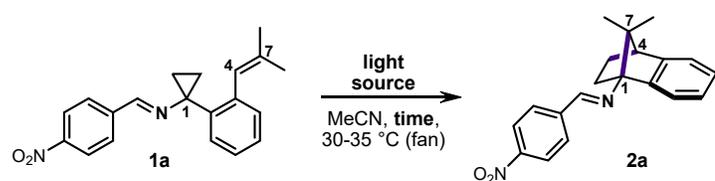


Figure 3: UV/Vis data and proposed mechanism of cyclopropane fragmentation

A) UV/Vis data for cyclopropylimines **1b** and **1a** and 1-aminoNB **2a** collected at 50 μ M in MeCN; B) UV/Vis data collected at 10 mM in MeCN; C) Structures and data summary; ^[a]molar absorptivities (ϵ) estimated from peak absorbance at single concentration; D) Depiction of in-plane donation from cyclopropyl σ_{CC} to singly-occupied n_N orbital in $S_1(n,\pi^*)$ state.

To evaluate the viability of this mechanistic hypothesis, benzo-fused cyclopropylimine **1a** was exposed to a range of wavelengths to assess conversion to 1-aminoNB **2a** (see Figure 4). As there was no theoretical need for any additional reagents, the optimization was centered exclusively on light source. Irradiating degassed solutions of cyclopropylimine **1a** in dry acetonitrile quickly revealed a preference for 390 nm light, presumably progressing through the $S_1(n,\pi^*)$ state to fully consume starting material and afford the desired

product in 76% yield after 8 hrs of irradiation (entry 1; 200 μ mol scale reaction). In concordance with the above analysis, excitation of the $\pi \rightarrow \pi^*$ transition with 300 nm light (entry 2) did not proceed to product, and in fact, returned starting material in nearly quantitative yield. Light sources less optimally-aligned with the $n \rightarrow \pi^*$ transition maxima (~ 385 nm) predictably provided less conversion, with the 370 nm light source outperforming the 440 nm light source as expected (51% vs. 13% yield, respectively; entries 3 and 4). The utility of the 390 nm light was further demonstrated in a continuous flow setting (entry 5); the optimized batch processing yield was nearly recapitulated (73% vs. 76%) while improving the rate of production and indicating potential for translation into an industrial setting, where flow photochemistry has drawn substantial interest.⁴⁷ Significantly, this reactivity definitively requires light, as evidenced by the near quantitative recovery of starting material upon excluding light from the reaction or employing purely thermal conditions at 120 °C in a sealed tube (entries 6 and 7, respectively).



Trial	Light Source	Time	Isolated Yield	Recov. SM
1	390 nm Kessil lamp	8 hrs	76%	0%
2	300 nm Rayonet lights	12 hrs	0% ^[a]	98%
3	370 nm Kessil lamp	8 hrs	51%	27%
4	440 nm Kessil lamp	8 hrs	13%	63%
5 ^[b]	390 nm Kessil lamp	1.3 hrs	73%	0%
6	[no light] ^[c]	12 hrs	0%	>99%
7	[no light; 120 °C]	12 hrs	0%	99%

Figure 4: Optimization of light source for photochemical production of 1-aminoNBs

Reactions were run on ~ 200 mmol scale and degassed prior to irradiation via three freeze-pump-thaw cycles; all reactions run in 2 dram borosilicate vials except entry 2 (quartz tube) and entry 5 (TPFA tubing), see Supporting Information; ^[a]No product was isolated, but an estimated 1-2% was detected by crude ¹H NMR; ^[b]Trial 5 was run in continuous flow (see Supporting Information for details on flow apparatus); ^[c]Vial was wrapped in black electrical tape to exclude light prior to exposure to standard batch conditions.

Evaluation of the reaction scope was performed on a variety of cyclopropylimines with fused aryl and heteroaryl rings. The (hetero)aryl fusion arose from the chosen approach for starting material synthesis, which converted commercially-available 2-halo-(hetero)aryl nitriles to the desired cyclopropylimines via a three-step sequence: 1) a modified Kulinkovich cyclopropanation,⁴⁸⁻⁵⁰ 2) Schiff base formation, and 3) Suzuki coupling (see Supporting Information for detailed synthetic procedures). All cyclopropylimine starting materials were subjected to the optimized 390 nm conditions, and the isolated yields of 1-aminoNB products (isolated as the Schiff base) are provided in Figure 5.

Starting with the substituted benzene series, both neutral and electron-withdrawing substituents were well-tolerated (**2c-2g**), with the substitution even providing some benefit en route to fluorinated systems **2d** and **2e** (isolated in 80% and 83% yield, respectively). The location of the substituent appeared to be ineffectual. Even a C11-methyl group was viable (providing 1-aminoNB **2c** in 75% yield), despite the potential for 1,5-H-atom abstraction by the C7-radical intermediate. In addition to the C10- and C9-fluoro species mentioned above, C9-chloro and C9-trifluoromethyl 1-aminoNBs **2f** and **2g** were generated in good yield. Interestingly, upon transitioning to an electron-donating methoxy group, substitution locale played a major role in reaction progression, affording C9-methoxy 1-aminoNB **2h** in good yield (65%) yet producing only 29% of the C8-methoxy 1-aminoNB **2i**; it is suspected that the C8 functionality inhibits progression via A_{1,3} interactions that alter the conformational preferences of the cyclopropane motif, but electronic factors could also contribute to the above observation. Heteroarene fusions were also amenable to the photochemical methodology, providing structurally-unique thiophene-fused (**2j**) and pyridine-fused (**2k** and **2l**) 1-aminoNBs. While 11-*aza* 1-aminoNB **2k** was produced in good yield (73%) in line with the electron-deficient series discussed above, the 8-*aza* system **2l** was isolated in substantially lower yield (20%); of note, both the starting material and product for this latter system offer an excellent site for metal chelation, thus it is unclear whether the low yield is attributable to inherent inefficiency in the photochemical transformation, to deleterious radical additions into the pyridine, or to the unwanted participation of trace palladium retained from the Suzuki coupling. In regards to varied substitution on the aliphatic portion of the norbornane core, this methodology tracked with our prior observations with *N,N*-dialkylaminocyclopropanes, necessitating functionality at C7 to stabilize the C7-radical of diyl intermediate. For mono-substituted systems, the *anti:syn* ratio of 1-aminoNB products was consistently close to 2:1 in favor of the *anti* isomer for C7-alkyl systems, whether the original olefin geometry is *E* or *Z*; C7-methyl 1-aminoNB **2m** was formed in a 2.2:1 *anti:syn* ratio from the *Z*-isomer, while C7-propyl 1-aminoNB **2l** was isolated in a 1.7:1 *anti:syn* ratio from the *E*-isomer. Similarly to above, the fluorinated systems **2p** and **2q** were produced in higher yields than the corresponding benzo-fused 1-aminoNB **2l** (58% and 57% vs. 45%). Interestingly, the C7-carboxylate product **2o** was formed with complete selectivity for the *anti*-isomer (46% yield) likely due to steric factors.

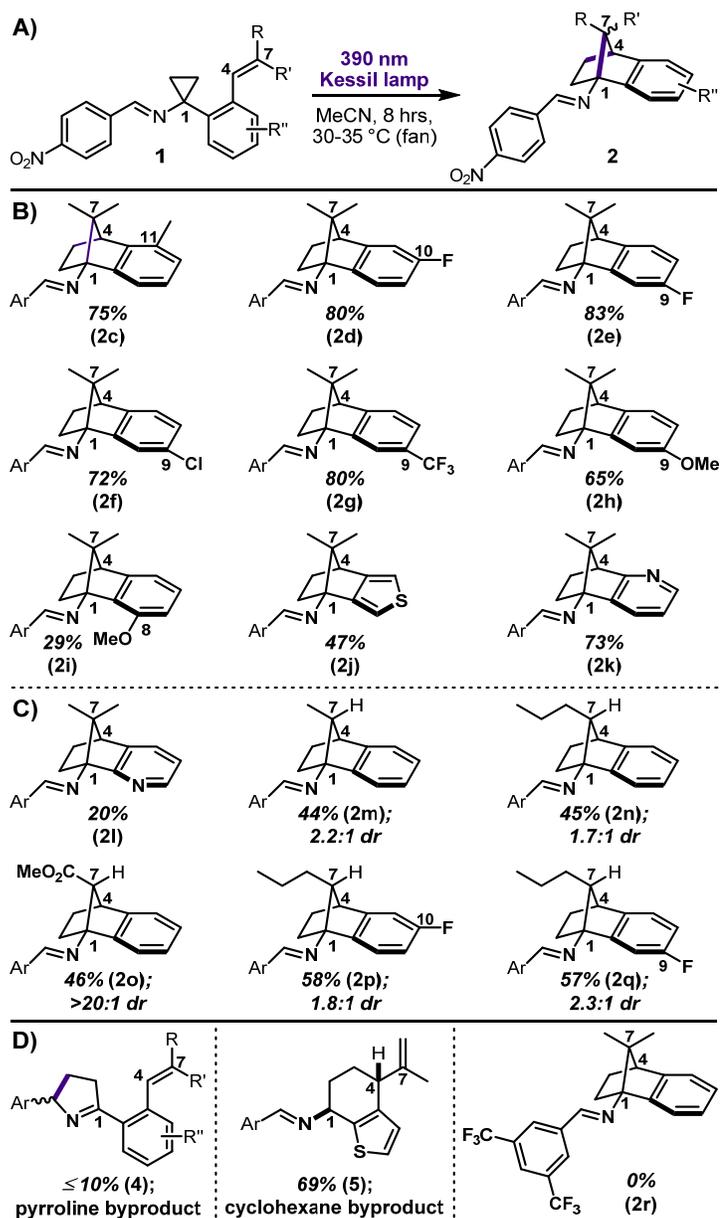


Figure 5: Reaction Scope

A) Generic reaction scheme; all reactions were run on ~200 mmol scale and degassed via three freeze-pump-thaw cycles prior to exposure to optimized conditions; Ar = 4-nitrophenyl. B) Arene modifications. C) C7-substitution effects. D) Deviations from desired reactivity.

During the course of evaluating the substrate scope, a number of observations were made that merit discussion. While most cyclopropylimines were fully consumed under the standard conditions and generated the 1-aminoNB as the only appreciable product, the lower-yielding substrates tended to return starting material and afford isolable quantities of the pyrroline byproduct **4** (upwards of 10% yield, typically with electron-rich substrates); this byproduct was not unexpected given the prior reports on this rearrangement (*vide supra*), but it is interesting that this pathway can be suppressed by employing more electron-deficient systems, an effect that may

be attributable to the interplay of olefin electronics and the *6-exo-trig* cyclization. Intriguingly, only a 2,3-thiophene-fused cyclopropylimine provided any evidence for incomplete radical cyclization pathways, producing cyclohexane **5** in 69% yield (the corresponding 1-aminoNB, not shown, was isolated in <10% yield); whether the distonic diyl intermediate is terminated through electron-transfer or H-atom abstraction pathways is unknown at this time, but that deleterious pathway is uncompetitive in any other substrate evaluated. Lastly, a 3,5-bis(trifluoromethyl)benzimine system provided further support for the importance of the nitro motif in our masked *N*-centered radical strategy, as the corresponding cyclopropylimine was unable to facilitate the production of 1-aminoNB **2r** upon irradiation at 390 nm or at shorter wavelengths (see Supporting Information).

Significantly, this masked *N*-centered radical strategy is not limited to intramolecular chemistry. Employing cyclopropylimine **1b** in the presence of styrenyl systems (**6**) enabled intermolecular formal [3+2] cycloadditions, thus producing 2-aryl cyclopentylamines **7a** and **7b** as the Schiff bases in ~60% yield as ~1:1 mixtures of the *syn* and *anti* isomers (see Figure 6); the ability to deprotect these systems to the free amines (see Supporting Information) provides a complementary set of cyclopentylamine building blocks to the anilino-cyclopropane-derived systems from Zheng and co-workers.⁵¹

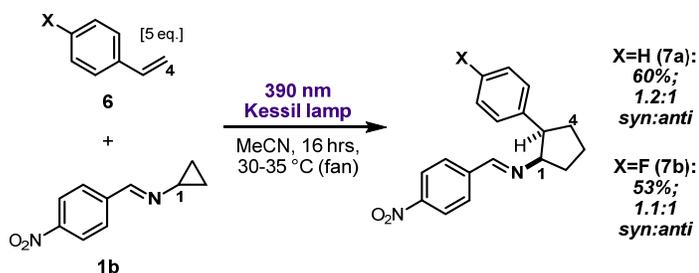


Figure 6: Intermolecular formal [3+2] cycloadditions employing masked *N*-centered radical strategy

Reactions were run on 400 μmol scale and degassed via three freeze-pump-thaw cycles prior to irradiation.

As a preliminary means of showcasing the utility of the 1-aminoNB products and thus the masked *N*-centered radical strategy, a number of post-irradiation functionalizations were performed on the benzo-fused norbornane scaffold **2a** (see Figure 7). Initial removal of the Schiff base proceeded cleanly, as anticipated, to reveal the C1-NH₂ 1-aminoNB target **8**. Alternatively, coupling the photochemical method with Schiff base formation and/or removal in a one-pot fashion was proven to be viable (see Supporting Information for further details), though the two-step sequence shown here has thus far led to the highest yields of 1-aminoNB **2s**. Manipulation of the free amine of 1-aminoNB **2s** can be achieved through standard methods, as demonstrated through acetylation to acetamide **2t**. Direct conversion of the Schiff base product **2a** to acetamide **2t** proceeded in higher yield than the two-step deprotection-acetylation sequence, suggesting the potential to couple the deprotection and *N*-functionalization procedures together en route to alternative targets. Further investigation of these multi-transformation sequences, particularly in a continuous flow setting, are anticipated to provide more optimal processes; efforts toward this end will be reported in due course. Notably, 1-aminoNB **2s** itself offers a great deal of synthetic flexibility in addition

to standard uses of amine functionality (e.g. nucleophilic aromatic substitution, C-N coupling reactions; not shown). The bridgehead amine can also serve as a precursor to a bridgehead cation (via the bridgehead diazonium species **8**). This methodology was originally developed as a means of understanding S_N1 mechanisms,⁵² and variations have been developed to generate 1-hydroxy, 1-halo, and 1-aryl norbornanes^{32,53,54} from these unique cationic species; conditions to afford the former³¹ were recapitulated herein, providing 1-hydroxynorbornane **9** in 74% yield. Perhaps the most significant manipulation was the conversion of C7-CO₂Me 1-aminoNB **2o** to the C7-methylene 1-aminoNB **2v**, as the latter provides the closest spatial occupancy to the analogous aniline system (potentially critical for the execution of our 1-aminoNB bioisosterism strategy outlined in our prior manuscript¹⁸). This was achieved through saponification of the the C7-CO₂Me to provide the C7 carboxylic acid (**2u**), which was reductively decarboxylated through a photoredox catalysis strategy. Given the prevalence of carboxylic acid manipulations now available, this sequence indicates the potential for rapid diversification of these 1-aminoNB scaffolds. Collectively, through incorporation of functionality in the cyclopropylimine starting materials or post-irradiation manipulations, this methodology enables the production of a variety of substituted 1-aminoNBs, all of which are structurally-distinct from building blocks currently available to the drug discovery community.

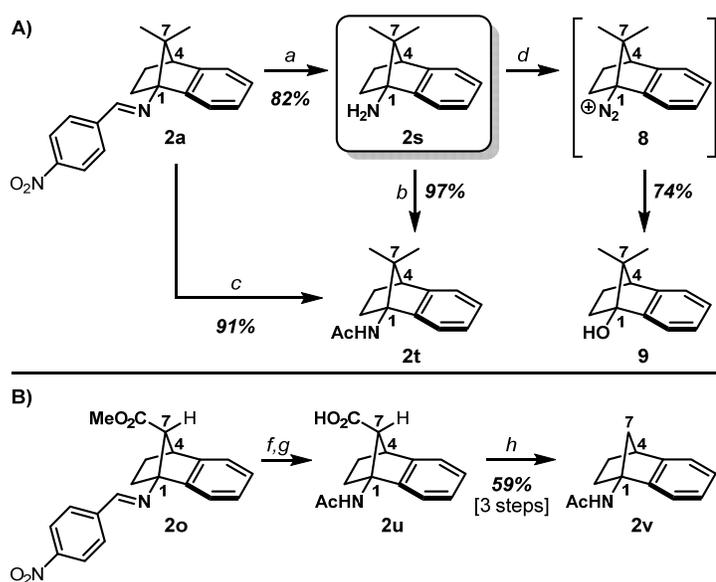


Figure 7: Post-irradiation functionalization of 1-aminoNBs

A) Bridgehead manipulations; Reagents and conditions: *a*) AcOH, H₂O, MeCN, rt; *b*) Ac₂O, NEt₃, DMAP, CH₂Cl₂, rt; *c*) Ac₂O, pTsOH·H₂O, DCE, 75 °C; *d*) NaNO₂, 2 M H₂SO₄ (aq), 1:1 DMF:H₂O, 0 °C to rt. B) Preparation of C7 methylene 1-aminoNB **2v**; Reagents and conditions: *a*) Ac₂O, pTsOH·H₂O, CH₂Cl₂, 40 °C; *b*) 1:1 EtOH:1 M KOH (aq), 75 °C; *c*) [Ir(dF(CF₃)ppy)₂(dtbbpy)](PF₆) (2 mol%), K₂HPO₄, Two Blue Kessil lamps, DMF, 30-35 °C (fan-controlled).

Discussion

The work detailed above demonstrates the operational-simplicity and unique reactivity offered by our masked *N*-centered radical strategy. Initiating a radical cyclization sequence from the *N*-centered radical character of an excited state imine is, to our knowledge, a fundamentally new transformation in synthetic photochemistry. Terminating the radical processes via regeneration of the imine obviated the need for any reagent beyond the light source itself, which conveniently lies in the violet region of the spectrum and thus avoids unwanted excitation of common functional groups (cross-reactivity that can plague the utility of traditional UVB photochemistry). The intermolecular reactivity briefly introduced above illustrates the potential to extend this concept well beyond 1-aminoNB synthesis. Importantly, this new mode of reactivity ultimately enabled the production of the originally-targeted C1-NH₂ 1-aminoNBs, facilitating downstream applications of these saturated building blocks. As the Schiff base is both introduced and removed via simple and mild transformations, it was an ideal surrogate for the amine radical cation-driven reactivity previously developed. This new photochemical transformation thus provides a key motif for our aniline bioisosterism program while opening new avenues for the modern synthetic photochemist.

Experimental Procedures

General procedure of the photochemical conversion of cyclopropylimines (1) to 1-aminoNBs (2):

In a dry vial under inert atmosphere, cyclopropylimine **1** was dissolved in dry MeCN (0.1 M). Reaction mixture was degassed with three freeze-pump-thaw cycles. The reaction was irradiated with 390 nm light for 8 hrs (for 200 mmol-scale reactions), controlling the temperature between 30-35 °C with a fan. The mixture was partitioned between 1:1 saturated NaHCO₃ (aq.):water and ether. Phases were separated, and the aqueous phase was further extracted with ether three times. Combined organics were washed with brine, dried over anhydrous magnesium sulfate, filtered to remove solids, and concentrated *in vacuo*. The crude residue was purified via flash chromatography over basic alumina to afford the desired 1-aminoNB as the Schiff base (**2**).

For detailed experimental procedures and characterization data for all cyclopropylimines and 1-aminoNBs presented above, see the Supporting Methods.

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Author Information

Declaration of Interests

The authors declare no competing financial interests.

Associated Content

Equipment employed for photochemical reactions. Reaction optimization, time course profile, and related investigations of the conversion of aminocyclopropane starting materials to 1-aminoNBs **2a** or **2s**. Procedures for collecting spectroscopic data, and related mechanistic data. Detailed experimental procedures and characterization for the preparation of all novel compounds.

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only reagent: **VIOLET LIGHT**

