Radical Reactions

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

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Abstract: *This report details the development of a masked N-centered radical strategy that harvests the energy of light to drive the conversion of cyclopropylimines to 1-aminonorbornanes. This process employs the N-centered radical character of a photoexcited imine to facilitate the homolytic fragmentation of the cyclopropane ring and the subsequent radical cyclization sequence that forms two new C–C bonds en route to the norbornane core. Achieving bond-forming reactivity as a function of the N-centered radical character of an excited state Schiff base is unique, requiring only violet light in this instance. This methodology operates in continuous flow, enhancing the potential to translate beyond the academic sector. The operational simplicity of this photochemical process and the structural novelty of the (hetero)aryl-fused 1-aminonorbornane products are anticipated to provide a valuable addition to discovery efforts in pharmaceutical and agrochemical industries.*

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. elbasvir[6]). 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 cations[10]) and can be paired with additional catalytic protocols (e.g. Ni-based cross-coupling,[11] enantioselective Lewis acid catalysis[12]). 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 space[15] 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-aminoNBs[18] (see Figure 1 A) 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-NH_2 1-aminoNBs. Circumventing this limitation would require another means of accessing open-shell character at nitrogen (see Figure 1 B). Nitrogen-centered radicals have drawn a great deal of interest in recent years, largely driven by photochemical innovation.[24,25] Prominent alternatives to amine radical cations include amidyl or imidyl radicals arising from oxidation of N–H bonds[26,27] via proton-coupled electron transfer (PCET)[28] or from N–X bonds via homolysis,[29–31] reduction,[32] or even oxidation[33] by employing α-aminoxy carboxylic acid auxiliaries popularized by the groups of Leonori[34,35] and Studer.[36,37] Alternatively, it was hypothesized that initiation of our desired fragmentation-cyclization sequence could be accomplished not from a *discrete* N-centered radical but a *temporaneous* N-centered radical. More specifically, a cyclopropylimine would serve as a masked N-centered radical, revealing the nitrogen-based radical character only upon excitation. Directing the focus to aryl aldehydes 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 (and could perhaps be accomplished in a catalytic sense in conjunction with the photochemistry; see

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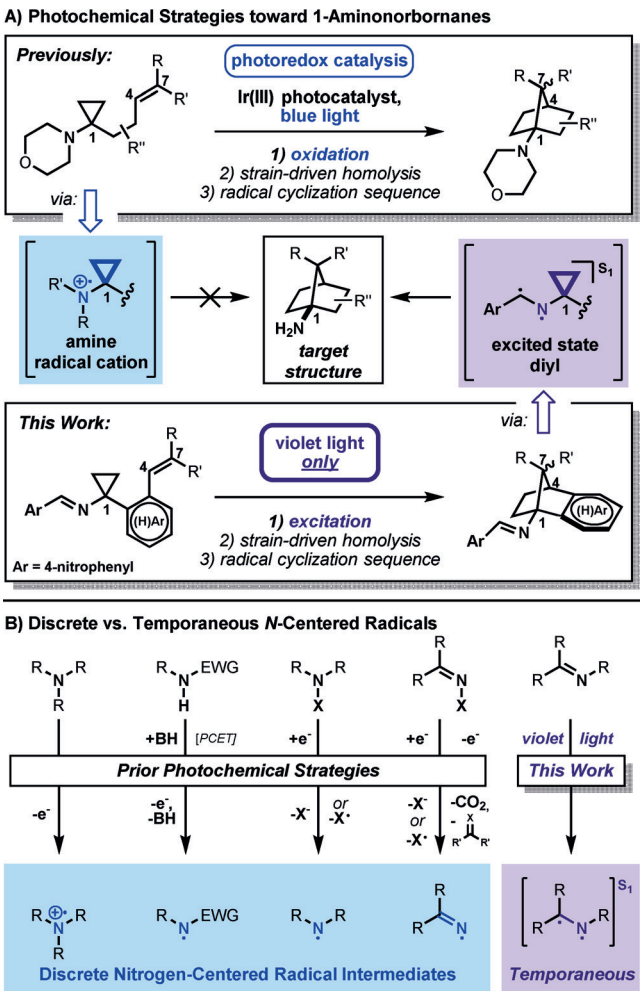


Figure 1. 1-Aminonorbornanes through photochemical innovation: A) Comparison of our photochemical strategies toward 1-aminonorbornanes. B) Comparison of existing approaches for the production of nitrogen-centered radicals with our masked N-centered radical strategy.

Supporting Information), this strategy appeared to offer an efficient solution to the need for C1-NH_2 1-aminoNBs.

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.[38,39] For instance, photoisomerizations of *N*-aryl benzimines are prone to thermal equilibration back to the *E*-isomer,[38] and aza-photocycloadditions tend to require specialized systems, specifically *N*-acyl imines.[38–40] Similarly, achieving an aza variant of the Norrish type II cyclization required an intricately designed oxazolinone from Hoffmann, Abe, and co-workers.[41] Importantly, despite the discrepancies between imine and carbonyl photochemistry, the mechanistic rules that govern excited state reactivity still hold; for example, photochemical electrocyclic ring opening and ring closure reactions proceed through the $^1(\pi,\pi^*)$ state in concordance with Woodward–Hoffmann rules.[38] One example of an imine-specific rearrangement is the photo-racemization of dihydropyrazine (−)-**3** (see Figure 2A),[42] facilitated by the non-classical bond structure available to [2.2.1] bicyclic systems with open-shell character adjacent to the bridgehead position.

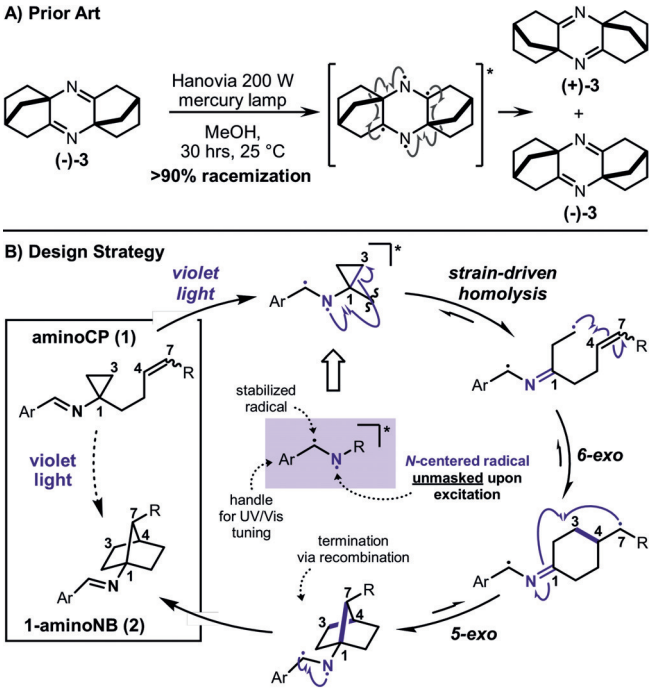


Figure 2. Imine-based photochemistry and the design of our masked N-centered radical strategy: A) Photo-racemization of dihydropyrazine (−)-**3** with UV light[42] (of note, all necessary electron-pushing arrows are depicted, but this is not expected to be a concerted process). B) Design principles behind our masked N-centered radical strategy for the synthesis of 1-aminoNBs.

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 materials[43–46] or from downstream products of cyclopentadiene-acrylate Diels–Alder reactions[47–50] (only one radical-based closure[51] existed before our work[18]).

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 relay reactions from excited state 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[52,53] and Eaton.[54] Termination of both radicals is

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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 is reported herein.

Results and Discussion

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-nitrobenzimine **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[38,39]). 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.[55] Importantly, the relatively large resolution[39,56] 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, where the in-plane association of a nucleophilic σ-bond with the electrophilic singly-occupied lone pair on oxygen drives the requisite bond scission.[55] 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** ($\Delta\lambda_{max}\approx+100$ nm relative to acetaldehyde[56]) 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.

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

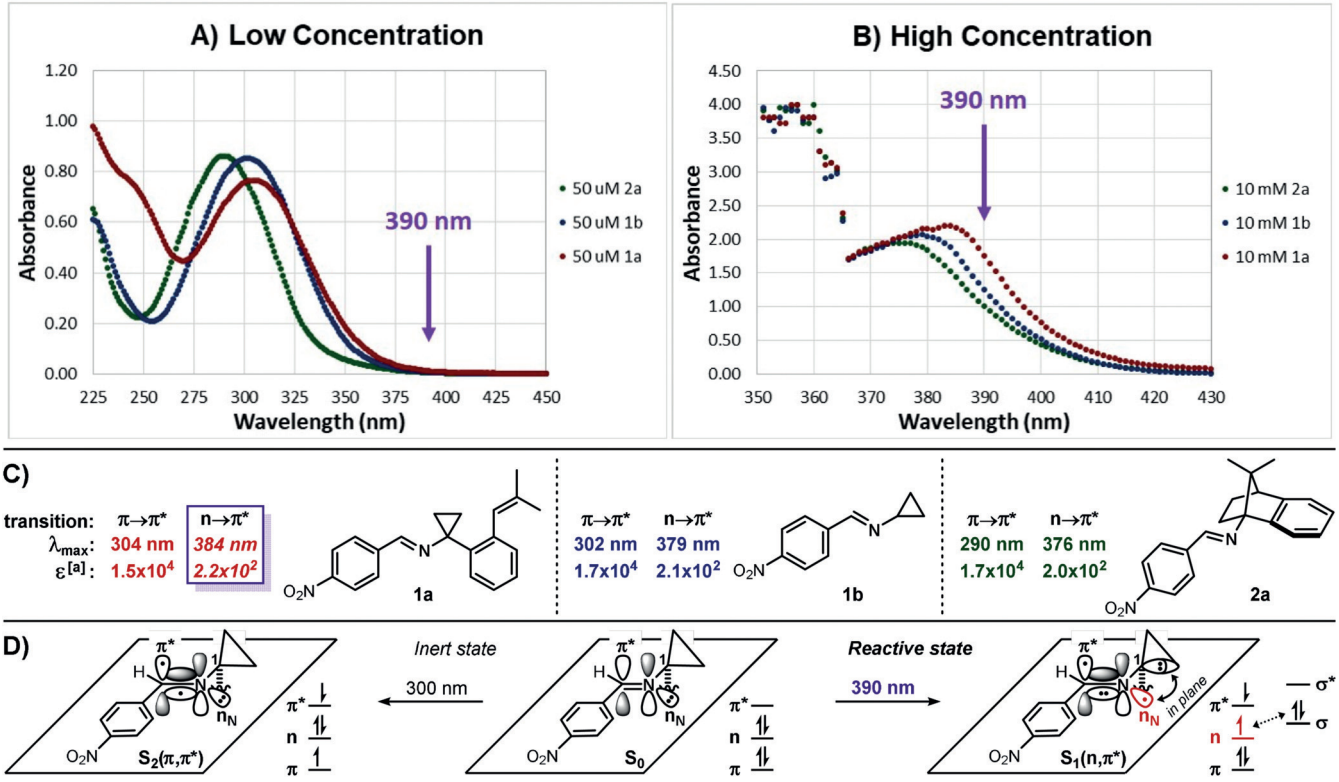
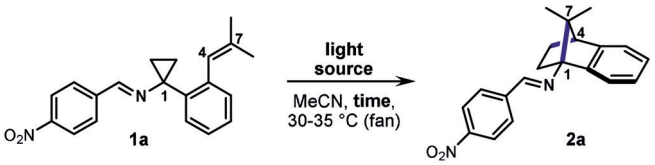


Figure 3. UV/Vis data and proposed mechanism of cyclopropane fragmentation: A) UV/Vis data for cyclopropylimines **1b** and **1a** and 1-aminoNB **2a** collected at 50 μM in MeCN. B) UV/Vis data collected at 10 mM in MeCN. C) Structures and data summary; [a]molar absorptivities (ε) estimated from peak 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.

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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 μmol 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 ^{1}H 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.

fully consume starting material and afford the desired product in 76% yield after 8 hrs of irradiation (entry 1; 200 μmol scale reaction). In concordance with the above analysis, excitation of the π→π* transition with 300 nm light (entry 2) did not proceed to product, and in fact, returned starting material in nearly quantitative recovery. Light sources less optimally-aligned with the n→π* 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.[57] 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).

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,[58–60] 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 irradiation 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

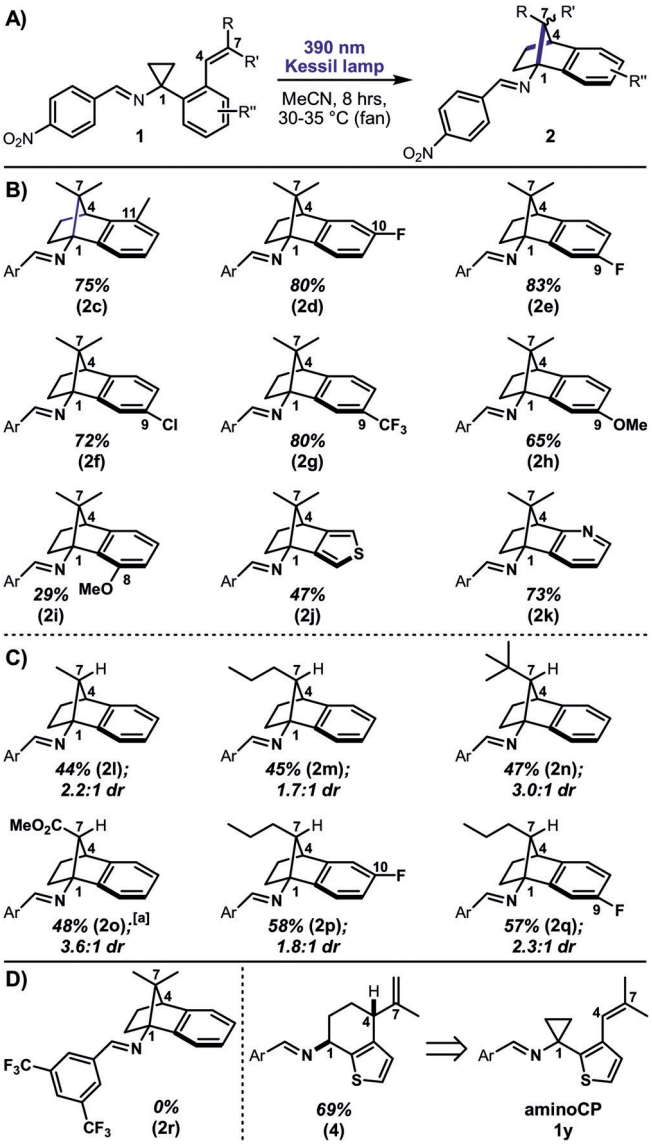


Figure 5. Reaction scope: A) Generic reaction scheme; all reactions were run on ≈200 μmol scale and degassed via three freeze-pump-thaw cycles prior to exposure to optimized conditions; Ar = 4-nitrophenyl. B) Arene modifications. C) C7-substitution effects. [a] C7-CO_2Me substrate proceeded in 3.6:1 *anti*:*syn* dr based on crude ^{1}H NMR, but was isolated in 48% yield in >20:1 dr (an additional 10–15% of a 1:5 *anti*:*syn* mixture was collected along with minor impurities). D) Deviations from designed reactivity.

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-

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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**) 1-aminoNBs (of note, while 11-*aza* 1-aminoNB **2k** was produced in 73% yield, the related 8-*aza* system was isolated in only 20% yield; see pg. S86 of Supporting Information for more details). 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, with steric bulk only minimally increasing the selectivity for the *anti* isomer (e.g. C7-*tert*-butyl system **2n**, 3.0:1 dr); this ratio was also independent of the original olefin geometry as C7-methyl 1-aminoNB **2l** was formed in a 2.2:1 *anti*:*syn* ratio from the *Z*-isomer, while C7-propyl 1-aminoNB **2m** 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 **2m** (58% and 57% vs. 45%). Interestingly, the C7-carboxylate product **2o** was formed with the highest selectivity for the *anti*-isomer (48% yield of *anti* isomer; 3.6:1 dr in crude reaction mixture), suggesting that electronic factors can also serve a minor role.

During the course of evaluating the substrate scope, a number of observations were made that merit discussion. In regards to the role of the nitro motif in our masked N-centered radical strategy, it was proven to be necessary, given that a 3,5-bis(trifluoromethyl)benzimine system was unable to facilitate the production of 1-aminoNB **2r** upon irradiation at 390 nm or at shorter wavelengths (see Supporting Information). Secondly, a 2,3-thiophene-fused cyclopropylimine **1y** provided an intriguing cyclohexane byproduct (**4**) in good yield (69%) rather than the desired 1-aminoNB ($\approx$6%). This represents the only evidence for premature termination pathways competing with the desired radical cyclization sequence; even the closely-related 3,4-thiophene-fused system **2j** did not produce detectable quantities of this byproduct, suggesting strict electronic requirements for the undesired termination. It is not known whether the distonic diyl intermediate progresses to cyclohexane **4** through electron-transfer or H-atom abstraction pathways at this time, nor is it known whether or not this pathway is coupled to the production of the minor pyrroline byproduct ($\approx$10% yield; see pg. 120 of Supporting Information). Of note, the photochemical cyclopropylimine-pyrroline rearrangement has been reported[61–63] (and could be achieved, albeit inefficiently, by irradiating model cyclopropylimine **1b** under standard conditions), but this was not an appreciably competitive pathway. The majority of these transformations generated the desired 1-aminoNBs as the only detectable product, speaking to the overall efficiency of the reaction design despite the implementation of highly-reactive intermediates (i.e. singlet excited states, carbon-centered radicals). In fact, cyclopropylimine **1y** was the only substrate tested that produced isolable quantities of the pyrroline byproduct; see pg. S11 for control experiments and further discussion of this rearrangement as contextualized with our methodology.

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**. Initial removal of the Schiff base proceeded cleanly, as anticipated, to reveal the C1-NH_2 1-aminoNB target **2s** (see Figure 6A). Alternatively, coupling the photochemical method with Schiff base formation and/or removal in a one-pot fashion was proven to be viable (see pg. S8 of Supporting Information), 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. 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 **5**). This methodology was originally developed as a means of delineating S_N1 mechanisms,[64] and variations have been developed to generate 1-hydroxy, 1-halo, and 1-aryl norbornanes[45,65,66] from these unique cationic species; conditions to afford the former[44] were recapitulated herein, providing 1-

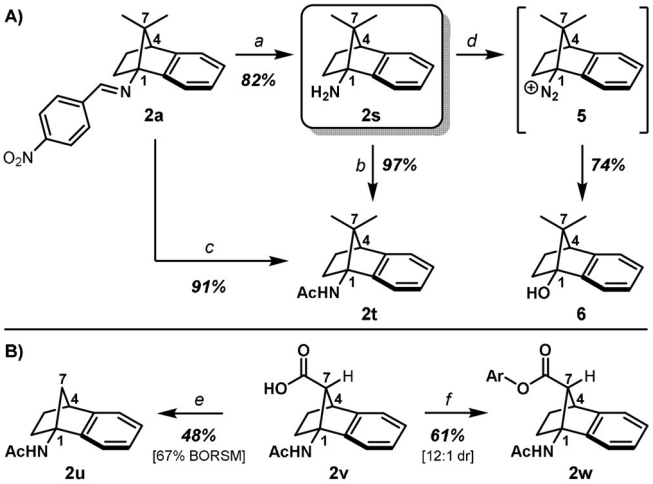


Figure 6. Post-irradiation functionalization of 1-aminoNBs: A) Bridgehead manipulations; Reagents and conditions: a) AcOH, H_2O, MeCN, rt; b) Ac_2O, NEt_3, DMAP, CH_2Cl_2, rt; c) Ac_2O, pTsOH·H_2O, DCE, 75 °C; d) $NaNO_2$, 2 M H_2SO_4 (aq), 1:1 DMF:H_2O, 0 °C to rt. B) Manipulation of C7-CO_2H 1-aminoNB **2v**; Reagents and conditions: e) [Ir(dF(CF$_3$)ppy)$_2$(dtbbpy)](PF$_6$) (2.5 mol%), K_2HPO_4, Two H150 Blue Kessil lamps, 1:1 iPrOH:DMF, 30–35 °C (fan-controlled); f) Ir(dF(CF$_3$)ppy)$_2$(dtbbpy)](PF$_6$) (2.5 mol%), $NiBr_2$·DME (20 mol%), dtbbpy (25 mol%), K_2CO_3, methyl 4-bromobenzoate, Two H150 Blue Kessil lamps, MeCN, 30–35 °C (fan-controlled); Ar = (4-CO_2Me)-C_6H_4.

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hydroxynorbornane **6** in 74% yield. Perhaps the most significant manipulation was the conversion of C7-CO_2Me 1-aminoNB **2o** to the C7-methylene 1-aminoNB **2v** (see Figure 6B). The C7-methylene system provides the closest spatial occupancy to the aniline congener, which could prove critical for the execution of our 1-aminoNB bioisosterism goals (outlined in our prior manuscript[18]). This was achieved through photochemical reductive decarboxylation of a C7-carboxylic acid species (**2u**). Given the prevalence of carboxylic acid manipulations now available, this sequence indicates the potential for rapid diversification of these 1-aminoNB scaffolds. One such attempt yielded *O*-arylated species **2w** via a photochemical Ir^{III}/Ni^{II} co-catalyzed transformation inspired by MacMillan lab research. Of note, while the chosen conditions more closely mimic the decarboxylative cross-coupling methodology,[67] the reaction yielded the product previously ascribed to an energy transfer-mediated transformation.[68] This result communicates the complexity associated with deconvoluting the reactivity available via these co-catalytic photochemical processes,[11] further incentivizing rigorous mechanistic evaluation of these reaction subtypes.[69] Significantly, whether 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.

Conclusion

The work detailed above demonstrates the operational-simplicity and unique reactivity offered by our masked N-centered radical strategy. Initiating a radical C–C bond fragmentation/C–C bond-forming 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). Importantly, this new mode of reactivity ultimately enabled the production of the originally-targeted C1-NH_2 1-aminoNBs, facilitating downstream applications of these saturated buildings 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 Section

In a dry vial under inert atmosphere, cyclopropylimine **1** was dissolved in dry MeCN (0.1M). Reaction mixture was degassed with three freeze-pump-thaw cycles. The reaction was irradiated with 390 nm light (Kessil PR-160 model) for 8 hrs (for 200 μmol-scale reactions), controlling the temperature between 30–35 °C with a fan. The mixture was partitioned between 1:1 saturated $NaHCO_3$ (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**). No unexpected or unusually high safety hazards were encountered. For detailed experimental procedures and characterization data for all cyclopropylimines and 1-aminoNBs presented above, see the Supporting Information.

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Conflict of interest

The authors declare no conflict of interest.

Keywords: 1-aminonorbornane · cyclopropylimine · excited state diyl · imine photochemistry · N-centered radical

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