Synthesis of Bridged Bi-cyclic Amines by Transannular Amination of Remote C–H Bonds: Synergistic Activation by Light and Heat

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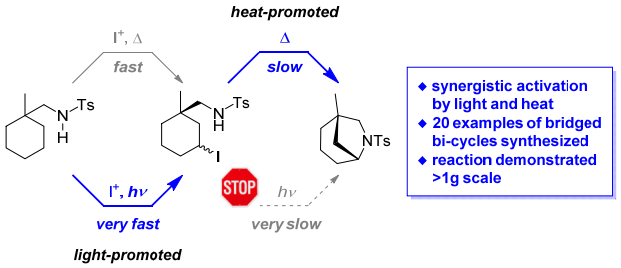
Supporting Information Placeholder

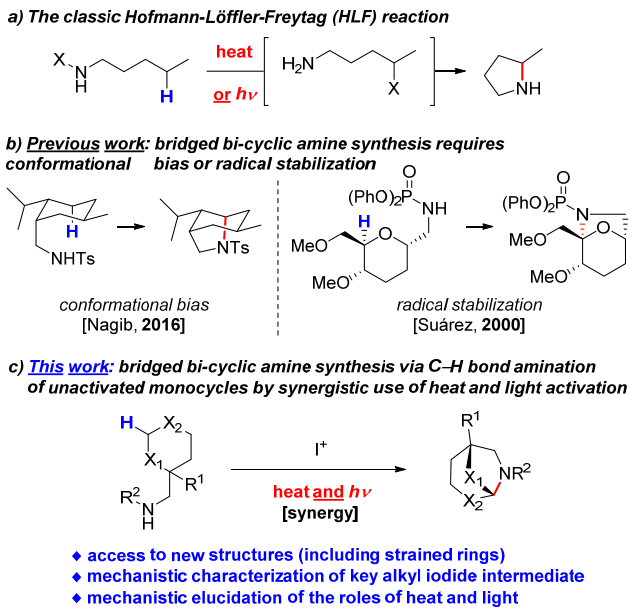


ABSTRACT: Construction of complex aza-cycles is of interest to drug discovery due to the prevalence of nitrogen-containing heterocycles in pharmaceutical agents. Herein, we report an intramolecular transannular C–H amination approach to afford value-added and complexity-enriched bridged bi-cyclic amines. Guided by DFT and NMR investigations, we determined the unique roles of light and heat activation on the bi-cyclization mechanism. We applied both light and heat activation in a synergistic fashion achieving gram-scale bridged aza-cycle synthesis.

In drug discovery, the rapid synthesis of bioactive compounds is enabled by access to diverse arrays of building blocks.[1] General approaches toward complex aza-cycles would positively impact drug design, given the prevalence of nitrogen-containing heterocycles in pharmaceutical agents.[2] Bridged bi-cyclic amines can be difficult to synthesize, but are of significant interest in drug discovery because they have high sp^3 content, a parameter known to correlate with clinical success.[2c, 3] Moreover, the incorporation of rigid bridged bi-cyclic amines into bioactive structures can reduce *in vivo* metabolism,[2b] provide access to unique substituent vectors,[2b, 4] and favorably alter physicochemical properties.[2b] Currently, strategies to synthesize diverse bridged amines are limited. Instead, state-of-the-art methodologies typically target the related classes of spirocyclic or fused aza-cycles,[4a, 5] or target specific ring types in the context of natural product synthesis.[4, 6] As a consequence, bridged aza-cycles remain underrepresented in medicinal chemistry optimization campaigns, not because of a lack of interest, but because of the barrier to synthesize these structures.

In this work, we report a general approach to saturated, medium-sized, bridged bi-cyclic nitrogen heterocycles (Scheme 1). Our work is motivated by Bode's bi-cyclic morpholine synthesis using olefin-amine and aldehyde starting materials.[7] We approached bridged amines in a conceptually distinct manner, relying instead on the construction of a new C–N bond via C–H functionalization onto an existing mono-cyclic amine. To accomplish this goal, we drew inspiration from the Hofmann-Löffler-Freytag (HLF) reaction (Scheme 1a),[8] a common approach toward pyrrolidine synthesis.[8c] To our surprise, this robust transformation has rarely been used in bridge formation, likely due to the increased ring-strain of bi-cycles. As a consequence, conformational bias and/or radical stabilization is typically required for productive bridged aza-cycle formation (Scheme 1b).[8c] Herein, we describe a broadly applicable method toward

a diversity of complex bridged aza-cycles not restricted to activated C–H bonds or conformationally biased scaffolds (Scheme 1c). Our mechanistic studies highlight the importance of the activation method, revealing that heat and light accelerate different elementary steps in the transannular C–H amination and are therefore synergistic. Ultimately, this work has led to 20 bridged aza-cycles containing diverse functionality and structure on up to gram-scale.

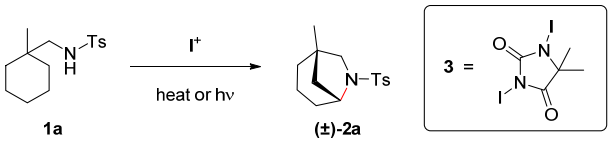


Scheme 1. a) The HLF reaction toward pyrrolidines. b) Previous work: bridged bi-cyclic aza-cycles rely on conformational restriction or radical stabilizing functional groups. c) This work: a comprehensive approach toward bridged bi-cyclic pyrrolidines.

We initiated our investigations with mono-cyclic sulfonamide **1a** which would produce bridged bi-cyclic amine (±)-**2a** upon intramolecular C–H bond amination (Table 1).[9] The modified Suárez conditions developed by Nagib[10] failed to provide the desired product using light activation (Table 1, entry 2); instead, when we applied heat activation, we observed (±)-**2a** (entry 3). This observation is striking, given that known HLF reactions proceed through *either* heat or light activation. Employing triiodide as the halogenating agent failed to yield the bi-cyclization product (entry 4), while I_2 produced (±)-**2a** in modest yield (entry 5), further supporting a mechanistic distinction from Nagib's report.[10] Using *N*-iodosuccinimide (entry 7), *N*-iodosaccharin (entry 8), or *N*-iodohydantoin (entry 9) as the halogenating agent afforded enhanced levels of product formation, as did raising the reaction temperature to 80 °C (entry 10). Other solvents were less effective, as were other halogenating reagents (Cl^+ or Br^+).

The observation that heat and light activation each afford disparate results prompted us to investigate the reaction mechanism. While blue LEDs failed to promote the desired reaction (Table 1, entry 3), Hg-lamp irradiation, which provides higher intensity and shorter wavelengths of light, produced alkyl iodide (±)-**5a**, with only trace amounts of desired product (±)-**2a** (Scheme 2). This experiment suggests that light-mediated N–I bond homolysis and hydrogen atom transfer (HAT) occurs, but light alone is ineffective in promoting cyclization. In contrast, early quenching of the heat-mediated reaction (<50% conversion) revealed the presence of both the alkyl iodide intermediate (±)-**5a** and product (±)-**2a**, indicating that elevated temperature promotes HAT and rapid cyclization. Next, carrying out the reaction at 70 °C, we observed only (±)-**5a**-*syn* by *in situ* NMR. In contrast, the Hg-lamp-promoted reaction produced an equimolar mixture of (±)-**5a**-*syn* and (±)-**5a**-*anti*.[11] Because we observe build-up of alkyl iodide (±)-**5a**-*syn* under thermal conditions, we speculate that rapid S_N2 cyclization of (±)-**5a**-*anti* proceeds immediately upon its formation, precluding detection. We hypothesize that halogenation of a carbon- centered radical occurs indiscriminately in both the light- and heat-mediated reactions to form both diastereomers of alkyl iodide (±)-**5a**, but cyclization to (±)-**2a** only occurs effectively under thermal activation. Furthermore, epimerization of the alkyl iodide intermediate takes place, likely via isodesmic exchange, which is consistent with our kinetic data (see the Supporting Information.[12] Comparing Hg-lamp irradiation with thermal activation in a head-to-head fashion, we observed that (±)-**5a** was formed faster under Hg-lamp irradiation. Accordingly, the synergistic application of heat and photoirradiation using a 1000 W LED flood lamp provided significant rate acceleration, and reduced loading of **3** in a gram-scale experiment (Table 1,

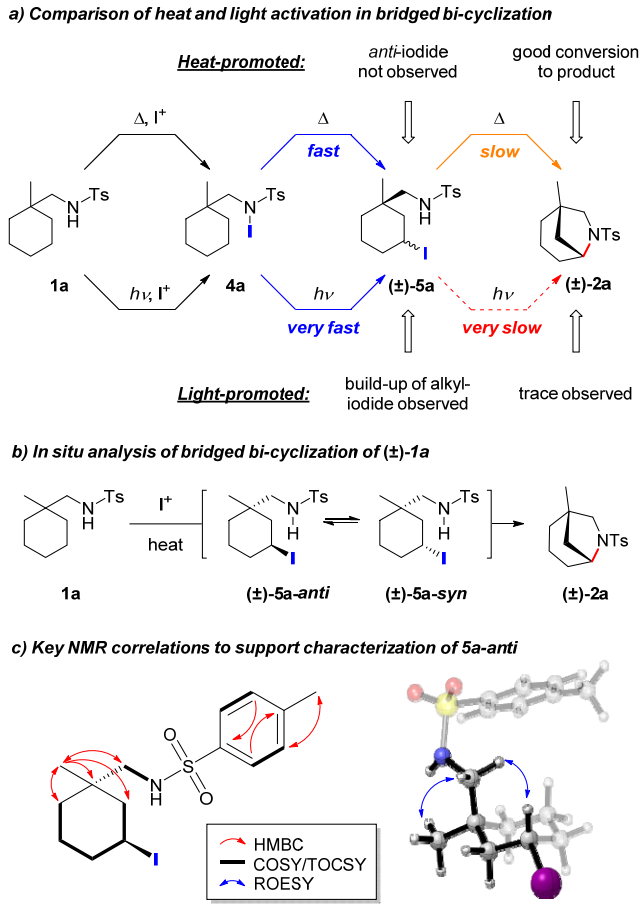
Table 1. Reaction optimization of the bridged bi-cyclization via intramolecular C–H bond amination.[a]



1a (±)-2a

entry	halogenating reagent; equiv	activation mode;[b] time	yield (%)[c]
1	none	blue LED or 50 °C, n/a	0
2	NaI, $PhI(OAc)_2$; 4 equiv	blue LED, 24 h	0
3	NaI, $PhI(OAc)_2$; 4 equiv	50 °C, 24 h	48
4	$(^nBu_4N)I_3$; 4 equiv	50 °C, 24 h	0
5	I_2; 4 equiv	50 °C, 24 h	37
6	pyridine•I–Cl; 4 equiv	50 °C, 24 h	16
7	*N*-iodosuccinimide; 4 equiv	50 °C, 24 h	54
8	*N*-iodosaccharin; 4 equiv	50 °C, 24 h	66
9	*N*-iodohydantoin (**3**); 4 equiv	50 °C, 24 h	80
10	*N*-iodohydantoin (**3**); 4 equiv	80 °C, 24 h	>90 (46)[d]
11	*N*-iodohydantoin (**3**); 4 equiv	80 °C, 72 h	(38)[e]
12	*N*-iodohydantoin (**3**); 2 equiv	1000 W, 50 °C, 6 h	(30)[f]

[a]Conditions: **1a** (0.05 mmol), halogenating reagent (0.2 mmol), MeCN (1 mL), 24 h. [b]Reaction mixtures were activated by either light or heat or both, as specified. [c]Conversion to desired product (±)-**2a** was determined by LCMS. [d]Isolated yield on a 0.2 mmol scale. [e]Isolated yield on a 1 g (3.6 mmol) scale: 0.2 M. [f]Isolated yield on a 2 g (7.2 mmol) scale: 0.2 M. Synergistic activation with light and heat provided enhanced rates. See text for details.



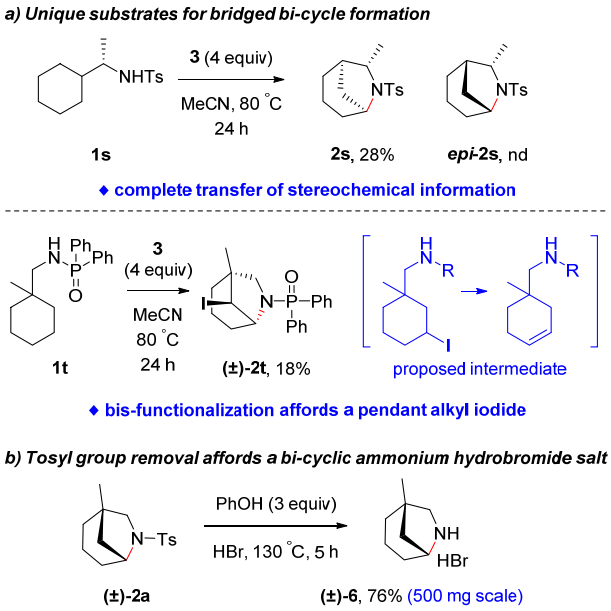
Scheme 2. a) Mechanistic hypothesis for heat and light activation in the formation of bridged bi-cycles. b) Formation of an alkyl iodide intermediate *en route* to bridged bi-cycle (±)-**2a**. c) Key NMR data for characterization of (±)-**5a**-*anti*.

entry 12, light & heat, compared to Table 1, entry 11, heat), affording 600 mg of (±)-**2a** (2.1 mmol) in 6 h.

For practical reasons, we used only heat activation for milligram-scale experiments.[13] We examined mono-cyclic amine starting materials that contained diverse backbone functionality, including substrates bearing different functional groups, heteroatoms, linker lengths, and ring sizes (Table 2, entries 1–9). Different sulfonyl activating groups on nitrogen were tolerated in the reaction (entry 2). Ester-bearing substrate **1c** underwent cyclization to afford (±)-**2c**, a bi-cyclic γ-aminobutyric acid (GABA, entry 3). When benzannulated and heterocyclic sulfonamides (±)-**1c**–**h** were subjected to the reaction conditions, we obtained bi-cyclic tetrahydronaphthalene (±)-**2d** (entry 4), tetrahydroisoquinoline (±)-**2e** (entry 5), and tetrahydropyrans (±)-**2f**–**i** (entries 6–9). Of note, bi-cyclic *N*,*O*-aminals would be challenging to access using alternative strategies.[14] Additionally, a tertiary aliphatic fluoride remained intact in the amination (entry 7), and a tetrahydropyran-containing bi-cyclic α-amino acid could be accessed (entry 8), albeit as a mixture of diastereomers (3:1 dr)—presumably resulting from epimerization at the ester bearing stereocenter. Given the observation that a *N*- or *O*-atom can enhance isolated yields (entries 4–9),[15] we found the HAT barrier for **1a** was 4.6 kcal mol^{-1} higher in energy than for **1g** (DFT; see the Supporting Information), which can potentially explain this effect. Moreover, it is also feasible that neighboring heteroatoms may promote an S_N1 pathway through an oxonium or iminium intermediate.

The conditions identified for amination onto six-membered rings were readily extended to five-, seven-, and eight-membered rings (Table 2, entries 10–18). Cyclopentane-derived substrate **1j** was readily converted to the corresponding bi-cyclic amine product (±)-**2j** in synthetically useful yields (entry 10), and cycloheptane- and cyclooctane-derived substrates **1l** and **1m** undergo bi-cyclization to afford (±)-**2l** (entry 12) and (±)-**2m** (entry 13), respectively. Substrate (±)-**1k**, which was isolated as a 3:1 mixture of *trans* and *cis* diastereomers, was readily converted to a single bi-cyclic product, (±)-**2k** (entry 11). Cyclobutanes were unproductive in the bi-cyclization (not shown). Notably, transannular C–H bond amination without the methylene linker effectively led to bi-cyclic amines (±)-**2n**–**r** (entries 14-18). While amines directly attached to a cycloheptane undergo rapid bi-cyclization, substrates bearing smaller rings, including cyclohexanes, did not react efficiently (not shown). Bicyclization also proceeded smoothly for substrates bearing ester (**1o**, entry 15) or nitrile (**1p**, entry 9) functionalities in place of the quaternary methyl, forming bi-cyclic α-amino acid and α-amino nitrile derivatives, respectively. To our delight, amide- and oxepane-derived sulfonamides (±)-**1q** and (±)-**1r**, were likewise competent substrates for the transannular bi-cyclization, forming (±)-**2q** (entry 17) and (±)-**2r** (entry 18), respectively.

Next, when we applied chiral mono-cyclic sulfonamide **1s** as a substrate, we observed only one diastereomer of the anticipated product (**2s**, Scheme 3a). The high level of stereochemical communication highlights the utility of our strategy toward chiral bridged aza-cycles. The 1,5-HAT barrier *en route* to **2s** is 3.1 kcal mol^{-1} lower in energy than the corresponding transition state to *epi*-**2s** (DFT; see the Supporting Information). Beyond chirality transfer, contemporaneous with Nagib's account,[16] we observed aza-cycle (±)-**2t** with a pendant alkyl iodide when



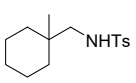
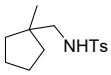
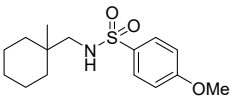
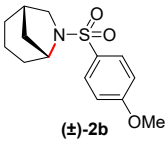
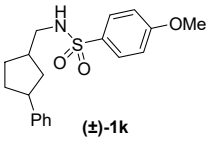
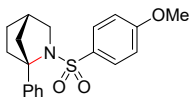
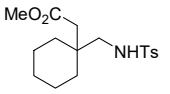
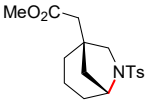
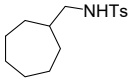
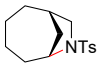
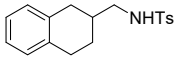
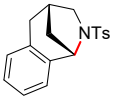
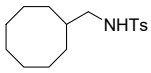
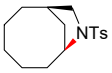
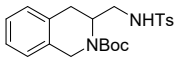
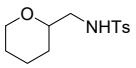
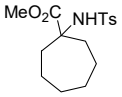
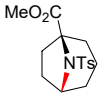
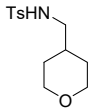
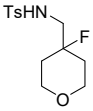
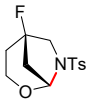
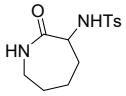
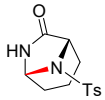
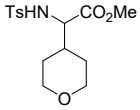
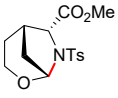
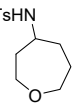
Scheme 3. a) Bridged bi-cyclization is stereospecific, and a bridged bis-functionalization: iodoamination via double C–H bond activation. b) Bridged sulfonamides are readily deprotected.

using a phosphinyl activating group on nitrogen instead, presumably forming through an olefin intermediate. Finally, removal of the tosyl activating group on (±)-**2a** was successful

upon treatment with HBr and phenol, affording the N–H azacycle **(±)-6** (Scheme 3b) as a hydrobromide salt on a 500 mg scale.

In conclusion, we have developed a robust and functional-group-tolerant method for C–H bond amination based on HLF reactivity, providing a general approach to bridged bi-cyclic amines. These scaffolds are of interest to the medicinal chemistry and academic communities alike. Bridged bi-cyclic amines with rich functional group diversity have been prepared, and our reaction can successfully be carried out on gram scale. Informed by the elucidation of alkyl iodide intermediates, we deconvoluted the roles of light and heat activation, providing evidence that light promotes N–I bond homolysis and HAT, while heat promotes S_N2 ring closure. Expansion of this technology to fused and spirocyclic bi-cyclic amines, a deeper understanding of selective C–H bond amination, and further optimization of multi-gram scale building block syntheses are the subject of ongoing investigation and will be reported in due course.

Table 2. Substrate scope of bridged six-, seven-, eight-, and nine-membered bi-cyclic amines from insertions into five-, six- seven-, and eight-membered rings. General reaction conditions: starting material (0.2 mmol), *N*-iodohydantoin (0.8 mmol), MeCN (4 mL), 24 h, 80 ºC. Isolated yields reported. [a]Isolated yield on a 1 g (3.6 mmol) scale. [b]3:1 d.r. was determined by ^{1}H NMR analysis of the crude product.

entry	starting material	product	yield	entry	starting material	product	yield
1	 **1a**	 **(±)-2a**	46% (38%)[a]	10	 **1j**	 **(±)-2j**	44%
2	 **1b**	 **(±)-2b**	60%	11	 **(±)-1k** 3:1 *trans*/*cis*	 **(±)-2k**	64%
3	 **1c**	 **(±)-2c**	41%	12	 **1l**	 **(±)-2l**	42%
4	 **(±)-1d**	 **(±)-2d**	42%	13	 **1m**	 **(±)-2m**	17%
5	 **(±)-1e**	 **(±)-2e**	66%	14	 **1n**	 **(±)-2n**	30%
6	 **(±)-1f**	 **(±)-2f**	58%	15	 **1o**	 **(±)-2o**	47%
7	 **1g**	 **(±)-2g**	87%	16	 **1p**	 **(±)-2p**	39%
8	 **1h**	 **(±)-2h**	47%	17	 **(±)-1q**	 **(±)-2q**	21%
9	 **(±)-1i**	 **(±)-2i**	57% 3:1 d.r.[b]	18	 **(±)-1r**	 **(±)-2r**	55%

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

Experimental procedures; characterization data; kinetic data; ^{1}H and ^{13}C NMR spectra, DFT calculations and Cartesian coordinates

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The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript. ‡↑These authors contributed equally.

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13. Small scale LED set-ups, such as the one described in Table 1, entry 2, did not afford productive acceleration or conversion to desired product. Commonly employed set-ups (e.g., Kessil lamps, LED plates) were likewise ineffective. We posit that the high power of the 1000 W flood lamp is important for the synergistic acceleration. Performing the reaction in flow was also ineffective due to fouling of the reaction tubing.
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