Selective Piperidine Synthesis Exploiting Iodine-Catalyzed C_{sp}^3-H Amination under Visible Light

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ABSTRACT: A route to selective piperidine formation through intramolecular catalytic C_{sp}^3-H amination is described. This hydrocarbon amination reaction employs a homogeneous iodine catalyst derived from halogen coordination between molecular iodine and a terminal oxidant. It relies on visible light initiation and proceeds within two catalytic cycles that comprise a radical C-H functionalization and an iodine-catalyzed C-N bond formation. Under these conditions, the commonly observed preference for pyrrolidine synthesis based on halogenated nitrogen intermediates within the Hofmann-Löffler domain is effectively altered in favor of a free radical promoted piperidine formation. The protocol is demonstrated for a total of 30 applications.
KEYWORDS: *amination, C-H functionalization, halogen bonding, iodine, light initiation.*

Intramolecular amination of remote aliphatic C-H bonds is of particular conceptual interest as it streamlines existing protocols for the preparation of saturated N-heterocycles.[1] These compounds are usually accessible by classic radical chemistry,[2] in which modified Hofmann-Löffler reactions have demonstrated a unique potential.[3] We recently initiated exploration into iodine-catalyzed Hofmann-Löffler reactions[4] that provide the expected access to pyrrolidines from position-selective C-H functionalization based on intramolecular 1,5-H abstraction[3,5] through a nitrogen centered radical pathway (Figure 1, top).

In contrast, the related C-H amination strategy toward the piperidine core is significantly more challenging as the required 1,6-H abstraction from nitrogen-centered radicals is kinetically disfavored.[6] Consequently, a C-H amination strategy owards piperidines has remained elusive.[7] Piperidines represent important structural subunits in molecules of pharmaceutical, biological and medicinal interest, and exercise important pharmacophoric properties.[8] In fact, a recent analysis on the occurrence of nitrogen heterocycles in FDA approved pharmaceuticals identified the piperidine core as the most frequent member.[9] As a result, piperidine synthesis within intramolecular amination of remote C-H bonds would constitute an important synthetic advance. We here report on conditions for such a selective synthesis for the first time (Figure 2, bottom).

To override the given "innate" preference for pyrrolidine formation, we decided to pursue conditions that would preferentially generate free radicals outside the amidyl radical manifold involved in the Hofmann-Löffler pathway.[3] Within such a scenario, free radical hydrogen atom abstraction should address the weakest C-H bond and could be predicted by the introduction of carefully pre-organized substitution.[10,11]

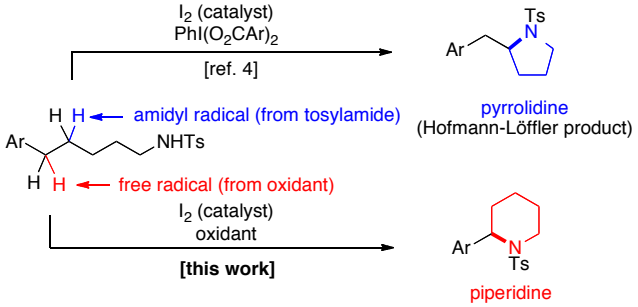
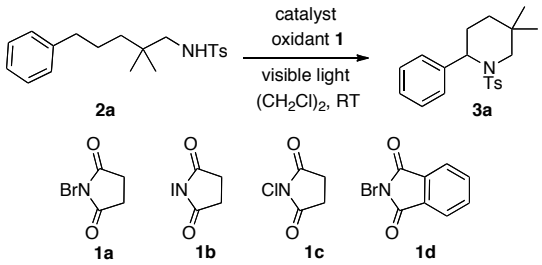


Figure 1. Position-selective intramolecular C-H amination for pyrrolidine and piperidine synthesis.

We previously reported that iodinated reagents such as NIS **1b** effectively provide intermediates for exclusive Hofmann-Löffler reactions.[12] As a consequence of this observation and in order to prevent potential background reactions, we turned to less reactive bromine-based reagents. Catalytic amounts of molecular iodine[13] were pursued to generate low amounts of free radicals as the reaction carriers and thus to minimize potential side reactions. These halide reagent combinations provide the desired gateway to the elusive piperidine formation. Table 1 provides insight in the optimization of catalytic reaction conditions that allow for selective piperidine synthesis within C-H amination.

Table 1. Iodine-catalyzed piperidine formation: optimization.

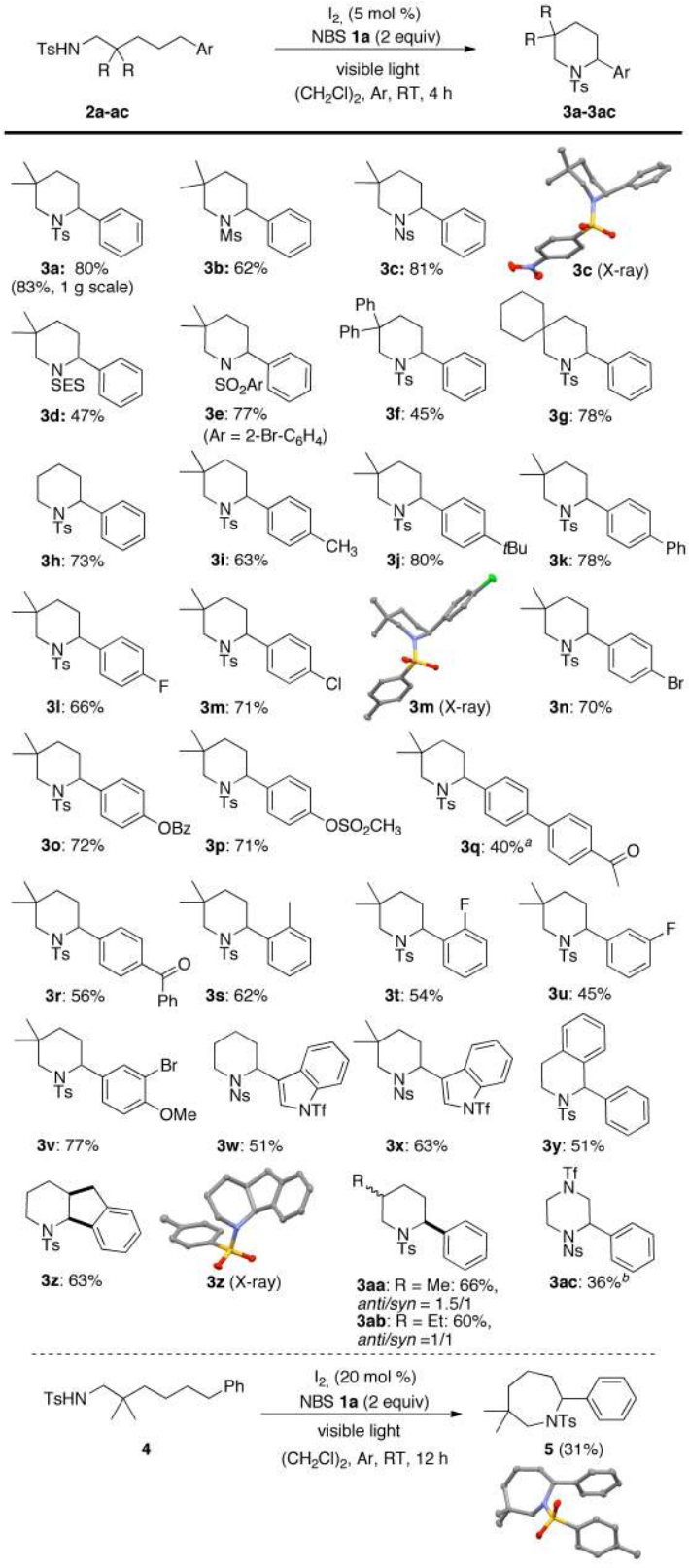


entry	catalyst	oxidant (equiv)	time [h]	yield [%][a]
1	I_2 (5 mol%)	**1a** (1.2)	4	47
2	I_2 (5 mol%)	**1a** (1.6)	4	62
3	I_2 (5 mol%)	**1a** (2.0)	2	80
4	I_2 (5 mol%)	**1b** (2.0)	12	34
5	I_2 (5 mol%)	**1c** (2.0)	12	n.d.[b]
6	I_2 (5 mol%)	**1d** (2.0)	12	72
7	-	**1a** (2.0)	12	0
8[c]	I_2 (5 mol%)	**1a** (2.0)	12	0
9	KI (10 mol%)	**1a** (2.0)	12	50
10	TBAI (10 mol%)	**1a** (2.0)	12	30
11[d]	I_2 (5 mol%)	**1a** (2.0)	12	73
12[e]	I_2 (5 mol%)	**1a** (2.0)	12	67
13[f]	I_2 (5 mol%)	**1a** (2.0)	12	0

[a]Isolated yield after purification. [b]n.d. = not determined (observation of trace amounts of **3a** in the crude NMR). [c]Reaction in the dark lab. [d]Reaction in CH_2Cl_2. [e]Reaction in MeCN. [f]Reaction in THF.

The reaction was developed with **2a** as substrate and departed from the observation that a combination of visible light exposure, 5 mol% molecular iodine and *N*-bromo succinimide (NBS) **1a** provided a selective transformation to the desired piperidine **3a** (entry 1). Subsequent rise of the amount of oxidant to 2 equivalents provided **3a** in 80% yield (entries 2,3) without detection of the corresponding pyrrolidine. This observation proofs that the current conditions are capable of overriding conventional Hofmann-Löffler chemistry. Related iodo and chloro derivatives NIS **1b** and NCS **1c** provided significantly decreased reactivity (entries 4,5) accompanied by formation of the undesired pyrrolidine, while *N*-bromo phthalimide **1d** gave a comparable yield of 72% (entry 6). Control experiments verify that no formation of **3a** is obtained without the iodine catalyst or in the absence of light (entries 7,8). Alternative iodine catalyst sources andreactions in alternative solvents gave lower yields (entries 9-13).

Under the optimized conditions, the scope of the reaction was explored (Scheme 1). For tosylamide **2a**, the reaction was extended to a 1g-scale. Several additional sulfonimides **2b-e** including mesyl, nosyl, trimethylsilylethylsulfonyl (SES) and 2-bromophenyl sulfonyl also provide the corresponding piperidination products **3b-e**. Use of different substituents in the chain is demonstrated for **3f**,**g** and the reaction could be extended to the synthesis of the unsubstituted 2-phenyl piperidine **3h**.



Scheme 1. Piperidine Formation from C-H Amination: Scope (0.2 mmol scale). Yields refer to isolated material after purification. All reactions proceed with >90% selectivity in favor of piperidine formation (>95% yield based on recovered starting material). [a]1.6 equiv. of NBS. [b]20 mol% I_2, white LED.

Common organic substituents are well tolerated on the arene group as demonstrated for derivatives **3i-3v**. These examples include 2-, 3- and 4-disubstitution patterns as well as higher substitution and as for **3q,r** also include carbonyl derivatives, which are non-compatible with the corresponding light induced iodine-catalyzed Hofmann-Löffler reaction.[4] The reaction also proceeds for heteroaromatic (**3w,x**) and dibenzylic derivatives (**3y**), and yields diastereomerically pure piperidine **3z** from cyclic stereocontrol, while acyclic stereocontrol is not possible under the reaction conditions (**3aa** and **3ab**). The C-H amination scope also includes related heterocycles such as the pharmaceutically relevant piperazine core **3ac.** For compounds **3c**, **3m** and **3z** their constitution was unambiguously established by single crystal X- ray analyses.[14]

It is noteworthy that potentially competing pyrrolidine formation was not observed in any of these cases. While the reactions were usually conducted with tosylamides as the representative sulfonamide groups, the use of SES and Ns enables a convenient approach to the corresponding free piperidines.[14] The reaction conditions could also be extended to the selective formation of a seven-membered derivative **5**, using an increased catalyst loading. It demonstrates the inherent potential of the current methodology for the synthesis of more advanced nitrogen heterocycles such as azepanes as well.

This novel C-H amination reaction is rationalized by the following merger of two catalytic cycles (Figure 2).

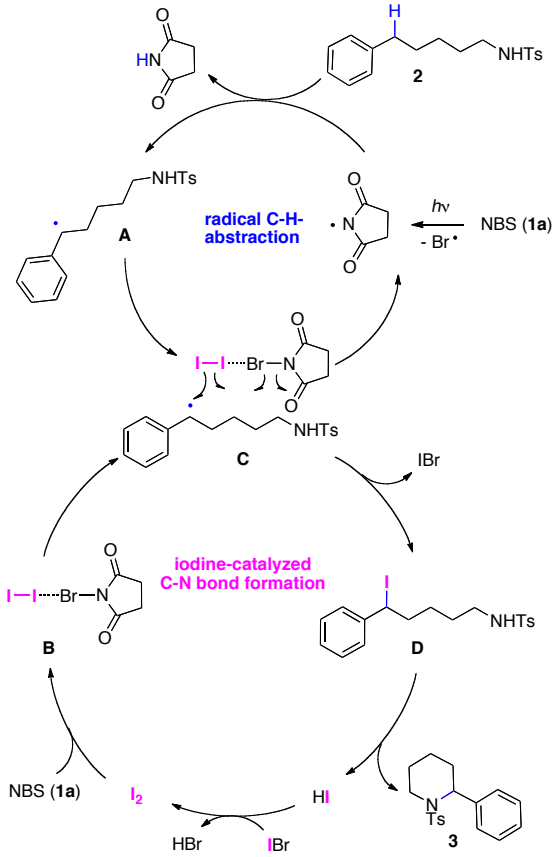
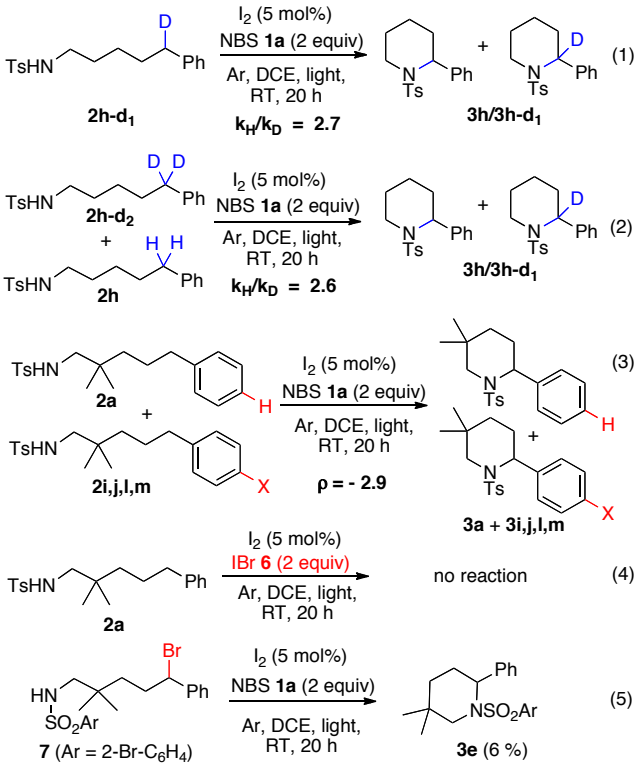


Figure 2. Position-selective intramolecular C-H amination.

It initiates from visible light-assisted homolytic cleavage of the N-Br bond in NBS.[15] The N-centered succinimidoyl radical then abstracts a hydrogen atom at the benzylic position of the substrate **2**. The respective benzylic C-H bonds are of lower BDE than the competing ones, which provides the required selectivity within this free radical reaction step.[16] Control experiments with deuterated staring materials **2h-d$_1$** and **2h-d$_2$** provide intra- and intermolecular kinetic istope effects of 2.6 and 2.7, respectively (Scheme 2, eq. 1,2).[14]



Scheme 2. Control Experiments.

These results suggest the intramolecular radical C-H abstraction to be the slow step of the reaction, which is further corroborated for a Hammett correlation with a ρ-value of -2.9 (eq. 3). The intermediary benzylic radical **A** abstracts an iodine atom from a halogen-bonded[17] I_2-NBS adduct **B** to generate IBr **6** and the intermediary benzyl iodide **D** and regenerates the succinimide radical.[18] The formation of the latter closes the catalytic cycle of radical C-H functionalization. The benzylic iodide undergoes nucleophilic substitution to the pyrrolidine product **3**.[19] The liberated HI regenerates the molecular iodine catalyst upon reaction with IBr **6**. This compound could potentially engage in radical halide formation itself, but is unproductive under the current conditions as demonstrated by a control experiment (Scheme 2, eq. 4). Molecular iodine recoordinates NBS **1a** within a halogen bonding mode,[17] which closes the second catalytic cycle of iodine catalysis. Closely related species such as I_2-*N*-chloropthalimide had been invoked previously by Ishihara in iodolactonization reactions.[20,21] The postulation of a free radical mechanism outside the classical N-centered radical from N-halogenation as in the Hofmann-Löffler scenario is in agreement with the observation that molecular iodine does not convert tosylamides into their N-iodinated derivatives.[4] However, upon polarization by halogen bonding with the N-bromo succinimide **1a** the radical pathway to C-H functionalization is switched on. The postulated pathways do not involve direct benzylic bromination with NBS **1a**. This is in agreement with the observation that benzyl bromide derivative **7** does not cyclize to piperidine **3e** under the reaction conditions (Scheme 2, eq. 5) and thus con-

stitutes a dead-end. Obviously, successful nucleophilic piperidine formation requires the more reactive benzyl iodide intermediate **D**.[14]

In summary, we have identified mild and uniform conditions for a selective iodine-catalyzed C-H amination of 2-aryl substituted piperidines. This reaction overrides the common preference for pyrrolidine formation within the Hofmann-Löffler manifold and significantly enlarges both the scope of light-induced iodine-catalysis and position-selective C-H amination reactions. In addition, it diversifies the chemical space of piperidines.

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Notes

The authors declare no competing financial interest.

ASSOCIATED CONTENT

Supporting Information. Experimental details, control experiments and compound characterization (PDF), and details on the X-ray analyses (CIF). The Supporting Information is available free of charge on the ACS Publications website.

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ABBREVIATIONS

NBS, N-bromo succinimide; DCE, dichloroethane.

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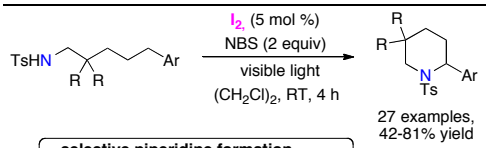

27 examples,
42-81% yield

- **selective piperidine formation**
- **benign light induced reaction**
- **radical C-H functionalization**
- **iodine-catalyzed C-N bond formation**