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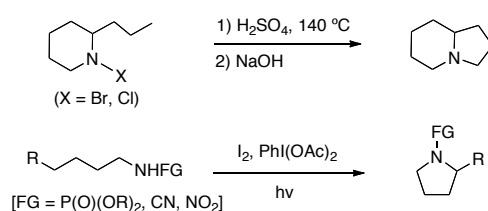
An Iodine Catalysed Hofmann-Löffler Reaction

Claudio Martínez,^[a] and Kilian Muñoz*^[a,b]

Dedicated to Professor Antonio Echavarren on the occasion of his 60th birthday

Abstract: Iodine reagents have been identified as economically and ecologically benign synthetic alternatives to transition metals, although their application as molecular catalysts in challenging C-H oxidation has remained elusive. An attractive iodine oxidation catalysis is now shown to promote the convenient conversion of ubiquitous carbon-hydrogen into carbon-nitrogen bonds with unprecedented complete selectivity. The reaction proceeds within two interlocked catalytic cycles comprising a radical chain reaction, which is initiated by visible light as energy source. This unorthodox synthetic oxidation strategy of direct amination of alkyl groups has no biosynthetic precedence and provides an efficient and straightforward access to a general class of saturated nitrogenated heterocycles.

Nitrogen-halogen bonds have a long history in the synthesis of pyrrolidines and related heterocyclic structures through the amination reaction of a distant carbon-hydrogen bond.^[1] For such approaches with preformed chlorinated and brominated amines, the transformation is known as Hofmann-Löffler reaction (Scheme 1, top). Despite the great attractiveness of such an approach toward aminated 5-membered ring compounds, the required rather harsh conditions have prevented wider application.^[1a,b] Modification of the common protocol include the *in situ* formation of the corresponding *N*-iodinated amides from the combined use of molecular iodine and a large excess of commonly available iodine(III) reagents^[2,3] with the requirement of an external light source (Scheme 1, bottom). These reactions usually start from electron-acceptor substituted nitrogen groups and were employed largely in steroid and carbohydrate chemistry.^[3]



Scheme 1. Hofmann-Löffler reactions: classical reaction conditions (top) and Suárez modification (bottom).

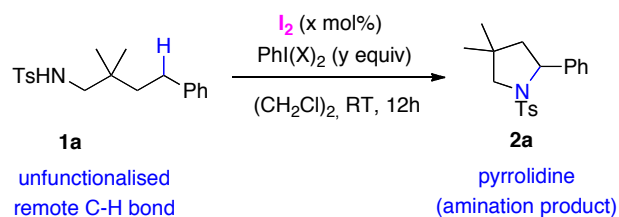
Although a significantly more desirable process from a synthetic standpoint, a variant catalytic in iodine remains a challenging task and has so far not been realised. Such a conceptually novel reaction is of fundamental interest, since it addresses the quest for a catalytic remote C-H amination process of unfunctionalised hydrocarbons based on an iodine derivative as a benign non-metallic catalyst. Molecular catalysis based on iodine^[4] has recently been considered an attractive, mechanistically distinct alternative to the far more common transition metal catalysis, although truly efficient protocols for C-N bond formation remain yet to be developed.^[5]

Table 1. Development of the iodine-catalysed visible light-induced C-H amination reaction: Reaction optimisation. Yields refer to isolated yields of **2a** after purification.

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Entry	I ₂ (x mol%)	X	y	Yield [%]
1	100	O ₂ CMe	3	67
2	20	O ₂ CMe	3	<10
3	100	O ₂ C <i>t</i> Bu	3	89
4	20	O ₂ C <i>t</i> Bu	3	78
5	20	O ₂ C <i>t</i> Bu	1	<10
6	20	<i>m</i> CBA	3	98
7	20	<i>m</i> CBA	1	98
8	5	<i>m</i> CBA	1	98
9	2.5	<i>m</i> CBA	1	98
10	1	<i>m</i> CBA	1	95
11	0.5	<i>m</i> CBA	1	76
12	0.1	<i>m</i> CBA	1	-
13†	5	<i>m</i> CBA	1	-
14§	0.5	<i>m</i> CBA	1	85
15¶	5	<i>m</i> CBA	1	98
16 ^f	2.5	<i>m</i> CBA	1	98

† Reaction in a dark laboratory (red light).

§ Reaction at 400 nm wavelength irradiation.

¶ Reaction on 13 mmol scale.

^f Reaction in the presence of 10 equiv of *m*CBAH.

The required fundament for such a reaction was explored for the representative compound **1a** (Table 1). Over-stoichiometric oxidation conditions^[3] could be employed, however, changing to catalytic amounts of iodine shut down the reaction (entries 1,2). This problem could be overcome by alteration of the carboxylate component of the hypervalent iodine reagent from acetate to pivalate. This oxidant did allow reducing the iodine amount to a catalytic 20 mol%, while similar results as in the stoichiometric reaction were maintained (entry 3 vs. 4). Still, a significant excess of iodine(III) reagent was required (entry 5). Further modification of the iodine(III) reagent to $\text{PhI}(\text{mCBA})_2$ [*m*CBA = 3-chlorobenzoate] provided quantitative yields of **2a**, even when a single equivalent of this oxidant was used (entries 6,7). The iodine catalyst could be successively lowered to 2.5 mol%, without loss in yield, and still 95% yield was obtained at 1 mol% catalyst loading. Reasonable conversion as still achieved at 0.5 mol%, while the amination no longer proceeds upon further decrease to 0.1 mol% (entries 8-12). The optimised conditions call for only a single equivalent of terminal oxidant, which demonstrates the effectiveness of the new reaction. Usually, iodine catalysed reactions require excess of terminal oxidants.^[4,6] Moreover, it is noteworthy that the catalytic use of iodine provides a significantly cleaner reaction outcome in the oxidation of **1a** than a comparable protocol using the overstoichiometric combination $\text{I}_2/3 \text{ PhI}(\text{OAc})_2$,^[5] which forms product mixtures.^[7] The reaction progresses under visible light upon convenient exposure to daylight. In contrast to initial reports on stoichiometric reagent combination,^[3] an external light bulb is no longer required, which greatly facilitates experimental setup. In the absence of light irradiation, amination does not occur (entry 13). The optimum wavelength within the visible light spectrum was deduced to be at 400 nm from a series of individual experiments at different wavelengths.^[7] An experiment using a diode to enable a defined irradiation at 400 nm indeed provided an outcome with slightly increased yield (85 vs 76%, entries 11, 14).^[7] To maintain operational simplicity, reactions were usually conducted upon exposure to daylight in the absence of a photo reactor. The versatility of these conditions was demonstrated for a reaction scale up to 13 mmol, which provided quantitative formation of **2a** (entry 15). The initial reaction between molecular iodine and the hypervalent iodine(III) reagent $\text{PhI}(\text{mCBA})_2$ should provide formation of $\text{I}(\text{mCBA})$ (Figure 1A),^[8] which is the active catalyst. With every turnover, the reaction from Table 1 generates two equivalents of carboxylic acid. However, presence of free acid does not influence the overall performance of the reaction. A control experiment starting in the presence of excess free carboxylic acid did not show any change in reaction outcome (Table 1, entry 16). In fact, the catalyst $\text{I}(\text{mCBA})$ might receive beneficial stabilisation through acid adduct formation. To confirm this hypothesis, we prepared and structurally characterised the related tetrabutylammonium derivative $\text{Bu}_4\text{N}[\text{I}(\text{mCBA})_2]$ **3**.^[9] The core anion $[\text{I}(\text{mCBA})_2]^-$ is depicted in Figure 1B and displays the expected linear coordination geometry at the central iodine atom. A cyclisation reaction of **1a** with this compound led to a reaction outcome comparable to catalytic cycloaminations. This suggests that the active catalyst $\text{I}(\text{mCBA})$ is stabilised by free acid to $\text{H}[\text{I}(\text{O}_2\text{CAr})_2]$, and

regenerated upon dissociation. As deduced from independent control experiments, hypoiodite catalysis is entirely ineffective for the present transformation as are related iodine species generated in the presence of alternative oxidants.^[7] Stoichiometric amounts of molecular iodine as the sole promoter also fail to induce the C-H amination reaction.

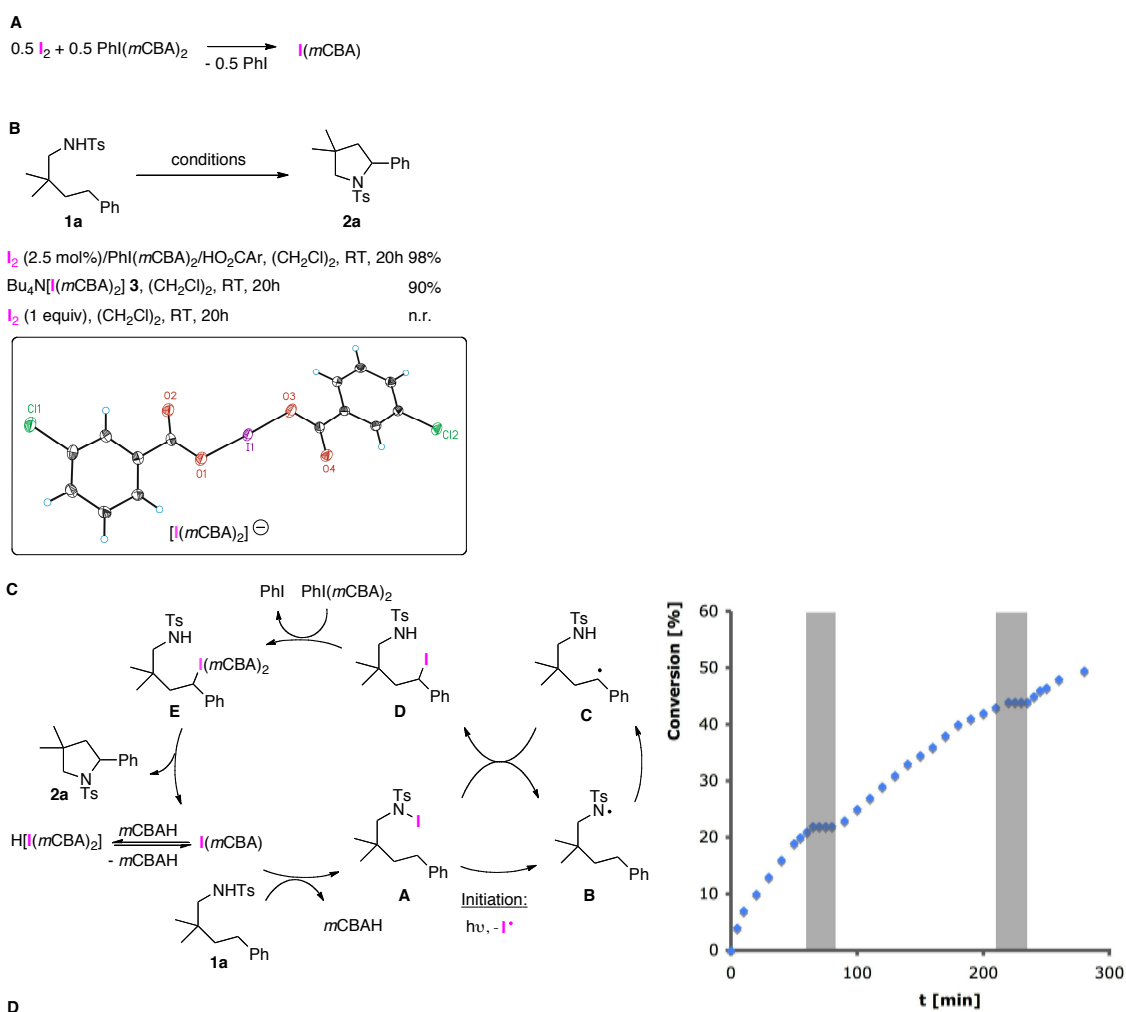
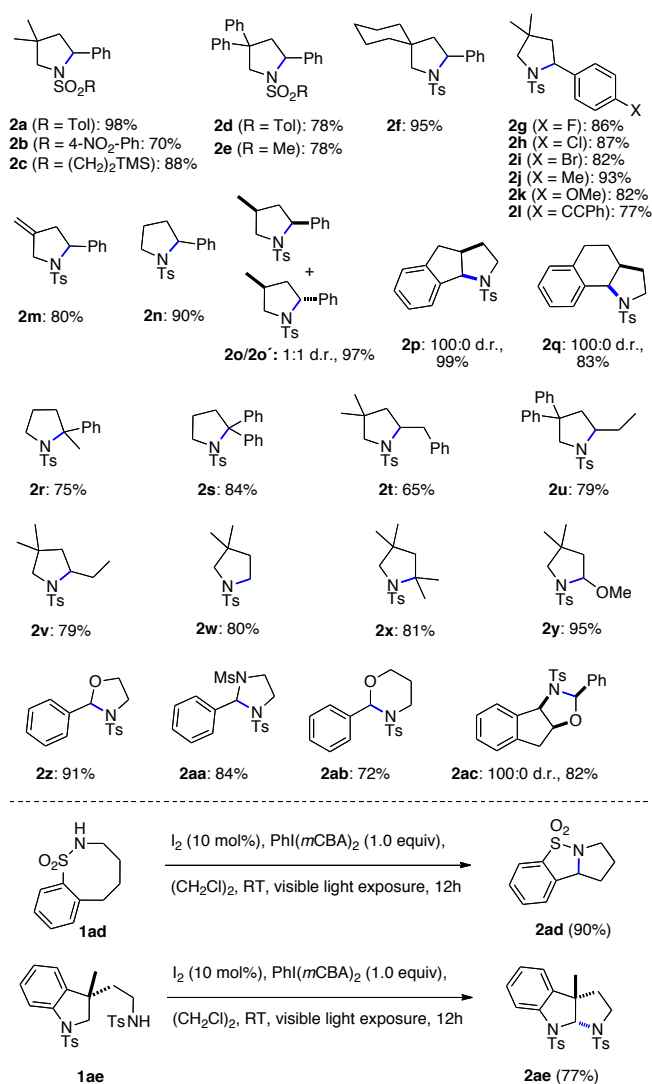


Figure 1. Mechanistic context of the iodine-catalysed visible light-induced C-H amination reaction: **A** catalyst formation, **B** control experiments, **C** catalytic cycle and **D** *in situ* NMR monitoring for the reaction progress in the presence (white background) and absence (grey background) of monochromatic light source. n.r. = no reaction.

The mechanistic rationale for the present iodine catalysis is given in Figure 1C. Once the I(mCBA) catalyst is generated, this compound promotes the N-I bond formation to generate the crucial intermediate **A** from **1a**. Apparently, the iodinated sulfonamide moiety in **A** represents the chromophore for the photochemically induced homolysis of the N-I bond. The resulting nitrogen centred radical **B** engages in 1,5-hydrogen atom abstraction from the benzylic position to generate the carbon centred radical **C**. This intermediate abstracts an iodine atom from another molecule **A** within a radical chain reaction^[10] to arrive at the iodinated intermediate **D**. Direct nucleophilic amination to **2a** at this stage appears possible, however, a significantly enhanced reactivity arises from oxidation to the alkyl iodine(III) intermediate **E**.^[11,12] This catalyst state benefits from an increased leaving group ability due to the character of iodine(III) as a nucleofuge.^[16] The latter assumption is corroborated by a Hammett correlation study with derivatives of **1a**.^[7] No electronic effect was observed for the manipulation at the benzylic position during formation of **2a**, which suggests this step to be comparably fast. An additional advantage of the alkyl iodine(III) intermediate **E** lies in the subsequent regeneration of the active catalyst I(mCBA) directly from **E**. Hence, the amination proceeds within an iodine(I/III) manifold,^[17] which ensures that the reaction cycle comprising the iodine catalyst proceeds with sufficient rate.

The nature of the C-H functionalisation reaction as a visible light-induced radical chain process is corroborated by an experimentally determined quantum yield of 44.^[7] The radical chain pathway contains the rate-limiting step of the reaction, which through the corresponding intramolecular isotope labelling experiment^[18] was demonstrated to be the hydrogen abstraction in the reaction step from **B** to **C** due to with a primary kinetic isotope effect of 4.0.^[7]

At suitable catalyst loading, the rate of the iodine-based catalytic cycle provides sufficient amount of the crucial intermediate **A** to keep the radical chain reaction operative. To this end, the limiting catalyst loading is around 0.5 mol%. Below this value the concentration of iodine catalyst is too low to maintain the concentration of **A** sufficiently high. This overall mechanistic context thus characterizes the difference between the present iodine catalysis from recent elegant developments using hypiodite catalysis for a selective C-H oxygenation in the alpha-position to carbonyl compounds.^[19] These reactions proceed through a single catalytic cycle and solely depend on regeneration of the involved electrophilic iodine.^[19b] In contrast, the present scenario of two intertwined synergistic cycles demands an efficient kinetic competence of the iodine catalyst to cooperate with the radical chain mechanism progressing in parallel, as the two cycles cannot operate one independently from the other.^[20] Upon eventual chain termination, the present reaction is re-initiated by visible-light-induced photochemical homolysis of **A**. This context was modelled by a nuclear magnetic resonance (NMR) experiment, in which the light-source was periodically switched off. Reaction monitoring revealed an expected 1-2% increase in yield due to the continuing radical chain progress, before further product formation ceased. At this point, re-admission of light led to re-initiation of the reaction (Figure 1D).



Scheme 2. Substrate scope of the iodine-catalysed C-H bond amination under visible-light-initiation. Conditions: I₂ (2.5 mol%), PhI(mCBA)₂ (1.0 equiv), (CH₂Cl)₂, RT, visible light exposure, 12h. The newly formed C-N bonds are marked in blue colour. Yields refer to isolated yields after chromatographic purification. All reactions proceeded with > 95% selectivity (> 95% yield based on recovered starting material).

The present iodine-catalysed heterocycle synthesis is of broad scope and can be conducted within the discussed scenario with hypervalent iodine as terminal oxidant. Scheme 2 displays several examples of this new catalytic platform, which is operationally simple and proceeds under mild conditions. In addition to tosylated compound **2a**, more labile sulfonyl groups such as nosyl (product **2b**) and SES (product **2c**) are tolerated.

The alkyl chain substitution can be varied (products **2d-f**) as can the substitution of its arene group, demonstrating tolerance towards common functional groups (products **2g-l**). As the acetylene in **2l**, a free alkene group remains also untouched in **2m**. Cyclisation proceeds equally well without alkyl chain substitution (product **2n**). Acyclic stereochemical information leads to formation of two diastereoisomers **2o**, **2o'** as a consequence of the radical reaction pathway, while cyclic stereocontrol within ring annelation furnishes single diastereoisomers (products **2p**, **2q**). The reaction is also applicable to the amination of tertiary benzylic positions (products **2r**, **2s**). However, the involvement of a benzylic position is not a requirement. For example, pyrrolidine **2t** is obtained from selective amination in homobenzylic position, and products **2u-x** demonstrate the applicability of the present iodine catalysed amination to the entire spectrum of unfunctionalised primary, secondary and tertiary C-H bonds. Finally, the scope includes C-H amination reactions alpha to heteroatoms as demonstrated for the four examples **2y-ab** and for the diastereoselective formation of **2ac**. To further demonstrate its synthetic potential, the catalytic C-H amination reaction was applied to the synthesis of more advanced alkaloid building blocks. For example, the reaction provides the tricyclic product **2ad** within a highly efficient transannular C-H amination reaction.^[21] The tryptamine derivative **1ae** undergoes selective formation of the cyclised amination product **2ae**, which opens new possibilities for the synthesis of polytryptamine alkaloids.^[22]

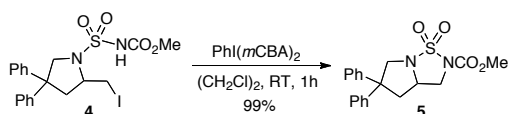
We have presented a unique iodine-catalyzed oxidative amination of saturated hydrocarbons that proceeds within two intertwined catalytic cycles. Within this context, it combines a radical chain reaction with an iodine catalysis that proceeds within the iodine(I/III) manifold. The reaction is operationally simple, proceeds under unprecedented mild conditions^[23] with only a single equivalent of oxidant and is conveniently initiated by visible light. This straightforward heterocycle synthesis from intramolecular C-H amination of alkyl groups provides an attractive iodine catalysed oxidation reaction that represents the first example of a Hofmann-Löffler-type amination reaction that is truly catalytic in halogen promoter. The reaction is of significant scope as it is applicable to the C-H amination of primary, secondary and tertiary hydrocarbon bonds. It compliments conventional metal catalysed variants and demonstrates the potential of iodine catalysis as a conceptual alternative.

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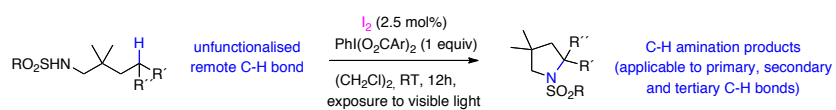
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COMMUNICATION



C. Martínez, K. Muñiz*

An Iodine Catalysed Hofmann-Löffler Reaction

Iodine does it! The first catalytic Hofmann-Löffler reaction proceeds with a combination of catalytic amounts of molecular iodine and a modified hypervalent iodine(III) reagent. The reaction proceeds under mildest catalytic conditions within an intramolecular C-H amination comprising primary, secondary and tertiary C-H groups.