Synthetic Methods

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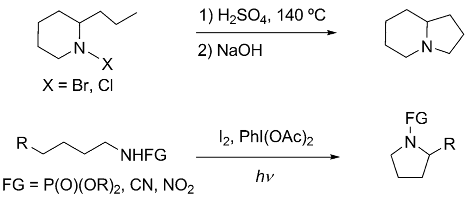
An Iodine-Catalyzed Hofmann–Löffler Reaction**

*Claudio Martínez and Kilian Muñiz**

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

Abstract: *Iodine reagents have been identified as economically and ecologically benign alternatives to transition metals, although their application as molecular catalysts in challenging C–H oxidation reactions has remained elusive. An attractive iodine oxidation catalysis is now shown to promote the convenient conversion of carbon–hydrogen bonds into carbon–nitrogen bonds with unprecedented complete selectivity. The reaction proceeds by two interlocked catalytic cycles comprising a radical chain reaction, which is initiated by visible light as energy source. This unorthodox synthetic strategy for the direct oxidative 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 the Hofmann–Löffler reaction (Scheme 1, top). Despite the great attractiveness of such an approach for the synthesis of aminated five-membered-ring compounds, the required rather harsh conditions have prevented wider application.[1a,b] Modifications of the common protocol include the in situ formation of the corresponding N-iodinated amides through 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 compounds having 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 has not yet been realized. Such a conceptually novel reaction is of fundamental interest, since it would amount to a catalytic remote C–H amination of nonfunctionalized 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 to be developed.[5]

The required principle for such a reaction was explored for the representative compound **1a** (Table 1). Overstoichiometric oxidation conditions[3] could be employed; however, changing to catalytic amounts of iodine shut down the reaction (entries 1 and 2). This problem could be overcome by changing the carboxylate component of the hypervalent iodine reagent from acetate to pivalate. With this oxidant it was possible to reduce the iodine amount to a catalytic 20 mol %, while the results remained similar to those obtained in the stoichiometric reaction (entry 3 vs. 4). Still, a significant excess of iodine(III) reagent was required (entry 5). Further modification of the iodine(III) reagent to $PhI(mCBA)_2$ (*m*CBA = 3-chlorobenzoate) provided quantitative yields of **2a**, even when a single equivalent of this oxidant was used (entries 6 and 7). The amount of the iodine catalyst could be successively lowered to 2.5 mol %, without loss in yield, and still 95 % yield was obtained at a catalyst loading of 1 mol %. Reasonable conversion was still achieved at 0.5 mol %, while the amination no longer proceeds upon further decrease of iodine to 0.1 mol % (entries 8–12). The optimized conditions call for only a single equivalent of terminal oxidant, which demonstrates the effectiveness of the new reaction. Usually, iodine-catalyzed reactions require an 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 reagent combination I_2/3 $PhI(OAc)_2$,[3f] which forms product mixtures.[7]

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[*] Dr. C. Martínez, Prof. Dr. K. Muñiz
Institute of Chemical Research of Catalonia (ICIQ)
Av. Països Catalans 16, 43007 Tarragona (Spain)
E-mail: kmuniz@iciq.es
Prof. Dr. K. Muñiz
Catalan Institution for Research and Advanced Studies (ICREA)
Pg. Lluís Companys 23, 08010 Barcelona (Spain)

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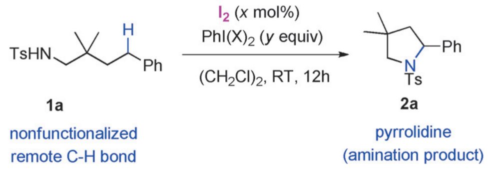
Table 1: Development of the iodine-catalyzed visible-light-induced C–H amination reaction.



Entry	I_2 (x mol%)	X	y	Yield [%][a]
1	100	O_2CMe	3	67
2	20	O_2CMe	3	<10
3	100	O_2CtBu	3	89
4	20	O_2CtBu	3	78
5	20	O_2CtBu	1	<10
6	20	*m*CBA	3	98
7	20	*m*CBA	1	98
8	5	*m*CBA	1	98
9	2.5	*m*CBA	1	98
10	1	*m*CBA	1	95
11	0.5	*m*CBA	1	76
12	0.1	*m*CBA	1	–
13[b]	5	*m*CBA	1	–
14[c]	0.5	*m*CBA	1	85
15[d]	5	*m*CBA	1	98
16[e]	2.5	*m*CBA	1	98

[a] Yields refer to isolated material of **2a** after purification. [b] Reaction in the dark laboratory (red light). [c] Reaction with irradiation at $\lambda = 400$ nm. [d] Reaction on 13 mmol scale. [e] Reaction in the presence of 10 equivalents of *m*CBAH.

The reaction progresses simply upon exposure to daylight. In contrast to initial reports on stoichiometric reagent combinations,[3] an external light bulb is not required, which greatly facilitates the 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 400 nm from a series of individual experiments at different wavelengths.[7] An experiment using a diode for defined irradiation at 400 nm indeed led to slightly increased yield (85 vs. 76%, entries 11 and 14).[7] To maintain operational simplicity, reactions were usually conducted by exposure to daylight in the absence of a photoreactor. 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 $PhI(mCBA)_2$ should lead to formation of I(*m*CBA) (Figure 1A),[8] which is the active catalyst. With every turnover, the reaction from Table 1 generates two equivalents of carboxylic acid. However, the presence of the free acid does not influence the overall performance of the reaction. A control experiment conducted with excess free carboxylic acid did not show any change in reaction outcome (Table 1, entry 16). In fact, the catalyst I(*m*CBA) might be stabilized by formation of an adduct with the carboxylic acid. To confirm this hypothesis, we prepared and structurally characterized the related tetrabutylammonium derivative $Bu_4N[I(mCBA)_2]$ (**3**).[9] The core anion $[I(mCBA)_2]^-$ displays the expected linear coordination geometry at the central iodine atom (Figure 1B). A cyclization

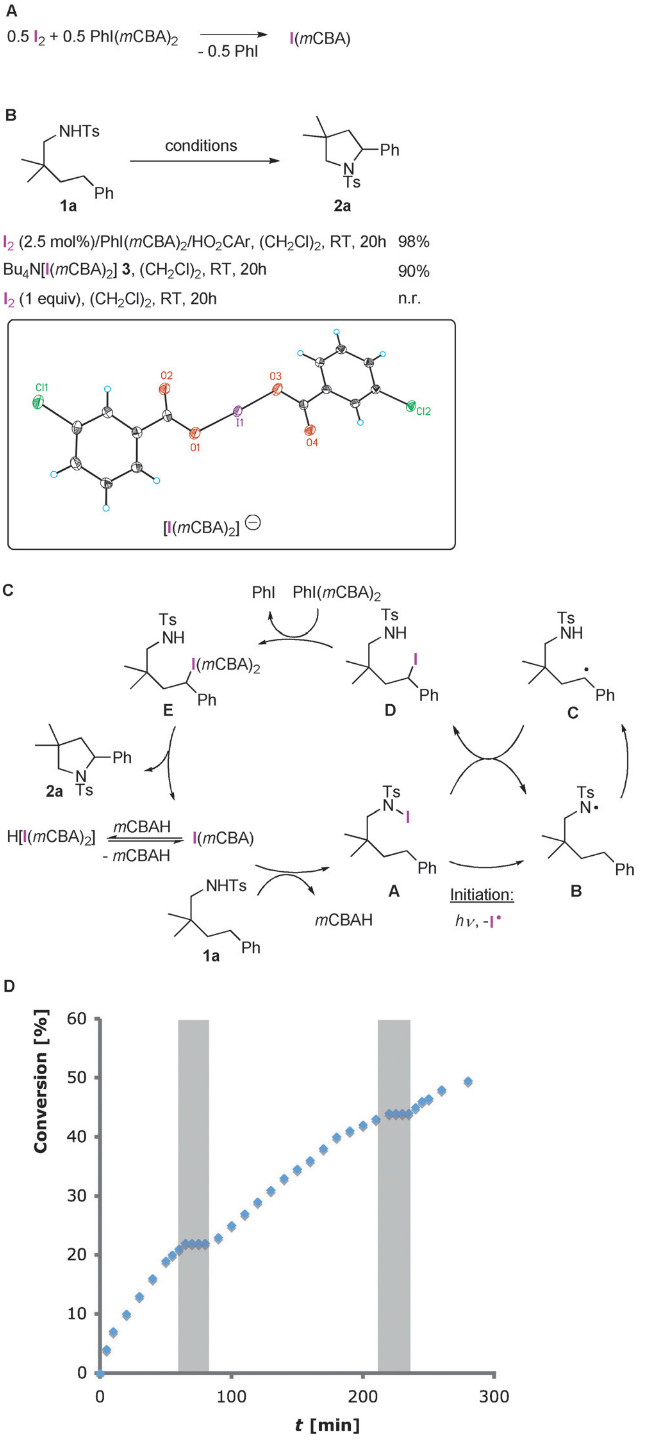


Figure 1. Mechanistic context of the iodine-catalyzed visible-light-induced C–H amination reaction: A) catalyst formation, B) control experiments, C) catalytic cycle, and D) in situ NMR monitoring for the reaction progress in the presence (white background) and absence (gray background) of a monochromatic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

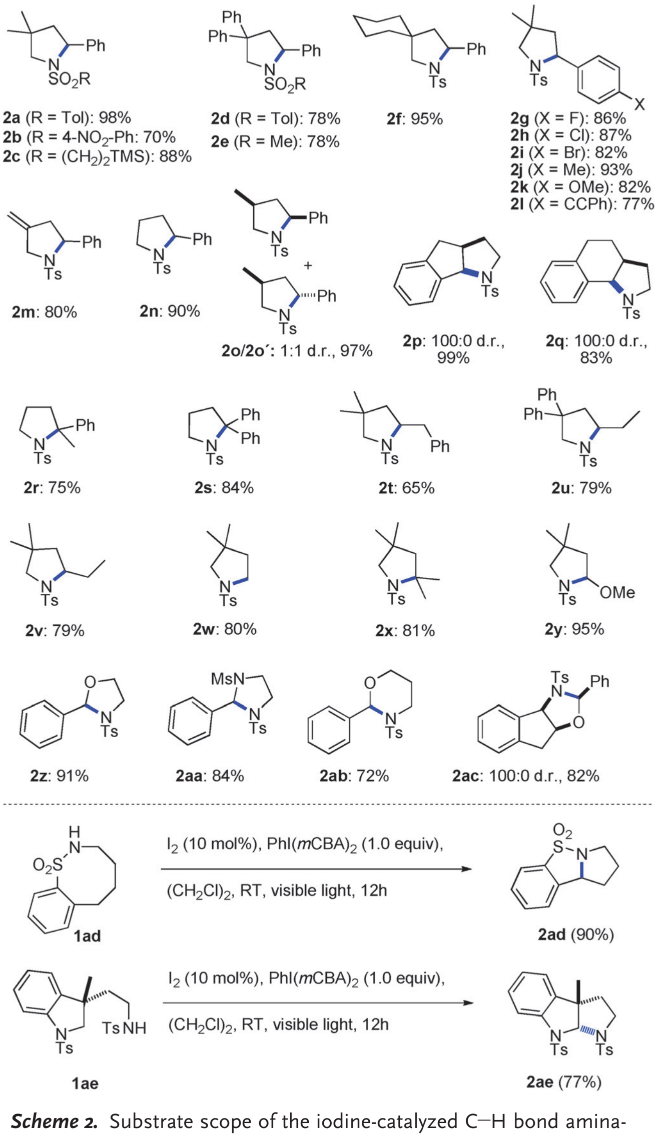
reaction of **1a** with this compound led to a reaction outcome comparable to that of catalytic cycloaminations. This suggests that the active catalyst I(*m*CBA) is stabilized by the free acid as $H[I(O_2CAr)_2]$ and regenerated upon dissociation. As deduced from independent control experiments, hypoiodite 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.

The mechanistic rationale for the present iodine catalysis is given in Figure 1C. Once the I(*m*CBA) 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-centered radical **B** engages in 1,5-hydrogen atom abstraction from the benzylic position to generate the carbon-centered radical **C**. This intermediate abstracts an iodine atom from another molecule of **A** in a radical chain reaction[10] to arrive at the iodinated intermediate **D**. Direct nucleophilic amination yielding **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 the 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(*m*CBA) 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 at a sufficient rate.

The nature of the C−H functionalization 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-labeling experiment[18] was demonstrated to be the hydrogen abstraction in the reaction step from **B** to **C** with a primary kinetic isotope effect of 4.0.[7]

At suitable catalyst loading, the rate of the iodine-based catalytic cycle provides a 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 the iodine catalyst is too low to maintain the concentration of **A** sufficiently high. This overall mechanistic context thus distinguishes the present iodine catalysis from recent elegant developments using hypoiodite catalysis for selective α-C−H oxygenation in 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 independently.[20] Upon eventual chain termination, the present reaction is re-initiated by visible-light-induced photochemical homolysis of **A**. This context was modeled by an 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, renewed exposure to light led to re-initiation of the reaction (Figure 1D).

The present iodine-catalyzed heterocycle synthesis is of broad scope and can be conducted within the discussed scenario with hypervalent iodine as the terminal oxidant. Scheme 2 displays several examples of this new catalytic platform, which is operationally simple and proceeds under mild conditions. In addition to the tosylated substrate (product **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



Scheme 2. Substrate scope of the iodine-catalyzed C−H bond amination under visible-light irradiation. Conditions: I$_2$ (2.5 mol%), PhI(*m*CBA)$_2$ (1.0 equiv), (CH$_2$Cl)$_2$, RT, visible light, 12 h. The newly formed C−N bonds are marked in blue. Yields refer to yields of isolated product after chromatographic purification. All reactions proceeded with >95% selectivity (>95% yield based on recovered starting material).

towards common functional groups (products **2g–l**). Both the acetylene in **2l** and the free alkene group in **2m** remain untouched. The cyclization proceeds equally well without substituents on the alkyl chain (product **2n**). Stereochemical information at an acyclic position leads to the formation of two diastereoisomers **2o**, **2o′** as a consequence of the radical reaction pathway, while stereocontrolled cyclization in the context of 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-catalyzed amination to the entire spectrum of non-functionalized primary, secondary, and tertiary C–H bonds. Finally, the scope includes C–H amination reactions α 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** in the context of a highly efficient transannular C–H amination reaction.[21] The tryptamine derivative **1ae** is transformed selectively into the cyclized aminal product **2ae**, which opens new possibilities for the synthesis of cyclotryptamine alkaloids.[22]

We have presented a unique iodine-catalyzed oxidative amination of saturated hydrocarbons that proceeds by means of two intertwined catalytic cycles. In this context, this reaction 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 through the intramolecular C–H amination of alkyl groups provides an attractive iodine-catalyzed 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 bonds. It compliments conventional metal-catalyzed variants and demonstrates the potential of iodine catalysis as a conceptual alternative.

Keywords: amination · C–H functionalization · homogeneous catalysis · iodine · oxidation

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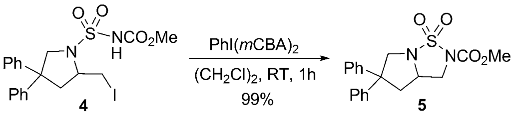

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