Engineering Molecular Iodine Catalysis for Alkyl-Nitrogen Bond Formation

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KEYWORDS: C-H Amination, Catalysis, Hofmann-Löffler reaction, Iodine, Oxidation.

ABSTRACT

An advanced protocol for the intramoleclar C-H amination of alkyl groups via amidyl radicals (Hofmann-Löffler reaction) under homogeneous iodine catalysis is reported. This protocol employs common *m*CPBA as terminal oxidant. It proceeds under mild conditions, with complete chemoselectivity, is compatible with radical intermediates and allows for the selective intramolecular amination reaction of secondary and tertiary hydrocarbon bonds and is not restricted to benzylic C-H amination. The involvement of an iodine(III) catalyst state in the C-N bond formation derives from selective oxidation at the stage of the corresponding alkyl iodide with *m*CPBA. Its formation is corroborated by quantum-chemical calculations. This new catalysis thus proceeds within a defined iodine(I/III) catalysis manifold.

Key Words

Amination, C-H Functionalisation, Hofmann-Löffler Reaction, Iodine, Oxidation, Radicals
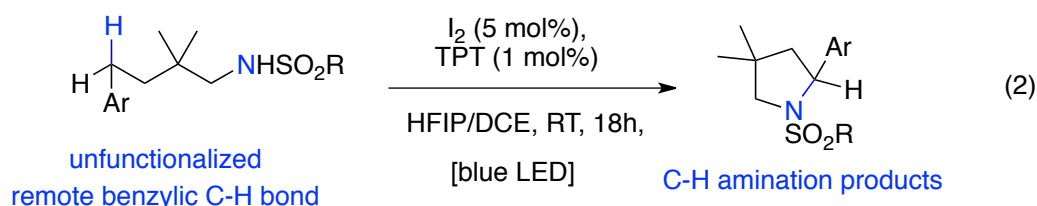
Introduction

Homogeneous oxidation catalysis based on molecular iodine[1] has emerged as a viable answer to the quest for alternative concepts complimenting conventional transition metal based transformations. Within this context, seminal iodine-catalyzed α-oxygenation reactions of ketones were developed by Ishihara.[2] We have recently presented selective Csp[3]-H amination reactions that constitute the first Hofmann-Löffler reactions employing only a catalytic amount of iodine (Scheme 1).[3] Despite the common feature of deriving from iodine catalysis, the two protocols display significantly different behavior depending on the respective re-oxidant. The initial protocol made use of a stoichiometric amount of a non-commercial iodine(III) reagent as terminal oxidant (eq. 1). This variant optimizes earlier stoichiometric protocols[4,5] and demonstrates a remarkably robust main group catalysis based on a defined iodine(I/III) manifold.[6] The broad scope of this catalytic transformation includes aliphatic primary, secondary and tertiary C-H bonds alike. The hypervalent iodine(III) reagent as terminal oxidant (i) provides an alkyliodine(III) intermediate for the observed general aliphatic C-N bond formation and (ii) leads to the generation of electrophilic iodine species I-O$_2$CR, as demonstrated independently.[3a,7,8] Despite the clean reaction conditions, the requirement for a preformed iodine(III) reagent may be considered less optimum from economic and practical perspectives. In search for a more economic re-oxidant, a terminal oxidation based on an organic photoredox catalyst was developed (eq. 2).[3b] This reaction proceeds under significantly more benign conditions, however, due to its iodine(-I/I) manifold, it is limited to the C-H amination at benzylic positions.

Iodine(I/III) catalysis: requirement for a preformed iodine(III) oxidant[3a]

$$(1)$$

unfunctionalized remote C-H bond

C-H amination products
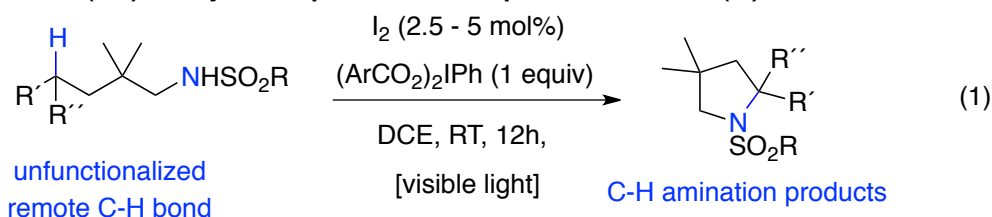
Iodine(-I/I) catalysis: limitation to benzylic C-H positions[3b]

$$(2)$$

unfunctionalized remote benzylic C-H bond

C-H amination products

Scheme 1. Iodine-catalyzed Hofmann-Löffler reactions using hypervalent iodine as terminal oxidant (1) or photoredox catalysis for terminal oxidation (2). Ar = 3-Cl-C$_6$H$_4$.

Despite its undisputable progress,[1] iodine redox catalysis still requires the development of defined general and benign re-oxidation conditions for a broader application in organic synthesis. Some interesting contributions have arisen in the recent past, which include the combination of molecular iodine with cleaner oxidants such as peracids or peroxides.[1,2] We here report on a modified protocol of increased economic nature for catalytic Hofmann-Löffler reactions of general substrate scope. It relies on a suitable engineering of the iodine catalyst, which is generated from molecular iodine as a single iodine component in combination with a commercial terminal oxidant.

2. Results and Discussion

2.1. Reaction Development

In previous investigation, we had disclosed that several attempts to implement common hypoiodite catalysis[2] for catalytic Hofmann-Löffler reactions were unsuccessful. In order to render the reaction more economic and replace the required preformed hypervalent iodine as terminal oxidant, we were intrigued to test whether common organic peroxides or peracids could promote the desired Hofmann-Löffler reaction (Table 1).[9] While *tert*-butyl hydroperoxide (TBHP) was completely ineffective (entry 1), peracetic acid showed some low conversion (entries 2,3). In contrast, *m*CPBA in acetonitrile/acetic acid directly provided a 52% of yield (entry 4). Using a limiting amount of this oxidant in acetonitrile, 44% product was observed (entry 5). Screening of alternative solvents in the presence of a three-fold excess of *m*CPBA revealed that acetonitrile represented the best solvent (entries 6-11). Finally, addition of *tert*-butanol as co-solvent provided quantitative conversion and 98% isolated yield of **2a** (entry 12), which was maintained at 2.2 equivalents of terminal oxidant (entry 13). Under these conditions, reduced iodine loadings of even 2.5 mol% provide lower, albeit synthetically useful yields (entries 13-15).

Table 1. Iodine-catalyzed Hofmann-Löffler reactions: Optimization of reaction conditions for *m*CPBA as terminal oxidant.
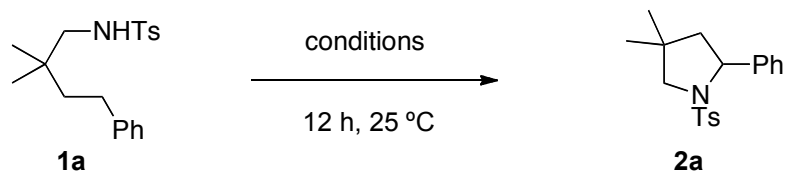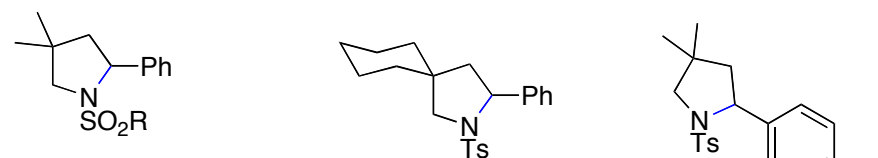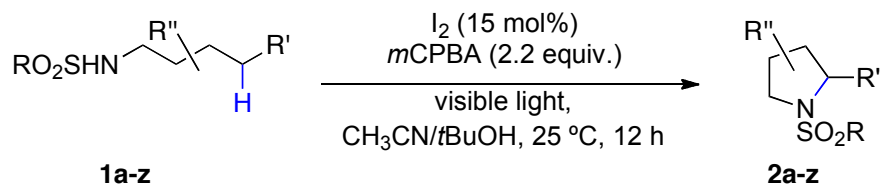

No	Conditions	Conversion[a]
1	I_2 (15%), TBHP (3.0 eq), CH_3CN/^tBuOH (1/1)	s.m
2	I_2 (15%), CH_3CO_3H (3 eq), DCE	12%
3	I_2 (15%), CH_3CO_3H (3 eq), CH_3CN	s.m
4	I_2 (15%), *m*CPBA (3 eq), CH_3CN/AcOH (1/1)	52%
5	I_2 (15%), *m*CPBA (1 eq), CH_3CN	44%
6	I_2 (15%), *m*CPBA (3 eq), PhCN	38%
7	I_2 (15%), *m*CPBA (3 eq), AcOH	32%
8	I_2 (15%), *m*CPBA (3 eq), TFE	37%
9	I_2 (15%), *m*CPBA (3 eq), MeOH	26%
10	I_2 (15%), *m*CPBA (3 eq), EtOAc	56%
11	I_2 (15%), *m*CPBA (3 eq), CH_3CN	60%
12	I_2 (15%), *m*CPBA (3 eq), CH_3CN/^tBuOH (1/1)	98%[b]
13	I_2 (15%), *m*CPBA (2.2 eq), CH_3CN/^tBuOH (1/1)	98%[b]
14	I_2 (5%), *m*CPBA (2.2 eq), CH_3CN/^tBuOH (1/1)	70%[b]
15	I_2 (2.5%), *m*CPBA (2.2 eq), CH_3CN/^tBuOH (1/1)	56%[b]

[a] Estimated conversion from integration of the ^{1}H NMR spectrum of the crude reaction product.

[b] Isolated yield after purification.

2.2. Scope of the iodine/*m*CPBA catalyzed Hofmann-Löffler reaction

Under the optimized conditions, a number of pyrrolidines were prepared from the corresponding linear sulfonamides **1a-aa** (Scheme 2). In agreement with earlier protocols,[3a] cyclization onto benzylic positions is straightforward and includes variation at the nitrogen substitution (**2b**), along the aliphatic chain (**2c,k**), at the arene (**2d-2i**, including an acetylenic group) and at the benzylic position (**2l,m**). The accurate screening of re-oxidants has identified *m*CPBA to provide suitable conditions for the important substrate class of C-H amination even at non-benzylic aliphatic positions (**2n-r**), including the new compounds **2o** and **2p/2p'**. Here, the synthesis of the α-tertiary amine derivative **2r** stands out, as it represents an uncommon synthetic access to this important class of compounds in natural alkaloids.[10] The reaction proceeds at alpha-position to heteroatoms (**2s**) and with excellent diastereoselectivity for cyclic stereocontrol (**2t-u**), while acyclic stereocontrol is not possible due to the involved radical pathway (**2v/v'**). Transannular C-H amination[11] is also possible (**2w**).

Reaction scheme:

RO_2SHN–(R'')–(R')–H [with H highlighted] →
Conditions: I_2 (15 mol%), $mCPBA$ (2.2 equiv.), visible light, $CH_3CN/tBuOH$, 25 °C, 12 h →
product pyrrolidine with R'', R', N–SO_2R

1a-z → **2a-z**

2a (R = Tol): 95%
2b (R = 4-NO_2-Ph): 63%[a]

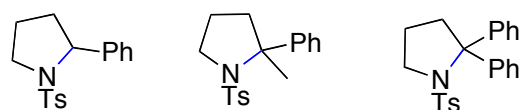**2c**: 99%

2d (X = F): 83%
2e (X = Cl): 82%
2f (X = Br): 73%
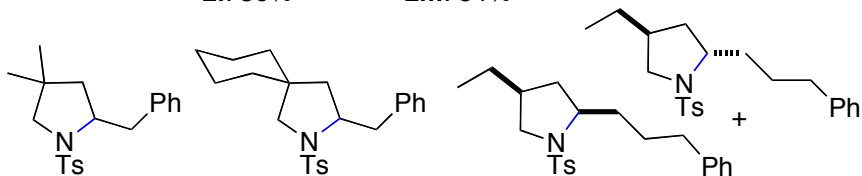**2g** (X = Me): 96%
2h (X = OMe): 99%
2i (X = CCPh): 58%

2k: 54%

2l: 36%[a]

2m: 84%[a]
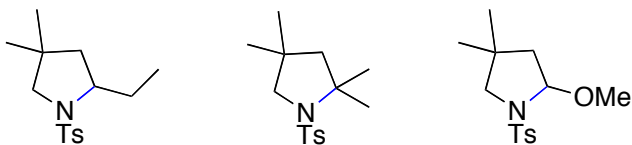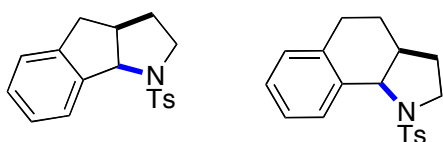
2n: 58%

2o: 54%

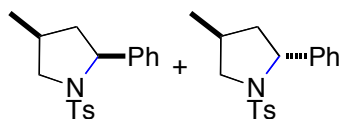**2p/2p´:** 1:1 d.r., 69%

2q: 65%
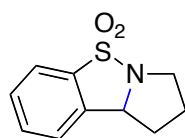
2r: 61%[a,b]

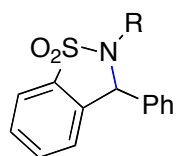**2s**: 60%

2t: 100:0 d.r., 96%
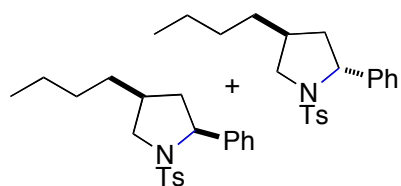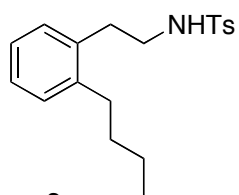
2u: 100:0 d.r., 85%

2v/2v´: 1:1 d.r., 94%

2w: 70%

2x (R = Me): 63%
2y (R = Et): 85%

2z/2z': 1:1 d.r., 67%

Bottom reaction:
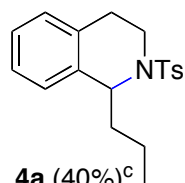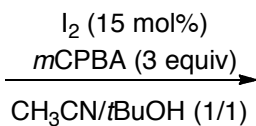
3a (structure with NHTs) →
**Conditions:** I_2 (15 mol%), $mCPBA$ (3 equiv), $CH_3CN/tBuOH$ (1/1) →
4a (40%)[c]

Scheme 2. Iodine-catalyzed Hofmann-Löffler reaction with *m*CPBA: Scope.

a Reaction in 1,2-dichloroethane. b with 3 equivalents of *m*CPBA. c >55% recovered starting material.

New substrates were investigated for the amination of **1x** and **1y**, which cyclized under the present conditions, while they are entirely unreactive under the previous ones.[3] Compound **1z** demonstrates that in the case of competitive secondary hydrocarbon bonds, the common 1,5-HAT[12,13] is preferred for the weaker benzylic C-H bond, thus providing **2z/2z'** as the exclusive amination products. The reaction was further expanded to an interesting example of six-membered ring formation. For the case of compound **3a**, clean formation of the corresponding tetrahydroisoquinoline **4a** was observed (40%, together with amost fully recovered remaining starting material). This example represents a rare case of a 1,6-HAT reaction,[14-16] which in the present case is the result of an impossible 1,5-HAT. However, the potentially competing α-elimination to an aldimine[6f] was not observed at all for this case. Noteworthily, previous iodine catalyses do not promote this particular reaction. In order to further demonstrate the difference between the individual protocols, we explored the performance of the benzyl methylether derivative **3b** (Scheme 3). While the iodine/iodine(III) system[3a] provides the expected C-H amination product **4c**, the present iodine/*m*CPBA variant promotes overoxidation to the lactam **4b**. Finally, the inherent reaction differences between the protocols of the reoxidants iodine(III) and *m*CPBA may open new synthetic possibilities. For the case of a substrate with a tertiary alcohol, clean Hofmann-Löffler cyclization is obtained for the substrates **5a,b** in the presence of the iodine/*m*CPBA system, yielding the pyrrolidine products **6a,b** in good isolated yields. In contrast, the iodine/iodine(III) system leads to concomitant opening of the tertiary alcohol to form ω-iodo ketones. Such a scission reaction had previously been reported by Barluenga and González for the use of a cationic iodonium reagent.[17] Since the active iodine species is also an electrophilic iodine(I) in the present case, ketone formation represents the expected outcome. However, the incorporation of the iodine into the carbon framework of the product prevents the progress of the catalytic Hofmann-Löffler cyclization, and, consequently, yields could not exceed the range of 10%. When conducting the reaction in the presence of equimolar reagent amounts, synthetically relevant yields of **7a,b** could be obtained.
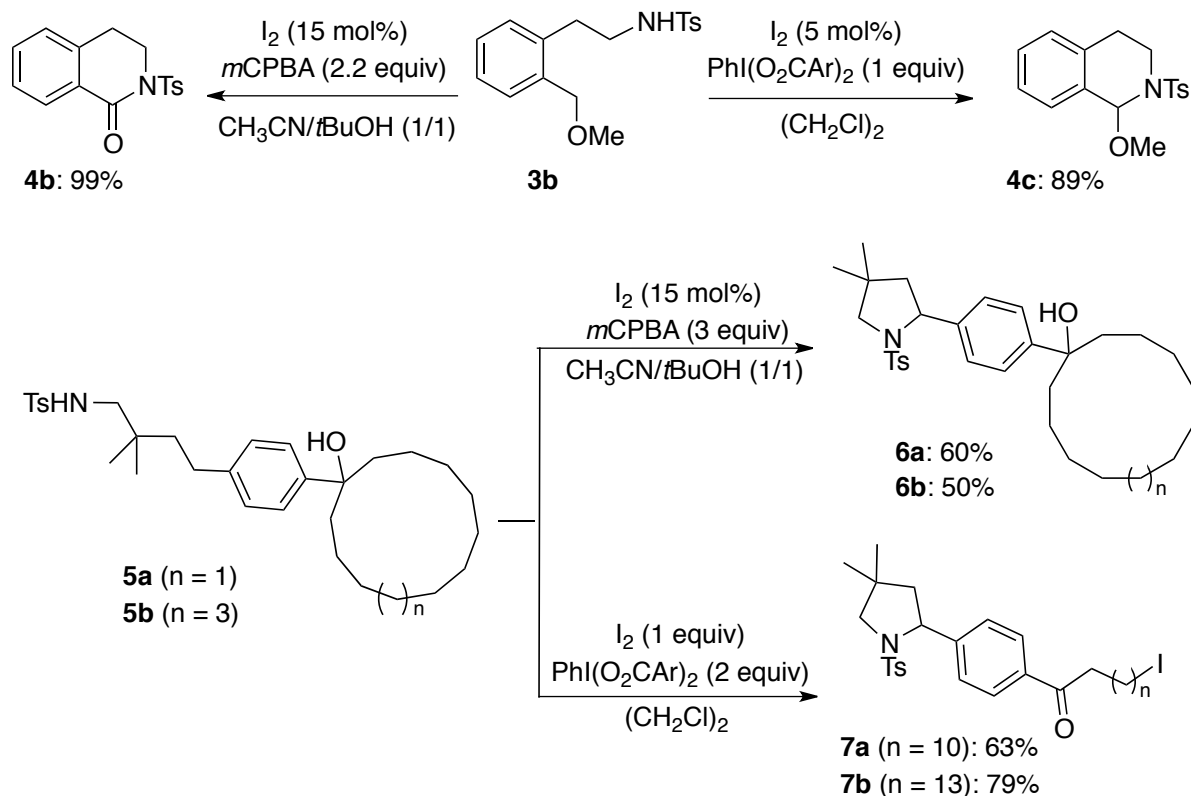
Scheme 3. Iodine-catalyzed Hofmann-Löffler reactions with *m*CPBA: Influence of the terminal oxidant. Ar = 3-Cl-C$_6$H$_4$.

2.3 Mechanistic Discussion

Several control experiments were conducted to gain insight into the mechanism of the present transformation (Scheme 4). At the outset, it is noteworthy that *m*CPBA as the optimum oxidant generates the 3-chlorobenzoate anion, which had been identified as a component in the best hypervalent iodine reagent in our earlier reaction.[3a] This could suggest that these two iodine catalyses actually proceed through the formation of identical iodine(I) states such as I-O$_2$CAr.[7] However, control experiments with the isolated compound **8** showed a completely different picture. First, a reaction employing **8** as catalyst source led to no reaction either with *m*CPBA alone or in the presence of additional free 3-chlorobenzoic acid. Next, it was observed that tetrabutylammonium iodide could also not serve as catalyst source upon oxidation with *m*CPBA.

1a → **2a**

conditions
visible light
CH$_3$CN/tBuOH, 12h, 25 °C
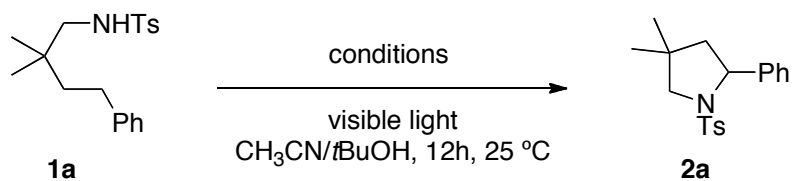
conditions

[(ArCO$_2$)$_2$I]NBu$_4$ **8** (30 mol%), mCPBA (1.5 eq)	No reaction
[(ArCO$_2$)$_2$I]NBu$_4$ **8** (30 mol%), mCPBA (1.5 eq) ArCO$_2$H (2 eq)	No reaction
INBu$_4$ (30 mol%), mCPBA (1.5 eq)	No reaction
IOtBu (1.2 equiv), c-C$_6$H$_{12}$	51%
IOtBu (30 mol%), c-C$_6$H$_{12}$, mCPBA (1.5 equiv)	83%
I$_2$ (15 mol%), mCPBA (2.2 eq), dark laboratory	No reaction

Scheme 4. **Control Experiments**. Ar = 3-Cl-C$_6$H$_4$.

These observations make an iodine(I) catalyst state IO$_2$CAr less probable. In view of the positive influence of the tBuOH co-solvent, the participation of $tert$-butyl hypoiodite IOtBu becomes an intriguing alternative. We investigated the participation of this reagent using its in situ formation following Wirth's protocol.[18] Indeed, a stoichiometric amount of this oxidant promotes a 51% isolated yield for the standard transformation of **1a** into **2a**. When IOtBu is employed as the catalyst source in the presence of mCPBA as terminal oxidant under standard conditions, the reaction outcome closely resembles the yield from the corresponding reaction with in situ catalyst formation.
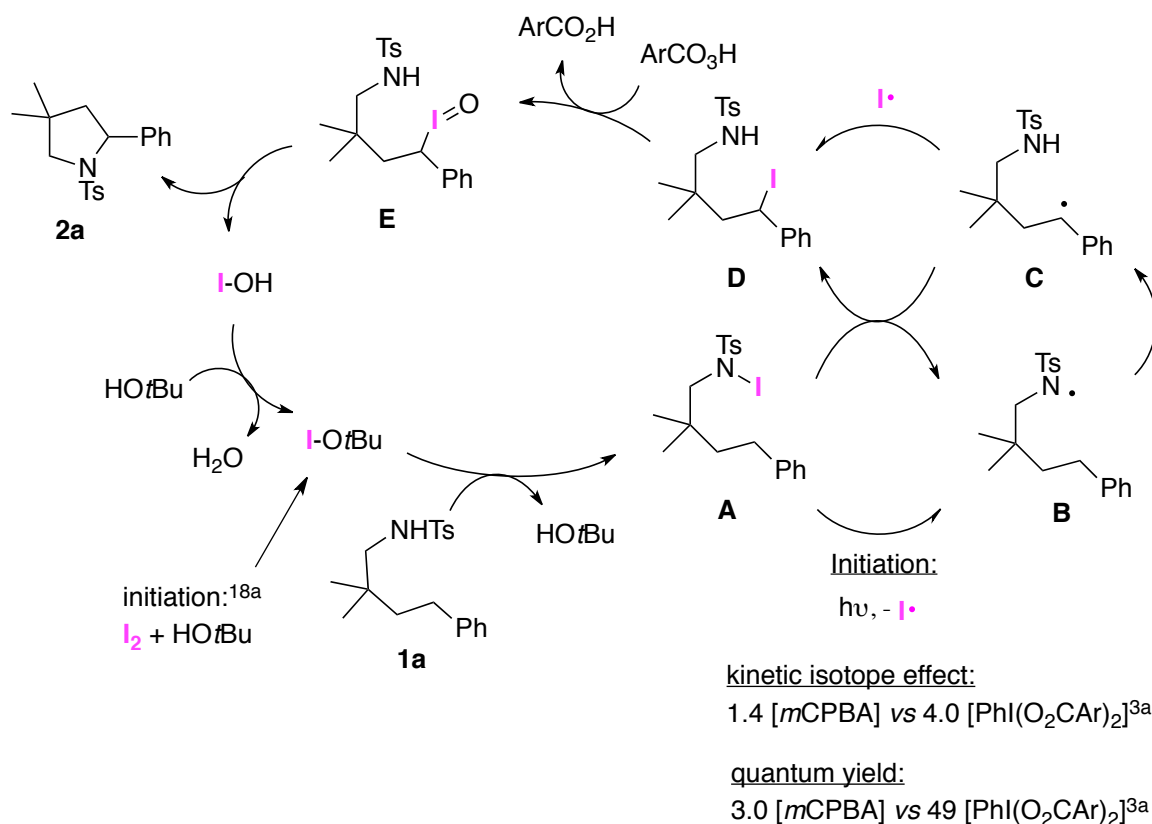
Figure 1. Catalytic cycle for the iodine-catalyzed Hofmann-Löffler reaction with *m*CPBA as terminal oxidant. Values for control experiments are given with the corresponding oxidant in brackets. Ar = 3-Cl-C$_6$H$_4$.

With these observations in hand, it is plausible to conclude that the reaction proceeds through an iodine catalysis that involves IO*t*Bu as a competent catalyst state (Figure 1). This compound is formed at the outset from molecular iodine and *t*BuOH.[18] Reaction with the substrate **1a** provides the crucial intermediate **A**. In the absence of *t*BuOH, intermediate **A** is directly formed from IOH.[3b] Obviously, this latter pathway is slower than the one through *t*BuOI, and this context explains the observed acceleration effect of *t*BuOH. Intermediate **A** then undergoes photolytic N-I bond cleavage as investigated previously.[3] This homolytic light-induced amidyl radical formation[19] is in agreement with the corresponding control experiment in the absence of light, which does not show product formation (Scheme 4). It obviously overrides the potentially competing unselective radical C-H iodination by the *t*BuOI reagent itself.[18a] The resulting intermediate **B** promotes a 1,5-HAT to **C**,[3,19,20] which engages in a radical chain reaction with **A**

to finally generated the aliphatic iodide **D**. Alternatively, radical recombination with iodine would provide the same outcome in a direct transformation. In view of the demonstrated successful reaction scope including aliphatic, non-benzylic C-H amination, it can be concluded that the reaction should involve an alkyl-iodine(III) intermediate **E** prior to nucleophilic C-N bond formation to product **2a**. The enhanced leaving group capacity[21] of alkyliodine(III) **E** over the comparable iodine(I) state **D** enables amination reactions outside the activated benzylic or neighboring heteroatom scaffold. This postulation of an alkyliodine(III) catalyst state **E** is in agreement with literature precedence on the formation of iodosyl alkanes from alkyl iodides upon oxidation with *m*CPBA.[22,23] A somewhat slower leaving group capacity than for related alkyl[(dicarboxy)iodine](III) intermediates[3] is generally expected for iodosyl derivative **E**. This assumption should affect the relative rate of C-N bond formation, and the subsequent nucleophilic substitution should be slightly slower than in the case of comparable di(acyloxy)iodosylalkanes,[3] which display a comparably higher nucleophuge character.[24] This observation is corroborated by Hammett studies[9] and by a pronounced observation of an electronic influence of the nitrogen substituent on the reaction. For a competition experiment between **1a** and **1b**, the less nucleophilic nosyl group displays a decreased reactivity and the two products are formed in a 1.7:1 ratio in favor of **2a** (Scheme 5).
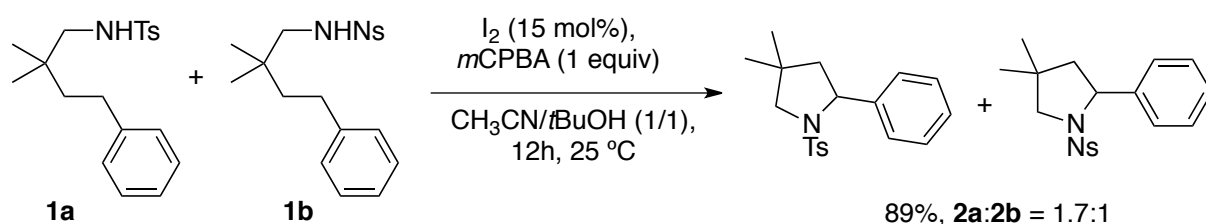
Scheme 5. Competition experiment between **1a** and **1b**. Conversion based on the terminal oxidant *m*CPBA as limiting agent.

In any case, the leaving group ability of the alkyliodine(III) intermediate is required to guarantee a sufficient rate in the iodine-based catalytic cycle, in particular for those examples, that promote amination of non-activated carbon atoms. In comparison to the previous catalytic Hofmann-Löffler reaction with iodine(III) $PhI(O_2CAr)_2$ as the terminal oxidant, the relative rates of the individual steps of both catalytic cycles are different. First, the 1,5-HAT step now occurs at comparably faster relative rate as suggested from the corresponding KIE of 1.4[9] measured for the

overall transformation from **1a** to **2a**. In addition, the observed quantum yield of only 3^9 suggests that significant interruption of the radical chain reaction occurs. This may be the result of partial radical recombination with an iodine radical at the intermediary state **B**, and due to the comparably slow regeneration of the crucial intermediate **A**, even at a comparably higher iodine catalyst loading.
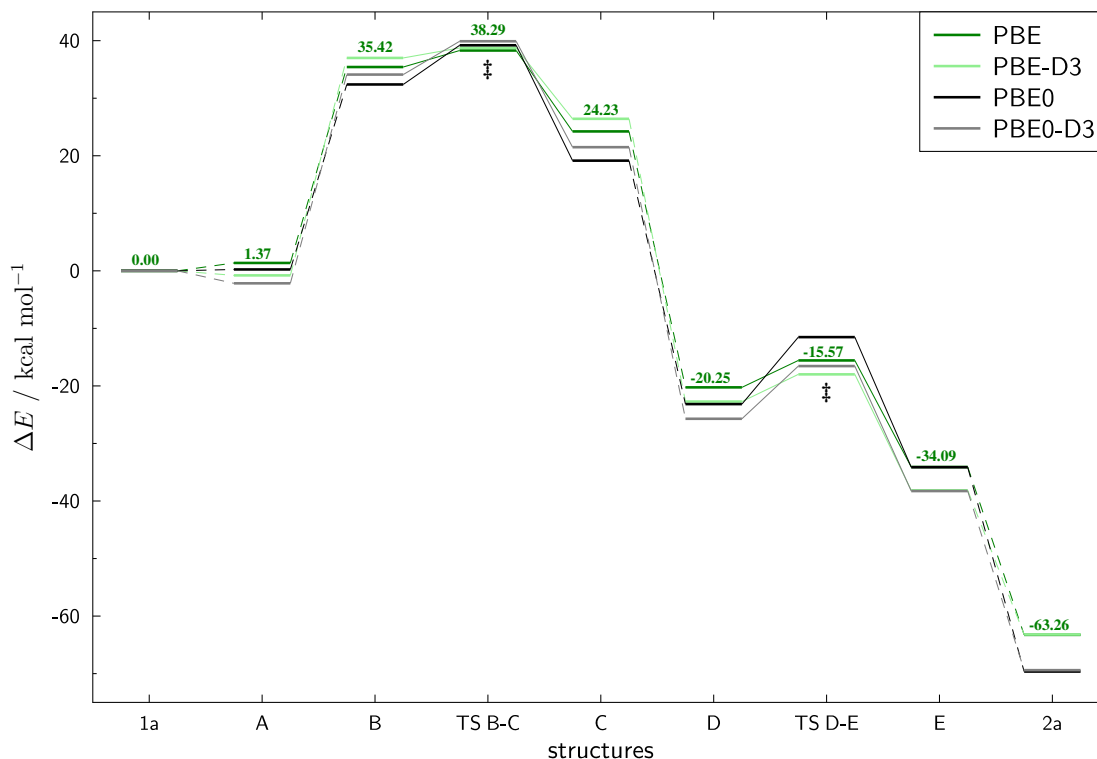
Figure 2. Electronic energy profile of the proposed catalytic cycle from Figure 1. All energies are calculated either with the PBE functional and with (light green) and without (dark green) D3 dispersion correction, or with the PBE0 hybrid functional again with (gray) and without (black) dispersion correction. Transition state energies, indicated by the double dagger, are connected to the energies of the minimum structures by solid lines, whereas the dashed lines connect minimum energies for which no transition state was calculated or already discussed previously.[3b] All structures were optimized with PBE/def2-TZVPP and the green numbers indicate the exact values for these relative energies.

In order to understand in more detail the mechanism and in particular the two crucial steps of 1,5-HAT and alkyliodine oxidation in particular, we carried out density functional theory calculations for the catalytic cycle from Figure 1. We optimized the structures with the PBE functional[25] and the def2-TZVPP basis set[26] in Turbomole[27] and solvent effects were modeled with the COSMO continuum model[28] employing a dielectric constant of $\varepsilon = 24.95$, which is the average of the dielectric constants of MeCN and *t*BuOH. Transition state structures were optimized with the QST3 transition state search[29] as implemented in Gaussian 09.[30] The effect of exact exchange and dispersion interaction on the energies was investigated with the PBE0 hybrid functional[31] and the empirical D3 dispersion correction,[32] respectively.

As in our previous work,[3b] we adopted a closed conformation for all structures but note that the relative energy barriers to the open structure are on the order of 2 kcal mol^{-1}. Figure 2 displays the electronic energy profile of the proposed catalytic cycle. As expected, the photochemical initiation step, corresponding to the homolytic N-I bond cleavage,[3b] leads to radical structure **B** that is destabilized by about 35 kcal mol^{-1} compared to structure **A**. The intramolecular radical transfer to form the more stable benzylic radical **C** is almost barrierless. Structure **D** is then significantly stabilized by a recombination with an iodine radical in the next step. The crucial iodine oxidation with *m*CPBA has a barrier (**TS D-E**) of 4.68 (11.63) kcal mol^{-1} as calculated with the PBE (PBE0) functional. The corresponding transition state structure is displayed in Figure 3. It is important to note, however, that both transition states have several vibrations with very low wave numbers (four (twelve) vibrations with less than 50 cm^{-1} for **TS B-C** (**TS D-E**)). Therefore, the concept of a transition state is not strictly valid but we can confirm that both transformations correspond to very flat regions of the potential energy hyper-surface. Despite the prominence of *m*CPBA in iodine(I/III) catalysis,[33] a more detailed picture on the course of the oxidation of organic iodine(I) compounds had not been generated previously. The detected low barrier now provides the rationale for the success of this particular oxidant.

The direct reaction from **D** to **2a** is endothermic, with energies ranging from 1.32 kcal mol^{-1} (PBE0) to 5.10 kcal mol^{-1} (PBE-D3), underlining the necessity of the iodine oxidation with *m*CPBA. It is interesting that for the alternative peroxide TBHP as oxidant (Table 1, entry 1) the corresponding transition state from **D** to **E** is significantly increased by almost 20 kcal/mol (see the Supporting Information), indicating that iodine(I) to iodine(III) oxidation is a kinetically less feasible process with this oxidant.[9,34] These results again demonstrate that the involvement of an

iodine(III) intermediate is crucial in order to provide kinetically competent pyrrolidine formation.

We further calculated the energy of a radical quenching reaction by a solvent molecule. For the most stable radical structure **C**, H-atom abstraction from an acetonitrile molecule has an enthalpic penalty of 12 kcal mol^{-1}, whereas it is as high as 19 kcal mol^{-1} for H-atom abstraction from *t*BuOH (both values are obtained from PBE/def2-TZVPP calculations). Even if present, these reactions do not affect the overall yield because they lead to regeneration of the starting material **1a**. However, they contribute an explanation to the comparably low quantum yield of the present radical chain.[34]
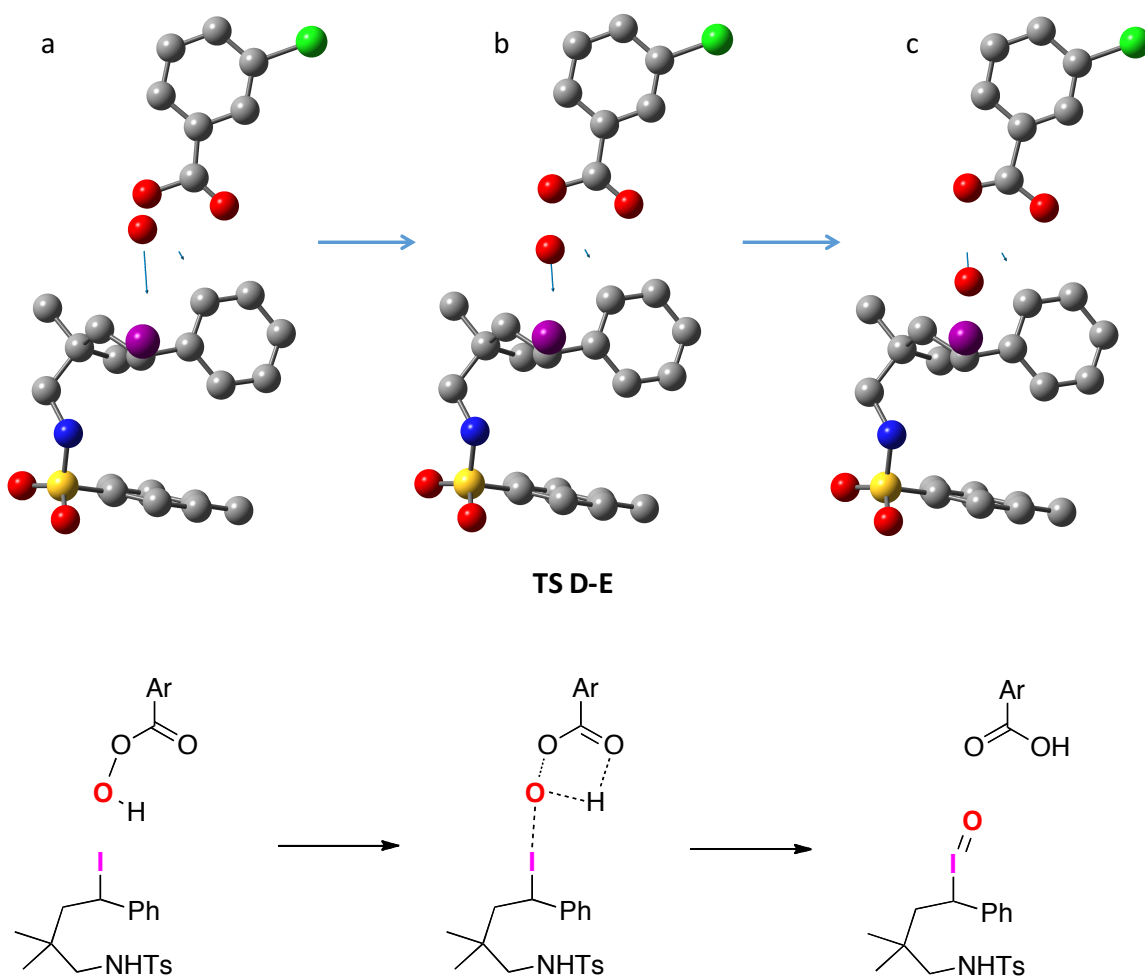
TS D-E

Figure 3. Three structures obtained from displacements along the imaginary vibrational mode corresponding to the transition state structure **TS D-E**. The transition state is shown in the middle (b), whereas the structure on the left (a) is closer to the starting structures *m*CPBA and **D** and the

structure on the right (c) resembles the oxidized structure **E**. Hydrogen atoms were removed for clarity.

The combined experimental and theoretical observations demonstrate that the development of catalytic iodine catalyzes for Hofmann-Löffler reactions require an accurate engineering of a number of different factors in order to arrive at suitably balanced rates for all involved individual steps. It includes the identification of *t*BuOH as a suitable co-solvent for stabilization of the electrophilic iodine catalyst in the form of *t*BuOI, *m*CPBA as a suitably rapid oxidant to generate the crucial alkyliodine(III) intermediate and acetonitrile as non-chlorinated solvent. As a consequence, the catalytic system based on *m*CPBA that is presented here is only the second catalytic reaction that is general for C-H amination of aliphatic positions including non-benzylic ones and it provides the advantage of employing only conventional bulk reagents and solvents.

3 Conclusion

We have identified suitable conditions for the selective intramolecular amination of aliphatic positions, which include activated and non-activated aliphatic C-H bonds. The reaction proceeds with high selectivity and synthetically useful yields. The robust homogeneous catalyst is conveniently generated in situ from molecular iodine and *tert*-butanol and is continuously regenerated from 3-chloro perbenzoic acid as terminal oxidant, which are all commodity reagents. The reaction represents the currently most economic variant of an iodine-catalyzed Hofmann-Löffler reaction. It proceeds through an iodine(I/III) catalytic manifold, which is active in the presence of visible light irradiation. Although related to alternative catalysis with an iodine(III) reagent as terminal oxidant, the present system shows significant changes in the rate of the relative steps of the catalytic cycle and for some substrate classes can even provide alternative reactivity. The present work thus demonstrates that careful engineering of molecular iodine catalysis can provide an entry into versatile improvement of the economic conditions of homogeneous catalysis.

ASSOCIATED CONTENT

Supporting Information. The Supporting Information is available free of charge on the ACS Publications website. The following files are available free of charge. Details on experimental procedures for the catalytic reactions, spectroscopic data for the products and xyz structure files for all molecules included in the calculations (PDF).

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Author Contributions

TD and CM conducted the experimental research and CJS and MR designed and conducted the theoretical investigation. The manuscript was written by KM after consultation with all authors. All authors have given approval to the final version of the manuscript.

Notes

The authors declare no competing financial interest.

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Synopsis

Oxidation to Iodine(III) Catalyst