Radical Chemistry

International Edition: DOI: 10.1002/anie.201604704
German Edition: DOI: 10.1002/ange.201604704

Triiodide-Mediated δ-Amination of Secondary C–H Bonds

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Abstract: *The C_δ–H amination of unactivated, secondary C–H bonds to form a broad range of functionalized pyrrolidines has been developed by a triiodide (I_3^-)-mediated strategy. By in situ 1) oxidation of sodium iodide and 2) sequestration of the transiently generated iodine (I_2) as I_3^-, this approach precludes undesired I_2-mediated decomposition which can otherwise limit synthetic utility to only weak C(sp^3)–H bonds. The mechanism of this triiodide-mediated cyclization of unbiased, secondary C(sp^3)–H bonds, by either thermal or photolytic initiation, is supported by NMR and UV/Vis data, as well as intercepted intermediates.*

In the synthetically enabling realm of C–H functionalization,[1] selective amination of unactivated C(sp^3)–H bonds is of primary interest because of the privileged nature of amines in medicines and materials.[2,3] Some creative solutions for this key synthetic challenge employ metallated amides and nitrenes.[4,5] Radical-mediated strategies also enable C–H amination, albeit with differing selectivities.[6] For example, nitrogen-centered radicals facilitate facile and selective hydrogen-atom transfer (HAT) leading to complementary C–H amination approaches.[2,6,7] Although the selectivity of single-electron-mediated strategies can be robust, the typically harsh means for generating these radicals have limited their synthetic utility —until recently.[8] In this vein, we sought to expand the scope and synthetic applicability of one of the most powerful transformations in this class by introducing a mild and general strategy for generating and harnessing the reactivity of nitrogen-centered radicals.

The Hofmann–Löffler–Freytag (HLF) reaction[9] converts acyclic amines into pyrrolidines by transposition of an N-haloamine to a δ-haloamine by selective 1,5-HAT (Figure 1a). Despite the harsh reaction conditions required to promote the classic HLF reaction[10] (through homolysis of a preformed haloamine in refluxing acid), this radical-mediated C_δ–H amination has enabled landmark syntheses (e.g. nicotine, gelsemicine).[2]

A major milestone in the development of HLF chemistry is a discovery by Suárez and co-workers, and it precludes the need for haloamine pre-formation (Figure 1b).[11] In this improved approach, generation of the N-centered radical is facilitated by direct oxidation of an amine with $Hg(OAc)_2$ or

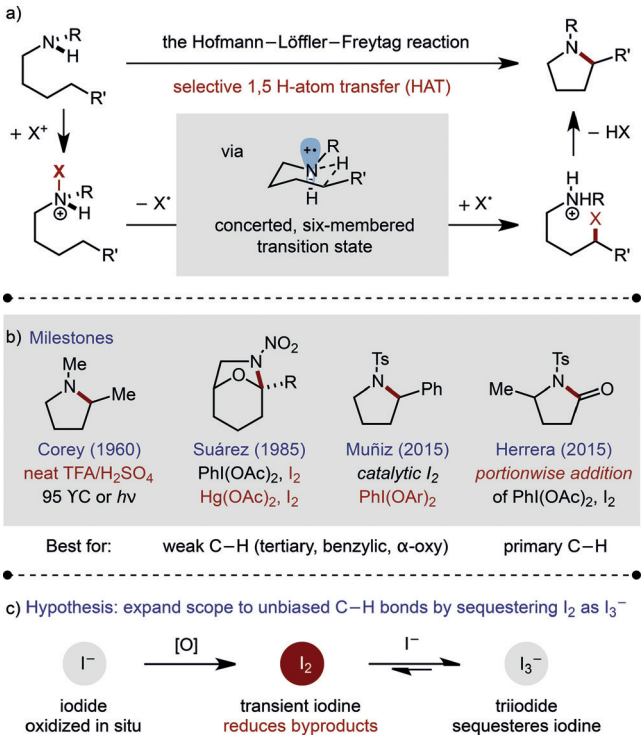

Figure 1. Development of Hofmann–Löffler–Freytag (HLF) reaction and our proposed triiodide strategy to significantly broaden scope and utility. TFA = trifluoroacetic acid, Ts = 4-toluenesulfonyl.

$PhI(OAc)_2$. Additionally, use of an electron-deficient nitrogen substituent replaces the need for strongly acidic conditions by promoting 1,5-HAT by a polarized aminyl radical intermediate. This modification enables C–H functionalization[12] of previously inaccessible, acid-sensitive molecules (e.g. carbohydrates).[13] However, this transformation remains generally limited to weak or activated C–H bonds (e.g. tertiary, benzylic, α-heteroatom).[14]

A major obstacle to functionalization of less biased substrates (e.g. secondary, nonbenzylic C–H bonds) derives from the requisite co-oxidant employed in this reaction. Specifically, iodine (I_2), and in situ generated acetyl hypoiodite (AcOI),[15] are prone to photoinitiated homolysis which leads to undesired oxidations of weaker C–H bonds.[16] To avoid these byproducts, HLF substrates are often designed with limited functionality and weak C_δ–H bonds to favor 1,5-HAT. Thus, the necessity of I_2 severely limits the scope and utility of such N-centered radical C–H functionalizations.

Recent attempts to overcome this limitation have focused on decreasing the reaction concentration of I_2, and thus AcOI.[17] Martínez and Muñiz have reported the first system which employs iodine as a catalyst, through the use of a tailored oxidant which facilitates efficient turnover of the

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Supporting information and the ORCID identification number(s) for the author(s) of this article can be found under http://dx.doi.org/10.1002/anie.201604704.

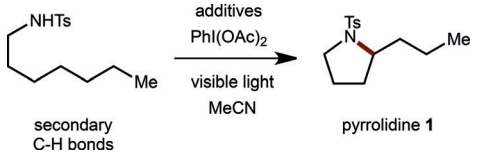
active iodine species (Figure 1b).[18] This innovative approach enables the use of sensitive functionality, such as alkenes and anisoles. Nonetheless, the protocol still requires weak C–H bonds or the incorporation of entropic bias. Another strategy to avoid unproductive I_2-mediated oxidations has been developed by Herrera and co-workers.[19] Through iterative oxidant addition, reaction efficiency could be improved for a range of primary C–H bond functionalizations, also allowing in situ subsequent oxidation to lactams.

In our strategy, we hypothesized that a solution to the I_2 problem entails slow, in situ I_2 generation from innocuous iodide (I^-) salts (Figure 1c). This approach allows 1) attenuated formation of transiently reactive AcOI, and 2) decreased generation of byproducts by in situ sequestration of I_2 as triiodide (I_3^-). We were inspired by the classical "iodine clock" experiment, where I_2 is formed by combination of iodide salts and an oxidant.[20] In the presence of excess I^-, the in situ generated I_2 forms I_3^-, because of a Lewis acid/base interaction between I^- and I_2. This equilibrium is well elucidated[21] and has been harnessed in battery technologies which employ an I^-/I_3^- electron shuttle.[22] Ultimately, we hypothesized that triiodide formation should minimize the concentration of I_2 in solution, thus allowing selective amination of unactivated C–H bonds within functionalized substrates.

To this end, we explored the cyclization of N-tosyl (Ts) heptyl amide, which contains unbiased, secondary C(sp^3)–H bonds at the δ position (Table 1). As expected, I_2-mediated conditions provide low yields of desired pyrrolidine (entry 1), leading instead to several, inseparable decomposition products. Next, we sought to test our hypothesis that I^- sequestration of I_2 as I_3^- prevents undesired byproduct pathways. Indeed, increasing NaI in the I_2-based conditions improved reaction efficiency (entries 3–5). We then sought to decrease initial I_2 concentration by relying on direct in situ oxidation of NaI. Again, increasing I^- (even in the absence of initial I_2) provides the cleanest and most efficient functionalization of this unbiased, secondary C(sp^3)–H bond (entry 9). We also observed that thermal initiation (50 °C, without added light) proved superior to visible-light irradiation in some cases (see the Supporting Information).

Having successfully developed a protocol for the δ-amination of unbiased, secondary C–H bonds, we applied this triiodide strategy to the cyclization of a wide range of amines bearing medicinally relevant functionalities. As illustrated in Table 2, the δ-functionalization of secondary C–H bonds is efficient and synthetically tractable by this triiodide strategy. Notably, selective functionalization of unactivated, secondary C(sp^3)–H bonds in the presence of weaker C(sp^3)–H bonds is accomplished under these reaction conditions [e.g. benzylic (**6–8**), α-oxy (**5**, **10**), α-CF_3 (**13**), and α-carbonyl (**11**, **12, 15, 16**): 65–75% yields]. We observed

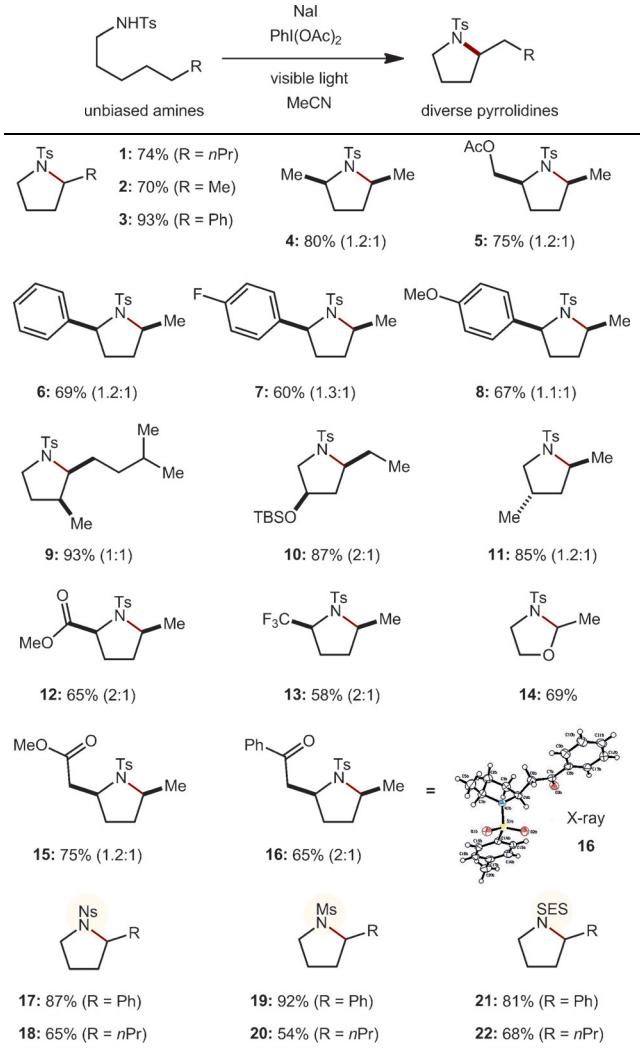
Table 1: Discovery of a triiodide-mediated C_δ–H amination.



Entry[a]	I_2 (equiv)	NaI (equiv)	Yield [%][b]
1	2	–	33
2	4	–	32
3	2	1	58
4	2	2	65
5	2	4	71
6	–	1	37
7	–	2	68
8	–	4	73
9	–	4	79 (74)[c]

[a] Reaction conditions: 0.2 mmol amide, $PhI(OAc)_2$ (4 equiv), 0.1 M MeCN, visible light, 4 h, 23 W compact fluorescent light (CFL). [b] Yields determined by ^1H NMR spectroscopy using an internal standard. [c] Yield of isolated product after a 9 h reaction time.

Table 2: Scope and generality of the triiodide-mediated C_δ–H amination.



Reaction conditions: 0.2 mmol amide, NaI (4 equiv), $PhI(OAc)_2$ (4 equiv), 0.1 M MeCN, visible light, 2–48 h, 23 W compact fluorescent light (CFL) or ambient light in fume hood at 50 °C. Yields are those of isolated products. Products **4–8**, **13–16** are obtained by thermal initiation, all others are photolytically initiated. Diastereomeric ratio (d.r.) indicated within parentheses. Ms = methanesulfonyl, Ns = nitrobenzenesulfonyl, SES = 2-trimethylsilylethanesulfonyl, TBS = *tert*-butyldimethylsilyl. X-ray structure of **16** is shown. Thermal ellipsoids are shown at 50% probability.[30]

exclusive C_δ–H amination in all cases, in lieu of competitive decomposition, or regioisomeric products.[23] Also, while the weak α-oxy C–H bonds of ethanolamine efficiently generate the oxazolidine **14**, cyclization of the amino acid analogue Ts-norleucine, is selective at a secondary C(sp^3)–H bond over the weaker
α-oxy C–H bonds (**12**). As expected in rapid, radical-mediated transformations, the diastereoselectivity of this amination is modest (1:1 to 2:1), although it is improved with nearby electron-deficient substituents [CO_2Me (**12**) and CF_3 (**13**)]. The major diastereomer obtained in all cases (except **11**) has been assigned as the *cis* isomer by NMR spectroscopy and confirmed by X-ray analysis of the β-keto pyrrolidine **16** (see the Supporting Information).

This C–H amination reaction exhibits a wide tolerance for biologically relevant functionality, including ethers, esters, ketones, arenes, and organofluorines (**5**–**16**). To further probe its synthetic utility, we investigated varying amine protecting groups. Although radical initiation and subsequent cyclization was limited for some protecting groups (e.g. Boc, Ac, TFA), all investigated sulfonamides underwent δ-amination, despite varied electronics of the aminyl radical in each case (**17**–**22**). Importantly, each of these sulfonamide pyrrolidine products is deprotected by an orthogonal method, including the synthetically valuable SES group, which is removed by fluoride-induced desilylation.[24]

Interestingly, this method exhibits unique, exclusive δ-selectivity, even in the presence of weaker C(sp^3)–H bonds. Unlike other protocols, which typically require tertiary or benzylic C–H bonds, this method appears to disfavor ring closure at unactivated tertiary C–H bonds. To further probe this seemingly divergent selectivity, we subjected a pair of menthol-derived amides to our I_3^--mediated conditions (Scheme 1). In the first competition experiment, C_δ–H amination is selective at the secondary over tertiary C–H bonds (**23** to **24** only). This atypical selectivity is notable given the additional observation that exocyclic ring formation is completely preferred over transannular cyclization (**25** to **26** only), as observed in a second competition experiment. In each case, only the pyrrolidine is obtained, thus further supporting the 1,5-HAT transition-state model.

This method is predicated on the mechanistic hypothesis that in situ I_2 generation in the presence of excess I^- favors I_3^- formation[21] and limits undesired I_2-based reactivity (Figure 1c). Our mechanistic hypothesis for the improved, triiodide-mediated process is supported by the observation of clean conversion of unactivated amines into pyrrolidines. Notably, ^{1}H NMR spectral data of this reaction shows significantly less impurities than the I_2-mediated reaction, thus suggesting a minimization of over-oxidation typically associated with I_2 and AcOI homolysis. As shown in Figure 2, the I_2-initiated reaction (red) results in multiple, inseparable byproducts, while the I^-/I_3^--mediated conditions (blue) affords clean conversion into the desired product **1** (green). These cleaner reaction profiles lead to increased pyrrolidine formation and simplified isolation.

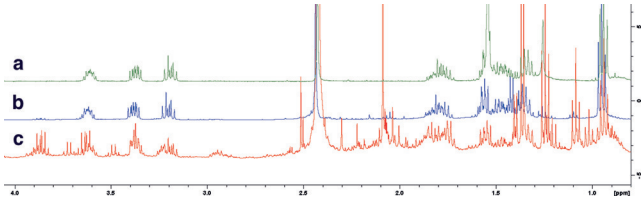
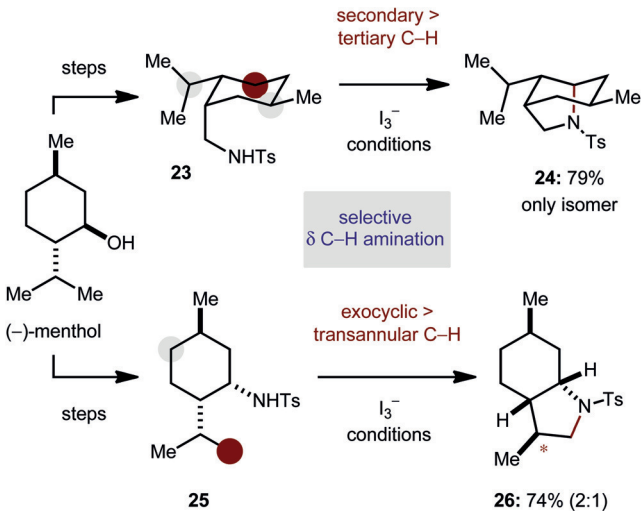


Figure 2. ^{1}H NMR spectra of the pyrrolidine product **1** (a; green) compared to crude reaction mixtures mediated by either I_3^- (b; blue) or I_2 (c; red).

Central to our hypothesis, I_3^- formation plays a key role in attenuating I_2-mediated decomposition. To confirm the presence of triiodide, we obtained UV/Vis spectroscopic data for the reactions depicted in Table 1. As illustrated in Figure 3, a strong absorbance at $\lambda = 360$ nm is observed, which is consistent with the presence of triiodide.[20] This I_3^- signal is absent in I_2-based conditions, but it is present and amplified with increasing quantities of NaI, including that of our reaction (4 equiv).

In the course of developing this triiodide-based protocol, we hypothesized that other salts might also be oxidized in situ to form the active oxidant. Interestingly, counterions apart from Na^+ (e.g. Li^+, K^+, Bu_4N^+) are uniformly inferior in promoting this transformation (see the Supporting Information). We propose this result is due to the beneficial role of the



Scheme 1. Atypical selectivities observed in this triiodide reaction.

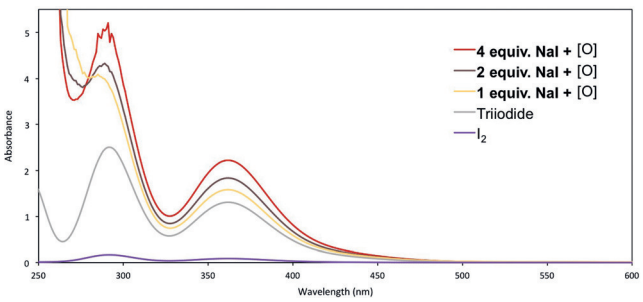
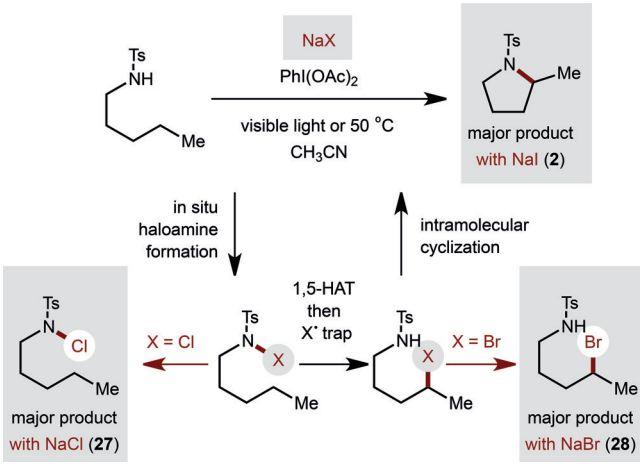


Figure 3. UV/Vis spectra of reaction mixtures confirm the presence of triiodide at varying concentrations of iodide.

basic NaOAc, which is formed in the reaction and may promote the final cyclization of the δ-iodo amide. While addition of exogenous bases provides varying levels of product formation, none are superior to the standard reaction conditions.

Interestingly, the use of sodium halide salts (NaX), in place of NaI, enabled isolation and characterization of two proposed intermediates (Scheme 2). For example, NaCl leads to exclusive formation of the haloamine (N–Cl) intermediate



Scheme 2. Proposed mechanism and intercepted intermediates.

27, which is not homolyzed[25] under these mild reaction conditions. Next, NaBr addition results in interruption of the cascade to form the C–Br bond of the intermediate **28** and halts the cyclization mechanism.[26] Lastly, among all NaX salts investigated, only NaI provides the cyclized product **2**, likely through the sequential formation of weak N–I and C–I bonds which are broken under these reaction conditions (BDE: C–I = 50.0 kcal mol^{-1}; N–I = 38.0 kcal mol^{-1}).[27] A radical-mediated mechanism is further supported by the decreased yields observed in the presence of typical traps, including TEMPO and galvinoxyl radicals or molecular oxygen (see the Supporting Information). Furthermore, neither over-oxidation[19] nor elimination[28] was observed for any substrate using this triiodide protocol.

In summary, we have developed a broadly applicable protocol for the C_δ–H functionalization of unbiased amines to access a range of biologically relevant pyrrolidines. This new transformation is predicated on a significant, mechanistic modification of the radical-mediated Suárez-HLF reaction. By replacing the electron-transfer mediating reagent, I_2, with an I_3^--based system, generated in situ from NaI, the typically observed byproducts are reduced significantly. In the absence of these alternate pathways associated with I_2 and AcOI homolysis, unbiased, secondary C(sp^3)–H bonds are now amenable to highly efficient aminations in the presence of a variety of biologically relevant functionalities. The application of this triiodide strategy for distal C–H functionalizations is expected to further enable the streamlined synthesis of complex molecules.

Acknowledgments

We gratefully acknowledge The Ohio State University (OSU) and the American Chemical Society Petroleum Research Fund for support of this research. We are also grateful for fellowship support to E.A.W. (OSU) and S.C.F (National Institutes of Health Chemistry-Biology Interface Training Program NIH GM08512). We also wish to thank Dr. Judith Gallucci (OSU) for assistance with X-ray crystallographic characterization.

Keywords: amination · C–H functionalization · radical chemistry · hydrogen atom transfer · triiodide

How to cite: *Angew. Chem. Int. Ed.* **2016**, *55*, 9974–9978
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[30] CCDC 1479777 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.

Received: May 13, 2016
Revised: June 2, 2016
Published online: July 7, 2016

