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

Ethan A. Wappes, Stacy C. Fosu, Trevor C. Chopko, and David A. Nagib

Department of Chemistry and Biochemistry The Ohio State University, Columbus, OH 43210 (USA)

Abstract

The δ C-H amination of unactivated, secondary C-H bonds to form a broad range of functionalized pyrrolidines has been developed via a triiodide (I_3^-)-mediated strategy. By in situ (i) oxidation of sodium iodide and (ii) sequestration of the transiently generated iodine (I_2) as I_3^- , this approach precludes undesired I_2 -mediated decomposition that can otherwise limit synthetic utility to only weak C-H bonds. The mechanism of this triiodide-mediated cyclization of unbiased, secondary C-H bonds, via thermal or photolytic initiation, is supported by NMR and UV-Vis spectroscopic data and intercepted intermediates.

Graphical Abstract

Keywords

C-H functionalization; radical chemistry; triiodide; amination; remote H abstraction

In the synthetically enabling realm of C-H functionalization,¹ selective amination of unactivated sp^3 C-H bonds is of primary interest due to 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.

Correspondence to: David A. Nagib.

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The Hofmann-Löffler-Freytag (HLF) reaction⁹ converts acyclic amines to pyrrolidines via transposition of an N-halo-amine to a δ -halo amine via selective 1,5-HAT (Figure 1). Despite the harsh conditions required to promote the classic HLF reaction¹⁰ (through homolysis of a pre-formed haloamine in refluxing acid), this radical-mediated δ C-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 coworkers, which precludes the need for haloamine pre-formation.¹¹ In this improved approach, generation of the N-centered radical is facilitated by *direct* oxidation of an amine with $\text{Hg}(\text{OAc})_2$ or $\text{PhI}(\text{OAc})_2$. Additionally, use of an electron-deficient nitrogen substituent replaces the need for strongly acidic conditions by promoting 1,5-HAT via a polarized aminyl radical intermediate. This modification enables C-H functionalization¹² 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, non-benzylic 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 photo-initiated homolysis that leads to undesired oxidations of weaker C-H bonds.¹⁶ To avoid these byproducts, HLF substrates are often designed with limited functionality and weak δ C-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 that employs iodine as a catalyst, through the use of a tailored oxidant that facilitates efficient turnover of the active iodine species.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 coworkers.¹⁹ Through iterative oxidant addition, reaction efficiency could be improved for a range of primary C-H bond functionalizations – also allowing for *in situ* subsequent oxidation to lactams.

Strategy

We hypothesized that a solution to the I_2 -problem entails slow, *in situ* I_2 -generation from innocuous iodide (I^-) salts (Eq 1). This approach allows for (i) attenuated formation of transiently reactive AcOI , and (ii) decreased generation of byproducts via *in situ* sequestration of I_2 as triiodide (I_3^-). We were inspired by the classical “iodine clock” experiment, where I_2 is formed via combination of iodide salts and an oxidant.²⁰ In the presence of excess I^- , *in situ* generated I_2 forms I_3^- , due to a Lewis acid/base interaction between I^- and I_2 . This equilibrium is well elucidated²¹ and has been harnessed in battery technologies that employ an I^-/I_3^- electron shuttle.²² Ultimately, we hypothesized that

triiodide formation should minimize the concentration of I_2 in solution, allowing for 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-H bonds at the δ position (Table 1). As expected, I_2 -mediated conditions provide low yields of desired pyrrolidine (entry 1, 33% yield), 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, up to 71% yield). 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-H bond (entry 9, 79% yield). We also observed that thermal initiation (50 °C, without added light) proved superior to visible light irradiation in some cases (see Supp Info).

Synthetic Utility

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 via this triiodide strategy. Notably, selective functionalization of unactivated, secondary C-H bonds in the presence of weaker C-H bonds is accomplished under these conditions (e.g. benzylic (**6–8**), α -oxy (**5**, **10**), α -CF₃ (**13**), and α -carbonyl (**11**, **12**, **15**, **16**): 65–75% yields). We observed exclusive δ C-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 oxazolidine **14**, cyclization of amino acid analog, Ts-norleucine, is selective at a secondary C-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 (**12**, CO₂Me & **13**, CF₃). The major diastereomer obtained in all cases (except **11**) has been assigned as the *cis* isomer by NMR and confirmed by X-ray analysis of β -keto pyrrolidine **16** (see Supp Info).

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 via an orthogonal method, including the synthetically valuable SES group, which is removed via fluoride-induced desilylation.²⁴

Interestingly, this method exhibits unique, exclusive δ -selectivity, even in the presence of weaker C-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, δ C-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, further supporting the 1,5-HAT transition state model.

Mechanistic Considerations

This method is predicated on the hypothesis that *in situ* I_2 generation in the presence of excess I^- favors I_3^- formation²¹ and limits undesired I_2 -based reactivity (Eq 1). Our mechanistic hypothesis for the improved, triiodide-mediated process is supported by the observation of clean conversion of unactivated amines to pyrrolidines. Notably, 1H NMR spectral data of this reaction shows significantly less impurities than the I_2 -mediated reaction, suggesting a minimization of over-oxidation typically associated with I_2 and AcOI homolysis. As shown in Figure 2, the I_2 -initiated reaction (**c**, red) results in multiple, inseparable byproducts, while the I^-/I_3^- mediated conditions (**b**, blue) affords clean conversion to desired product **1** (**a**, green). These cleaner reaction profiles lead to increased pyrrolidine formation and simplified isolation.

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 Supp Info). We propose this is due to a beneficial role of the basic NaOAc that 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 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 haloamine (N-Cl) intermediate **27**, which is not homolyzed²⁵ under these mild conditions. Next, NaBr addition results in interruption of the cascade to form the C-Br bond of intermediate **28** and halts the cyclization mechanism.²⁶ Lastly, among all NaX salts investigated, only NaI provides cyclized product **2**, likely through the sequential formation of weak N-I and C-I bonds that are broken under these reaction conditions (BDE: C-I = 50.0 kcal/mol; N-I = 38.0 kcal/mol).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 Supp Info). Furthermore, neither

over-oxidation¹⁹ nor elimination²⁸ was observed for any substrate using this triiodide protocol.

In summary, we have developed a broadly applicable protocol for the δ C-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, I₂, with an I₃⁻ based system, generated *in situ* from NaI, the typically observed byproducts are reduced significantly. In the absence of these alternate pathways, associated with I₂ and AcOI homolysis, unbiased, secondary C-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.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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References

1. For reviews on C-H functionalization, see: Bergman RG. *Nature*. 2007; 446:391. [PubMed: 17377575] Davies HML, Manning JR. *Nature*. 2008; 451:417. [PubMed: 18216847] Chen X, Engle KM, Wang D-H, Yu J-Q. *Angew. Chem. Int. Ed.* 2009; 48:5094. Lyons TW, Sanford MS. *Chem. Rev.* 2010; 110:1147. [PubMed: 20078038] Mkhali IAI, Barnard JH, Marder TB, Murphy JM, Hartwig JF. *Chem. Rev.* 2010; 110:890. [PubMed: 20028025] Colby DA, Bergman RG, Ellman JA. *Chem. Rev.* 2010; 110:624. [PubMed: 19438203] Gutekunst WR, Baran PS. *Chem. Soc. Rev.* 2011; 40:1976. [PubMed: 21298176] Roizen JL, Harvey ME, Du Bois J. *Acc. Chem. Res.* 2012; 45:911. [PubMed: 22546004] White MC. *Science*. 2012; 335:807. [PubMed: 22344434] Yamaguchi J, Yamaguchi AD, Itami K. *Angew. Chem. Int. Ed.* 2012; 51:8960. Wencel-Delord J, Glorius F. *Nat. Chem.* 2013; 5:369. [PubMed: 23609086]
2. Jeffrey JL, Sarpong R. *Chem. Sci.* 2013; 4:4092.
3. Vitaku E, Smith DT, Njardarson JT. *J. Med. Chem.* 2014; 57:10257. [PubMed: 25255204]
4. For seminal nitrenoid based sp³ C-H aminations, see: Breslow R, Gellman SH. *J. Am. Chem. Soc.* 1983; 105:6728. Espino CG, Du Bois J. *Angew. Chem. Int. Ed.* 2001; 40:598. Espino CG, Wehn PM, Chow J, Du Bois J. *J. Am. Chem. Soc.* 2001; 123:6935. Milczek E, Boudet N, Blakey S. *Angew. Chem. Int. Ed.* 2008; 47:6825. Lyaskovskyy V, Olivos Suarez AI, Lu H, Jiang H, Zhang XP, de Bruin B. *J. Am. Chem. Soc.* 2011; 133:12264. [PubMed: 21711027] Alderson JM, Phelps AM, Scamp RJ, Dolan NS, Schomaker JM. *J. Am. Chem. Soc.* 2014; 136:16720. [PubMed: 25386769] Yang M, Su B, Wang Y, Chen K, Jiang X, Zhang Y-F, Zhang X-S, Chen G, Cheng Y, Cao Z, Guo Q-Y, Wang L, Shi Z-J. *Nat. Commun.* 2014; 5:4707. [PubMed: 25140832] Kang T, Kim Y, Lee D, Wang Z, Chang S. *J. Am. Chem. Soc.* 2014; 136:4141. [PubMed: 24580093]
5. Other seminal sp³ C-H aminations include: Fraunhoffer KJ, White MC. *J. Am. Chem. Soc.* 2007; 129:7274. [PubMed: 17516648] Ochiai M, Miyamoto K, Kaneaki T, Hayashi S, Nakanishi W. *Science*. 2011; 332:448. [PubMed: 21512029] Antonchick AP, Samanta R, Kulikov K, Lategahn J. *Angew. Chem. Int. Ed.* 2011; 50:8605. He G, Zhao Y, Zhang S, Lu C, Chen G. *J. Am. Chem. Soc.* 2012; 134:3. [PubMed: 22191666] Nadres ET, Daugulis O. *J. Am. Chem. Soc.* 2012; 134:7.

- [PubMed: 22206416] Paradine SM, White MC. *J. Am. Chem. Soc.* 2012; 134:2036. [PubMed: 22260649] Michaudel Q, Thevenet D, Baran PS. *J. Am. Chem. Soc.* 2012; 134:2547. [PubMed: 22276612] Nguyen Q, Sun K, Driver TG. *J. Am. Chem. Soc.* 2012; 134:7262. [PubMed: 22519742] Hennessy ET, Betley TA. *Science*. 2013; 340:591. [PubMed: 23641113] He G, Zhang S-Y, Nack WA, Li Q, Chen G. *Angew. Chem. Int. Ed.* 2013; 52:11124. McNally A, Haffemayer B, Collins BSL, Gaunt MJ. *Nature*. 2014; 510:129. [PubMed: 24870240] Villanueva O, Weldy NM, Blakey SB, MacBeth CE. *Chem. Sci.* 2015; 6:6672. Huang X, Bergsten TM, Groves JT. *J. Am. Chem. Soc.* 2015; 137:5300. [PubMed: 25871027] Pandey G, Laha R. *Angew. Chem. Int. Ed.* 2015; 54:14875.
6. For reviews on N-centered radicals, see: Heusler K, Kalvoda J. *Angew. Chem. Int. Ed.* 1964; 3:525. Stella L. *Angew. Chem. Int. Ed.* 1983; 22:337. Fokin AA, Schreiner PR. *Chem. Rev.* 2002; 102:1551. [PubMed: 11996544] Zard SZ. *Chem. Soc. Rev.* 2008; 37:1603. [PubMed: 18648685]
7. a) Zhdankin VV, Krasutsky AP, Kuehl CJ, Simonsen AJ, Woodward JK, Mismash B, Bolz JT. *J. Am. Chem. Soc.* 1996; 118:5192. b) Sharma A, Hartwig JF. *Nature*. 2015; 517:600. [PubMed: 25631448]
8. For recent examples of mildly generated N-centered radicals, see: Zhang H, Pu W, Xiong T, Li Y, Zhou X, Sun K, Liu Q, Zhang Q. *Angew. Chem. Int. Ed.* 2013; 52:2529. Matcha K, Narayan R, Antonchick AP. *Angew. Chem. Int. Ed.* 2013; 52:7985. Sahoo B, Hopkinson MN, Glorius F. *J. Am. Chem. Soc.* 2013; 135:5505. [PubMed: 23565980] Cecere G, König CM, Allea JL, MacMillan DW. *J. Am. Chem. Soc.* 2013; 135:11521. [PubMed: 23869694] Zhang H, Song Y, Zhao J, Zhang J, Zhang Q. *Angew. Chem. Int. Ed.* 2014; 53:11079. Hu X-Q, Chen J-R, Wei Q, Liu F-L, Deng Q-H, Beauchemin AM, Xiao W-J. *Angew. Chem. Int. Ed.* 2014; 53:12163. Musacchio AJ, Nguyen LQ, Beard GH, Knowles RR. *J. Am. Chem. Soc.* 2014; 136:12217. [PubMed: 25127420] Allen LJ, Cabrera PJ, Lee M, Sanford MS. *J. Am. Chem. Soc.* 2014; 136:5607. [PubMed: 24702705] Lu D-F, Zhu C-L, Jia Z-X, Xu H. *J. Am. Chem. Soc.* 2014; 136:13186. [PubMed: 25166591] Romero NA, Margrey KA, Tay NE, Nicewicz DA. *Science*. 2015; 349:1326. [PubMed: 26383949] Jiang H, An X, Tong K, Zheng T, Zhang Y, Yu S. *Angew. Chem. Int. Ed.* 2015; 54:4055. Davies J, Booth SG, Essafi S, Dryfe RAW, Leonori D. *Angew. Chem. Int. Ed.* 2015; 54:14017. Choi GJ, Knowles RR. *J. Am. Chem. Soc.* 2015; 137:9226. [PubMed: 26166022] Yuan Y-A, Lu D-F, Chen Y-R, Xu H. *Angew. Chem. Int. Ed.* 2016; 55:534. Zhu L, Xiong P, Mao Z-Y, Wang Y-H, Yan X, Lu X, Xu H-C. *Angew. Chem. Int. Ed.* 2016; 55:2226.
9. a) Hofmann AW. *Chem. Ber.* 1883; 16:558. b) Löffler K, Freytag C. *Chem. Ber.* 1909; 42:3427.
10. a) Wolff ME. *Chem. Rev.* 1963; 63:55. b) Corey EJ, Hertler WR. *J. Am. Chem. Soc.* 1960; 82:1657.
11. De Armas P, Carrau R, Concepción JI, Francisco CG, Hernández R, Suárez E. *Tetrahedron Lett.* 1985; 26:2493.
12. Togo H, Katohgi M. *Synlett*. 2001; 2001:0565.
13. Francisco CG, Herrera AJ, Suárez E. *J. Org. Chem.* 2003; 68:1012. [PubMed: 12558429]
14. Although the use of $\text{Hg}(\text{OAc})_2$ oxidant allows for broader reaction scope in the Suárez-HLF reaction, the less toxic and synthetically preferred $\text{PhI}(\text{OAc})_2$ oxidant is only suitable for amination of weaker C-H bonds.
15. Courtneidge JL, Luszyk J, Pagé D. *Tetrahedron Lett.* 1994; 35:1003.
16. AcOI homolysis-derived radicals can oxidize α -aminyl C-H bonds. This byproduct-forming oxidation is competitive with 1,5-HAT for unactivated C-H bonds, which limits reaction scope to activated C-H bonds.
17. For an alternate strategy, see: Zhu C, Liang Y, Hong X, Sun H, Sun W-Y, Houk KN, Shi Z. *J. Am. Chem. Soc.* 2015; 137:7564. [PubMed: 26035639]
18. Martínez C, Muñoz K. *Angew. Chem. Int. Ed.* 2015; 54:8287.
19. Paz NR, Rodríguez-Sosa D, Valdés H, Marticorena R, Melián D, Copano MB, González CC, Herrera AJ. *Org. Lett.* 2015; 17:2370. [PubMed: 25932748]
20. Burgess AE, Davidson JC. *J. Chem. Educ.* 2012; 89:814.
21. Carter JS. *J. Chem. Soc.* 1928:2227.
22. Papageorgiou N, Maier WF, Grätzel M. *J. Electrochem. Soc.* 1997; 144:876.
23. Chen K, Richter JM, Baran PS. *J. Am. Chem. Soc.* 2008; 130:7247. [PubMed: 18481847]
24. Weinreb SM, Demko DM, Lessen TA, Demers JP. *Tetrahedron Lett.* 1986; 27:2099.
25. Qin Q, Yu S. *Org. Lett.* 2015; 17:1894. [PubMed: 25853884]

26. Reddy LR, Reddy BVS, Corey EJ. *Org. Lett.* 2006; 8:2819. [PubMed: 16774265]
27. Dean JA, Lange NA. *Lange's Handbook of Chemistry* (15th). 1999
28. Liu T, Mei T-S, Yu J-Q. *J. Am. Chem. Soc.* 2015; 137:5871. [PubMed: 25915558]
29. An NIS-based HLF reaction with similar scope to ref 18: O'Broin CQ, Fernández P, Martínez C, Muñoz K. *Org. Lett.* 2016; 18:436. [PubMed: 26782641]

Milestones

Corey (1960)
neat TFA/H₂SO₄
95 °C or *hν*

Suárez (1985)
PhI(OAc)₂, I₂
Hg(OAc)₂, I₂

Muñiz (2015)
catalytic I₂
PhI(OAr)₂

Herrera (2015)
portionwise add'n
of PhI(OAc)₂, I₂

Best for:

weak C-H's (tertiary, benzylic, α-oxy)

primary C-H's

Hypothesis: expand scope to **unbiased C-H bonds** by sequestering I₂ as I₃⁻

Figure 1.

Development of Hofmann-Löffler-Freytag (HLF) reaction and our proposed triiodide strategy to significantly broaden scope and utility.

Figure 2.
¹H NMR spectra of pyrrolidine product **1** (a, green) compared to crude reaction mixtures mediated by triiodide, I₃⁻, (b, blue) or iodine, I₂ (c, red).

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

Scheme 1.

Atypical selectivities observed in this triiodide reaction.

Scheme 2.
Proposed mechanism and intercepted intermediates.

Table 1Discovery of a triiodide-mediated δ C-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] Conditions: 0.2 mmol amide, PhI(OAc)₂ (4 equiv), 0.1 M MeCN, visible light, 4 hrs, 23 W compact fluorescent light (CFL).

^[b] Yields determined by ¹H NMR vs internal standard.

^[c] Isolated yield, 9 hr.

Table 2Scope and generality of the triiodide-mediated δ C-H amination.

Conditions: 0.2 mmol amide, NaI (4 equiv), PhI(OAc)₂ (4 equiv), 0.1 M MeCN, visible light, 2–48 hrs, 23 W compact fluorescent light (CFL) or ambient light in fume hood at 50 °C. Isolated Yields. Diastereomeric ratio (d.r.) indicated in parenthesis. Ns = nitrobenzenesulfonyl; Ms = methanesulfonyl; SES = 2-trimethylsilylethanesulfonyl. X-ray **16**^[29]