Organic LETTERS

Letter

pubs.acs.org/OrgLett

Chemoselective Intramolecular Functionalization of Methyl Groups in Nonconstrained Molecules Promoted by *N*-Iodosulfonamides

Nieves R. Paz,[†] Dionisio Rodríguez-Sosa,[†] Haydee Valdés,[§] Ricardo Marticorena,[†] Daniel Melián,[‡] M. Belén Copano,[†] Concepción C. González,*[,†] and Antonio J. Herrera*[,†]

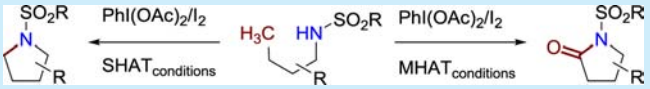
[†]Instituto de Productos Naturales y Agrobiología C.S.I.C., Av. Astrofísico Francisco Sánchez 3, 38206 La Laguna, Tenerife, Spain

[‡]Departamento de Química Orgánica, Universidad de La Laguna, Av. Astrofísico Francisco Sánchez s/n, 38206 La Laguna, Tenerife, Spain

[§]Departamento de Física Teórica, Atómica y Óptica, Universidad de Valladolid, Paseo de Belén 7, 47011 Valladolid, Spain

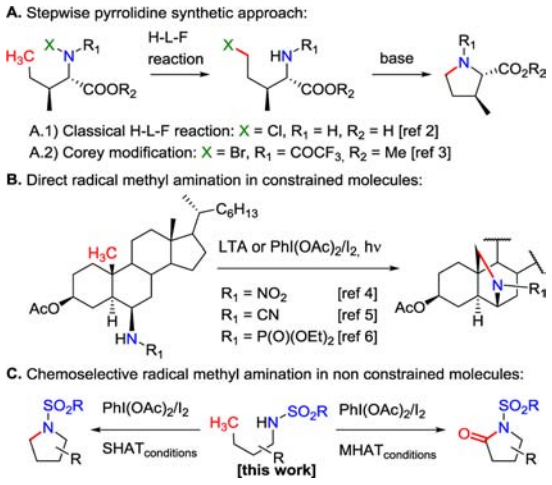
Supporting Information

ABSTRACT: Mechanistic evidence observed in Hofmann–Löffler–Freytag-type reactions has been crucial to achieve the chemoselective functionalization of methyl groups under mild conditions. Radical-mediated methyl iodination and subsequent oxidative deiodination are the key steps in this functionalization, where iodine chemistry has a pivotal role on the formation of the C–N bond. The concepts of single hydrogen atom transfer (SHAT) and multiple hydrogen atom transfer (MHAT) are introduced to describe the observed chemoselectivity.



The functionalization of the ubiquitous C–H bonds in organic molecules is certainly of high importance in the development of organic synthesis and currently remains one of the most challenging tasks in this field.[1] In this regard, the C(sp^3)–H bonds of methyl groups that are not directly influenced by other vicinal functional groups by inductive, conjugative, or hyperconjugative effects are of special interest due to their relatively low reactivity. Nitrogen-centered radicals have appeared in the literature as an intermediate capable of achieving methyl amination. Thus, Lavergne described a multistep procedure based on the original Hofmann–Löffler–Freytag (H–L–F) reaction, employing free amine group as precursor of *N*-radicals under strong acidic conditions (Scheme 1, eq A.1).[2] More recently, Corey reported a very efficient modification under neutral conditions via methyl bromination, utilizing *N*-trifluoroacetyl derivatives to optimize the intramolecular C–H abstraction pathway (Scheme 1, eq A.2).[3] The Suárez modification has also been used to accomplish the direct methyl amination in a one-pot procedure employing *N*-nitroamides,[4] *N*-cyanamides,[5] and *N*-phosphoramidates.[6] However, its application has been limited to cyclic systems with restricted geometry (Scheme 1, eq B).

Scheme 1. Intramolecular Radical Methyl Aminations



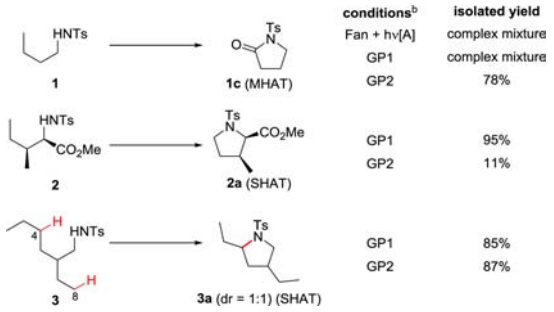
In our ongoing program, we have focused our attention in the direct intramolecular C–H amination of unactivated methyl groups employing nitrogen-centered radicals with the idea of developing chemoselective procedures to synthesize pyrrolidines and pyrrolidinones under mild conditions. The strategy is based on the direct sequential transformation C–H → C–I → C–N already proposed in H–L–F-type reactions[7] and employing its Suarez modification[8] to generate nitrogen-centered radicals (Scheme 1, eq C). We attempted to overcome the classical limiting scopes of previously reported methodologies[9,10] and tackle three major problems: suitable *N*-radical precursors, conformational restrictions, and control of the chemoselectivity.

In this work, we decided to reconsider the employment of sulfonamides as *N*-radical precursors, previously reported by Togo and Yokoyama,[11] to achieve the proposed functionalization, motivated by the success of Fan[12] in his intramolecular functionalization of methylene groups. Although Fan's optimized conditions were not efficient for obtaining the respective pyrrolidine derived from *N*-tosylamide **1**, we repeated the experiment under irradiation with two tungsten lamps (80 W) ($h\nu$[A]). Complete consumption of starting material and formation of a complex mixture of compounds was observed

Received: March 24, 2015
Published: May 1, 2015

DOI: 10.1021/acs.orglett.5b00866
Org. Lett. 2015, 17, 2370–2373

Scheme 2. Structure-Dependent Chemoselective Functionalization[a]



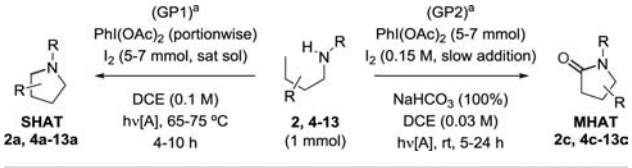
[a]SHAT = single hydrogen atom transfer, MHAT = multiple (*triple*) hydrogen atom transfer. [b]See the Supporting Information.

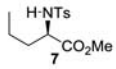
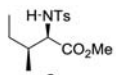
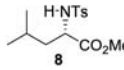
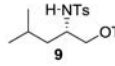
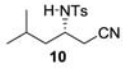
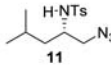
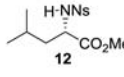
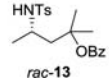
(Scheme 2). Mono- and polyiodo-containing compounds were detected by mass spectra of the mixture, indicating some functionalization. After testing many conditions, we found that use of an excess of $PhI(OAc)_2$ (600 mol %), $NaHCO_3$, more diluted conditions, and slow addition of a solution of iodine in DCE (keeping low concentrations of I_2), while the reaction mixture was irradiated at rt (denominated as GP2), led to a clean reaction to afford the 2-pyrrolidinone **1c** in 78% yield after purification. Thus, we assumed that the main problem to obtain the expected pyrrolidine does not rely only on the step of the transference of the hydrogen atom from the methyl group to the *N*-radical but also on the process of cyclization, leading, in this case, to the highly selective formation of an "over-oxidized" product.

Conversely, when the same procedure GP2 was used with compound **2**, only the corresponding pyrrolidine was obtained, as expected for constrained molecules, with a low conversion (73% of **2** was recovered). This result showed that the efficiency of this approach is highly dependent on the shape of each precursor. At this point, we were interested in finding general patterns of reactivity in order to favor the formation of pyrrolidines (**Na**)[13] or 2-pyrrolidinones (**Nc**),[13] considering that the cyclization step (highly influenced by the geometry of the molecule) is determinant in the chemoselectivity. In this regard, we found that use of an excess of iodine (saturated solution), more concentrated conditions (0.1 M in DCE), and portionwise addition of $PhI(OAc)_2$ while the reaction mixture was irradiated in a sealed tube that was allowed to reach 65−75 °C (named as GP1 conditions) were excellent conditions to convert compound **2** into the corresponding pyrrolidine **2a** in almost quantitative yields and complete chemoselectivity. However, a complex mixture was obtained when GP1 was applied to **1**. This suggests that, due to the entropic penalty to approach the amide group to the monoiodinated methyl position (Thorpe−Ingold effect),[14] the cyclization step is slow and would enable the competition of other intra- and intermolecular reactions. When compound **3** was submitted to either GP1 or GP2, pyrrolidine **3a** was obtained as the sole product without any stereoselectivity, evidencing that the methanediyl group is more reactive than the methyl group in both determining steps: first, in the HAT step due to enthalpic factors (ΔH_{C4-H} = 93.9 kcal mol^{-1}; ΔH_{C8-H} = 97.5 kcal mol^{-1}) (see the Supporting Information: DFT calculations) and, second, in the cyclization step due to the faster oxidative deiodination of a secondary monoiodinated carbon versus a primary one.[15] Moreover, the absence of "over-oxidized" product led us to consider the functionalization of the methyl groups as a particular matter.

Fortunately, when we used GP1 and GP2 to perform the fuctionalization with other butylamine derivatives (compounds **4**−**6**, Table 1, entries 1−6), we obtained the corresponding pyrrolidines and 2-pyrrolidinones with good yields and excellent chemoselectivity, indicating that these procedures were reliable.[16] In the same manner, GP1 and GP2 were efficient with the amino acid derivatives **7** and **8** obtaining good yields and chemoselectivities, as well as for the leucinol derivatives **9**−**11**.

Table 1. Chemoselective Functionalization of Methyl Groups



entry	substrate	procedure[a]	SHAT %(*syn*/*anti*)[b]	MHAT %(*syn*/*anti*)[b]
1		GP1	**4a**, 61	**4c**, 7
2	**4**	GP2	-	**4c**, 77
3		GP1	**5a**, 65	-
4	**5**	GP2	-	**5c**, 78
5		GP1	**6a**, 65	-
6	**6**	GP2	-	**6c**, 56
7		GP1	**7a**, 86	-
8		GP2	**7a**, 9	**7c**, 73
9	**7**	GP3[c]	-	**7c**, 83
10		GP1	**2a**, 95	-
11		GP2	**2a**, 11	-
12	**2**	$GP3_{Na2CO3}$[d]	-	**2c**, 81
13		GP1	**8a**, 81 (1:1.4)	**8c**, 8 (1:0)
14		$GP1_{Zn(OTf)2}$[e]	**8a**, 88 (1:1)	-
15		$GP1_{CSA}$[f]	**8a**, 93 (1.1:1)	-
16	**8**	GP2	-	**8c**, 72 (1.1:1)
17		GP1	**9a**, 72 (1:1.7)	**9c**, 5 (1:0)
18		GP2	-	**9c**, 88 (2.8:1)
19	**9**	GP1	**10a**, 32 (1:2.8)	**10c**, 40 (4:1)
20		$GP1_{CSA}$[f]	**10a**, 86 (1.3:1)	-
21	**10**	GP2	-	**10c**, 72 (2.5:1)
22		GP1	**11a**, 52 (1.5:1)	**11c**, 15 (1:1)
23		$GP1_{CSA}$[f]	**11a**, 36 (1:3)	**11c**, 23 (4.3:1)
24	**11**	GP2	-	**11c**, 68 (2:1)
25		GP1	**12a**, 69.5 (1:1.8)	**12c**, 24 (2.5:1)
26		$GP1_{CSA}$[f]	**12a**, 82 (1:1.2)	-
27	**12**	GP2	-	**12c**, 60 (1:1.1)
28		$GP1_{CSA}$	**13a**, 52 (1.7:1)	**13c**, 24 (1:0)
29	*rac*-**13**	GP2	-	**13c**, 83 (7.5:1)

[a]For more details on the reaction conditions, see the Supporting Information. [b]Total isolated yield (diastereoisomeric ratio). [c]GP3 same as GP2 but I_2 (1.4 mmol) added in one portion. [d]$GP3_{Na2CO3}$ same as GP2 but I_2 (1.0 mmol) added in one portion and Na_2CO_3 instead of $NaHCO_3$. [e]$GP1_{Zn(OTf)2}$ same as GP1 but I_2 (0.5 mmol) and $Zn(OTf)_2$ (0.6 mmol) were added. [f]$GP1_{CSA}$ same as GP1 but I_2 (0.6 mmol) and CSA (1.0 mmol) were added.

DOI: 10.1021/acs.orglett.5b00866
Org. Lett. 2015, 17, 2370−2373

Alternatively, we found that the formation of pyrrolidines could be optimized, for some substrates, employing $GP1_{Zn(OTf)2}$ or $GP1_{CSA}$, which combine catalytic amounts of iodine with a Lewis or Brønsted acids such as $Zn(OTf)_2$ or CSA (entries 14, 15, 20, and 26), although that behavior was not general (entry 23). On the other hand, the employment of Na_2CO_3 ($GP3_{Na2CO3}$) instead of $NaHCO_3$ (GP2) was highly efficient to improve the chemoselectivity toward the formation of the 2-pyrrolidinone **2c** (entry 12).

Replacement of the *N*-tosylamidyl group in compound **8** for the *N*-nosylamidyl group (compound **12**) led to very similar reactivity under GP1, $GP1_{CSA}$, or GP2 conditions. However, poor reactivity was observed when it was replaced by either diphenylphosphoramidyl or alkyl carbamate groups. Furthermore, no reactivity was observed with the trifluoroacetamidyl derivative (see the Supporting Information, Tables S14−S16).

Functional groups such as sulfonic esters, nitriles, and azides were tolerated by these procedures as shown with substrates **9**−**11**. Additionally, it was also proved that neither GP1 nor GP2 conditions induced epimerization in compound **7** (see the Supporting Information, Scheme S14).

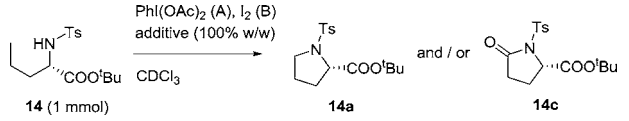
Finally, we evidenced that either GP1 or GP2 can be used to synthesize pyrrolidines and 2-pyrrolidinones with good stereoselectivities (Table 1, entries 28 and 29). It is important to notice the chemoselectivity observed in compounds with two methyl groups in the γ-position, such as **4** and **8**−**13**, where only one of the methyl groups was functionalized, especially under GP2 conditions. This chemoselectivity could be explained on the basis of the C−H BDE for the methyl and the mono- and diiodinated methyl groups (see Scheme S15, Supporting Information).

In order to elucidate the key of the chemoselectivity, we decided to synthesize compounds **14**, **14(I)** and **14(I_2)** and monitor their reactivity by ^{1}H NMR (see the Supporting Information, mechanistic studies section).

First, we checked that GP1 and $GP3_{Na2CO3}$ were good procedures to obtain **14a** and **14c** with good chemoselectivity in $CDCl_3$ as well (Table 2, entries 1 and 2). For both procedures, the *N*-iodoamide intermediate (**14_{N-I}**) established an equilibrium with **14**, while the reaction was kept in the dark. This equilibrium was reached much faster and further displaced toward **14_{N-I}** in the absence of Na_2CO_3 than in the presence of the base (entries 3 and 4). Additionally, this intermediate **14_{N-I}** did not undergo any reaction in the absence of light; however, wavelengths above 445 nm were efficient to initiate the methyl functionalization (entry 2). It is noteworthy that no intermediate was detected under the conditions of entry 1, while intermediates **14(I)** and **14(I_2)** were detected within the formation of lactam **14c**.

Second, we also found that the cyclization process did not involve a classical intramolecular nucleophilic substitution catalyzed by acids, since the evolution of **14(I)** in the absence of reagent or after separate addition of iodine, AcOH, CSA, $Zn(OTf)_2$, or $PhI(OAc)_2$, and either under irradiation with light or in the dark, no considerable evolution toward cyclic compound **14a** was observed (see the Supporting Information: Table S20, entries 1−7). Nevertheless, when **14(I)** was added to a previously stirred solution of $PhI(OAc)_2$ and I_2 in the dark and absence of Na_2CO_3 (Scheme 3, eq 1), it was completely converted into **14a** in less than 3 min. On the contrary, this cyclization was dramatically slowed down when it was carried out in the presence of a slurry of Na_2CO_3 (conditions C), where 87.5 h was necessary to achieve 50% conversion. Fortunately, when the reaction was performed in the absence of Na_2CO_3 at 5 °C (conditions B), it

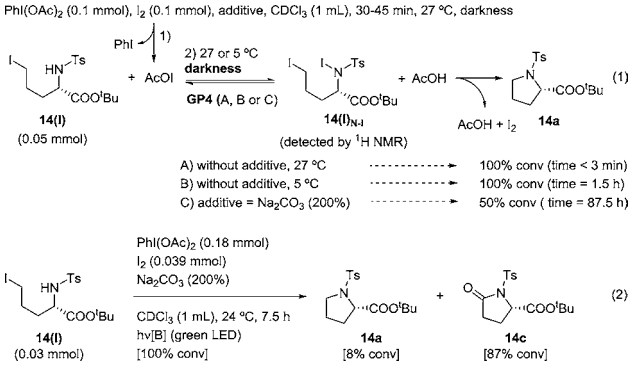
Table 2. NMR-Monitored Experiments with 14



entry	procedure[a]	A, B (mmol)	additive	[c] (M)	hν[b]	time (h)	conv[c] 14a	conv[c] 14c
1	GP1	4, 5	-	0.1	[A]	4.5	73	-
2	GP3	6, 1.4	Na_2CO_3	0.03	[A+ f]	6	4	88
3	GP3	2, 2	-	0.05	dark	0.4[d]	-	-
4	GP3	2, 2	Na_2CO_3	0.05	dark	3.6[e]	-	-

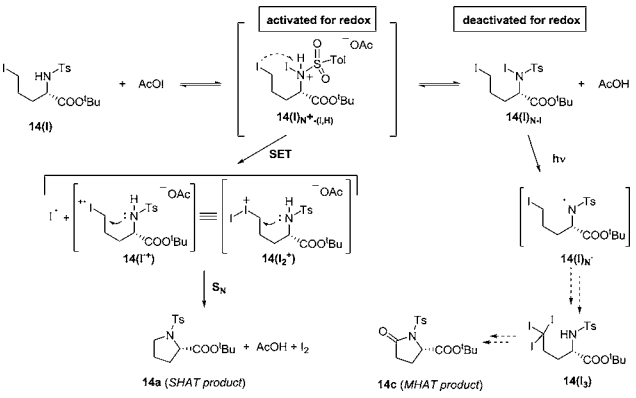
[a]GP1: $PhI(OAc)_2$ added portionwise, 60−65 °C; GP3: all reagents added in one portion, 26−27 °C. [b][A] = tungsten lamps (80 W), [A + f] = filtered light (λ > 445 nm). [c]Calculated by ^{1}H NMR. [d](**14**/**14_{N-I}**, 1:1.52) after 20 min. [e](**14**/**14_{N-I}**, 1:0.31) after 3.6 h.

Scheme 3. Evolution of 14(I) toward 14a or 14c



was possible to monitor it by ^{1}H NMR and plot the concentrations versus time for **14(I)**, **14a**, and **$14(I)_{N-I}$**, providing a graph consistent with a second-order pre-equilibrium first-order reaction, the pathway suggested in eq 1, where **$14(I)_{N-I}$** is proposed as an intermediate (Scheme 4 and Scheme S11, Supporting Information).

Scheme 4. Proposed Mechanism for the Cyclization Step (Key of Chemoselectivity)



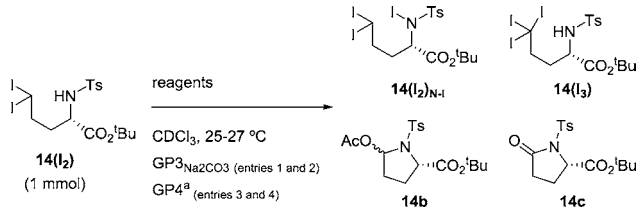
Therefore, we proposed that the cyclization step involved a mechanism of oxidative deiodination where the protonated *N*-iodoamide group of intermediate **$14(I)_{N-I}$** is responsible for the oxidative activation of the primary iodoalkane moiety.[17] As a consequence of the inhibition of the cyclization step by the presence of Na_2CO_3, further generation of *N*-radical species **$14(I)_N$**· is favored under irradiation and subsequent intra-

DOI: 10.1021/acs.orglett.5b00866
Org. Lett. 2015, 17, 2370−2373

molecular HAT reactions could take place (Scheme 4). As a result, the reaction continues toward the multiple (triple) iodination of the methyl group, leading to the formation of **14c** after cyclization.

Furthermore, we observed that **14(I$_2$)** could be efficiently transformed into **14c** employing the GP3$_{Na2CO3}$ (Table 3, entry

Table 3. Monitored Experiments with 14(I$_2$) by ^{1}H NMR



entry	reagents (mmol)	hν	time (h)	conv[b]	major product (conv)[b]
1	PhI(OAc)$_2$ (3.5), I$_2$ (1), Na$_2$CO$_3$ (100%)	[A]	2	87	**14c** (78.3)
2	PhI(OAc)$_2$ (10), I$_2$ (2), Na$_2$CO$_3$ (100%)	[A+f]	0.25	95.3	**14(I$_3$)** (87.2)[c]
3	PhI(OAc)$_2$ (4), I$_2$ (1)	-	3	100	**14b** (>95)
4	PhI(OAc)$_2$ (4), I$_2$ (1), Na$_2$CO$_3$ (200%)	-	3	12	**14b** (7)[d]

[a]GP4: reagents were stirred in $CDCl_3$ for 24 h prior to the addition of **14(I$_2$)**. [b]Calculated by ^{1}H NMR. [c]**14c** (8.1%) was also detected. [d]**14(I$_2$)$_{N-I}$** (22%) was also detected.

1) via cyclization of the pseudostable intermediate **14(I$_3$)** (entry 2). Likewise, we propose that an intramolecular redox activation is determinant in the formation of lactam **14c** (Scheme S12, Supporting Information). **14(I$_2$)** could also be almost quantitatively cyclized into **14b** (entry 3) following an oxidative deiodination mechanism in absence of light. This cyclization is much slower than in the case of **14(I)** toward **14a** and also does not compete with the third methyl-iodination process toward **14(I$_3$)** employing GP3$_{Na2CO3}$ under irradiation (compare entry 2 and entry 4, Scheme S12). Moreover, we elucidated that neither **14a** nor **14b** are intermediates toward **14c** under our reaction conditions (Scheme S16). Thus, we defined that the formation of pyrrolidines **Na** involves a single hydrogen atom transfer process (SHAT), while the formation of 2-pyrrolidinones requires a multiple hydrogen atom transfer process (MHAT).

In summary, the herein described tunable reactivity of *N*-iodo sulfonamides as radical precursors as well as oxidants of iodoalkanes can be used to achieve the chemoselective intramolecular functionalization of unactivated methyl groups. Consequently, we present a new methodology to synthesize pyrrolidines (SHAT process) or 2-pyrrolidinones (MHAT process) in a wide range of conformationally nonrestricted substrates. It has been useful to define the concept of SHAT/MHAT to refer to single or multiple oxidations at the same carbon center, which has been extended to achieve chemoselective fuctionalizations at unactivated methanediyl groups. These studies will appear in the literature in due course.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures, full characterization of products, DFT calculations, NMR-monitored experiments, additional schemes, and copies of NMR spectra. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b00866.

■ AUTHOR INFORMATION

Corresponding Authors

*E-mail: ccgm@ipna.csic.es.
*E-mail: ajherrera@ipna.csic.es.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was supported by the research programs ref CTQ2007-67492/BQU of the Ministerio de Educación y Ciencia, Spain, and Gobierno de Canarias ref ProID20100088. The COST Action CM1201 "Biomimetic Radical Chemistry" is also acknowledged. R.M. and D.R.-S. thank the Program JAE-C.S.I.C. for fellowships. We thank Dr. A. G. Santana (IPNA-CSIC) for helpful discussions.

■ REFERENCES

(1) For selected reviews on C(sp$_3$)−H functionalization in organic synthesis, see: (a) Godula, K.; Sames, D. *Science* **2006**, *312*, 67. (b) Davies, H. M. L.; Manning, J. R. *Nature* **2008**, *451*, 417. (c) Gutekunst, W. R.; Baran, P. S. *Chem. Soc. Rev.* **2011**, *40*, 1976. (d) Voica, A.-F.; Mendoza, A.; Gutekunst, W. R.; Fraga, J. O.; Baran, P. S. *Nature Chem.* **2012**, *4*, 629.

(2) Titouani, S. L.; Lavergne, J.-P.; Viallefont, P.; Jacquier, R. *Tetrahedron* **1980**, *36*, 2961.

(3) Reddy, L. R.; Reddy, B. V. S.; Corey, E. J. *Org. Lett.* **2006**, *8*, 2819.

(4) De Armas, P.; Francisco, C. G.; Hernández, R.; Salazar, J. A.; Suárez, E. *J. Chem. Soc., Perkin Trans. 1* **1988**, 3255.

(5) Carrau, R.; Hernández, R.; Suárez, E.; Betancor, C. *J. Chem. Soc., Perkin Trans. 1* **1987**, 937.

(6) Betancor, C.; Concepción, J. I.; Hernández, R.; Salazar, J. A.; Suárez, E. *J. Org. Chem.* **1983**, *48*, 4430.

(7) (a) Wolff, M. E. *Chem. Rev.* **1963**, *63*, 55. (b) Corey, E. J.; Hertler, W. R. *J. Am. Chem. Soc.* **1960**, *82*, 1657.

(8) (a) Hernández, R.; Rivera, A.; Salazar, J. A.; Suárez, E. *J. Chem. Soc., Chem. Commun.* **1980**, *20*, 958. (b) De Armas, P.; Carrau, R.; Concepción, J. I.; Francisco, C. G.; Hernández, R.; Suárez, E. *Tetrahedron Lett.* **1985**, *26*, 2493.

(9) For recent examples of radical-mediated aliphatic C−H amination reactions, see: Chen, H.; Chiba, S. *Org. Biomol. Chem.* **2014**, *12*, 42 and references cited therein.

(10) For a recent discussion on selective functionalization of methyl group employing *N*-radicals, see: Cherney, E. C.; Lopchuk, J. M.; Green, J. C.; Baran, P. S. *J. Am. Chem. Soc.* **2014**, *136*, 12592.

(11) (a) Togo, H.; Hoshina, Y.; Muraki, T.; Nakayama, H.; Yokoyama, M. *J. Org. Chem.* **1998**, *63*, 5193. (b) Katohgi, M.; Togo, H.; Yamaguchi, K.; Yokoyama, M. *Tetrahedron* **1999**, *55*, 14885.

(12) Fan, R.; Pu, D.; Wen, F.; Wu, J. *J. Org. Chem.* **2007**, *72*, 8994.

(13) (**Na**), (**Nb**), or (**Nc**): **N** refers to number of the precursor without any functionalization; **a** refers to pyrrolidine derivatives; **b** refers to 2-acetylpyrrolidine derivatives; **c** refers to 2-pyrrolidinone derivatives.

(14) Jung, M. E.; Piizzi, G. *Chem. Rev.* **2005**, *105*, 1735.

(15) Recommended ionization energies (IEs; in eV) of halopropanes (R−X → R−X$^{\bullet+}$) taken from: Lias, S. G. Ionization Energy Evaluation. In *NIST Chemistry WebBook, NIST Standard Reference Database Number 69*; Linstrom, P. J., Mallard, W. G., Eds.; National Institute of Standards and Technology, Gaithersburg, MD, http://webbook.nist.gov (retrieved September 19, 2014). $ICH_2-CH_2-CH_3$ (9.26); $CH_3-CHI-CH_3$ (9.19).

(16) The results obtained when other interesting selected conditions were employed are summarized in the Supporting Information.

(17) (a) Zefirov, N. S.; Zhdankin, V. V.; Koz'min, A. S. *J. Org. Chem.* **1985**, *50*, 1872. (b) Macdonalds, T. L.; Narasimhan, N. *J. Org. Chem.* **1985**, *50*, 5000. (c) Gallos, J.; Varvoglis, A. *J. Chem. Soc., Perkin Trans. 1* **1983**, 1999.

DOI: 10.1021/acs.orglett.5b00866
Org. Lett. 2015, 17, 2370−2373