Organic LETTERS

Letter

pubs.acs.org/OrgLett

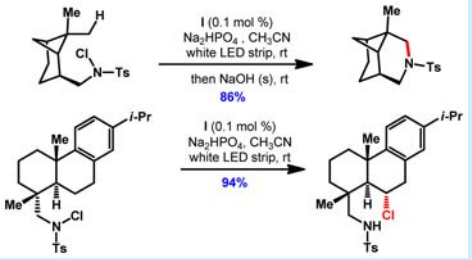
Visible-Light-Promoted Remote C(sp^3)−H Amidation and Chlorination

Qixue Qin and Shouyun Yu*

State Key Laboratory of Analytical Chemistry for Life Science, School of Chemistry and Chemical Engineering, Nanjing University, Nanjing, 210093, China

Supporting Information

ABSTRACT: A visible-light-promoted C(sp^3)−H amidation and chlorination of *N*-chlorosulfonamides (NCSs) is reported. This remote C(sp^3)−H functionalization can be achieved in weak basic solution at room temperature with as little as 0.1 mol % of a photocatalyst. A variety of nitrogen-containing heterocycles (up to 94% yield) and chlorides (up to 93% yield) are prepared from NCSs. Late-stage C(sp^3)−H functionalization of complex and biologically important (−)-*cis*-myrtanylamine and (+)-dehydroabietylamine derivatives can also be achieved with excellent yields and regioselectivity.



Selective and deliberate functionalization of inert C−H bonds, which has the potential to revolutionize the synthesis of complex molecules dramatically, is a long sought after goal in organic synthesis.[1] Nitrogen-centered radicals, which can be used directly to enable C−H amination/amidation, have not received much attention in the synthetic community.[2] The lack of methods for their effective generation and their high reactivity are possible reasons. Very recently, our group[3a] and others[3b−f] reported visible-light-induced C−H amidations of arenes and heteroarenes using different nitrogen sources (Figure 1a). The key step in these transformations is the formation of nitrogen-centered amidyl radicals from different precursors under visible light.[3,4] Despite significant advances, all these works focused on the amidation of C(sp^2)−H bonds. These promising results inspired us to exploit the feasibility of the more challenging C(sp^3)−H amidation under photoredox catalysis.[5]

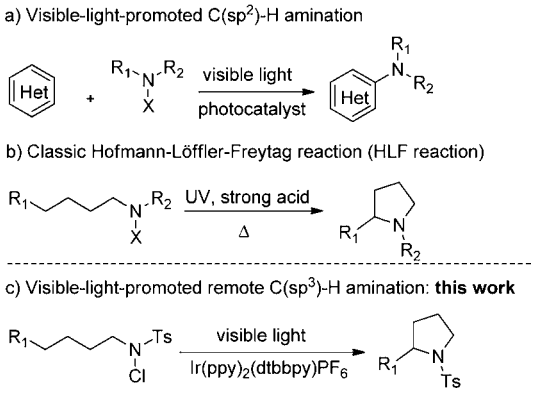


Figure 1. C−H amination/amidation.

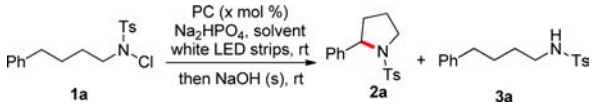
C(sp^3)−H functionalization is a formidable synthetic challenge due to activity and selectivity issues.[6] Efforts toward such a goal can be traced back to the historical Hofmann−Löffler−Freytag (HLF) reaction in the late 19th century (Figure 1b).[7] Later, numerous improvements were introduced to make this reaction more synthetically useful.[8] However, the requirement of ultraviolet photolysis, strongly acidic media, or oxidants restrains its applications in organic synthesis.[7−9] Due to the synthetic importance of remote C(sp^3)−H functionalization, as well as our research interests on visible-light-mediated radical chemistry,[10] we sought to develop a visible-light-promoted remote C(sp^3)−H functionalization of *N*-chlorosulfonamides (NCSs) that would address the synthetic limitations described above (Figure 1c).

Our efforts toward this goal initially focused on intramolecular cyclization of NCS **1a** ($E_p^{1a/1a-\bullet}$ = −0.470 V vs SCE). A solution of **1a** in CH_3CN was irradiated by white LED strips in the presence of photocatalyst $Ir(ppy)_2(dtbbpy)PF_6$ (**I**) and Na_2HPO_4 for 6 h at room temperature. After **1a** was consumed as monitored by TLC analysis, the reaction mixture was treated with solid NaOH directly and stirred for another 4 h. The desired pyrrolidine **2a** could be obtained in 52% NMR yield, together with a 40% yield of dechlorination product **3a** as a major byproduct (Table 1, entry 1). This encouraging result prompted us to improve this reaction further. It was found that the loading of the photocatalyst had an important impact on the outcome of this transformation. When more photocatalyst **I** (2 mol %) was employed, less desired product **2a** was produced with a comparable yield of side product **3a** (entry 2). When 0.5 mol % of **I** was used, a 79% NMR yield of **2a** was given together with a 13% yield of **3a** (entry 3). To our delight, when the photocatalyst loading was reduced to 0.1 mol %, the NMR yield of **2a** increased to 87% (83% isolated yield, entry 4). Various solvents, such as toluene, MeOH, EtOAc, DMSO,

Received: February 25, 2015
Published: April 8, 2015

DOI: 10.1021/acs.orglett.5b00582
Org. Lett. 2015, 17, 1894−1897

Table 1. Reaction Optimization[a]



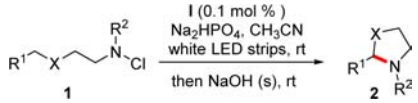
entry	PC	solvent	2a/%[b]	3a/%[b]
1	**I** (1 mol %)	CH_3CN	51	40
2	**I** (2 mol %)	CH_3CN	33	39
3	**I** (0.5 mol %)	CH_3CN	79	13
4	**I** (0.1 mol %)	CH_3CN	87(83[c])	9
5	**I** (0.1 mol %)	toluene	33	37
6	**I** (0.1 mol %)	CH_3OH	42	41
7	**I** (0.1 mol %)	EtOAc	trace	50
8	**I** (0.1 mol %)	DMF	63	30
9	**I** (0.1 mol %)	DMSO	trace	90
10	**I** (0.1 mol %)	THF	28	65
11	**I** (0.1 mol %)	CH_2Cl_2	58	28
12	**II** (0.1 mol %)	CH_3CN	69	24
13	**III** (0.1 mol %)	CH_3CN	79	9
14	**IV** (0.1 mol %)	CH_3CN	38	31
15	none	CH_3CN	NR	NR
16[d]	**I** (0.1 mol %)	CH_3CN	34	38
17[e]	**I** (0.1 mol %)	CH_3CN	NR	NR

[a]Reaction conditions: A solution of **1a** (0.2 mmol, 1.0 equiv), Na_2HPO_4 (0.24 mmol, 1.2 equiv), and photocatalyst in indicated solvent (3.0 mL) was irradiated by white LED strips for 6 h, and then the reaction mixture was treated with solid NaOH (0.24 mmol, 1.2 equiv) for another 4 h. [b]Yields were determined by ^1H NMR using CH_2Br_2 as an internal standard. [c]Isolated yield. [d]No Na_2HPO_4. [e]No irradiation. NR = no reaction.

THF, and CH_2Cl_2, were then examined (entries 5−11). However, none of them gave improved results. Other photocatalysts, such as $Ir(ppy)_3$ (**II**), $Ru(phen)_3(PF_6)_2$ (**III**), and $Ru(bpy)_3(PF_6)_2$ (**IV**), were not superior to photocatalyst **I** (entries 12−14). Control experiments verified the necessity of the base, irradiation, and photocatalyst (entries 15−17). Without visible light irradiation or a photocatalyst, the starting material **1a** was fully recovered. And without Na_2HPO_4, the yield of **1a** dropped to 34%.

After the optimized conditions were established, we next sought to explore the substrate scope of this visible-light-mediated intramolecular C(sp^3)−H amidation (Table 2). It was found that protecting groups on the nitrogen atom had a significant impact on the outcome of the reactions. Electron-rich NCS **1b** gave a slightly better isolated yield of the desired pyrrolidine **2b** (88%) while electron-deficient NCSs **1c** and **1d** gave much worse yields (42% for **2c** and 28% for **2d**). *N*-Chlorocarbamate **1e** ($E_p^{1e/1e^{-\bullet}}$ = −0.682 V vs SCE) and *N*-chloroalkyl amine **1f** could not go through this transformation, and the starting materials could be recovered fully due to their lower oxidative capacity compared to **1a**. A variety of 2-substituted pyrrolidines **2g−2j** were prepared in good to excellent yields (57−94%). 3-Substituted and 2,5-disubstituted pyrrolidines **2k** (86%) and **2l** (78%) were also accessible by means of this method. Notably, optically active isoleucine-derived 2,3-disubstituted pyrrolidines **2m** and **2n** could be provided as a single isomer with 85% and 56% yields, respectively. To our delight, acid-sensitive oxazolidines **2o** and **2p**, which are not accessible under classic HLF conditions, could be produced under our established conditions with moderate to good yields. Cyclic benzosulfonamides **2q** and **2r**

Table 2. Scope of Intramolecular C(sp^3)−H Amidation[a]



entry	substrate	product	yield (%)[b]
1	R = Ts (**1a**)	**2a**	83
2	R = *p*-MeOPhSO$_2$ (**1b**)	**2b**	88
3	R = *p*-NO$_2$PhSO$_2$ (**1c**)	**2c**	42
4	R = *o*-NO$_2$PhSO$_2$ (**1d**)	**2d**	28
5	R = Boc (**1e**)	**2e**	trace
6	R = CH_3 (**1f**)	**2f**	trace
7	R = H (**1g**)	**2g**	57
8	R = CH_3 (**1h**)	**2h**	94
9	R = *n*-Bu (**1i**)	**2i**	81
10	R = CH_2CN (**1j**)	**2j**	63
11	**1k**	**2k**	86
12	**1l**	**2l**	78 (dr = 3:2)
13	**1m**	**2m**	85
14	**1n**	**2n**	56
15	**1o**	**2o**	68
16	**1p**	**2p**	34
17	R = H (**1q**)	**2q**	46
18	R = CH_3 (**1r**)	**2r**	62

[a]Reaction conditions: A solution of **1** (0.2 mmol, 1.0 equiv), Na_2HPO_4 (0.24 mmol, 1.2 equiv), and **I** (0.1 mol %) in CH_3CN (3.0 mL) was irradiated by white LED strips for 4−18 h, and then the reaction mixture was treated with solid NaOH (0.24 mmol, 1.2 equiv) for another 4 h. [b]Isolated yield.

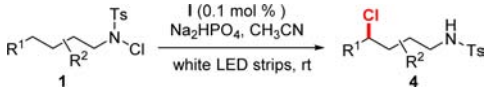
could be provided in satisfactory yields. It is worthy of note that **2q** is easily overoxidized under Suárez's modified conditions of the HLF reaction.[11]

Interestingly, when NCSs were subjected to standard conditions, but without adding solid NaOH, C(sp^3)−H chlorination products could be isolated. As shown in Table 3,

DOI: 10.1021/acs.orglett.5b00582
Org. Lett. 2015, 17, 1894−1897

a serial of chlorides **4a**–**4f** could be prepared in good yields (64–93%) with the assistance of this newly developed method.

Table 3. Scope of C(sp^3)–H Chlorination[a]



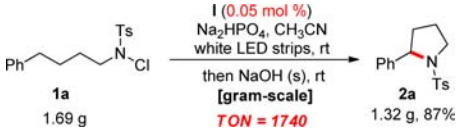
1 4

entry	1	product	yield (%)[b]
1	R = Ph, (**1a**)	**4a**	90
2	R = H (**1g**)	**4b**	64
3	R = *n*-Bu (**1i**)	**4c**	93
4	**1m**	**4d**	91
5	**1n**	**4e**	65
6	**1s**	**4f**	88 (dr = 2:1)

[a]Reaction conditions: A solution of **1** (0.2 mmol, 1.0 equiv), Na_2HPO_4 (0.24 mmol, 1.2 equiv), and **I** (0.1 mol %) in CH_3CN (3.0 mL) was irradiated by white LED strips for 4–12 h. [b]Isolated yield.

Encouraged by these results, we subsequently conducted the intramolecular C(sp^3)–H amidation on a gram scale, demonstrating its practicability. As shown in Scheme 1, when

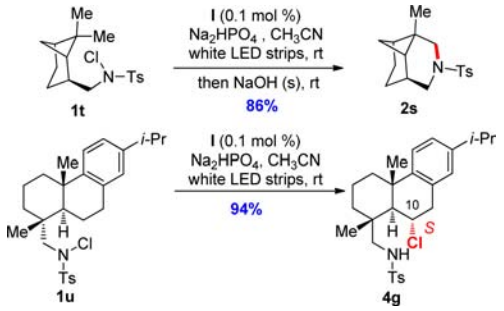
Scheme 1. Gram-Scale Preparation of 2a



1.69 g of NCS **1a** was amidated in the presence of as little as 0.05 mol % of the photocatalyst **I**, a comparative isolated yield of **2a** (87%, 1.32 g) was achieved with the turnover number (TON) = 1740.

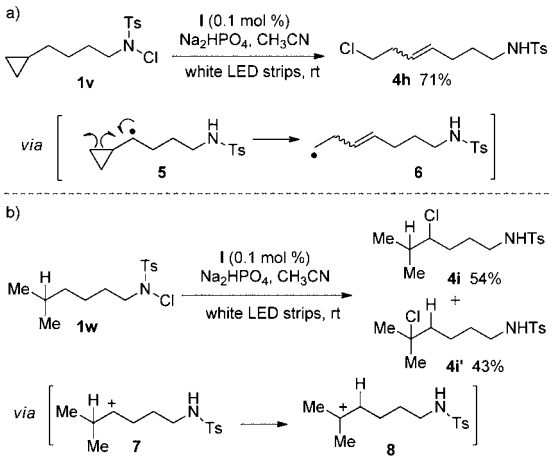
The mildness of the remote C(sp^3)–H functionalization conditions prompted us to investigate the feasibility of late-stage modification of complex and biologically important molecules. For example, matrix-2 protein inhibitor (−)-*cis*-myrtanylamine-derived NCS **1t**[12] was subjected to standard C(sp^3)–H amidation conditions, and piperidine **2s** was isolated in 86% yield as one isomer. A six-membered ring was formed instead of a five-membered ring due to conformation restriction.[13] When (+)-dehydroabietylamine-derived NCS **1u** went through C(sp^3)–H chlorination conditions, C10-chlorination product **4g** was produced in 94% yield as a sole product. Dehydroabietylamine derivatives possess broad interesting pharmacological activities, such as antitumor and antimalarial activities.[14] The structures and stereochemistry of **2s** and **4g** were established unambiguously by single crystal X-ray diffraction analysis (Scheme 2).[15]

Scheme 2. Late-Stage Functionalization of 1t and 1u



To understand the mechanism, a series of control reactions were conducted, as shown in Scheme 3. The reaction could be

Scheme 3. Control Experiments



terminated completely when TEMPO was introduced to the reaction mixture, which indicated that this reaction goes through a one-electron transfer pathway. The radical-based mechanism could be further supported by a radical clock experiment.[16] When cyclopropane-derived NCS **1v** went through this transformation, the ring-open product **4h** was obtained via the key intermediates **5** and **6** (Scheme 3a). When NCS **1w** was subjected to the standard chlorination conditions, 54% of desired chloride **4i** was isolated, together with rearrangement product **4i′** (43% yield) (Scheme 3b). Given that a radical 1,6-shift is unfavorable when a 1,5-shift is available, chloride **4i′** could be generated from carbocation **8**, which was formed from carbocation **7** through the Meerwein-type rearrangement. This phenomenon suggests that this reaction goes through a radical-polar crossover mechanism rather than a chain propagation mechanism. Light off/on and time profile experiments for **1a** and **1g** (for details, see Supporting Information) were also carried out to support this hypothesis. It was observed that the reaction progressed smoothly with light irradiation, but little conversion was observed when the light resource was removed. This experiment suggests that regeneration of the photocatalyst is necessary for the full consumption of NCSs.

On the basis of these observations, a plausible mechanism is proposed (Figure 2). First, the photocatalyst Ir^{III} is irradiated to the excited state Ir^{III}*, which is then oxidatively quenched by NCS **1a** with generation of Ir^{IV} and nitrogen-centered radical **9** respectively. Radical **9** undergoes an intramolecular 1,5-

DOI: 10.1021/acs.orglett.5b00582
Org. Lett. 2015, 17, 1894–1897

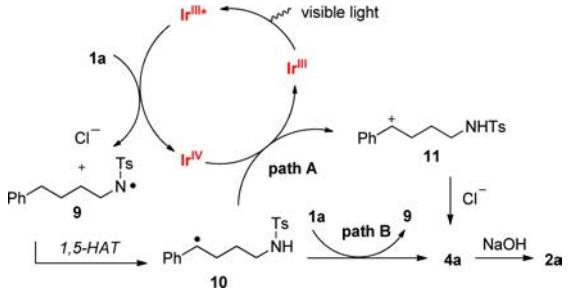


Figure 2. Proposed mechanism.

hydrogen atom transfer (HAT) to generate carbon-centered radical **10**. The radical **10** is oxidized to carbocation **11** by Ir^{IV} with regeneration of Ir^{III} (path A). Cation **11** is finally trapped by chloride to give chlorination product **4a**. At this stage, a short chain propagation mechanism (path B) cannot be ruled out completely.

In summary, we have described a visible-light-promoted remote C(sp^3)−H functionalization in the presence of 0.1 mol % of a photocatalyst. This remote C(sp^3)−H amidation and chlorination from NCSs can be achieved in weak basic solution at room temperature. The reaction can be scaled up to gram scale with as litlle as 0.05 mol % of the photocatalyst. A variety of nitrogen-containing heterocycles and chlorides are prepared from NCSs in good to excellent yields. Late-stage C(sp^3)−H functionalization of complex and biologically important (−)-*cis*-myrtanylamine and (+)-dehydroabietylamine derivatives can also be achieved. We expect this powerful protocol to be of broad utility in the synthesis and modification of biologically important *N*-containing heterocycles, as well as natural products, which are not easily accessible by means of a conventional HLF reaction and other variants.

■ ASSOCIATED CONTENT

Supporting Information

Full experimental, CIF information, and characterization data for all compounds are provided. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: yushouyun@nju.edu.cn.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

Financial support from the 863 program (2013AA092903), the National Natural Science Foundation of China (21472084 and 81421091), and the Natural Science Foundation of Jiangsu Province (BK20131266) is acknowledged. We thank Dr. Yue Zhao for the refinement of the single crystal data.

■ REFERENCES

(1) For recent selected reviews on C−H functionalization: (a) Engle, K. M.; Mei, T.-S.; Wasa, M.; Yu, J.-Q. *Acc. Chem. Res.* **2012**, *45*, 788. (b) Wencel-Delord, J.; Dröge, T.; Liu, F.; Glorius, F. *Chem. Soc. Rev.* **2011**, *40*, 4740. (c) Sun, C.-L.; Li, B.-J.; Shi, Z.-J. *Chem. Rev.* **2011**, *111*, 1293. (d) Lyons, T. W.; Sanford, M. S. *Chem. Rev.* **2010**, *110*, 1147.

(2) For selected recent reviews on nitrogen-centered radicals, see: (a) Chiba, S. *Chimia* **2012**, *66*, 377. (b) Hofling, S. B.; Heinrich, M. R. *Synthesis* **2011**, 173. (c) Minozzi, M.; Nanni, D.; Spagnolo, P. *Chem.—Eur. J.* **2009**, *15*, 7830.

(3) (a) Qin, Q.; Yu, S. *Org. Lett.* **2014**, *16*, 3504. (b) Allen, L. J.; Cabrera, P. J.; Lee, M.; Sanford, M. S. *J. Am. Chem. Soc.* **2014**, *136*, 5607. (c) Kim, H.; Kim, T.; Lee, D. G.; Roh, S. W.; Lee, C. *Chem. Commun.* **2014**, *50*, 9273. (d) Song, L.; Zhang, L.; Luo, S.; Cheng, J.-P. *Chem.—Eur. J.* **2014**, *20*, 14231. (e) Brachet, E.; Ghosh, T.; Ghosh, I.; König, B. *Chem. Sci.* **2015**, *6*, 987. (f) Greulich, T. W.; Daniliuc, C. G.; Studer, A. *Org. Lett.* **2015**, *17*, 254.

(4) (a) Hu, X.-Q.; Chen, J.-R.; Wei, Q.; Liu, F.-L.; Deng, Q.-H.; Beauchemin, A. M.; Xiao, W.-J. *Angew. Chem., Int. Ed.* **2014**, *53*, 12163. (b) Musacchio, A. J.; Nguyen, L. Q.; Beard, G. H.; Knowles, R. R. *J. Am. Chem. Soc.* **2014**, *136*, 12217. (c) Cecere, G.; König, C. M.; Alleva, J. L.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2013**, *135*, 11521. (e) Schmidt, V. A.; Quinn, R. K.; Brusoe, A. T.; Alexanian, E. J. *J. Am. Chem. Soc.* **2014**, *136*, 14389.

(5) For selected reviews on visible-light photoredox catalysis, see: (a) Prier, C. K.; Rankic, D. A.; MacMillan, D. W. C. *Chem. Rev.* **2013**, *113*, 5322. (b) Xi, Y.; Yi, H.; Lei, A. *Org. Biomol. Chem.* **2013**, *11*, 2387. (c) Xuan, J.; Xiao, W.-J. *Angew. Chem., Int. Ed.* **2012**, *51*, 6828. (d) Narayanam, J. M. R.; Stephenson, C. R. J. *Chem. Soc. Rev.* **2011**, *40*, 102. (e) Yoon, T. P.; Ischay, M. A.; Du, J. *Nat. Chem.* **2010**, *2*, 527.

(6) For recent reviews on C(sp^3)−H functionalization: (a) Yuan, J.; Liu, C.; Lei, A. *Chem. Commun.* **2015**, *51*, 1394. (b) Chiba, S.; Chen, H. *Org. Biomol. Chem.* **2014**, *12*, 4051. (c) Jeffrey, J. L.; Sarpong, R. *Chem. Sci.* **2013**, *4*, 4092. (d) Hartwig, J. F. *Chem. Soc. Rev.* **2011**, *40*, 1992. (e) Newhouse, T.; Baran, P. S. *Angew. Chem., Int. Ed.* **2011**, *50*, 3362. (f) Cho, S. H.; Kim, J. Y.; Kwak, J.; Chang, S. *Chem. Soc. Rev.* **2011**, *40*, 5068. (g) Gutekunst, W. R.; Baran, P. S. *Chem. Soc. Rev.* **2011**, *40*, 1976.

(7) (a) Löffler, K.; Freytag, C. *Ber.* **1909**, *42*, 3427. (b) Hofmann, A. W. *Ber.* **1883**, *16*, 558. For selected reviews, see: (c) Mackiewicz, P.; Furstoss, R. *Tetrahedron* **1978**, *34*, 3241. (d) Neale, R. S. *Synthesis* **1971**, 1. (e) Wolff, M. E. *Chem. Rev.* **1963**, *63*, 55.

(8) (a) Baran, P. S.; Chen, K.; Richter, J. M. *J. Am. Chem. Soc.* **2008**, *130*, 7247. (b) Fan, R.; Pu, D.; Wen, F.; Wu, J. *J. Org. Chem.* **2007**, *72*, 8994. (c) Reddy, L. R.; Reddy, B. V. S.; Corey, E. J. *Org. Lett.* **2005**, *8*, 2819. (d) Francisco, C. G.; Herrera, A. J.; Suárez, E. *J. Org. Chem.* **2003**, *68*, 1012. (e) Betancor, C.; Concepcion, J. I.; Hernandez, R.; Salazar, J. A.; Suárez, E. *J. Org. Chem.* **1983**, *48*, 4430. (f) Baldwin, S. W.; Doll, T. J. *Tetrahedron Lett.* **1979**, *20*, 3275. (g) Ban, Y.; Kimura, M.; Oishi, T. *Chem. Pharm. Bull.* **1976**, *24*, 1490.

(9) (a) Shi, Y.; Yang, B.; Cai, S.; Gao, S. *Angew. Chem., Int. Ed.* **2014**, *53*, 9539. (b) Cherney, E. C.; Lopchuk, J. M.; Green, J. C.; Baran, P. S. *J. Am. Chem. Soc.* **2014**, *136*, 12592.

(10) (a) Jiang, H.; Cheng, Y.; Zhang, Y.; Yu, S. *Org. Lett.* **2013**, *15*, 4884. (b) Jiang, H.; Cheng, Y.; Wang, R.; Zheng, M.; Zhang, Y.; Yu, S. *Angew. Chem., Int. Ed.* **2013**, *52*, 13289.

(11) Katohgi, M.; Togo, H.; Yamaguchi, K.; Yokoyama, M. *Tetrahedron* **1999**, *55*, 14885.

(12) Hu, W. H.; Zeng, S. G.; Li, C. F.; Jie, Y. L.; Li, Z. Y.; Chen, L. *J. Med. Chem.* **2010**, *53*, 3831.

(13) (a) Kimura, M.; Ban, Y. *Synthesis* **1976**, 201. (b) Dupeyre, R. M.; Rassat, A. *Tetrahedron Lett.* **1973**, *14*, 2699.

(14) Aicher, T. D.; Damon, R. E.; Koletar, J.; Vinluan, C. C.; Brand, L. J.; Gao, J. P.; Shetty, S. S.; Kaplan, E. L.; Mann, W. R. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 2223.

(15) CCDC 1042250 (**2s**) and CCDC 1042176 (**4g**) contain the supplementary crystallographic data for this paper.

(16) (a) Bowry, V. W.; Lusztyk, J.; Ingold, K. U. *J. Am. Chem. Soc.* **1991**, *113*, 5687. (b) Griller, D.; Ingold, K. U. *Acc. Chem. Res.* **1980**, *13*, 317.

DOI: 10.1021/acs.orglett.5b00582
Org. Lett. 2015, 17, 1894−1897